ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY

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ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY

ANTIBIOTICA-PROFYLAXE IN DE GALWEGCHIRURGIE

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF.DR.C.J.RIJNVOS
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
20 mei 1992 om 15.45 uur

DOOR

WILLEM SIMON MEIJER
GEBOREN TE 'S-GRAVENHAGE

PROMOTIECOMMISSIE:

Promotor:	Prof.Dr.J.Jeekel
Co-promotor:	Dr.Ir.P.I.M.Schmitz
Overige leden:	Prof.Dr.M.F.Michel
	Prof.R.van Strik
	Prof.Dr.O.T.Terpstra

To my parents,
Marion, Susan, Evert-Jan

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VOORWOORD

De herhaalde opmerking van mijn vader "een niet-gepromoveerde specialist is een halve specialist" is voor mij de voornaamste drijfveer geweest om dit proefschrift te schrijven. Hoewel het idee van een promotie-onderzoek al lang door mijn hoofd speelde, is het toch bij toeval zover gekomen. Na deelname van de heelkundige afdeling van het Sint Clara Ziekenhuis (Rotterdam) aan een multicentrisch onderzoek over antibiotische behandeling van een geperforeerde blindedarmontsteking onder leiding van Dr.J.C.J.Wereldsma, chirurg uit het Sint Franciscus Gasthuis (Rotterdam), werd door hem het voorstel gedaan de samenwerking te continueren. Gedacht werd aan een nieuwe antibiotica-studie, met eveneens een nieuwe studie-coördinator. Gaarne ben ik op zijn voorstel ingegaan. Met medewerking van chirurgen en microbiologen uit het Sint Clara Ziekenhuis en Sint Franciscus Gasthuis te Rotterdam werd een protocol opgesteld voor een prospectieve multicentrische studie: de GALANT-trial. GALANT werd afgeleid van GALweg en ANTibiotica.

Het is niet mogelijk om iedereen, die aan de totstandkoming van dit proefschrift heeft bijgedragen, persoonlijk te bedanken. Allen die hebben meegewerkt aan de trial wil ik hartelijk danken, vooral de trial-coördinatoren, apothekers en microbiologen van de deelnemende klinieken. Door uw aller inzet is het mogelijk gebleken een grote multicentrische studie tot een goed einde te brengen.

Enkelen wil ik in het bijzonder noemen. Ten eerste mijn promotor, Prof.Dr.J.Jeekel. Beste Hans, ik dank je zeer voor de tijd die je geïnvesteerd hebt in het kritisch doornemen van het manuscript. De meeste dank ben ik zonder meer verschuldigd aan Dr.Ir.P.I.M. Schmitz, mijn co-promotor. Beste Paul, wat jij voor mij, voor de studie en voor dit proefschrift hebt betekend, is zeer veel en moeilijk onder woorden te brengen. Voor je inbreng, enthousiasme, behulpzaamheid en vriendschap ben ik je zeer erkentelijk. Je hulp betrof niet alleen de statistische bewerking van de Galant-trial, maar vooral ook de meta-analyse. Daarnaast ben ik je dankbaar voor alle nuttige adviezen bij de publicatie van een aantal hoofdstukken van dit proefschrift.

De begeleiding en statistische bewerking van de Galant-trial werd financiëel mogelijk gemaakt door Glaxo B.V.. In het bijzonder wil ik Paul Jonker en Arthur Storm hiervoor dankzeggen. Hun belangstelling voor de studie en de hulp bij het bewerken van een aantal trial-formulieren werd zeer gewaardeerd. De begeleiding van

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Cora Bouman wil ik bedanken voor het inbrengen van alle gegevens in de computer, een enorm werk, waar ik zelf geen gat meer in zag.

Laraine Visser was onmisbaar voor de Engelse vertaling c.q. tekstuele correcties.

Mijn collegae chirurgen van het Sint Clara Ziekenhuis te Rotterdam, alsook de chirurgische arts-assistenten, hebben mij regelmatig "gespaard" en steeds belangstelling getoond voor mijn promotie-onderzoek. Hiervoor ben ik hen zeer erkentelijk.

Mijn echtgenote en kinderen werden het meest getroffen door mijn tijdelijke "afwezigheid". Maar mijn aandacht zal nu weer op andere, meer huislijke, zaken gericht zijn, dus: Susan en Evert-Jan, proefschrift wordt weer proefwerk!

CONTENTS

Chapter 1

INTRODUCTION

INTRODUCTION

1.1 Introduction

Even in health, man's environment is one of ubiquitous bacterial presence. As a consequence all wounds are, to a certain extent, contaminated, if only from the normal skin flora. Along with a number of other factors, the development of a wound infection is related to the degree of this bacterial contamination[1,2]. Prior to Pasteur's studies on bacteriology and Lister's application of them to wounds most, if not all, wounds became infected. The treatment of established wound infections, however, is beyond the scope of this thesis. Attention will focus on the prevention of wound infections. Lowering the incidence of wound infections can be directed to (1) destroying organisms after they have reached the wound, and (2) preventing the arrival or growth of organisms in subcutaneous tissues. The aim of antibiotic prophylaxis is to prevent any bacteria, released into the operative field at the time of surgery, from multiplying[3,4]. The use of antibiotics for prophylaxis has only recently been accepted as a useful adjuvant to the established principles of antisepsis in surgery.

In cholecystectomy, the problems of operative mortality and serious morbidity have been largely solved. At present, the most common complication of traditional cholecystectomy is wound infection[5]. The importance of reducing this source of morbidity is obvious. Presented in this thesis is a randomized study designed to assess the efficacy of a preoperative, single-dose prophylaxis of cefuroxime.

This introductory chapter of the thesis includes some historical aspects of asepsis, antisepsis, and antimicrobial prophylaxis of wound infection, as well as the history of cholecystectomy. The aetiology of wound infections and the bacteriology of bile are also discussed in this chapter. Furthermore the basic principles of antibiotic prophylaxis and the objectives of the study are outlined. The following five chapters include the original studies. At the end of the thesis a general discussion and conclusions drawn from the study are presented. The thesis is concluded with a summary.

1.2 Historical aspects

1.2.1 Asepsis and antisepsis

Postoperative infections have been a source of problems for as long as surgery existed. A little over 100 years ago the mortality rate due to infected wounds approached levels up to 90 per cent. Generally, pus was the expected concomitant of wounds, but there was virtually no understanding of how it was produced. At that time, even those who accepted the principle that disease could be transmitted from person to person failed to see the connection between contamination and the gangrenous complications of surgical wounds. It was Ignaz Philipp Semmelweis (1818-1865; *Figure 1.1*) who noted that the annual mortality rate on one of the obstetrical wards of the Allgemeines Krankenhaus in Vienna reached almost 20 per cent, mainly due to puerperal fever. He discovered that the physicians and students usually came to the ward to examine patients directly from the autopsy room. Furthermore, he noted that the patients succombing to infections were usually those in a row of beds conforming to the routine of examination that day. His next step was to require physicians and students under his charge to scrub hands with soap and water and soak them in a chlorinated lime solution before entering

Figure 1.1 *Portrait of Ignaz Semmelweis, in 1857, who realized that fatal fevers after childbirth were caused by contamination on doctors' hands*

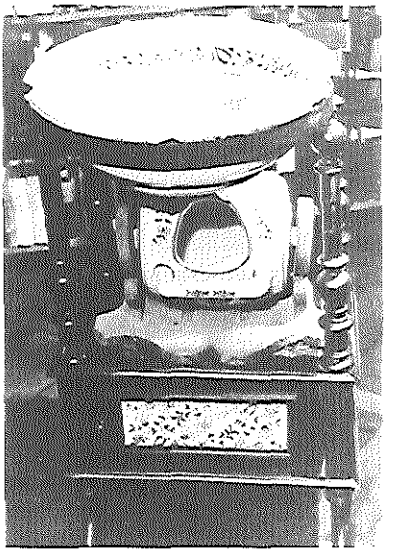

Figure 1.2 *Basin and stand used by Ignaz Semmelweis to scrub his hands before examining each patient*

the clinic or ward (*Figure 1.2*) and to repeat this after each examination. Over the next months, the obstetrical mortality rate declined to a low of 1.2 per cent. Semmelweis may be credited with being the first to construct a statistically tested system of asepsis (keeping germs away from the patient) before the germ theory had arrived[6].

Trained as a chemist, Louis Pasteur (1822-1895) discovered that bacteria acted differently on two types of tartaric acid crystals and he applied these observations to the problems of beet alcohol production (for the French wine industry), which a local manufacturer had asked him to investigate. Pasteur demonstrated that microscopic live creatures (microbes) are responsible for fermentation, and that some of these organisms grow in the presence of oxygen (aerobic) while others exist in the absence of free oxygen (anaerobic). The result was an entirely new focus; the germ concept of infection gradually developed and wound complications were viewed with a new perspective.

Joseph Lister (1827-1912), a British surgeon, noticed that broken bones over which the skin was intact usually healed without complication, but complicated fractures commonly developed infections and drainage of pus[7]. He thought that something circulating in the air was responsible - possibly invisible particles which he called "disease dust". When the work of Pasteur was brought to his attention, he appreciated the connection between his own observations on wounds and the microscopic bacteria involved in fermentation. Therefore, Lister sprayed carbolic acid over the patient during an operation in order to kill any bacteria before they could multiply in the wound (*Figure 1.3*)[8].

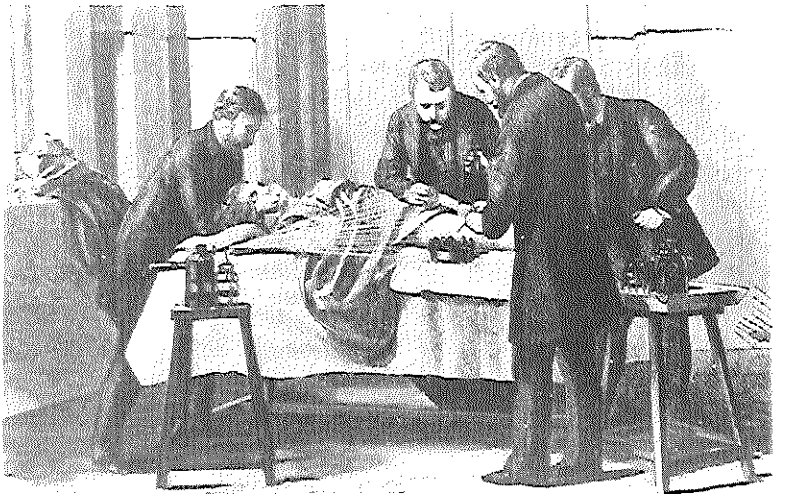

Figure 1.3 *Antiseptic surgery (1882) depicting use of Lister carbolic spray as antiseptic precaution during an operation*

Many surgeons failed to see the implications of the revelation that infections in wounds came from something "foreign" introduced at operation. They focused on the antiseptic itself (carbolic acid) and the mechanics of its use in sprays and soaks, thereby missing entirely the main concept. Later on, the principles and practice of aseptic surgery were further developed in Germany by Von Bergmann (1836-1907), assisted by Schimmelbusch (1860-1895)[9,10].

Ways of fighting microorganisms were given by the ideas and works of Paul Ehrlich (1854-1915). The advent of sulfonamides for the treatment of bacterial infections was a direct, though delayed, outgrowth of Ehrlich's demonstration that dyes could be antibacterial agents. Ehrlich had set in motion the activities of the 20th century that were to revolutionize the therapy of microbial diseases. In 1929, Alexander Fleming (1881-1955) reported in the British Journal of Experimental Pathology his observations on the antibacterial action of *Penicillium noctatum*, with the suggestion that the mold culture could be used to inhibit bacteria as a help in obtaining their culture isolation[11]. Whatever Fleming may have thought of the eventual usefulness of what he called penicillin, there was virtually no further research until Howard Florey and Ernst Chain from Oxford, England made studies in 1941, which convinced them that penicillin had great therapeutic potential. Other types of antibiotics followed in rapid order. Streptomycin was obtained from *Streptomyces griseus* in 1944. Since 1948 many other similar agents have entered the medical armamentarium, each with a special potency but also with its own limitations.

1.2.2 Antimicrobial prophylaxis of wound infections

After the discovery of penicillin in 1929, antibiotics were fairly extensively used in surgical procedures during the 1940s and 1950s. Although the initial use of antimicrobial prophylaxis was excessive and poorly focused, early studies reported no benefit[12-16], or even higher infection rates with such prophylaxis[17,18]. Many of these studies, however, were retrospective and badly controlled; moreover the basic principles of antimicrobial prophylaxis were not well understood. In fact, as many patients already had an infection, this could be seen as a "therapeutic" use of antibiotics. The disadvantages of prophylaxis were also emphasized, including the risks of hematological and hypersensitivity reaction, development of resistance and the masking of concomitant infectious diseases.

From reports published by Howes and Miles *et al.* it became apparent that the immune system of tissue, namely reaction of the wound to existing bacteria, was in fact active for only 1-3 hours after development of the wound[19,20]. Burke (1961) demonstrated that if penicillin, erythromycin, chloramphenicol or tetracyclin was injected 0-1 hour previously, the reaction to live *Staphylococcus aureus*, intracutaneously injected or

delivered via experimental incisions, was the same as the reaction to dead cultured staphylococci[21]. Burke, who was the first to speak of "prophylactic" antibiotics, proposed that the antibiotic should be given early in order to achieve an effective tissue concentration at the moment of entry of bacteria. This proved to be the scientific basis of antimicrobial prophylaxis. Based on these experimental studies, Linton suggested preoperative administration of clinical antibiotics[22]. This was evaluated prospectively by Bernard and Cole[3]. In their randomized study on gastrointestinal and gallbladder procedures 66 patients received, 1-2 hours preoperatively, an intramuscular injection of a combination of penicillin, methicillin and chloramphenicol. Compared with 79 patients receiving placebo only, there was a significant reduction in percentage wound infections from 21 to 5 per cent.

The clinical importance of preoperative administration of prophylactic antibiotics was established in a retrospective study on abdominal perforation wounds[23], and in the much-cited prospective study of Stone *et al* [24]. In the latter study it appeared that the group of patients receiving antibiotics 1-4 hours postoperatively had the same percentage wound infections as those receiving no antibiotics. Increasing numbers of studies continue to demonstrate the beneficial effects of antimicrobial prophylaxis. Currently, prophylaxis is a generally accepted procedure, providing that basic principles are observed (see *Chapter 1.4*).

1.2.3 Gallstone disease and cholecystectomy

As early as 2,000 B.C. there was anatomic knowledge of the liver, bile ducts and gallbladder, as demonstrated by clay models of sheep livers made by the Babylonians[25]. Despite this knowledge, the recognition of gallstones was not recorded until the 5th century. Alexander (525-606), a Greek physician, described concretions within the bile ducts[26]. In the 13th and 14th centuries observations of human gallstones were made with increasing frequency. Gradually, physicians began to associate the presence of gallstones with symptoms of abdominal pain, peritoneal inflammation and jaundice. Recognition of the manifestations of gallstones by physicians in the 16th and 17th centuries, when specific diagnostic methods were absent, is remarkable.

The possibility of surgical treatment of cholelithiasis had its origin in the 17th century. Johannus Jaenis has received credit for the first cholecystolithotomy in 1673 but, apparently, he extracted gallstones from a biliary fistula following spontaneous drainage of a suppurative gallbladder[27]. In 1743, Jean Louis Petit, a French surgeon, reported the puncture of an enlarged gallbladder by trocar and cannula, probably being the first invasive procedure of the gallbladder[28]. On June 15, 1867, John S. Bobbs of Indianapolis, U.S.A. performed the first elective cholecystostomy for hydrops of the gallbladder, or an appendage of this, on a 30-year-old patient[29].

From animal studies and various experiments in the mortuary, Carl Langenbuch of Berlin (1846-1901; *Figure 1.4*) concluded that the absence of the gallbladder had no adverse effects. The easiest way to perform this was via a laparotomy and extirpation of the gallbladder following ligation of the cystic duct and artery. Late in June, 1882 a 43-year-old man with episodes of colic for 16 years, was referred to him as chief of the Lazarus Hospital. An operation was set for the 15th of July. Before the operation measures of extraordinary exactness were taken to secure aseptic conditions. On that day Langenbuch performed the first cholecystectomy in man[30]. The next morning the patient was found to be without pain and enjoying a cigar. He was discharged early September, 1882. The operation was universally criticized. Robert Lawson Tait, a great pioneer in the field of abdominal surgery, advocated cholecystostomy as the procedure of choice in gallstone disease. He saw no reason for removing the gallbladder merely

Figure 1.4 Carl Langenbuch (1846-1901)

because of the presence of stones. Moreover, he opined that gallstones were derived from the intrahepatic bile ducts, and removal of the gallbladder would not change this condition[31]. Langenbuch, however, maintained that the gallbladder should be removed not because it contained stones, but because it formed them[32].

The controversy on cholecystostomy and cholecystectomy would last for several decades and retarded the further development of cholecystectomy. In 1890, eight years after the first operation, only 47 cholecystectomies had been performed by twenty surgeons[33]. Nowadays, approximately 400,000 cholecystectomies in the United States[34], 43,000 in the United Kingdom[35] and 17,000 cholecystectomies in The Netherlands[36] are performed every year.

1.3 Aetiology of wound infections

1.3.1 Exogenous and endogenous contamination

The cause of postoperative wound infection is multifactorial. Infection can be considered as the negative result of the degree and type of bacterial contamination on the one hand, and the patient's local defence mechanism on the other. The source of bacterial contamination was initially thought to be exclusively exogenous, caused by non-sterile instruments, personnel or operation room air. Even contamination via the patient's skin was generally seen as being exogenous. Since the times of Lister and Semmelweis much research has focused on prevention of exogenous contaminations: disinfecting the hands of surgeons and operating personnel[37]; cleaning the skin around the area to be operated[38,39]; use of surgical masks[40]; cleaning the air in the operation room by means of ultraviolet rays[41,42], positive pressure ventilation[43], and laminar flow[44]. Many of these aseptic and antiseptic techniques have generated strict rules, which should be observed by all operation department personnel[45,46]. Through these means, effective control of the major sources of exogenous bacteria has been achieved.

In spite of this, the percentage of wound infections did not reduce significantly[47]. This is attributable to the fact that, apart from exogenous forms, endogenous contamination is also possible. These endogenous contaminations stem from bacterial flora in the intestinal, urogenital or respiratory tracts - thus from the patient self[48]. Endogenous contamination of a wound, caused by opening of infected viscera, is the most frequently occurring cause of wound infections in abdominal operations[49]. In biliary tract surgery endogenous contamination is mainly due to infected bile[50].

1.3.2 Bacteriology of bile

In the normal gallbladder, bile is generally sterile. In diseases of the gallbladder bile may be infected; the reported incidence of bactobilia is variable, ranging from 8-42 per

cent[51-55]. It is well established that bacteria are more common in bile if the patient is jaundiced particularly if biliary obstruction is due to stones or a benign bile duct stricture, with significant lower numbers of bacteria in the bile of patients with malignant obstruction. The most frequently occurring diseases with infected bile include acute cholecystitis, choledocholithiasis, jaundice due to obstructive gallstones and biliodigestive fistula. Infection is also more common in patients aged over 70 years and patients with a resolving acute cholecystitis[56-58].

Infected bile is usually colonized by more than one organism. The more complex the pathology the greater the chance of mixed infections. More complicated cases are also characterized by a greater number of bacteria; these can be high as 10^6 per ml bile in patients with common bile duct stones or strictures[59]. In approximately 45 per cent of the patients with infected bile anaerobes are present, nearly always as part of a mixed infection[60]. The most frequently occurring aerobes are *Escherichia coli*, *Klebsiella* species and *Streptococcus faecalis*, whereas *Bacteroides fragilis* and other *Bacteroides* species form the largest genus of anaerobics[61,62]. *Clostridium perfringens* is sometimes present, but seldom of clinical relevance.

Furthermore Chetlin and Elliot, in a retrospective study of 1421 gallbladder operations, found that the chance of wound infection was 40 times greater in patients with infected bile[63]. Correlation between positive gallbladder cultures and wound infections with the same microorganisms has been confirmed by others[53,56,59,61].

1.4 Basic principles of antibiotic prophylaxis

Antimicrobial prophylaxis is defined as the use of antibiotics to prevent infection. This does not involve prevention of secondary infections of wound or drain, but concerns only those infections caused by contamination during the operative procedure. Surgical antibiotic prophylaxis has defined principles governing the absolute and provisionally established requirements for antibiotics. Needless to say, antimicrobial prophylaxis is no alternative for inferior surgical practice or insufficient aseptic management. The general principles of antibiotic prophylaxis are:

(1) Antimicrobials should be directed against the organisms most likely to be encountered in that particular operation;
(2) Antibiotics should be present in target tissues at the time of incision;
(3) The agent should be for short-term use and adequate plasma and tissue levels should be maintained for the duration of the operation and the immediate postoperative period only;
(4) The operations should have a significant risk of contamination or postoperative infection (i.e. clean-contaminated, contaminated and dirty operations);

(5) In situations where postoperative infection is rare, prophylaxis should be given only when infection would have catastrophic results;

(6) Potent antibiotics used for resistant organisms should not be used prophylactically (exceptions include those operations where infection could prove disastrous);

(7) The benefits of prophylaxis should outweigh the risks, e.g. the antibiotic should have no toxic effects and should not contribute to the emergence of antibiotic-resistant bacteria.

1.5 Aims of the study

(1) Assessment of the mode of current antibiotic prophylaxis in biliary tract surgery in The Netherlands. Herefore, a questionnaire was sent to the Chairmen of the Departments of Surgery of all Dutch hospitals. The results of this enquiry are presented in *Chapter 2*.

(2) A study on the traditional cholecystectomy was conducted in The Netherlands. Recent data from the Public Health Information Center about frequency, mortality and morbidity of cholecystectomy are reported in *Chapter 3*.

(3) The value of antibiotic prophylaxis in biliary tract surgery was reviewed by meta-analysis. The results of this meta-analysis are presented in *Chapter 4*.

(4) Assessment of the efficacy of single-dose prophylaxis of a short-acting antimicrobial in high risk biliary surgery. Herefore, a new major trial was designed in which single-dose cefuroxime was compared with multiple-dose cefuroxime. The results of this trial are presented in *Chapter 5*.

(5) Assessment of the cost effects of different prophylactic regimens in biliary surgery and potential cost savings, based on the results of the abovementioned studies. The cost aspect are reported in *Chapter 6*.

(6) The thesis is concluded with a general discussion and conclusions (*Chapter 7*).

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Chapter 2

ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY – CURRENT PRACTICE IN THE NETHERLANDS

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ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY – CURRENT PRACTICE IN THE NETHERLANDS

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2.1 Introduction

Although wound infections are not common after biliary tract operations, infections vary from 15 to 30 per cent when antibiotic prophylaxis is not used[1,2]. Meta-analysis of several randomized trials has confirmed the effectiveness of prophylaxis, with a stronger effect in patients at high risk[3]. Although many studies indicate that single-dose prophylaxis is effective, there is no consensus about timing and optimal duration of prophylaxis[3-5]. We, therefore, assessed the influence of data in the literature on the surgical practice in The Netherlands as well as the influence of different types of residency in general surgery.

2.2 Methods

In October 1988, a questionnaire (*Appendix A*) was sent to the Chairmen of the Departments of Surgery of 175 hospitals registered in the Yearbook 1987/1988 of the Association of Surgeons of The Netherlands. The questionnaire was sent with a pre-paid reply envelope. No follow-up was given to non-responders. The surgical clinics in The Netherlands are classified into three categories:

1. **A-clinic:** University or affiliated teaching hospital in general surgery with 6-years residency (32 clinics with 293 consultant surgeons and senior registrars);
2. **B-clinic:** teaching hospital with two-years residency in general surgery (23 clinics with 124 consultant general surgeons); and
3. **C-Clinic:** no training programme in general surgery (112 clinics with 375 consultant general surgeons).

The questionnaire sought information about: 1. Details of antibiotic use in elective cholecystectomy, 2. high risk factors as an indication for antibiotic prophylaxis, 3. details of agents used, and 4. treatment of acute cholecystitis.

The study comprised 167 out of a total of 175 departments of surgery, because cholecystectomy is seldom performed in children's hospitals and cancer centres, eight were excluded from the study.

2.3 Results

Eighty per cent (133/167) of the surgical clinics responded to the questionnaire (*Table 2.1*). One respondent refused to participate in the enquiry. The results of 132 hospitals i.e. a total of 652 surgeons are included in the study.

2.3.1 Antibiotic prophylaxis

Antibiotic prophylaxis is used in elective cholecystectomy in 100 surgical clinics, routinely in eight and selectively in 92 (*Table 2.2*). The high risk factors and the indications for antibiotic prophylaxis are listed in *Table 2.3*. The most frequent indications for prophylaxis are immuno-suppressive therapy (59 per cent) and recent rigors (54 per cent of the clinics). Morbid obesity is rarely considered an indication for prophylaxis (7 per cent of the clinics). The number of indications vary per hospital (mean per hospital 3.3). On an average, indications for prophylaxis are more often used in A-clinics (mean 4.0) than in B- or C-clinics (mean 3.3 and 3.0) (*Table 2.3*).

2.3.2 Antimicrobial agents

In the 100 hospitals with antibiotic prophylaxis in elective cholecystectomy, cephalos-

Table 2.1 *Response to the questionnaire sent to 175 hospitals in The Netherlands*

	Number of clinics (percentage)			
	A-clinic	B-clinic	C-clinic	Total
No response	2 (6)	5 (22)	27 (24)	34 (20)
Response	30 (94)	18 (78)	85 (76)	133 (80)
Total	32 (100)	23 (100)	112 (100)	167 (100)

Table 2.2 *Antibiotic prophylaxis in 132 hospitals in The Netherlands*

	Number of clinics (percentage)			
	A-clinic	B-clinic	C-clinic	Total
Never	3 (10)	3 (16)	26 (31)	32 (24)
Routinely	2 (7)	0	6 (7)	8 (6)
Selectively	25 (83)	15 (84)	52 (62)	92 (70)
Total	30 (100)	18 (100)	84 (100)	132 (100)

Table 2.3 *Specification of indications for antibiotic prophylaxis in 92 hospitals in The Netherlands*

	Number of clinics (percentage)			
	A-clinic	B-clinic	C-clinic	Total
Indications				
1. Age over 60-70 years	11 (44)	7 (47)	12 (23)	30 (33)
2. Rigors <1 week before operation	15 (60)	10 (67)	25 (48)	50 (54)
3. Attack of acute cholecystitis <1 month before operation	11 (44)	6 (40)	17 (33)	34 (37)
4. Jaundice	15 (60)	6 (40)	17 (33)	38 (41)
5. Stones or planned exploration of the common bile duct	16 (64)	4 (27)	22 (42)	42 (46)
6. Former biliary tract operation	10 (40)	1 (7)	7 (13)	18 (20)
7. Diabetes mellitus	6 (24)	2 (13)	11 (21)	19 (21)
8. Obesity	2 (8)	1 (7)	3 (6)	6 (7)
9. Immuno-suppressive therapy	8 (32)	10 (67)	36 (69)	54 (59)
10. Other	5 (20)	3 (20)	7 (13)	15 (16)
Number of indications				
1 to 4	15 (60)	12 (80)	44 (85)	71 (77)
5 to 8	10 (40)	3 (20)	8 (15)	21 (23)

porins account for 65 per cent (65/100), and penicillins for 21 per cent (21/100) of the agents used. First generation cephalosporins (cefazolin, cefradine) comprise 29 per cent (19/65) of all cephalosporins prescribed, second-generation (cefuroxime, cefamandole, cefamycine) 63 per cent (43/65), and third-generation (cefotaxime, ceftriaxone) eight per cent (6/65). Cefuroxime is most commonly used (36/65), followed by cefazolin (18/65). In 37 per cent metronidazole is added to cephalosporin.

Penicillins (ampicillin, amoxycillin, amoxycillin/clavulanic acid and piperacillin) are used in 21 surgical clinics, and in 14 of these clinics in combination with metronidazole or gentamicin. From the remaining 14 hospitals seven use metronidazole alone or in combination with gentamicin, and seven clinics have no fixed antibiotic regimen.

Table 2.4 *Duration of antibiotic prophylaxis in 100 hospitals in The Netherlands*

	Number of clinics (percentage)			
	A-clinic	B-clinic	C-clinic	Total
Single-dose	8 (30)	2 (13)	18 (31)	28 (28)
4-24 hours	17 (63)	11 (74)	29 (50)	57 (57)
2-5 days	2 (7)	2 (13)	9 (16)	13 (13)
Variable	0	0	2 (3)	2 (2)
Total	27 (100)	15 (100)	58 (100)	100 (100)

2.3.3 Duration of antibiotic prophylaxis

Single-dose prophylaxis is adopted in 28 clinics using prophylaxis (28 per cent). Multiple-dose regimens from four to 24 hours postoperatively are used in 57 clinics (57 per cent), and prophylaxis for more than 24 hours postoperatively in 13 surgical clinics (13 per cent) (*Table 2.4*).

2.3.4 Acute cholecystitis

The treatment of choice in acute cholecystitis is an emergency operation in 82 per cent (108/132) of the surgical clinics. Antibiotics are used less than 48 hours in 73 clinics, between two and six days in 20 clinics and in 15 clinics antibiotics are not used (*Table 2.5*).

- An *elective operation* as soon as possible is the treatment of choice in 15 per cent of the surgical departments (20/132). Peri-operative prophylaxis (less than 48 hours) is used in 14 clinics, in three the antibiotic treatment is started immediately after admission to the hospital, and in three clinics antibiotics are not used.
- Initial *conservative therapy* followed by delayed elective surgery is the treatment of choice in three hospitals (two per cent). Under specific circumstances (e.g. poor general condition of the patient), conservative treatment is stated as alternative to acute or elective operation in another eight surgical departments.

The use of cephalosporins does not vary clearly between operations for chronic and those for acute cholecystitis: most surgeons use the same antibiotic throughout. From the 32 hospitals without a regimen of antibiotic prophylaxis in elective cholecystectomy, 16 do administer antibiotics for treatment of acute cholecystitis, four clinics use no antibiotics at all, in the remaining 12 clinics the antibiotic regimen was not indicated.

Table 2.5 *Treatment of acute cholecystitis in 132 hospitals in The Netherlands*

Management	Number of clinics (percentage)			
	A-clinic	B-clinic	C-clinic	Total
Emergency operation	25 (83)	16 (89)	67 (80)	108 (82)
- perioperative prophylaxis	20	9	44	73
- antibiotics > 48 hours	3	2	15	20
- no antibiotics	2	5	8	15
Elective operation as soon as possible	5 (17)	2 (11)	13 (15)	20 (15)
- perioperative prophylaxis	4	1	9	14
- starting antibiotics immediately after admission	0	1	2	3
- no antibiotics	1	0	2	3
Initial conservative treament	0	0	3 (4)	3 (2)
- with antibiotics	0	0	1	1
- without antibiotics	0	0	2	2
Varied management	0	0	1 (1)	1 (1)

2.4 Discussion

The enquiry about the mode of antibiotic prophylaxis in biliary tract surgery seems representative of the current practice in The Netherlands. The results reflect the policy of 652 out of a total of 792 surgeons (82.3 per cent). It is uncertain, however, whether all surgical departments have a fixed prophylaxis protocol. A response rate of 80 per cent of the clinics is somewhat lower than a similar enquiry in the United Kingdom (response rate of 90 per cent)[6], but far higher than that of a national survey in Italy (response rate of 45.6 per cent)[7].

Almost one-third of the patients with chronic cholecystitis and two-thirds of the patients with acute cholecystitis have positive bile cultures[8,9]. The presence of bacteria in bile is related to postoperative wound infection[10]. Ideally, only patients with infected bile should be given prophylactic antibiotics. Although several studies have identified subsets of patients at high risk for postoperative infectious complications[11,12], selective

prophylaxis has been disappointing in practice[13] and can easily lead to errors or omission[14]. Moreover, it is difficult to identify a truly low risk group[15]. Therefore, routine antibiotic prophylaxis in all cholecystectomies is probably the best policy, particularly in A- and B-clinics with residents. Also in Scotland there have been significant increases over the last five years in the routine use of prophylactic antibiotics during elective cholecystectomy (from 21 to 53 per cent of the surgeons)[16].

Since many antibiotics have proven to be effective in prophylaxis[3], the choice of antimicrobial agent seems rather irrelevant. Serum and tissue levels of antibiotics appear to be more important than bile concentrations[1]. Of course, individual factors and local patterns of bacterial resistance have to be considered. In general, it is advisable to reserve those antibiotics for prophylaxis that have the least side effects, and not to use antibiotics that may be required for therapy[17]. Cephalosporins are most commonly used because of the spectrum of activity in vitro and the rare toxicity. Although Enterococcus presents a gap in the antimicrobial spectrum, cephalosporins have a proven efficacy and ensure adequate serum and tissue levels. There is no evidence that second- or third-generation cephalosporins are associated with a lower postoperative infection rate[18,19].

The incidence of anaerobic bacteria in bile is low, especially at elective cholecystectomy and the clinical importance is not evident[9]. Metronidazole is the current choice of supplement therapy for possible anaerobic infections.

Biliary tract operations are a popular area for study of single-dose prophylaxis. Overall, the results of the trials support the single-dose regimen[3,20]. Still, only 28 surgical departments have adopted single-dose prophylaxis. Several trials on single-dose prophylaxis are directed to the effect of long-acting agents like third-generation cephalosporins[21-24]. There is only little information about single-dose short acting agents. However, it is well established that prophylaxis beyond 24 hours has no additional effect[4].

It is generally accepted that prophylaxis should be given to patients at risk of endogenous infection[1,25]. By definition, these patients with bactobilia have bacterial contamination of bile, which is common in acute cholecystitis[1,17,26,27]. Therefore, antibiotic prophylaxis in the surgical management of patients with acute cholecystitis is mandatory.

In the management of acute cholecystitis this enquiry shows a strong preference for emergency surgery (82 per cent). The literature shows a preference for so-called early surgery, especially in elderly patients[26-30]. However, the question may have been misinterpreted because "emergency surgery" and "elective surgery as soon as possible" were not defined in the questionnaire. Emergency surgery can be defined as surgical intervention within 24 hours after admission[28], as acute surgery within 12 hours of seriously ill patients, almost always concomitant diffuse peritonitis, or as acute surgery

due to failed conservative treatment (5-25 days after onset of symptoms)[26]. Early surgery can be defined as intervention between 24 hours and seven days[28], or as operation within 24-72 hours after onset of symptoms[26]. Since definitions were omitted in the questionnaire, the exact timing of the operation is unknown.

The subdivision of the surgical clinics into three categories shows some interesting findings, like the 31 per cent of C-clinics that never use antibiotics in elective cholecystectomy, and the low percentage of single-dose prophylaxis in B-clinics (13 per cent). Also the four per cent of C-clinics with initial conservative treatment of acute cholecystitis is remarkable. In some way the differences in policy between the three categories must be related to the presence or absence of residents.

It is clear from this enquiry that some surgeons always use antibiotics and others do not. Apparently, surgical practice is often based on personal preference and not on published data. In all, the use of antibiotic prophylaxis in biliary surgery in The Netherlands is more or less in agreement with the policy of surgeons in the United Kingdom and Italy[6,7].

Because prophylaxis for more than 24 hours has no additional effect and the prophylaxis in the management of acute cholecystitis is mandatory, antibiotic prophylaxis in biliary tract surgery is inappropriate in at least 31 Dutch hospitals (23 per cent).

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Chapter 3

CHOLECYSTECTOMY IN THE NETHERLANDS: FREQUENCY, MORTALITY AND MORBIDITY (1987-1989)

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CHOLECYSTECTOMY IN THE NETHERLANDS: FREQUENCY, MORTALITY AND MORBIDITY (1987-1989)

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3.1 Introduction

The "traditional" cholecystectomy, until recently one of the most commonly performed operations of the digestive tract, is currently being replaced by laparoscopic cholecystectomy and, to a lesser extent, by extracorporeal shock wave lithotripsy. The advantages include a shorter postoperative recovery time and, therefore, shorter hospitalization, less pain and a quicker resumption of normal activities - factors which undoubtedly offer related savings in costs. Moreover it offers a better cosmetic result. On the other hand sepsis, peritonitis, distended bowel and pregnancy are absolute contraindications for laparoscopic cholecystectomy. Other, relative contraindications include acute cholecystitis, cholangitis, acute pancreatitis, common duct stones, portal hypertension and coagulopathy[1]. With these new techniques, however, no definite conclusions can yet be drawn concerning mortality and morbidity. The first series of patients show favourable results[2,3].

Even with the current rapid development in gallbladder surgery, the traditional cholecystectomy remains the gold standard against which new techniques are evaluated. Therefore, a study on this procedure was conducted in The Netherlands. Use was made of data from the Public Health Information Center (SIG) for the period 1987-1989. Apart from frequency and mortality, postoperative complications (namely, wound infection and wound dehiscence) are investigated. The results on frequency and mortality are compared with those from the period 1979-1981, the data for which was supplied by the Medical Registry Foundation (SMR)[4].

3.2 Methods

Data for the years 1987-1989 are based on the number of registered hospitalizations (about 99 per cent), rounded off to "Total Netherlands" by the Public Health Information Center. In order to achieve a reasonable comparison with data from 1979-1981, which represented only 95 per cent of the patients concerned, the data were extrapolated to 100 per cent. Frequencies were calculated per 100.000 of the total population in the period concerned, using data from the Central Statistics Office[5].

Operation code 535 (gallbladder extirpation) of the Classification of Operations was used as a basis for the retrieval of computer data[6]. Code 535 is subdivided into cholecystectomy without (code 535.0) and with common bile duct exploration (code 535.1). As mortality and morbidity are closely related to a number of risk factors, the following subgroups were investigated by means of cross tabulation: (1) patients aged 70 years and over, (2) patients operated for acute cholecystitis, and (3) patients, in which the common bile duct has been opened (code 535.1). In the Classification of Diseases acute cholecystitis is listed under codes 574.0, 574.3 or 575.0[7]. Chronic cholecystitis (codes 574.1, 574.2, 574.4 or 574.5) and other diseases of the gallbladder (codes 575.1-575.9) are combined and reported under "remainder".

3.2.1 Definitions

Mortality is defined as the number of patients dying during hospitalization for surgery divided by the number of operated patients, irrespective of the duration of hospitalization or cause of death.

Morbidity is defined as the number of patients with one or more complications, if these are registered under the Classification of Diseases codes 996-999 or E870-E876[7], divided by the number of operated patients.

Wound infections include all postoperative infections registered under code 998.5 of the Classification of Diseases[7]. These include wound abscess, intra-abdominal or subphrenic abscess, as well as sepsis.

Wound dehiscence is listed under code 998.3 of the Classification of Diseases[7].

3.3 Results

3.3.1 Frequency

The frequency distribution for cholecystectomy in the periods 1979-1981 and 1987-1989 is given in *Table 3.1.* In the first period, 53.453 cholecystectomies were performed (after extrapolation to 100 per cent), whereas in the second period 41.869 operations were performed: the crude number decreased by 21.7 per cent and by 25.5 per cent, when calculated per 100.000 of the total population. The number of gallbladder extirpations with choledochotomy (code 535.1) decreased by 43.8 per cent. The male/female ratio in both periods was 1:2.6.

3.3.2 Mortality

The overall mortality rate of 41.869 cholecystectomies (code 535) was 1.4 per cent (*Table 3.2*) (compared to 1.9 per cent in the period 1979-1981). Age proved to be an important risk factor: the mortality rate for patients below 70 years of age was 0.5 per

Table 3.1 *Number of cholecystectomies per 100.000 of the total population in the periods 1979-1981 and 1987-1989, and the reduction in the number of cholecystectomies performed in the second compared with the first period*

Operation Code*	1979-1981†	1987-1989‡	Reduction (%)
535.0	297.8	236.8	61.0 (20.5)
535.1	81.6	45.9	35.7 (43.8)
535	379.4	282.7	96.7 (25.5)

† SMR (Medical Registry Foundation) data extrapolated to 100%
‡ SIG (Public Health Information Center) data
* Code 535: cholecystectomy; code 535.0: cholecystectomy without common bile duct exploration; code 535.1: cholecystectomy with common bile duct exploration.

Table 3.2 *Mortality of 41,869 cholecystectomies (code 535), 35,064 without (code 535.0), and 6,805 with common bile duct exploration (code 535.1) in the period 1987-1989; Cross tabulation of diagnosis (acute cholecystitis and the remainder) and age group (younger or older than 70 years of age); Number of deceased patients (%)*

Operation Code		Age (years)		
		<70 (%)	≥70 (%)	Total (%)
535.0	- acute	12 (0.5)	54 (3.9)	66 (1.8)
	- remainder	89 (0.4)	232 (3.9)	321 (1.0)
	- total	101 (0.4)	286 (3.9)	387 (1.1)
535.1	- acute	8 (1.9)	28 (7.6)	36 (4.5)
	- remainder	39 (1.0)	141 (6.9)	180 (3.0)
	- total	47 (1.1)	169 (7.0)	216 (3.2)
535	- acute	20 (0.7)	82 (4.6)	102 (2.2)
	- remainder	128 (0.4)	373 (4.7)	501 (1.3)
	- total	148 (0.5)	455 (4.7)	603 (1.4)

cent and 4.7 per cent for patients aged 70 years and over. Acute cholecystitis also increased the mortality rate: 2.2 per cent compared to 1.3 per cent for all other gallbladder diseases. With opening of the biliary tract (code 535.1) the mortality rate was 3.2 *versus* 1.1 per cent for gallbladder extirpations without common bile duct exploration (code 535.0).

Table 3.3 *Postoperative morbidity, wound infections and wound dehiscence of 41.869 cholecystectomies (code 535) in the period 1987-1989, 35,064 without (code 535.0), and 6.805 with common bile duct exploration (code 535.1), per age group. Number of patients with complication(s) (%)*

	Age (years)		
	<70 (%)	≥70 (%)	Total (%)
Morbidity			
Operation code			
- 535.0	768 (2.8)	529 (7.2)	1297 (3.7)
- 535.1	276 (6.3)	225 (9.4)	501 (7.4)
- 535	1044 (3.2)	754 (7.7)	1798 (4.3)
Wound infection			
Operation code			
- 535.0	282 (1.0)	188 (2.6)	470 (1.3)
- 535.1	96 (2.2)	68 (2.8)	164 (2.4)
- 535	378 (1.2)	256 (2.6)	634 (1.5)
Wound dehiscence			
Operation code			
- 535.0	36 (0.1)	38 (0.5)	74 (0.2)
- 535.1	6 (0.1)	28 (1.2)	34 (0.5)
- 535	42 (0.1)	66 (0.7)	108 (0.3)

3.3.3 Morbidity

The overall percentage of postoperative complications was 4.3 per cent (*Table 3.3*); 3.2 per cent for patients under 70 years of age, and 7.7 per cent for those aged over 70 years. With acute cholecystitis the incidence of complications was almost double that of operations for other gallbladder diseases (7.3 *versus* 3.9 per cent, respectively; not mentioned in *Table 3.3*). Similarly, a choledochotomy resulted in doubling of the incidence of complications: 7.4 *versus* 3.7 per cent.

3.3.4 Wound infection

About 35 per cent of all postoperative complications were caused by wound infections. The overall percentage of wound infections was 1.5 per cent (*Table 3.3*). Older patients are at higher risk for wound infections than younger ones: 2.6 *versus* 1.2 per cent. With acute cholecystitis the incidence of wound infection was almost doubled (2.7 *versus* 1.4 per cent; not mentioned in *Table 3.3*). A similar result was seen with common bile duct exploration: 2.4 per cent incidence of wound infections against 1.3 per cent when the common bile duct was not opened.

3.3.5 Wound dehiscence

The overall percentage for wound dehiscence was 0.3 per cent (*Table 3.3*). For patients aged over 70 years the risk of wound dehiscence was sevenfold (0.7 *versus* 0.1 per cent), after choledochotomy double (0.5 *versus* 0.2 per cent) and with acute cholecystitis threefold (0.7 *versus* 0.2 per cent, not mentioned in *Table 3.3*).

3.4 Discussion

In the light of the fast growing popularity of laparoscopic cholecystectomy, an analysis of the "traditional" gallbladder extirpation in The Netherlands was performed in the period 1987-1989. Although only a randomized study could indicate the actual advantages of both techniques - such a study, for various reasons, would be difficult to realize[8]. The reported low mortality rates of laparoscopic cholecystectomies may well reflect the fact that the patients were a select population undergoing elective surgery[3].

An increase of the number of cholecystectomies would be expected, because of a high prevalence of gallstones in the older age categories in an "aging population"[5,9]. Instead, the number of gallbladder operations decreased by 25.5 per cent in a relatively short period of about 8 years. Similarly, in Sweden there has been a steady decreasing frequency of cholecystectomies in the period 1969-1982[10]. A possible explanation for this was attributed to a reduction in the prevalence of gallstones, especially among young women[11]. However, no obvious decrease has been observed in established risk factors such as obesity, fertility and use of oral contraceptives or postmenopausal estrogens. On the contrary, it is suggested that the frequency of cholecystectomies does not reflect the prevalence of gallstones, but rather factors such as operation indication, and availability of surgeons and hospital beds[12,13]. In a study of Thijs *et al.* there appeared to be a high prevalence of silent gallstones, especially in the oldest age groups[9]. The fact, that asymptomatic gallstones are no longer an indication for cholecystectomy, appears to be the main reason for the decrease in the number of gallbladder extirpations[14,15]. This corresponds to a decrease in admission rates for gallstone disease in the period 1970-1985[16].

The decrease in the number of choledochotomies in the same time period is dramatic (43.8 per cent). There is no evidence for a change in the incidence of common duct stones. The decrease could be explained, in part, by a reduction in the number of gallbladder extirpations. In fact common duct stones present few specific symptoms and are often found coincidentally at operation. In addition, there has been a comparatively steady reduction in common bile duct explorations, from 21.5 per 100 cholecystectomies in 1979-1981 to 16.3 in 1987-1989. The main reason for this appears to be the

Table 3.4 *Number of cholecystectomies with common bile duct exploration (code 535.1), per 100.000 of the population, per age group in the years 1980 (extrapolated SMR data), 1987 and 1989 (SIG data). The relative reduction (%) is stated above the arrows*

Age (years)	Period 1980		1987		1989
< 70	18.8	- 40.2% →	11.2	- 8.0% →	10.3
≥ 70	126.9	- 41.9% →	73.7	- 23.6% →	56.3

SMR = Medical Registry Foundation
SIG = Public Health Information Center

introduction of endoscopic sphincterotomy. This procedure is the therapy of choice, especially for older and/or seriously ill patients[17,18]. In the last years, there is indeed evidence of a marked decrease in the number of choledochotomies in patients aged 70 years and over (*Table 3.4*).

Concerning mortality, the results of this study correlate well with reports in the literature. Generally, the mortality rate is about 1 per cent[4,19,20]. Basically, all complications harmful to the patient could be attributed to the postoperative morbidity. Comparison of the reported incidence of complications (4.3 per cent) is difficult, because the definitions of complications are not given in the literature. With careful registration of all complications following biliary tract surgery an overall percentage of even 34 per cent has been reported and after common duct exploration this value is reported to be as high as 46 per cent[21]. Generally, only the clinically relevant complications are considered. Under-reporting of postoperative complications due to non-registered data is a well-known phenomenon, especially in retrospective studies. In the literature, wound infections following biliary surgery have been reported for 0-30 per cent of the cases. Such a variety can exist due to the following factors: (1) definition of wound infection, (2) selection of patients, (3) use of antibiotic prophylaxis, and (4) under-reporting in retrospective studies. Doubt no longer exists about the effectiveness of antibiotic prophylaxis, with the most marked effects observed in high risk patients[22]. In The Netherlands antibiotic prophylaxis is widely applied[23], which partly explains its favourable results. With subcostal incision, wound dehiscence is reported in 1.1 per cent of the cases, whereas with medial laparotomies the incidence is higher (2.3-4.1 per

cent)[21,24]. Wound dehiscence appears to be related to pulmonary complications and ileus in the postoperative course. Age seems to play a less important role in these cases[24].

The cross tabulation clearly indicates the marked effect of risk factors. Age 70 years and over, acute cholecystitis and common duct exploration account for a significant increase in mortality and morbidity. Finally, a brief remark about statistical interpretation of the results. It is generally accepted that statistics of demographic data, involving large numbers, results in statistical significance for nearly all the factors. Therefore calculation of, for example, P-values is of little use.

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Chapter 4

META-ANALYSIS OF RANDOMIZED, CONTROLLED CLINICAL TRIALS OF ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY

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META-ANALYSIS OF RANDOMIZED, CONTROLLED CLINICAL TRIALS OF ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY

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4.1 Introduction

Results of many controlled clinical trials seem to provide clear answers to the value of antibiotic prophylaxis in biliary tract surgery[(Appendix 4A: 2a,10a,11a,16a,21a,22a,32a,33a,35a)]. However, some studies did not show any statistically significant difference in wound infection rates between treatment and control groups[(Appendix 4A: 8a,12a,24a,39a)] so that there are conflicting results concerning the effectiveness of prophylaxis in biliary surgery.

Experimental animal studies have demonstrated the relationship between timing of antimicrobial administration and its prophylactic efficacy[1,2]. In one prospective, clinical trial[(Appendix 4A: 36a)] it was demonstrated that antibiotic prophylaxis reduces the risk of postoperative infection after biliary tract operations if begun before operation. The experimental and clinical studies showed that effective systemic antibiotic prophylaxis requires that the antibiotic is present in the tissue at the time that contamination occurs[3]. Several other aspects of antibiotic prophylaxis are still the subject of debate. Although another animal model showed the efficacy of single-dose prophylaxis[4], clinical studies have not provided definite answers [(Appendix 4A: 20a,23a,29a,37a,45a,46a,58a)].

Additionally, reviews of reported prophylaxis studies have identified important methodological problems that question the published conclusions[5-11]. Guglielmo *et al.*[10] included biliary tract operations in their review and concluded on the basis of ten studies that antibiotic prophylaxis in biliary tract surgery reduces the incidence of wound infection only in high risk patients.

The sample size of randomized, controlled clinical trials is one of the most important reasons for controversy in antibiotic prophylaxis. Usually trials are too small to detect clinically important differences. The optimal duration of prophylaxis, the value of the newer generation cephalosporins, and the effectiveness of prophylaxis in low risk patients are other subjects of debate[9,12-15]. We decided to perform a systematic overview, also called meta-analysis[16-22], because pooling the data from many trials

might overcome the problem of small sample sizes of individual trials and give a more precise estimate of the effectiveness of antibiotic prophylaxis. Looking at subgroups by meta-analysis might solve some of the controversial problems. Therefore, consideration included the following subgroups: single dosage *versus* multiple dosage, low risk *versus* high risk, and first generation *versus* second and third generation cephalosporins.

We also examined whether inadequacies of the trials analysed had any impact on the final outcome. This was determined by use of a scoring system designed to assess the quality of randomized, controlled clinical trials[23].

4.2 Methods

4.2.1 Definitions

Biliary tract operations. All operations on the gallbladder and/or common bile duct, including cholecystectomy, exploration of the common bile duct and choledochoenterostomy were included.

Wound infection. There is a wide variation in the definition of wound infection in the analysed trials and sometimes no definition is given at all. Discharge of pus from the wound was most commonly used. Purulent exudate from the wound and non-purulent exudate that yielded pathogens on culture was used by others. We have classified wound sepsis into major and minor infections. Wound infection was considered major if there was discharge of pus irrespective of culture results. Redness and wound edge necrosis were consisered minor infections if there was no constitutional disturbance or delay in patient's recovery.

High risk patients. All patients meeting one or more of the following ten criteria were included: (a) acute cholecystitis within 4 weeks of surgery; (b) emergency cholecystectomy; (c) common duct stone or ductal exploration; (d) jaundice at the time of surgery; (e) age over 60 years; (f) previous biliary tract surgery; (g) morbid obesity; (h) non-visualization of the gallbladder on oral cholecystography; (i) diabetes mellitus; and (j) concomitant alimentary procedures.

4.2.2 Selection of trials

Because randomization is necessary to avoid selection bias, this overview was restricted to randomized, controlled trials of prophylaxis in biliary tract surgery. Randomization between two or more treatment groups, and between one or more treatment groups and a control group were both allowed. If a study consisted of more than two treatment arms, only two were used in the analysis.

All randomized clinical trials of biliary tract surgery alone or of general and gastrointestinal surgery (if biliary tract operations were specified and analysed separately) which met the following criteria were included: (a) published between 1965 and 1988; (b) antimicrobials were given to prevent infection (prophylaxis); (c) wound infection was one of the end-points. If data on the same set of patients were published more than once, only one study was included.

An extensive search has been carried out using the literature databases, *Current Contents*, reference lists, review articles and proceedings of international congresses. The initial search was performed by a computer-assisted examination throughout 1988 of two literature databases, MEDLINE and MEDLARS-2 (Deutsches Institut für medizinische Dokumentation und Information, FRG). References were retrieved by the following keywords: biliary surgery, cholecystectomy, prospective, randomized trial and prophylaxis. A manual search of *Current Contents* (1985-1988) was performed using the following keywords: biliary, biliary tract, cholecystectomy, clinical trial, prophylactic, prophylaxis, prospective, prospective study and randomized. The reference list of each retrieved report was scanned for potential eligible studies. Review articles were consulted. Because there is a tendency not to publish "negative" trials, we also looked for unpublished studies in proceedings of international congresses on chemotherapy.

Only trials with comparable treatment arms can be pooled. If possible, we classified each trial into one of the three following groups (in each group a different comparison of treatments was studied): treatment regimen *versus* control or placebo (group I); treatment with first generation cephalosporins *versus* treatment with second or third generation cephalosporins (group II); and single-dose *versus* multiple-dose regimen (group III). Most of the trials could be classified in this manner.

4.2.3 Statistical methods

For each of the three groups of trials a meta-analysis was performed using the percentage of wound infection as an endpoint. We distinguished two different measures for assessment of differences in effect between treatment regimens. First, we calculated the differences in percentage wound infection (treatment minus control in group I trials; first minus second or third generation cephalosporins in group II trials; and single-dose minus multiple-dose administration in group III trials). Secondly, the odds ratio was computed for each trial. In the group I trials this is the ratio of the odds of the presence of wound infection in the treated group to the odds of the presence of wound infection in the control group. An odds ratio equal to one indicates no effect of treatment, a ratio less than one means a beneficial treatment effect, a ratio greater than one means a harmful treatment effect. The odds ratio was similarly defined in the group II trials (a ratio less than one means a preference for first generation cephalosporins) and the

group III trials (a ratio less than one means a preference for single-dose administration). Besides the estimates of percentage differences and odds ratios, 95 per cent confidence intervals were computed for each trial separately, while a common percentage difference (with 95 per cent confidence interval) and a common odds ratio (with 95 per cent confidence interval) were estimated using the methods described by DerSimonian and Laird[24]. Estimates and confidence intervals for the odds ratios were graphically displayed on a log scale[25]. A test of homogeneity of both percentage differences and odds ratios was performed using the method also described by DerSimonian and Laird[24].

In the group I trials several factors were studied which might explain the heterogeneity of treatment effect differences. We used linear regression analysis for the percentage differences and logistic regression for the odds ratios. On the basis of these results subgroups of trials were formed for which common effect estimates were calculated.

4.2.4 Criteria for subgroup meta-analysis

We studied whether the treatment effects in the group I trials (treatment *versus* control) differed in relation to one of the following six criteria: (1) route of administration of the prophylaxis (intravenous, intramuscular, local or combination); (2) the use of single or multiple doses; (3) the definition of wound infection, major *versus* minor plus major; (4) the moment of wound inspection, i.e. in hospital or during follow-up; (5) first *versus* second or third generation cephalosporins; and (6) administration of the treatment in "high" or "low" risk patients. A trial was classified as high risk when at least 50 per cent of the patients in the trial were high risk patients. Trials not classified as high risk were considered low risk.

4.2.5 Assessment of study quality

For assessing the quality of randomized, controlled trials we used a scoring system (*Table 4.1*) based on that of Chalmers *et al.*[26] and modified by Evans and Pollock[23]. Basically it is a checklist of 31 questions: 15 are about design and conduct of the trial, eight are about analysis and eight are about presentation. Quality scores ranging from zero to 100 were given to each study. The quality assessment of the first ten studies was performed by two reviewers and the outcomes were compared. When questions were poorly defined it was difficult to answer "yes" or "no", and different interpretations had a remarkable influence on the outcome. After postulating special criteria for those questions we were able to obtain identical results from the two reviewers. The remaining trials were then scored only by one reviewer (W.S.M.). Details of the special criteria used for this scoring system are available from the authors.

Table 4.1 *Scores for design and conduct, analysis and presentation of reports of clinical trials*

	Yes	No
Design and conduct		
Is the sample defined?	2	0
Are exclusions specified?	2	0
Are known risk factors recorded?	3	0
Are therapeutic regimens defined?	5	0
Is the experimental regimen appropriate?	5	0
Is the control regimen appropriate?	5	0
Were appropriate investigations carried out?	2	0
Are endpoints defined?	5	0
Are endpoints appropriate?	5	0
Have numbers required been calculated?	2	0
Was patient's consent sought?	1	0
Was the randomization blind?	3	0
Was the assessment blind?	4	0
Were additional treatments recorded?	4	0
Were side effects recorded?	2	0
Analysis		
Withdrawals: are they listed?	3	0
is their fate recorded?	4	0
are there fewer than 10%	4	0
Is there a comparability table?	3	0
Are risk factors stratified?	3	0
Is the statistical analysis of proportions correct?	3	0
Is the statistical analysis of numbers correct?	3	0
Are confidence intervals reported?	2	0
Are values of both test statistic and probability given?	1	0
In negative trials is the Type II error considered?	4	0
Presentation		
Is the title accurate?	2	0
Is the abstract accurate and helpful?	3	0
Are the methods reproducible?	3	0
Are the sections clear-cut?	2	0
Can the raw data be discerned?	2	0
Are the results credible?	3	0
Do the results justify the conclusions?	3	0
Are the references correct?	2	0
Total	100	0

4.3 Results

All 78 retrieved trials, which were eligible according to the criteria described above, are listed in the appendices (*Chapter 4.5*). From these trials 18[(Appendix 4B: 1b-18b)] have been withdrawn for various reasons: (1) study not eligible for one of the three groups of meta-analysis[(Appendix 4B: 1b-15b)]; (2) sample size less than ten[(Appendix 4B: 16b)]; and (3) abstract with incomplete data[(Appendix 4B: 17b,18b)]. Sixty studies accepted for meta-analysis were divided into three groups depending on randomization (some studies with more than two treatment arms could be classified in more than one group):

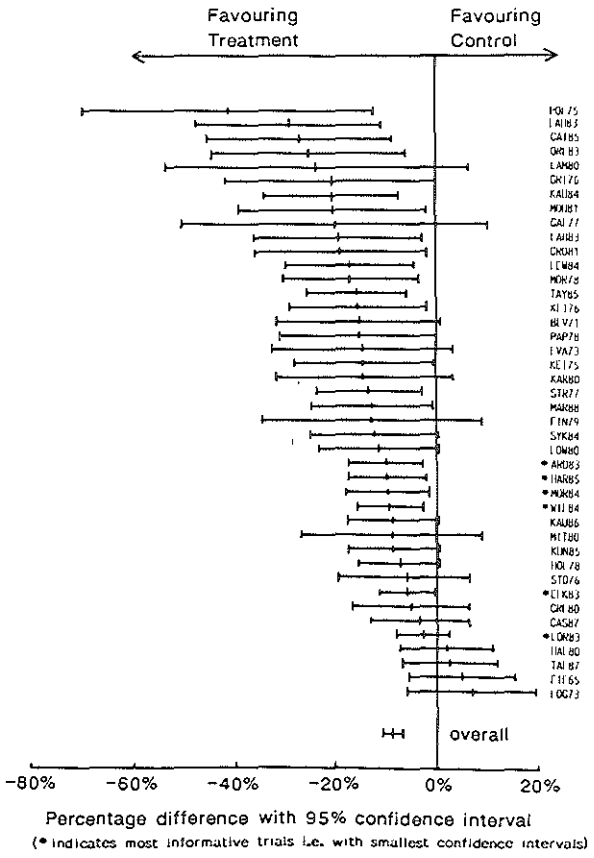

Figure 4.1 *Percentage differences with 95 per cent confidence intervals for 42 trials comparing treatment* versus *control and common 95 per cent confidence interval. *Most informative trials, i.e. those with the smallest confidence intervals*

I. Treatment regimen *versus* control or placebo (42 trials)[Appendix 4A: 1a-41a];

II. First generation cephalosporins *versus* second or third generation drugs (11 trials)[Appendix 4A: 42a-52a];

III. Single-dose *versus* multiple-dose regimen (15 trials)[Appendix 4A:3a,5a,9a,37a, 46a,51a,53a-60a].

4.3.1 Group I trials

The overall percentage difference between wound infection in the treated group and wound infection in the control group is 9 per cent in favour of antibiotic treatment (95 per cent confidence interval 7-11 per cent; *Figure 4.1*). The corresponding results for

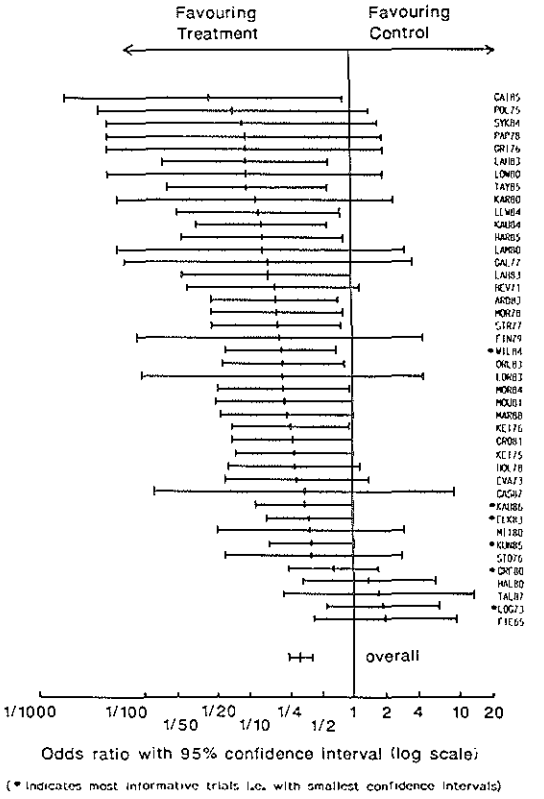

Figure 4.2 *Odds ratios with 95 per cent confidence intervals (log scale) for 42 trials comparing treatment* versus *control and common 95 per cent confidence interval. *Most informative trials, i.e. with the smallest confidence intervals*

the odds ratios (*Figure 4.2*) is 0.30 in favour of antibiotic treatment (95 per cent confidence interval 0.23-0.38). In terms of percentage differences the test revealed significant heterogeneity (P<0.005) in contrast to the odds ratios (P>0.10).

In the subgroup analyses of the group I trials only two factors appeared to have a significant effect on the percentage differences: (a) high risk (administration of the treatment in high or low risk patients) and (b) inspection time (the moment of wound inspection, in hospital or during follow-up). Therefore, we formed four subgroups: (1) low risk patients with early (in hospital) wound inspection; (2) low risk patients with late (follow-up) wound inspection; (3) high risk patients with early wound inspection; and (4) high risk patients with late wound inspection. Common estimates and 95 per cent confidence intervals were calculated within each subgroup for the percentage differences (*Figure 4.3*) and the odds ratios (*Figure 4.4*). The percentage differences were respectively 8, 10, 13 and 25 per cent.

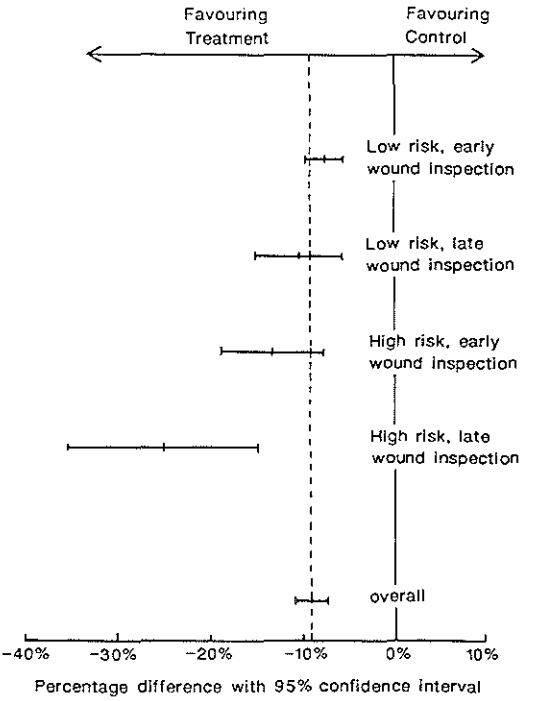

Figure 4.3 *Common percentage differences with 95 per cent confidence intervals for four subgroups of 42 trials comparing treatment* versus *control*

4.3.2 Assessment of study quality

None of the items which score study quality was associated with the heterogeneity in percentage differences. The distribution of the quality sum-scores for design and conduct, analysis, presentation, and overall score (maximum values of 50, 30, 20 and 100 respectively) of the 40 papers (42 trials) from group I are shown in *Table 4.2*.

Table 4.2 *Distribution of scores as specified in Table 4.1 for 40 reports of 42 trials comparing treatment* versus *control*

	Range	Mean (s.d.)
Design and conduct	17-42	29.0 (5.9)
Analysis	4-21	10.2 (3.5)
Presentation	2-17	9.2 (3.3)
Total	34-66	48.5 (7.9)

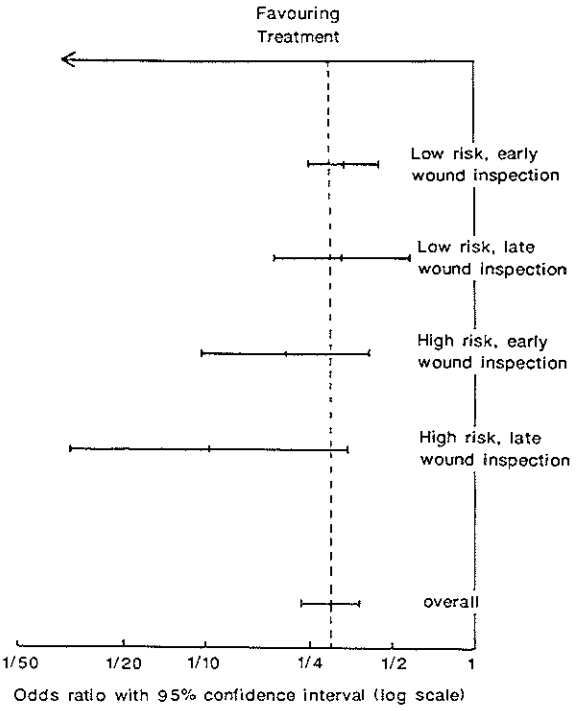

Figure 4.4 *Common odds ratios with 95 per cent confidence intervals (log scale) for four subgroups of 42 trials comparing treatment* versus *control*

4.3.3 Group II trials

Percentage differences and odds ratios for the 11 trials in group II (first generation cephalosporins *versus* second or third generation) did not reveal any significant differences. The common percentage difference is 0.5 per cent in favour of the newer generation (95 per cent confidence interval -1.5 per cent to +2.5 per cent; *Figure 4.5*); the common odds ratio is 1.18 in favour of the newer generation (95 per cent confidence interval 0.69-2.00; *Figure 4.6*).

4.3.4 Group III trials

From the 15 group III trials (single-dose *versus* multiple-dose regimen) we also

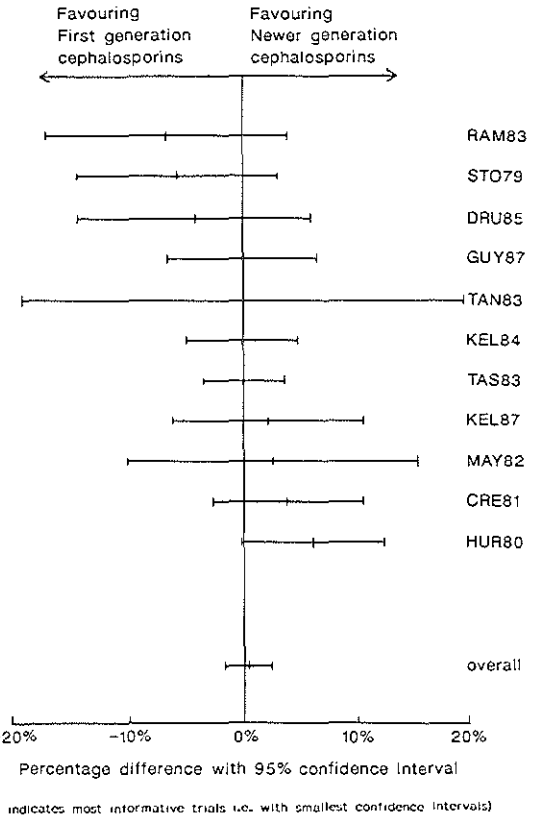

Figure 4.5 *Percentage differences with 95 per cent confidence intervals for 11 trials comparing first* versus *second or third generation cephalosporins and common 95 per cent confidence interval. *Most informative trials, i.e. with the smallest confidence intervals*

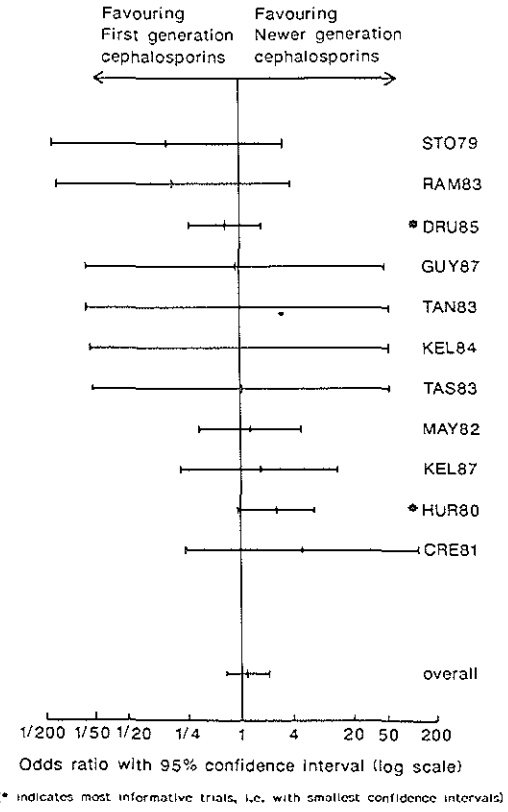

Figure 4.6 *Odds ratios with 95 per cent confidence intervals (log scale) for 11 trials comparing first* versus *second or third generation cephalosporins and common 95 per cent confidence interval. *Most informative trials, i.e. with the smallest confidence intervals*

could not detect any significant difference. Here, the common percentage difference is 0.4 per cent favouring single-dose therapy (95 per cent confidence interval from -1.1 per cent to +1.9 per cent; *Figure 4.7*), while the common odds ratio is 0.80 favouring single-dose therapy (95 per cent confidence interval 0.41 to 1.57; *Figure 4.8*).

4.4 Discussion

Although wound infections are not common after cholecystectomy (0-30 per cent are quoted in the literature), improvement is still a worthwhile aim because cholecystectomy is one of the most common operations on the digestive system. Many controlled

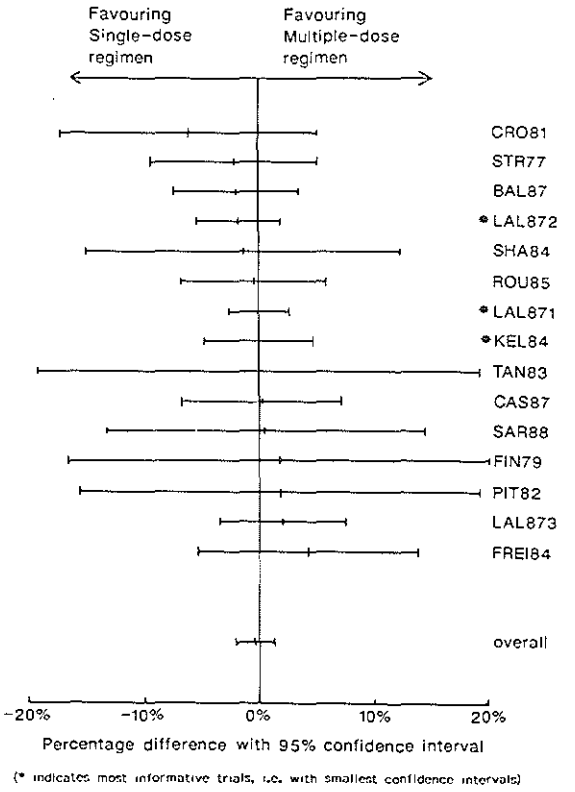

Figure 4.7 *Percentage differences with 95 per cent confidence intervals for 15 trials comparing single-dose* versus *multiple-dose regimens and common 95 per cent confidence interval. *Most informative trials, i.e. with the smallest confidence intervals*

clinical trials have been performed to show the effectiveness of prophylactic antimicrobials, or to show whether one treatment is better than another. Individually, most trials are too small to detect small differences with sufficient statistical power. If we assume a 15 per cent infection rate without treatment, the expected infection rate with antibiotic prophylaxis is approximately 6 per cent since we showed a 9 per cent overall difference. To demonstrate that such difference is statistically significant (with a 90 per cent power and use of one-sided testing alpha = 0.05) it is necessary to study a total of at least 350 patients. The size of the largest study in this meta-analysis was 330 patients(Appendix 4A: 6a).

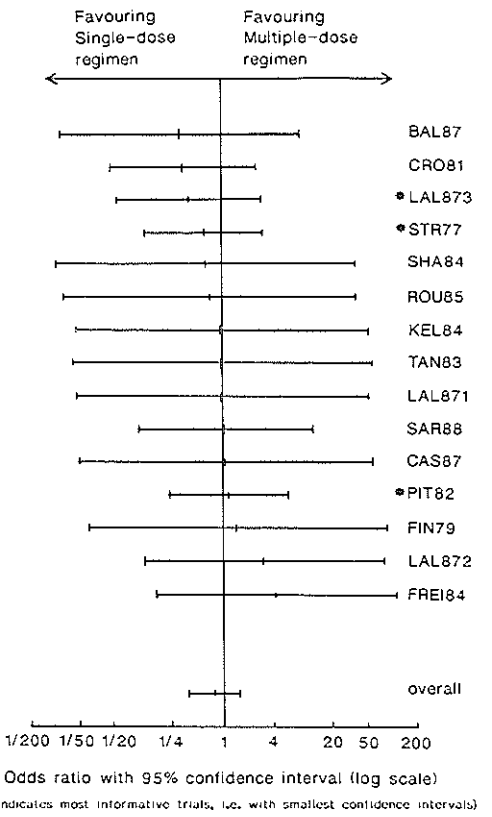

Figure 4.8 *Odds ratios with 95 per cent confidence intervals (log scale) for 15 trials comparing single-dose* versus *multiple-dose regimens and common 95 per cent confidence interval. *Most informative trials, i.e. with the smallest confidence intervals*

To obtain a stable estimate of the effect of prophylactic antibiotics and more reliable answers to several subjects of debate, such as single-dose prophylaxis and the use of newer cephalosporins, we have performed this meta-analysis.

Only prospective randomized trials were included in the analysis to overcome selection bias. Results of trials with pooled data from all kinds of general or gastro-intestinal operations may be different from biliary tract surgery alone. Therefore, only biliary tract operations have been included in this meta-analysis. To avoid publication bias as much as possible, we decided to include all trials we could retrieve, including abstracts from proceedings of international congresses. Trials with a sample size less then ten were withdrawn from analysis. Because of study heterogeneity, included trials

have been divided into three groups: (I) treatment *versus* no-treatment control; (II) first generation *versus* second or third generation cephalosporins; and (III) single-dose *versus* multiple-dose regimens.

For assessment of the effectiveness of antibiotic prophylaxis we used two different measures: the difference in percentage wound infection and the odds ratio. Although the odds ratio has certain favourable mathematical properties, the difference in percentages is easier to interpret. The data did not show a preference for one of these measures, and generally both measures led to the same results, with exception of the test for homogeneity in the group I trials. We found a 9 per cent difference in wound infection percentage, favouring antibiotic treatment *versus* controls. The demonstrated effectiveness of prophylaxis in biliary tract surgery is evidence against further use of no-treatment controls. Future trials should be performed *versus* a proven prophylactic regimen, for instance a first generation cephalosporin.

Besides the effectiveness of antibiotic prophylaxis we found a stronger protective effect in high risk patients. In addition, the timing of wound inspection had an important influence on treatment effect. Late (follow-up) wound inspection showed a higher infection rate than early (in hospital) wound inspection. Percentage differences in the four subgroups (low risk, early inspection; low risk, late inspection; high risk, early inspection; high risk, late inspection) are 8, 10, 13 and 25 per cent respectively (all favouring treatment). The variation in definition of wound infection had no influence on treatment effect: there was no significant difference between major alone and major plus minor wound infections. Nevertheless, a better and widely accepted definition of wound infection is warranted to make comparison of different trials more reliable.

Results of the scoring system for study quality showed striking inadequacies in most analysed trials. These findings are quite comparable to a similar quality assessment of reports of antibacterial prophylaxis in colorectal surgery[27]. However, none of the different items of the score system had a significant influence on treatment effect.

The meta-analyses of the trials from group II and III showed that no greater benefit could be detected for the newer generation cephalosporins (in comparison with first generation the common percentage difference is 0.5 per cent) and for use of a multiple-dose regimen (in comparison with a single-dose regimen the common percentage difference is 0.4 per cent). From the confidence intervals it can be deduced that a difference larger than 2 per cent is unlikely. Even if a 2 per cent difference were to be considered as interesting, a clinical trial to detect such a difference with statistical significance would need to include many thousands of patients. The small confidence intervals (3-4 per cent width) suggest that the choice of prophylactic agent can be made largely on the basis of cost.

An interesting question is whether meta-analysis can replace future clinical trials. The answer is no. Clinical trials in antimicrobial research should be carried out because one trial based on a single protocol, provided that sufficient patient numbers can be acquired, will always avoid the heterogeneity disadvantages inherent in an overview. One of the reasons for conducting such an analysis is to identify the need for and planning of major trials. Trials which have as primary objectives the comparison of single-dose *versus* multiple-dose regimens or first *versus* newer generation cephalosporins will almost certain fail to detect any clinically or statistically significant differences with respect to wound infection rates. However, it has to be noted that almost all of the 15 group III trials (single *versus* multiple dosage) compared a multiple-dose, short-acting, first generation cephalosporin with a single-dose, long-acting, third generation cephalosporin. Therefore, we feel that a major trial comparing single *versus* multiple dosage of the same antimicrobial is still worthwhile.

Although it is widely accepted that the first dose of prophylactic antibiotics should be given before operation, this was confirmed by only one prospective trial[Appendix 4A: 36a]. Recently, another randomized, double-blind trial[28] failed to show any advantage to starting antibiotics before operation. We endorse the view of Brumfitt and Hamilton-Miller, who made a plea for further studies into the timing of administration of prophylactic antibiotics[29].

In conclusion, antibiotic prophylaxis in biliary tract surgery is effective, especially in high risk patients. Late (follow-up) wound inspection essentially influenced the treatment effect reported. The choice of antimicrobial agent can largely be made on the basis of its cost. Future trials must be directed to timing and duration of antibiotic prophylaxis, such as the need of a first dose before operation and single *versus* multiple dosage of the same antimicrobial.

4.5 References

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APPENDIX 4A. Published Trials Accepted for meta-analysis

(1) Studies used for comparison of treatment versus *control (publication 21a contains two trials)*

1a. Bevan PG, Williams JD. Rifamide in acute cholecystitis and biliary surgery. *Br Med J* 1971; **3**: 284-7.

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3a. Castoldi R, Ferrari G, Di Palo S *et al.* Prophylactic use of cefotaxime in biliary surgery: comparison of single dose versus multiple dose schedule. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987: 1182-4 (Abstract).

4a. Creve U, Hubens A. Single-dose parenteral antibiotic prophylaxis in gastrointestinal surgery. *Acta Chir Belg* 1980; **79**: 27-33.

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9a. Finch DRA, Taylor L, Morris PJ. Wound sepsis following gastrointestinal surgery: a comparison of topical and two-dose systemic cephradine. *Br J Surg* 1979; **66**: 580-2.

10a. Galland RB, Mosley JG, Saunders JH *et al.* Prevention of wound infection in abdominal operations by peroperative antibiotics or povidone-iodine. A controlled trial. *Lancet* 1977; **ii**: 1043-5.

11a. Griffiths DA, Simpson RA, Shorey BA *et al.* Single-dose peroperative antibiotic prophylaxis in gastrointestinal surgery. *Lancet* 1976; **ii**: 325-8.

12a. Halsall AK, Welsh CL, Craven JL *et al.* Prophylactic use of metronidazole in preventing wound sepsis after elective cholecystectomy. *Br J Surg* 1980; **67**: 551-2.

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17a. Kaufman Z, Dinbar A. Single dose prophylaxis in elective cholecystectomy. *Am J Surg* 1986; **152**: 513-6.

18a. Keighley MRB, Baddeley RM, Burdon DW *et al.* A controlled trial of parenteral prophylactic gentamicin therapy in biliary surgery. *Br J Surg* 1975; **62**: 275-9.

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trial using one dose cephamandole. *Aust N Z J Surg* 1985; **55**: 19-22.

21a. Lahtinen J, Alhava EM, Katila M-L *et al.* Prophylactic antibiotics for acute cholecystitis treated by early surgery. A double-blind, controlled trial. *Proceedings of the 13th International Congress on Chemotherapy*, Vienna, 1983; SE 7.19/1, Part 68: 28-32 (Abstract).

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(2) Studies used for comparison of first versus *second or third generation cephalosporins*

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52a. Tasker DG, O'Malley V, Lewis P *et al.* Cefotaxime in the prophylaxis of wound infection following cholecystectomy. *Proceedings of the 13th International Congress on Chemotherapy*, Vienna, 1983; SE 7.19/3, Part 69: 22-5 (Abstract).

(3) Studies used for comparison of treatment given in single versus *multiple dose*

(In addition, publications 3a, 5a, 9a, 37a, 46a, 51a were used; publication 56a contains two trials.)

53a. Balbo G, Farina EC, Garino M *et al.* Single-shot versus short-term prophylaxis with mezlocillin in biliary tract surgery. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987: 1193-4 (Abstract).

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56a. De Lalla F, De Nunno T. Mezlocillin prophylaxis in high-risk biliary tract surgery. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987: 1443-5 (Abstract).

57a. Pitt HA, Postier RG, Gadacz TR *et al.* The role of topical antibiotics in "high-risk" biliary surgery. *Surgery* 1982; **91**: 518-24.

58a. Roufail WM. Comparison of cefonicid and cefoxitin for prophylaxis in biliary tract surgery. *Adv Ther* 1985; **2**: 225-32.

59a. Sarr MG, Parikh KJ, Sanfey H *et al.* Topical antibiotics in the high-risk surgical patient. A prospective, randomized study. *Am J Surg* 1988; **155**: 337-42.

60a. Shatney CH. Antibiotic prophylaxis in elective gastro-intestinal tract surgery: a comparison of single-dose pre-operative cefotaxime and multiple-dose cefoxitin. *J Antimicrob Chemother* 1984; **14** (Suppl B): 241-5.

APPENDIX 4B. Trials withdrawn from meta-analysis

(1) Studies not eligible for one of the three groups of meta-analysis

1b. Ambrose NS, Morris DL, Burdon DW *et al.* Comparison of selective and nonselective single-dose antibiotic cover in biliary surgery. *World J Surg* 1987; **11**: 101-4.

2b. Germiniani R, Bragherio L, De Nunno R *et al.* Single dose antibiotic prophylaxis in elective biliary surgery: cefotaxime versus ceftriaxone. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987: 1189-92 (Abstract).

3b. Gillen P, Ryan W, Peel ALG. A prospective randomised controlled trial of mezlocillin versus netilmicin in biliary surgery. *Ann R Coll Surg Engl* 1985; **67**: 376-8.

4b. Greenall MJ, Atkinson JE, Evans M *et al.* Single dose prophylaxis of surgical wound sepsis: which route of administration is best? A controlled clinical trial of intra-incisional against intravenous cephaloridine. *J Antimicrob Chemother* 1981; **7**: 223-7.

5b. Guyot L, Legue E, Kwantes M *et al.* Initial curative antibiotherapy in biliary surgery. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987: 1409-11 (Abstract).

6b. Harnoss B-M, Hirner A, Dibbelt A *et al.* Peri-operative antibiotic prophylaxis in cholecystectomy: two prospective randomised trials. *Chemotherapy* 1987; **33**: 297-301.

7b. Jensen LS, Anderson F, Gjøde P *et al.* Preoperative cefuroxime v. long-term ampicillin and metronidazole in high-risk biliary and gastric surgery. *Acta Chir Scand* 1987; **153**: 193-7.

8b. Kujath P, Hugelschaffer Ch, Kunz E *et al.* Antibiotic prophylaxis in the surgery of bile ducts - ciprofloxacin versus ceftriaxone. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987: 1185-8 (Abstract).

9b. Murray WR, Bradley JA. Antibiotic prophylaxis in elective biliary surgery. *Res Clin Forums* 1983; **5**: 97-101.

10b. Pollock AV, Evans M. The prophylaxis of surgical wound sepsis with cephaloridine - experiences in 2491 general surgical operations and reporting a controlled clinical trial

against framycetin. *J Antimicrob Chemother* 1975; **1** (Suppl): 71-83.

11b. Pollock AV, Leaper DJ, Evans M. Single dose intra-incisional antibiotic prophylaxis of surgical wound sepsis: a controlled trial of cephaloridine and ampicillin. *Br J Surg* 1977; **64**: 322-5.

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13b. Targarona EM, Munoz Ramos C, Roset F *et al.* Single dose antibiotic prophylaxis in high risk biliary surgery. A prospective randomized comparative trial between cefonicid and mezlocillin. *2nd World Congress on HPB Surgery*, Amsterdam, 1988: PO 107 (Abstract).

14b. Wilson SE, Hopkins JA, Williams RA. A comparison of cefotaxime versus cefamandole in prophylaxis for surgical treatment of the biliary tract. *Surg Gynecol Obstet* 1987; **164**: 207-12.

15b. Yellin AE, Berne TV, Heseltine PNR *et al.* Sulbactam-Ampicillin (SA) *versus* Moxalactam as an adjunct to surgery for acute cholecystitis. *Proceedings of the 17th International Congress on Chemotherapy*, Istanbul, 1987: 1420-1 (Abstract).

(2) Studies with sample size of less than ten

16b. Louie TJ, Blanchard R, Yaffe C *et al.* Randomized, double-blind comparison of cefotaxime, cefoxitin, cefazolin or placebo as prophylaxis during gastric, small bowel or complicated biliary surgery. *J Antimicrob Chemother* 1984; **14** (Suppl B): 255-62.

(3) Studies with incomplete data (Abstracts)

17b. Dewar EP. Piperacillin prophylaxis in biliary surgery. *Proceedings of the 13th International Congress on Chemotherapy*, Vienna, 1983, SE 7.19/1, Part 68: 33-5 (Abstract).

18b. Karran S, Papachristodoulou AJ, Moore L *et al.* Single dose chemoprophylaxis in 500 biliary operations. *Proceedings of the 15th Congress of the European Society for Surgical Research*, Brussels, 1980; SS97: 88-9 (Abstract).

Chapter 5

PROPHYLACTIC USE OF CEFUROXIME IN BILIARY TRACT SURGERY: RANDOMIZED, CONTROLLED DOUBLE-BLIND MULTICENTRE TRIAL OF SINGLE-DOSE *VERSUS* MULTIPLE-DOSE IN 1004 HIGH RISK PATIENTS

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PROPHYLACTIC USE OF CEFUROXIME IN BILIARY TRACT SURGERY: RANDOMIZED, CONTROLLED DOUBLE-BLIND MULTICENTRE TRIAL OF SINGLE-DOSE *VERSUS* MULTIPLE-DOSE IN 1004 HIGH RISK PATIENTS

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5.1 Introduction

Biliary tract operations are a popular area for study of single-dose antibiotic regimens. In placebo-controlled trials in which patients received a single-dose of cefazolin, cefuroxime, cefamandole, cefotaxime, gentamicin or cotrimoxazole, the antimicrobial group showed lower rates of postoperative wound infections[1-10]. In comparative trials single-dose cefotaxime, cefotetan, ceftriaxone and moxalactam were as effective as multiple-dose cefazolin or cefoxitin[11-15]. In spite of all efforts, duration of antibiotic prophylaxis remains a subject of debate. Questions about the efficacy and effectiveness of single-dose prophylaxis of short-acting antibiotics *versus* single-dose of long-acting agents and *versus* multiple doses of short-acting agents are yet to be answered. Because the sample size of most published trials was too small, clinically important differences could not be detected. In a meta-analysis of randomized, controlled clinical trials in biliary surgery the comparison of wound infection rates in patients treated with single-dose *versus* multiple-dose regimens did not reveal any significant effect[16]. However, in almost all included studies a single-dose, long-acting antibiotic has been compared with a multiple dosage of a short-acting agent. It is impossible to assess from these trials whether single-dose regimens of short-acting antibiotics are as effective in preventing infection as multiple-dose regimens of short-acting agents. Therefore, we conducted a randomized, controlled double-blind multicentre evaluation of single *versus* multiple dosage of cefuroxime in biliary surgery patients with infection risk factors. Since the value of prophylactic antibiotics in high risk biliary surgery is now well established, it was considered unethical to use placebo or a no-treatment control group to compare the incidence of sepsis.

5.2 Patients and methods

5.2.1 Patient population

Patients were enrolled between February 1, 1987 and May 31, 1990 at 14 Dutch hospitals (The Galant-Trial Study Group). Eight of these 14 clinics are affiliated teaching hospitals in general surgery with a 6-year residency. The other 6 hospitals have no training programme in general surgery. Ethical Committee approval was obtained from each participating hospital. All patients scheduled for biliary tract surgery were eligible for the study if they presented with at least one of the risk factors detailed in *Table 5.1*. These factors are associated with an increased risk of positive bile cultures[17-20]. Patients with an acute cholecystitis or an emergency operation were also eligible.

5.2.2 Exclusions (before randomization)

Patients were not eligible if they met one of the following exclusion criteria: Allergy to cephalosporins, haemodynamic instability, severe renal insufficiency (creatinin > 300 μmol/l), pregnancy or lactation, any antibiotic therapy within one week before operation, immuno-suppressive therapy, concomittant intraabdominal procedures as appendectomy or gastric resection, and resection of the common bile duct (Whipple's procedure).

5.2.3 Treatment regimens

Cefuroxime, a second generation cephalosporin with an elimination half-life of less than 1.5 hours, was chosen because this agent is considered a suitable antimicrobial drug for prophylaxis in surgery involving the gastrointestinal tract above the caecum. It has a wide range of activity against most species of bacteria present in the intestine[21]. In several studies cefuroxime was effective in the reduction of wound sepsis following biliary surgery[22-25]. In addition, most participating institutes already used cefuroxime for prophylaxis of their surgical procedures.

All study patients received cefuroxime 1.5 g as a rapid intravenous infusion at the time of induction. Subsequently, 8 and 16 hours postoperatively patients received either 0.75 g of cefuroxime intravenously (mixed in 100 ml saline with 1 ml riboflavin; Group II) or an identical appearing placebo intravenously (1 ml riboflavin in 100 ml saline; Group I).

In order to minimize the effects of different operation techniques on the results, cholecystectomy was standardized as much as possible: routine draining of the subhepatic space during a maximum of 48 hours; no irrigation of the abdominal cavity or subcutaneous tissues; closure of the fascia with a running monofilamentous suture; atraumatic closure of the skin. Violation of this protocol was no reason for withdrawal from analysis.

Table 5.1 *Distribution of risk factors in 1004 eligible patients* and the incidence of bacteria in bile per inclusion criterion (high risk factor)#*

Risk factor	Number of patients (percentages)					
	Group I† (n = 501)	Group II (n = 503)	P-value	Total number of patients	Number of obtained bile specimens (%)	Number of positive bile cultures (%)
Age ≥ 60 years	417 (83.2)	406 (80.7)	0.30	823	766 (93)	292 (38.1)
Jaundice (bilirubin ≥ 50 μmol/l)	51 (10.2)	36 (7.2)	0.09	87	82 (94)	38 (46.3)
Acute attack of cholecystitis within 1 month before operation	156 (31.1)	159 (31.6)	0.87	315	297 (94)	124 (41.8)
Stones in common bile duct	73 (14.6)	53 (10.5)	0.06	126	114 (90)	59 (51.8)
Previous biliary tract surgery	10 (2.0)	13 (2.9)	0.53	23	19 (83)	13 (68.4)
Chills or fever within 1 week before operation	18 (3.6)	12 (2.4)	0.26	30	17 (57)	17 (100)

* More than one risk factor could be present in one patient.
\# In 70 of the 1004 patients no bile culture was obtained.
† Group I is the single-dose treatment arm, group II is the multiple-dose treatment arm.

5.2.4 Randomization and blinding

Randomization was accomplished by computer-generated sheets retained in the hospital pharmacies. At each hospital, patients eligible for the study were randomly assigned separately in blocks of 10 to receive a single or multiple dosage of cefuroxime. Block randomization was used to ensure a balanced assignment to the two regimens within each institution.

Postoperative cefuroxime or placebo was supplied by the institute's pharmacist in identical appearing vials. The treatment codes were not known by the surgeon, other medical personnel, or the patient. The only way to break the code was to contact the pharmacist retaining the randomization list. As a consequence, drug assignments were not known during any follow-up evaluation or during data-processing.

5.2.5 Definitions

Wound infections were graded as follows: (0) no sign of infection; (I) minor infection: erythema, stitch abscess or skin edge necrosis; (II) major infection: purulent discharge and superficial or deep wound dehiscence. The presence of pus may be detected within a few days of an operation (in hospital wound infection) or its appearance may be delayed for as long as three weeks (delayed wound infection).

Bacteremia was defined as positive blood cultures and/or chills with rectal temperature higher than 39°C or axillary temperature higher than 38.5°C.

Urinary tract infection was defined as otherwise unexplained fever with local symptoms of urinary tract infection and/or positive urine culture.

Pneumonia was defined as purulent sputum as well as otherwise unexplained pulmonary infiltrates and either fever or respiratory symptoms.

Acute cholecystitis was defined as acute abdominal pain existing more than 24 hours but less than one week, with tenderness in the right upper abdomen and/or palpable gallbladder, leucocytosis $>10 \times 10^9$/l and/or rectal temperature higher than 38°C, or axillary temperature higher than 37.5°C, and optionally proven gallstones or pathological HIDA-scan.

5.2.6 Surveillance of postoperative infection

Wounds were assessed at day five and day ten postoperatively (or the day before discharge from the hospital). In addition, all patients were reviewed in the outpatient department four to six weeks after discharge from the hospital to detect any evidence of late sepsis. Wounds and drain sites were inspected by the surgeon or resident responsible for postoperative patient care. In case of unexplained fever radiological and bacteriological assessment of respiratory or urinary infections was made in the postoperative period. All data were recorded on specially designed study-forms (*Appendix C*).

5.2.7 Other data

Many other variables were recorded for each patient: duration of hospital stay; type and duration of symptoms; previous abdominal diseases and operations; preoperative radiological examinations; medication within two weeks before operation; length and weight of the patient; relevant physical examination; type and timing of shaving of the operative site; date and duration of the operation; time of administration of the first dose of the antibiotic; details of the surgical procedure including the surgeon (consultant or resident), incisional technique, condition of the gallbladder and common bile duct, and type of drainage; protocol violations; pathological findings of the gallbladder; antibiotic usage in the postoperative period; complications as wound haematoma, ileus, thromboembolic and cardiac events; date of onset of wound infection or other complications; date of discharge from the hospital and cause of death.

5.2.8 Bacteriological assessment

Samples of gallbladder bile were aspirated aseptically during operation and sent to the laboratory in a syringe with a rubber stopper on the needle. Deep wound swabs were obtained after closure of the abdominal cavity, and other wound swabs were taken in the postoperative period in case of wound drainage. All materials were dispatched to the bacteriology departments immediately, or stored in transport medium for later culture. Specimens were cultured aerobically and anaerobically. The media for aerobic cultures were 5 per cent sheep blood, chocolate, MacConkey and PA agar plates. For anaerobic cultures specimens were plated onto anaerobic sheep blood agar and sheep blood agar with vancomycin, colistin and nystatin, and incubated in an anaerobic tent. The aerobic plates were examined after 24, 48 and 72 hours for bacterial growth. The anaerobic plates were examined at 48 and 72 hours.

5.2.9 Number of patients

Calculation of the sample size for this study was based on the following two assumptions: (a) the percentage of grade I (minor) or grade II (major) wound infection in the multiple-dose treatment group is ten; (b) the percentage of grade I or grade II wound infection in the single-dose treatment group is at least 15. Testing will be based on significance level alpha = 0.05 (two-sided), and a power (1 − beta) of 95 per cent. Using these parameters it can be shown that 1174 patients in each treatment arm (2348 patients in total) are necessary.

During the enrollment of patients it became evident that the accrual (within a reasonable duration of approximately 3 years) would not be more than 50 per cent of the planned number. New power calculations, however, have led to the conclusion that the final number of approximately 1000 patients (500 in each trial arm) is appropriate for two

reasons: (a) the original sample size calculation was based on "overall" wound infections (10 per cent *versus* 15 per cent), while major wound infections (approximately 5 per cent in the multiple-dose treatment group) are clinically more significant. Assuming that we want to detect at least five percent more major infections in the single-dose treatment group, in that case a smaller number of patients is required; (b) the detection of a significant difference between the five, respectively ten percent major wound infections with 500 patients in each treatment group has a power of approximately 80 per cent, which is often used in sample size calculations.

5.2.10 Withdrawals

A sufficient number of patients were randomly assigned to ensure that 1000 would meet the criteria for evaluation. After randomization no exclusion was allowed, but patients were withdrawn from analysis if they did not meet one of the inclusion criteria, or if they met one of the exclusion criteria. In addition, patients were withdrawn if no eligible procedure was performed (i.e. irresectable carcinomas), or postoperative follow-up could not be performed (lost to follow-up or death within four weeks after surgery). If the study medication was inadvertently omitted or another antibiotic was given as prophylaxis, the patient was included in the analysis on the basis of the intention-to-treat principle.

5.2.11 Statistical analysis

Percentages or two-way tables were analysed with the chi-square test. For two by two tables with small expected frequencies Fisher's exact test was used. If relevant, 95 per cent confidence limits were calculated for the difference of two percentages. Approximately continuous data were tested with the Mann-Whitney-U test. Logistic regression analysis was used to detect prognostic factors in the development of major wound infections.

5.3 Results

5.3.1 Patient population

In the period of enrollment approximately 2500 patients were scheduled for eligible procedures. This number has been extrapolated from data of two hospitals in which the inclusion and exclusion criteria of *all* cholecystectomy patients were registered precisely. A total of 1077 from these 2500 patients were randomly assigned to receive 1.5 g cefuroxime preoperatively and either cefuroxime or placebo at 8 and 16 hours post-operatively. The reasons for not including the remainder in the randomization were: (a) the absence of an inclusion criterion (± 850 patients); (b) existence of an exclusion criterion (± 470 patients); (c) the surgeon's omission or refusal to allow the patient to participate (± 100 patients). The number of patients included in the analysis and the total number of

randomized patients were 1004 of 1077 (93 per cent, ranging from 88 per cent to 100 per cent in the participating hospitals; *Table 5.2*). A total of 73 patients were withdrawn from analysis after randomization for the reasons shown in *Table 5.3*. Two major wound infections developed in this group of patients (2.7 per cent). From the 1004 analysed patients 689 (68 per cent) were included on the basis of one risk factor, 243 patients (24 per cent) had two risk factors, 60 patients (6 per cent) had three and 11 patients (1 per cent) had four risk factors. One patient was included with all five risk factors present.

Base-line characteristics of the 1004 patients included in the analysis, are shown in *Table 5.4*. There were no important differences between the two treatment groups with regard to the variables shown, or any other evaluated parameters. Only a previous gastric resection showed a significant higher incidence in the multiple-dose treatment group (40 *versus* 23 patients; p=0.03). Selected characteristics of the surgical procedures are shown in *Table 5.5*. Cholecystectomy was performed through a right subcostal incision in 90 per cent of the cases. Common bile duct exploration was planned in 126 patients, but ultimately performed in 207 (20.6 per cent). Opening of the common bile duct, with or without choledochoscopy, revealed common bile duct stones in only 56 per cent of the

Table 5.2 *Participating hospitals, period of participation, number of randomized and eligible patients and their proportion (in percentages)*

Hospital	Period of participation (month/year)	Number of patients randomized	eligible	Proportion eligible/ randomized
St.Ignatius Hospital	2/88 - 2/89	27	25	93
Reinier de Graaf Gasthuis	5/87 - 12/89	100	92	92
Van Weel-Bethesda Hospital	3/87 - 11/89	74	70*	95
Groot Ziekengasthuis	9/88 - 5/90	42##	38	90
Bronovo Hospital	4/89 - 1/90	18	18*	100
Rode Kruis Hospital	4/89 - 6/90	25	22*	88
St.Joseph Hospital	3/87 - 11/89	42	39	93
Eudokia Hospital	11/87 - 11/89	48	45	94
St.Franciscus Gasthuis	6/87 - 3/90	121	113*	93
St.Clara Hospital	2/87 - 6/90	272	258*	95
Zuiderziekenhuis	4/87 - 6/90	82#	73	89
Schieland Hospital	4/87 - 12/89	80#	76	95
Hospital Rivierenland	6/87 - 4/90	149	45	92
St.Maartens Gasthuis	3/87 - 5/90	97#	90*	93
Total	2/87 - 6/90	1077	1004	93

* one patient included on the basis of intention-to-treat
\# one patient died

Table 5.3 *Reasons for withdrawal from analysis after randomization**

Reason	Number of patients	
	Group I	Group II
No inclusion criterion present	10	7
Another antibiotic given within 1 week before the day of surgery	6	9
Incomplete follow-up after surgery	5	3
Patient died before completion of follow-up	4	1
No biliary operation performed	7	3
Concomittant disqualifying procedure performed including Wipple's procedure	5	4
Immuno-suppressive medication at the time of operation	4	2
Haemodynamic instability of the patient at the time of operation	0	3
Total	41	32#

* In six patients the study medication was inadvertently omitted; they are included in the analysis on the basis of the intention-to-treat principle

\# Binomial test, $p > 0.05$

cases. A dilated duct on peroperative cholangiography was frequently the only reason for exploration of the common bile duct.

5.3.2 Protocol violations

Modifications to the "standardized" technique of cholecystectomy was never reason for withdrawal of the patient from analysis, but the modifications were noted on the patient-form as protocol violation: (a) no draining of the subhepatic space in 5 per cent; (b) irrigation of the abdominal cavity in 9 per cent; (c) irrigation of the subcutaneous tissue at the end of the operation in 1.8 per cent; (d) closure of the fascia with nonabsorbable materials in 6 per cent; (e) closure of the fascia with interrupted sutures in 3.7 per cent; and (f) closure of the skin with traumatic sutures in 21 per cent of the cases. None of the above protocol violations showed a significant difference between the two treatment groups ($p > 0.1$) nor any significant effect on the development of major wound infections ($p > 0.1$).

Table 5.4 *Base-line characteristics of the patients studied* *

Characteristic	Group I (n = 501)	Group II (n = 503)	P-value
Female	344 (68.7)	346 (68.8)	0.97
Age - yr (mean ± SD)	66.0 ± 11.8	64.7 ± 12.4	0.09
Body-mass index (mean ± SD)#	25.9 ± 3.9	26.4 ± 4.0	0.18
Acute cholecystitis	109 (21.8)	113 (22.5)	0.79
Acute admission to the hospital	184 (36.7)	191 (38.0)	0.68
Emergency operation	33 (6.6)	42 (8.3)	0.29
Preoperative length of stay >1 day	160 (31.9)	161 (32.0)	0.98
Diabetes mellitus	44 (8.8)	31 (6.2)	0.11
Cardiovascular diseases	176 (35.1)	171 (34.0)	0.71
Chronic respiratory disease	35 (7.0)	39 (7.8)	0.64
Previous gastric resection	23 (4.6)	40 (8.0)	0.03

* Unless otherwise indicated, values are numbers of patients. Percentages are in parentheses.
\# Body-mass index is calculated as weight in kilogram divided by square of height in meters.

5.3.3 Mortality

Five patients (mean age 70.8 yr, range 64-80 yr) died within four days after surgery and were withdrawn from analysis. Four patients were randomized in the single-dose treatment group. All five patients had a cardiac history; in four patients the probable cause of death was myocardial infarction. There were no signs of septic complications. One patient with signs of a hypovolemic shock and liver failure showed massive bleeding from the liver and liver cell necrosis at autopsy.

5.3.4 Bacteriological assessment

Bile culture specimens were obtained from 934 (93 per cent) patients. Overall, bile cultures were positive in 34.2 per cent (319/934), ranging from 38.1 to 100 per cent for the various risk factors (*Table 5.1*). The predominant aerobic organisms were *Escherichia coli* (187 isolates), streptococci (111 isolates), *Klebsiella* sp. (71 isolates) and staphylococci (17 isolates) (*Table 5.6*). The predominant anaerobic bacteria were *Clostridium* (33 isolates, including 28 *C.perfringens* isolates) and *Bacteroides* sp. (15 isolates, including 8 *B.fragilis* isolates). Polymicrobial colonization was present in 115 instances (36 per cent).

Table 5.5 *Details of the surgical procedures in 1004 patients**

Procedure		Number of patients (percentage)	
Incision:	right subcostal	906	(90.2)
	medial	69	(6.9)
	paramedial	27	(2.7)
	other	2	(0.2)
Cholecystectomy:	antegrade	745	(74.2)
	retrograde	259	(25.8)
Peroperative cholangiography		320	(31.9)
Common bile duct exploration		207	(20.6)
Choledochoscopy		115	(11.5)
Choledocho-enterostomy		10	(1.0)
Spillage of bile:	none	810	(80.7)
	moderate	165	(16.4)
	severe	29	(2.9)

* There were no statistically significant differences between the two study groups.

5.3.5 Postoperative infections

The follow-up evaluations at day 5, day 10 (or the day before discharge from the hospital), and at 4 to 6 weeks postoperatively occurred in all patients. Minor wound infections were detected in 64 patients (6.4 per cent) and 42 patients (4.2 per cent) developed a major wound infection (*Table 5.7*). Differences between the two study groups were not statistically significant ($p = 0.78$ and $p = 0.52$, respectively). The estimated difference in major wound infection rates between the two study groups was 0.8 per cent (95 per cent confidence interval from −1.7 per cent to +3.3 per cent). Delayed wound infections developed in 22 patients (2.2 per cent): 14 minor and 8 major wound infections. Deep wound dehiscence was observed in 11 patients, 9 of whom were in the single-dose group ($p = 0.04$).

Fever postoperatively (>39°C and/or >38°C during ≥4 days) was noted in 109 patients (11 per cent). Fever was unexplained in 47 patients, otherwise related to pneumonia, urinary tract infection, bacteremia, or wound infection. The overall incidence of pneumonia was 2.1 per cent (21 patients), urinary tract infection 4.3 per cent (43 patients) and bacteremia 1.9 per cent (19 patients). Differences between the two study groups were not statistically significant.

Table 5.6 *Organisms isolated from 323 positive bile cultures, 221 positive cultures of peroperative wound swabs and 26 positive cultures of draining wounds postoperatively*

Organisms	Number of isolates		
	Bile	Wound (peroperatively)	Wound (postoperatively)
No. of specimens(%)	323 (100)	221 (100)	26 (100)
Aerobic			
Gram-positive			
Streptococci	111 (34)	43 (19)	9 (35)
Staphylococci	17 (5)	66 (30)	10 (38)
Gram-negative			
Escherichia coli	187 (58)	65 (29)	16 (62)
Klebsiella	71 (22)	19 (9)	3 (12)
Enterobacter	16 (5)	7 (3)	2 (8)
Proteus	12 (4)	3 (1)	1 (4)
Pseudomonas	1 (0.3)	3 (1)	0 (0)
Anaerobic			
Gram-positive			
Clostridium	33 (10)	6 (3)	0 (0)
Streptococci	5 (1.5)	2 (1)	0 (0)
Gram-negative			
Bacteroides	15 (5)	4 (2)	0 (0)
Other organisms	41 (13)	52 (24)	4 (15)
Total number of isolates	509	270	45

5.3.6 Wound infections per hospital

The wound infection rate per hospital (with 95 per cent confidence interval) is presented in *Figure 5.1*. The overall wound infection rate was 4.2 per cent (range 0 - 8.9 per cent; 95 per cent confidence interval from 3.0 to 5.6 per cent). The lowest incidence of wound infection was seen in the clinics with the lowest number of randomized patients. These lower numbers were mostly due to a shorter time of participation to the trial. The difference in overall wound infection rates between the two ultimates (Eudokia Hospital and St.Maartens Gasthuis) is statistically significant (Fisher exact test, $p = 0.05$). Differences in wound infection rates between the two study groups within hospitals were not statistically significant.

Table 5.7 *Comparison of the results of the study in the two groups**

		Group I (n=501)	Group II (n=503)	P-value
Wound infection				
Minor		33 (6.6)	31 (6.2)	0.78
Major		23 (4.6)	19 (3.8)	0.52
Wound dehiscence		9 (1.8)	2 (0.4)	0.04
Delayed wound infection:	minor	6 (1.2)	8 (1.6)	0.46
	major	2 (0.4)	6 (1.2)	0.08
Other infectious complications				
Fever#		60 (12.0)	49 (9.7)	0.26
Bacteremia		10 (2.0)	9 (1.8)	0.80
Urinary tract infection		19 (3.8)	24 (4.8)	0.44
Pneumonia		12 (2.4)	9 (1.8)	0.50
Mortality†				
Sepsis-related		0 (0)	0 (0)	
Non-septic		2 (0.4)	0 (0)	0.25
Patients receiving antibiotics postoperatively other than trial medication		56 (11.2)	37 (7.4)	0.04
Length of postoperative stay				
mean ± S.D.		11.8 ± 5.4	11.7 ± 7.1	0.02
median (range) in days				
Uncomplicated (n = 899)		10 (4 - 49)	9 (4 - 45)	
Major wound infections (n = 42)		18 (9 - 44)	15 (5 - 72)	
Other septic complications (n = 172)		13 (4 - 41)	10 (4 - 72)	
Overall (n = 1004)		10 (4 - 49)		

* Unless otherwise indicated, values are numbers of patients (percentages in parentheses)
\# Temperature > 39°C or ≥ 38°C during ≥ 4 days
† Five deaths were withdrawn from analysis

5.3.7 Prognostic factors

Analysis of the 1004 included patients with respect to prediction of major wound infection (42 patients) revealed several univariate significant prognostic factors. With logistic regression three factors were selected with high prognostic value considered in a multivariate analysis: (a) previous gastric surgery; (b) local tenderness in the right upper abdomen; (c) perforation of the gallbladder (durante operationem or spontaneously). *Table 5.8* summarizes the results of the logistic regression. From this model it can be derived that if none of the three prognostic factors are present (319 patients) there is a probability of

1 per cent of a major wound infection. If only one factor is present (514 patients) this probability is approximately 3.5 per cent, while if at least two of these factors are present (171 patients) the probability of a major wound infection is at least 10 per cent.

From the literature it is suggested that many other factors may affect normal wound healing, including body mass index, hospitalization exceeding one week immediately prior to operation, shaving the operative site one day before surgery, duration of the operation, and wound haematoma. None of these factors revealed any prognostic effect on the development of major wound infections in this study.

5.3.8 Additional antibiotics

Overall, additional antibiotics postoperatively were used in 93 patients (9.3 per cent) with a significant difference between the two study groups ($p = 0.04$). In 74 patients (7.4 per cent) the antibiotics were given for septic complications: 43 in the single-dose group *versus*

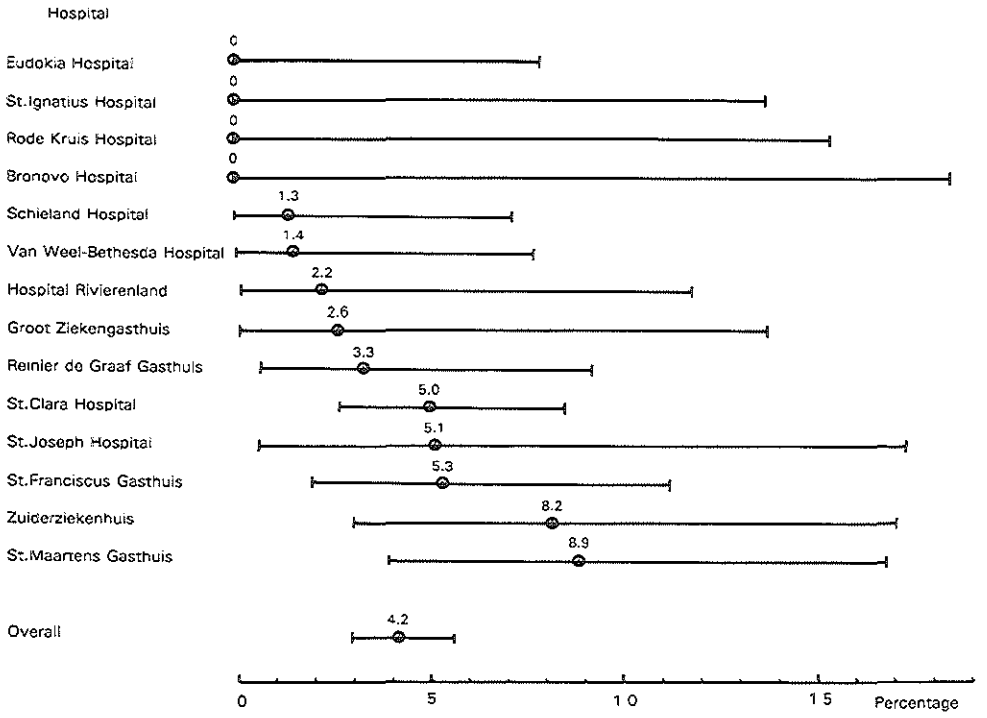

Figure 5.1 *Major wound infection rate per hospital (percentage and 95% confidence interval)*

Table 5.8 *Multivariate prognostic factors of major wound infection using logistic regression*

Factor	Logistic Coefficient	Standard Error	P - Value
Previous gastric surgery	1.18	0.48	0.014
Local tenderness in the right upper abdomen	1.35	0.45	0.003
Perforation of the gallbladder	1.29	0.33	<0.001

31 in the multiple-dose group (p = 0.12). The septic complications were: bacteremia (8 patients), urinary tract infection (21 patients), pneumonia (12 patients), minor wound infection (4 patients), major wound infection (5 patients), multiple factors (11 patients), and unexplained fever (13 patients). In other instances antibiotics were administered prophylactically to prevent septic complications due to ERCP or T-tube-cholangiography.

5.3.9 Other outcomes

No significant differences between the two study groups were noted with respect to the other recorded data. The incidence of carcinoma of the gallbladder was 1.5 per cent (15 patients). Acute acalculous cholecystitis was seen in only 7 patients (0.7 per cent), corresponding to 3.2 per cent of patients with an acute cholecystitis. In 30 patients (3.0 per cent) a chronic acalculous cholecystitis was noted and eight cholecystectomy patients had no gallstones nor signs of cholecystitis.

5.3.10 Adverse effects

Only one instance of urticaria was noted in the group of 1077 randomized patients. No correlation to the antibiotic therapy was suspected in the patients who died.

5.4 Discussion

Results of the present study show that one dose of a short-acting agent (half-life time less than 1.5 hr) is as effective as a three-dose regimen in preventing major wound infections. Therefore, the duration of antibiotic prophylaxis should not be extended by multiple dosage of a short-acting agent. However, mean hospital stay, additional antibiotics in the postoperative period and development of deep wound dehiscence showed statistically significant differences at the expense of single-dose prophylaxis. These differences might correlate to the duration of prophylaxis. Possibly, long-acting agents will overcome these problems, but this cannot be concluded from this study. Anyway, it is obvious that these factors will play a major role in a cost-benefit analysis.

There is no reasonable explanation for a previous gastric resection being a prognostic factor in the development of major wound infections. A direct relationship between the length of operation and wound infection has been reported[17], but in our 42 patients who developed a major wound infection, the duration of surgery was not significantly prolonged. The second prognostic factor was local tenderness in the right upper abdomen. This is one of the symptoms of acute cholecystitis, a condition with a high incidence of bactobilia. Although acute cholecystitis does not necessarily imply an infective etiology, approximately half of the patients have positive bile cultures[18-20]. The present study showed a 47.4 per cent incidence of bactobilia in acute cholecystitis. Perforation of the gallbladder was the third prognostic factor. Subsequent severe spillage of bile is best related to the development of wound infections. It concurs with the "primary lodgment" theory of Miles *et al.*, in which direct contact of bacteria to the wound is presumed to be the origin of wound infections[27,28].

It is accepted that wound infections are usually caused by biliary micro-organisms[29-31]. In 26 out of 42 major wound infections the drainage was cultured, from which 22 were positive. Eighteen (82 per cent) were associated with positive bile cultures, and in 14 of the 22 cases (64 per cent) the same organism was isolated from the subcutaneous tissue as had been previously cultured from the biliary tract. The most common organism cultured in bile and infected wounds was *Escherichia coli*. On the other hand, we found that staphylococci were uncommon in bile (5 per cent), and rather frequent in major wound infections (38 per cent). This finding has been reported by others[32-34]. Staphylococcus epidermidis was frequently grown from the subcutaneous tissues, and appeared to be of pathogenic significance in 5 patients (23 per cent). Although cefuroxime is less effective against *Streptococcus faecalis*, *Bacteroides fragilis* and *Pseudomonas* species (<50 per cent sensitivity), these organisms seem to play a minor role in the development of major wound infections. From the bacteriological assessment it is concluded that both endogenous and exogenous contamination were cause of wound sepsis. We conclude that prophylactic antibiotics should also be effective against the exogenous wound contaminants.

Whether or not all patients having cholecystectomy should receive antibiotic prophylaxis, remains controversial. It is generally accepted that patients undergoing biliary tract operations are at a higher risk of developing postoperative sepsis if bacteria are present in their bile at the time of operation[29,34-37]. The incidence of bile colonization in low risk patients lies within the range of 8-19 per cent[29,36-38], and in high risk patients within the range of 30-45 per cent[18,29,39]. Although antibiotic prophylaxis may not be essential in patients without risk factors undergoing biliary tract surgery, a beneficial effect has been reported in other clean operations[40].

Many clinically important questions can only be answered in multicentre trials to provide a sufficient number of patients. The organization and conduct of such a trial is

difficult, time consuming and often expensive. Therefore, it is disappointing that most trials failed to detect statistically significant differences because their sample sizes were too small[16], and also that many trials showed striking inadequacies with regard to the study quality[41].

Finally, a few remarks on the recent development and fast growing popularity of laparoscopic cholecystectomy. The principles of prophylaxis are not changed by minimal invasive surgery. Although wound complications seem to play a minor role, there is a better chance of intraabdominal spillage of bile. As long as no alternative has proven its efficacy, antibiotic management in laparoscopic cholecystectomy should be identical to the management in traditional cholecystectomy.

5.5 References

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Chapter 6

COST ASPECTS OF ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY

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COST ASPECTS OF ANTIBIOTIC PROPHYLAXIS IN BILIARY TRACT SURGERY

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6.1 Introduction

In addition to our prospective trial on single-dose and multiple-dose cefuroxime prophylaxis in high risk patients undergoing biliary surgery[1], it is interesting to look at the effects on costs. The effects consist of two main elements: (1) the cost of antimicrobial agents, and (2) the cost of wound infections. The cost of prophylactic antibiotics accounts for 30 per cent of the total cost of antimicrobial agents used in hospitals. Wound infection will add at least 3-7 days of hospitalization as well as delay the patient's return to productive activities[2,3]. It is important to realize that hospital per diem costs and duration of stay dominate the health care expenses to such extent that they overshadow most other expenses. Therefore, we will focus on the cost of additional nursing- days. Due to the cost structure of Dutch hospitals and the application of an all-in tariff, there is no detailed cost differentiation after treatment.

In this study only the variable costs of a nursing-day will be considered; this because the number of cholecystectomies compared with the total number of admissions is relatively small and, therefore, the cost effect of wound infections after biliary surgery would barely be reflected in the total hospital costs. Although the effect of a wound infection, namely the increase of postoperative hospitalization, has a certain influence on the cost structure of hospitals (i.e. hospital budget), this aspect is beyond the scope of this investigation.

6.2 Materials and methods

For calculations on the cost effects of single-dose and multiple-dose cefuroxime prophylaxis in high risk biliary surgery we have adapted the results of a randomized controlled double-blind multicentre trial, in which 501 patients were treated with single-dose cefuroxime and 503 patients with a three-dose regimen[1]. Overall, the trial showed 42 major wound infections (4.2 per cent). No statistically significant difference was

found between the two study groups (p = 0.52); 23 major wound infections (4.6 per cent) in the single-dose group (group I) and 19 infections (3.8 per cent) in the multiple-dose group (group II). For comparisons and other calculations we decided to use the wholesale price guide of drugs (Farmacotherapeutisch Kompas 1990-1991), although the actual drug acquisition cost is usually less than the wholesale price. Most hospitals purchase at least one antibiotic through competitive bargaining or a collective purchase arrangement.

For comparison of antibiotic prophylaxis with placebo or no-treatment controls we have used the results of a meta-analysis of randomized, controlled clinical trials in biliary tract surgery[4]. In terms of wound infection rates, a 9 per cent overall difference was found in favour of antibiotic prophylaxis. Derived from the meta-analysis (see *Figure 4.3*) the estimated wound infection rate in high risk patients without the use of prophylactic antibiotics was 18 per cent.

Costs of a nursing-day on a surgical ward were based on the 1990 data from the Department of Economics of the Sint Clara Hospital, Rotterdam, a general district hospital with 584 beds. The variable costs of one nursing-day are estimated at 104 Dutch guilders (Dfl.) (*Table 6.1*). These data will be applied to compare the costs of different antibiotic regimens combined with the costs of resulting wound infections. For convenience, calculations will be performed on the results of 500 operated patients, equal to the number of patients in groups I and II of the randomized trial. The calculated amounts in guilders will be rounded off.

Results of an investigation on antibiotic prophylaxis in biliary tract surgery in The Netherlands have given detailed information about the agents used (*Chapter 2*), and recent numbers of cholecystectomies performed in The Netherlands were derived from

Table 6.1 *Construction of the variable costs of a nursing-day, based on the 1990 data from the Dept. of Economics of the St.Clara Hospital, Rotterdam*

Nursing-day		Cost (Dfl.)
Nursing-staff		62.50
Nutrition		20.70
Medical attendance		0.40
Rental and laundry (Dfl. 5.69 + Dfl. 0.91)		6.60
	Subtotal	90.20
General charge (15 per cent)		13.80
	Total	104

the National Health Information Centre (*Chapter 3*). This information has been adapted to estimate potential savings.

6.3 Results

6.3.1 Cost of a major wound infection

In uncomplicated cases, the randomized controlled trial showed a median postoperative hospitalization of 10 days in group I and 9 days in group II. The median postoperative stay increased to 18 and 14 days, respectively, in cases of major wound infection (*Table 6.2*). Overall, the development of a major wound infection has added 6.5 days to the postoperative hospital stay, in line with findings from others studies[2,3]. The cost of a major wound infection is calculated as follows: 6.5 (days) × Dfl. 104 (variable costs of a nursing-day) = Dfl. 676.

6.3.2 Calculation of cost effects

If: C = cost of the antibiotic regimen
P = probability of a major wound infection
W = cost of a major wound infection (Dfl. 676)
n = number of patients (set to 500)
T = total excess cost of n treated patients $T = n(C + PW)$.

Then:

(A) In case of no treatment:

$C_0 = 0$ and $P_0 = 0.18$

$T_0 = n(C_0 + P_0W) = 500 \times \{0 + (0.18 \times \text{Dfl. } 676)\} =$
$= 500 \times \text{Dfl. } 121.68 = \text{Dfl. } 60{,}840$

(B) In case of single-dose cefuroxime prophylaxis:

$C_1 = \text{Dfl. } 28.15$ and $P_1 = 0.046$

$T_1 = n(C_1 + P_1W) = 500 \times \{\text{Dfl. } 28.15 + (0.046 \times \text{Dfl. } 676)\} =$
$= 500 \times \text{Dfl. } 59.25 = \text{Dfl. } 29{,}625$

(C) In case of multiple-dose cefuroxime prophylaxis:

$C_2 = \text{Dfl. } 56.53$ and $P_2 = 0.038$

$T_2 = n(C_2 + P_2W) = 500 \times \{\text{Dfl. } 56.53 + (0.038 \times \text{Dfl. } 676)\} =$
$= 500 \times \text{Dfl. } 82.22 = \text{Dfl. } 41{,}110$

Another way of expressing the cost effects of different antibiotic regimens is to calculate the average excess cost of preventing one major wound infection in a certain number of patients (n), and compare the results with the excess cost of contracting one infection.

Table 6.2 *Postoperative duration of hospitalization in relation to the type of infection. Data are based on results of the randomized controlled trial (Chapter 5) (n = number of patients)*

	Group I (single-dose)			Group II (multiple-dose)			Overall
	n	days of postoperative hospitalization	Median (range)	n	days of postoperative hospitalization	Median (range)	Median
Uncomplicated	347	3690	10 (4-49)	352	3636	9 (4-45)	10
Minor wound infection	32	380	12 (4-21)	31	345	9 (5-40)	11
Major wound infection	23	435	18 (9-44)	19	333	14 (8-48)	16.5
Other septic complications*	53	775	12 (7-41)	56	928	12 (7-72)	12
Subtotal	455	5280		458	5242		
Non-septic complications	46	607	11 (6-27)	45	620	11 (7-49)	11
Total	501	5887	10 (4-49)	503	5862	10 (4-72)	10

* Fever, bacteremia, pneumonia, urinary tract infection

Single-dose cefuroxime prophylaxis versus *no treatment*
Excess cost to prevent infections: $n(C_1 - C_0) = 500 \times$ Dfl. 28.15 = Dfl. 14,075
Number of prevented infections: $n(P_0 - P_1) = 500 \times 0.134 = 67$
Excess cost to prevent one major wound infection:

$n(C_1 - C_0) / n(P_0 - P_1) =$
= Dfl. 14,075 / 67 = Dfl. 210

Multiple-dose cefuroxime prophylaxis versus *no treatment*
Excess cost to prevent infections: $n(C_2 - C_0) = 500 \times$ Dfl. 56.53 = Dfl. 28,265
Number of prevented infections: $n(P_0 - P_2) = 500 \times 0.142 = 71$
Excess cost to prevent one major wound infection:

$n(C_2 - C_0) / n(P_0 - P_2) =$
= Dfl. 28,265 / 71 = Dfl. 389

Multiple-dose versus *single-dose cefuroxime prophylaxis*
Excess cost to prevent infections: $n(C_2 - C_1) = 500 \times$ Dfl. 28.38 = Dfl. 14,190
Number of prevented infections: $n(P_1 - P_2) = 500 \times 0.008 = 4$
Excess cost to prevent one major wound infection:

$n(C_2 - C_1) / n(P_1 - P_2) =$
= Dfl. 14,190 / 4 = Dfl. 3,547

The excess cost to prevent one major wound infection by using single-dose or multiple-dose cefuroxime compared with no treatment is lower than the excess cost of contracting one infection (Dfl. 676). However, the excess cost of preventing one infection by multiple-dose cefuroxime compared with single-dose prophylaxis is much higher (Dfl. 3,547) than getting one infection (Dfl. 676). Thus, in this evaluation single-dose cefuroxime prophylaxis is more cost-effective.

6.3.3 Further observations

In the first part of this cost evaluation we focused on the costs of antimicrobial agents and wound infections. There are indications from the literature that prophylactic antibiotics might prevent other septic complications as well. A significant reduction in postoperative chest infection from 32 to 9 per cent was demonstrated in a prospective trial of elective cholecystectomy patients[5]; reduction in infection was confirmed in a trial of patients undergoing head and neck surgery[6]. In a meta-analysis of randomized controlled trials of antibiotic prophylaxis in abdominal hysterectomy the pooled data showed a statistically significant reduction of urinary tract infections, febrile episodes and the usage of additional antibiotics when prophylaxis was compared with placebo[7]. Benefit of prophylaxis on the duration of postoperative hospital stay could not be demonstrated ($p > 0.05$), although a one-day difference was noted (8.7 *versus* 7.7 days of mean hospitalization)[7]. In two other studies standard febrile morbidity was partially prevented by antibiotic prophylaxis[8,9].

The prospective Galant-trial revealed significant differences ($p<0.05$) between the two study groups with respect to (a) length of postoperative hospitalization, (b) use of additional antibiotics, and (c) the incidence of wound dehiscence. Supported by findings of the aforementioned studies it is suggested that the observed differences are affected by different prophylactic regimens. Related costs to these differences can be estimated as follows:

(a) Duration of postoperative hospital stay

In subgroups of patients with septic complications differences in median postoperative hospital stay were observed. From *Table 6.2* can be derived that the total duration of hospitalization in group I patients (single-dose prophylaxis) with septic complications showed an increase of 354 days, while the increase in group II patients (multiple-dose prophylaxis) was limited to 253 days. The excess cost was calculated on the basis of

Table 6.3 *Cost of additional antibiotics postoperatively, derived from the randomized controlled trial (Chapter 5)*

Agent	Day-price*	Group I (single-dose)		Group II (multiple-dose)	
		Total number of days of administration	Total cost (Dfl.)	Total number of days of administration	Total cost (Dfl.)
Amikacin	129.30	5	646.50	0	0
Amoxycillin	2.17	32	69.44	53	115.01
Ampicillin	3.56	15	53.40	0	0
Cefradine	13.30	0	0	16	212.80
Cefotaxime	45.50	5	227.50	0	0
Cefuroxime	84.45	92	7769.40	41	3462.45
Cotrimoxazole	1.41	65	91.65	31	43.71
Doxycycline	2.01	7	14.07	15	30.15
Flucloxacillin	7.34	34	249.56	7	51.38
Gentamicin	22.50	6	135	18	405
Metronidazole	9.00	25	225	16	144
Netilmicin	58.50	10	585	0	0
Nitrofurodantoin	1.89	44	83.16	26	49.14
Norfloxacine	4.27	18	76.86	31	132.37
Oxytetracyclin	30.88	4	123.52	0	0
Piperacillin	132.70	9	1194.30	7	928.90
Total		371	11,540	261	5,575

* Wholesale prices in Dutch guilders (Farmacotherapeutisch Kompas 1990-1991)

the variable costs of an additional nursing-day:
Excess cost in group I patients: 354 × Dfl. 104 = Dfl. 36,800
Excess cost in group II patients: 253 × Dfl. 104 = Dfl. 26,300

(b) Additional antibiotics
Not all additional antibiotics were used for the treatment of septic complications. However, in this evaluation only the cost of additional antibiotics prescribed for septic complications were included. The excess cost of additional antibiotics was calculated on the basis of wholesale prices (*Table 6.3*): Excess cost in group I patients: Dfl. 11,540
Excess cost in group II patients: Dfl. 5,575

(c) Deep wound dehiscence, re-admissions and re-operations
We have found 11 wound dehiscences in 42 patients with a major wound infection (26 per cent). This is in accordance with the results of a study of 1491 patients who underwent medial laparotomy; from 128 patients (8.6 per cent) with a wound infection, 20 per cent developed a wound dehiscence and 40 per cent an incisional hernia compared with 0.7 and 12.7 per cent, respectively, in patients without a wound infection[10]. Wissing (1988) concluded that wound dehiscence and incisional hernias are closely related to wound infections, although other complications as pneumonia and ileus are equally important[10]. In our study 4 of 11 patients with a wound dehiscence (36 per cent) were re-admitted and operated for incisional hernias.

Three other re-admissions were necessary for patients with a subhepatic mass or abscess: one patient in group I and two patients in group II. The excess cost of re-admissions (Dfl. 4,900) was estimated on the basis of an average hospital stay of 7

Table 6.4 *Estimated cost effects of single-dose (group I)* versus *multiple-dose (group II) cefuroxime prophylaxis*

	Group I (n=501)	Group II (n=503)
	(costs in Dfl.)	
Prophylactic antibiotics	14,100	28,400
Increased hospitalization due to septic complications	36,800	26,300
Additional antibiotics for septic complications	11,540	5,575
Re-operations/re-admissions for septic complications	24,500	9,800
Total cost	86,940	70,075

Table 6.5 *Cost of prophylactic regimens in biliary tract surgery in 132 Dutch hospitals (1988)*

Prophylactic regimen		Duration of prophylaxis (range in hours#)	Total cost of prophylaxis* (range in Dfl.)
ampicillin		0 - 24	3.60 - 74.04
benzylpenicillin		72	6.32
cefamandol		24	59.16
cefazolin		0 - 24	15.02 - 60.08
cefotaxim		24	86.19 - 114.92
cefoxitin		0 - 24	46.27 - 97.64
cefuroxime		0 - 24	14.19 - 84.45
clavulanate-potentiated amoxycillin		0 - 120	16.20 - 81
metronidazole		120	179.25
piperacillin		0	46.55
ampicillin	+ metronidazole	72	181.50
cefamandole	+ metronidazole	24	73.05 - 102.63
cefazolin	+ metronidazole	0 - 24	26.97 - 95.93
cefotaxime	+ metronidazole	0 - 48	52.48 - 301.54
cefradin	+ metronidazole	48	147
ceftriaxon	+ metronidazole	72	204.57
cefuroxime	+ metronidazole	0 - 72	23.99 - 360.90
gentamicin	+ metronidazole	0 - 48	33.55 - 116.50
tobramycin	+ metronidazole	24	108.84
amoxicillin	+ gentamicin	24 - 48	35.20 - 231.96
ampicillin	+ gentamicin	24 - 120	48.90 - 579.90
clavulanate-potentiated amoxycillin	+ gentamicin	24	71.30
cefuroxime	+ gentamicin	24	91.26
flemoxin	+ gentamicin	72	96.69
clindamycin	+ gentamicin	24 - 48	96.72 - 193.44
amoxicillin	+ tobramycin	0	56.87
cefamandol	+ tobramycin	24	158.16
clavulanate-potentiated amoxycillin	+ doxycycline	0	33.07
ampicillin + gentamicin + clindamycin		24	191.50

* Based on wholesale prices in Dutch guilders (Farmacotherapeutisch Kompas 1990-1991)
\# Single-dose prophylaxis is indicated as 0 hours

days at the mean cost of hospital admission in The Netherlands in 1988[11], increased by 10 per cent for 1990.
Excess cost in group I patients: 5 × Dfl. 4,900 = Dfl. 24,500
Excess cost in group II patients: 2 × Dfl. 4,900 = Dfl. 9,800

Table 6.6 *Cost of prophylactic regimens in biliary tract surgery and potential savings in 132 Dutch hospitals, derived from the results of a questionnaire performed in 1988 (Chapter 2)*

Cost of prophylactic regimen (Dfl.)*	Number of clinics	Average cost (Dfl.)	Potential savings (Dfl.)
unknown	6	?	?
none	26	0	?
1 - 50	36	31.15	0
50 - 100	41	75.29	152,010
100 - 200	17	139.46	140,380
≥ 200	6	302.76	136,890
		Total savings	429,280

* Costs are based on wholesale prices in Dutch guilders (Farmacotherapeutisch Kompas 1990-1991)

The overall results of these calculations are listed in *Table 6.4*. The difference in costs between the two study groups was Dfl. 16,865 in favour of multiple-dose cefuroxime prophylaxis. Surprisingly, this does not correspond with the previous finding that single-dose prophylaxis was more cost-effective than a multiple dosage. On the assumption that septic complications are beneficially influenced by prophylactic antibiotics, the overall outcome might be in favour of the more expensive multiple-dose regimen. Since the financial consequences are significant, further investigation is warranted to confirm these findings.

6.3.4 Potential cost savings

An inventory of antibiotic prophylaxis in biliary tract surgery in The Netherlands has been made (*Chapter 2*). Drugs, duration of prophylaxis, and total cost of the antibiotic regimens (based on wholesale prices) are listed in *Table 6.5*. Subsequently, 132 Dutch clinics were subdivided in groups according to the total cost of their prophylactic regimen (*Table 6.6*). Assuming that a prophylactic regimen of less than Dfl. 50 is efficacious, potential savings were estimated by multiplying the average excess cost of the antibiotic regimen by the number of clinics involved and by the average number of cholecystectomies performed per clinic each year (derived from *Chapter 3*). Potential savings up to Dfl. 400,000 per year can be achieved using a more rational (cost-effective) antibiotic prophylaxis nationwide. It has to be mentioned that competitive bargaining or collective purchase arrangements were not considered.

A system for monitoring, effective surveillance and reporting might also help to

decrease the risk of infection and improve the quality of patient care. Prevention of infection includes high standards of housekeeping, antisepsis and asepsis, as well as careful surgical techniques. Many of these measures are a matter of discipline of the personnel involved. There are indications that all these measures might lead to a substantial reduction in the overall wound infection rate. For example, a one per cent reduction would prevent about 140 major wound infections after 13,956 cholecystectomies performed each year in The Netherlands. In that case, the estimated savings are 140 × Dfl. 676 (cost of a major wound infection) = Dfl. 94,640.

6.4 Discussion

The economic importance of surgical wound infection has already been emphasized by Terry (1985)[12]. Although prophylactic antibiotic regimens are established as being superior to placebo[4], reports on cost effects are scarce. Only a few studies can be mentioned. In a study of 1036 patients undergoing elective surgical procedures Jones *et al.* (1987) calculated a saving of $ 90.30 per patient when using cefotaxime instead of cefoxitin[13]. Garcia-Rodriguez *et al.* (1989) performed a cost-benefit analysis immediately following a prospective trial of single-dose cefotaxime prophylaxis *versus* four doses of cefoxitin in gastroduodenal and biliary surgery[14]. The authors found that cefotaxime resulted in a significant reduction of costs. However, the benefits are unclear and not specified. For many reasons comparison of our results with other cost analyses is hazardous; different agents are used, hospital costs and cost structure of hospitals may be incomparable, and the value of money and percentage of inflation can affect the results considerebly. Therefore, the discussion has to be confined to some general remarks, while the results of our calculations can only be applied to the present situation in The Netherlands.

Obviously, preventing wound infections is most beneficial to the patients concerned. But who else benefits? The words "cost-effective" and "cost-beneficial" are confusing, because they might have a variety of meanings, depending on who benefits. Most hospitals have no way of tracking patient outcomes from various therapies given, to even evaluate cost-effectiveness. A common cost-containment strategy in hospitals is to select the least expensive drug from a group of agents largely equivalent in terms of efficacy and toxicity. Indeed, cost savings can be achieved by introducing a less expensive antibiotic regimen (i.e. single-dose instead of multiple-dose cefuroxime prophylaxis) as we have demonstrated. From the results it can be concluded that both single-dose and multiple-dose cefuroxime prophylaxis are cost-effective compared with no prophylaxis, whereas single-dose prophylaxis is less expensive than multiple-dose cefuroxime prophylaxis.

The conclusion that single-dose cefuroxime prophylaxis is more cost-effective than a multiple dosage might be short-sighted if prophylactic antibiotics affect other septic complications to such an extent that the duration of postoperative hospital stay, the use of additional antibiotics, and the incidence of re-admissions or re-operations are reduced. In that case the final outcome might be quite different. The excess cost of multiple-dose cefuroxime did counterbalance the excess cost of infectious morbidity after single-dose cefuroxime prophylaxis, and we have estimated a difference of Dfl. 16,865 in favour of multiple-dose cefuroxime prophylaxis if these effects are taken into account. Apparently, multiple-dose cefuroxime was more efficacious than a single dosage. Although there is no clear evidence that newer, more powerful antibiotics are more efficacious in terms of wound infection than the established first-generation cephalosporins, the effect on septic complications other than wound infection were not mentioned[4,15-18].

In general, the more frequently a drug is administered the more expensive the total cost will be. However, since postoperative infectious complications are much more expensive than any difference in drug costs, the choice of a drug for prophylaxis should be based upon its clinical efficacy, not its cost. This is in contrast with a previous conclusion in *Chapter 4*. Reduction of postoperative hospitalization and, thus, in nursing-days always reduces costs, but this also has an impact on the hospital budgetting system, such as that introduced in The Netherlands in 1983. Therefore, the definite outcome of the cost effects can not be accurately determined and recommendations for an optimal antibiotic prophylaxis in biliary surgery in The Netherlands can not yet be given. Moreover, different assumptions or estimates have to be identified in order to test the sensitivity of the results and conclusions to such changes.

6.5 References

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Chapter 7

GENERAL DISCUSSION AND CONCLUSIONS

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7.1 Discussion

From the results of the questionnaire on the current practice of antibiotic prophylaxis in biliary surgery in The Netherlands (*Chapter 2*) it was concluded that prophylaxis was inappropriate in at least 31 hospitals (23%). We realize, however, that the questionnaire is only a still-frame during an evaluating process. Meanwhile, in some of the hospitals antibiotic prophylaxis might have been adjusted to modern practice as new drugs are introduced, more is known about the value of single-dose prophylaxis and more is learned about the emergence of resistant organisms. In 1988, single-dose prophylaxis was employed in only 28 clinics; this number has probably since increased, because single-dose prophylaxis is now frequently recommended as the standard therapy in biliary surgery. Reasons for inappropriateness in the 31 clinics were attributed to the duration of prophylaxis for longer than 24 hours and the absence of prophylaxis in cases of acute cholecystitis. These observations are in accordance with a similar questionnaire survey conducted in England in 1987[1]; prophylaxis was inappropriate in 20% of cases in biliary surgery due to the duration of use, choice of agents, and absence of prophylaxis in high risk patients. In a recent prospective survey of antibiotic use at five clinical departments of the Khon Kaen University, Thailand, 82.4% of the prescriptions for surgical prophylaxis were inappropriate, mostly due to delayed and excessive length of treatment[2]. In addition to these results, we should be aware that inappropriate use is an important factor in the rising cost of prophylactic antibiotics[3].

In 1976 the Dutch Health Council advised hospitals to formulate guidelines for use of antibiotics[4]. An inventory and comparison of these guidelines was performed in 1988-1989[5]. The results of this evaluation showed that guidelines are too often formulated in a non-committal way. This might explain our observation that within some hospitals surgeons use different prophylactic antibiotics for the same type of operation. We feel that a Hospital Infection Control Committee should be responsible for the control of infections within hospitals. This committee should develop imperative, written standards for an efficacious and cost-effective antibiotic prophylaxis. We can no longer afford the luxury of providing all physicians with an "open account" to order any drug or test that comes in mind.

The frequency of cholecystectomies in The Netherlands decreased by 25% within a period of eight years (1981-1989; *Chapter 3*). This is in line with findings in Sweden[6], but in contrast with recently published data in the USA and the UK. Maki *et al.* (1984) reported 400,000 cholecystectomies each year in the USA[7], whereas a number of 500,000 was published recently[8]. Crumplin *et al.* (1985) mentioned 43,000 cholecystectomies in the UK[9] *versus* 50,000 as stated by Walsh and Russell recently[8]. The registered frequency of postoperative morbidity of biliary surgery in The Netherlands (SIG data 1987-1989) is only 4.3 *versus* 34% in a study of Crumplin *et al.*[9]. Undoubtedly, the Dutch results are underestimated. As long as complications are not properly defined, comparison between different studies is hazardous.

As the number of published and unpublished clinical trials continue to increase, there is a need for systematic synthesis of research results (*Chapter 4*). Meta-analysis is a relatively new statistical tool, a more rigorous approach than the traditional narrative research review. Simple addition of successes across all trials to give an overall average is an inadequate way of pooling results. As far as the results are concerned, our meta-analysis can be compared with two recently published meta-analyses of randomized controlled trials of antibiotic prophylaxis[10,11]. All three meta-analyses revealed a significant difference in wound infection rates in favour of the use of prophylactic regimens compared with placebo or no-treatment controls. We found an overall difference of 9% (95% confidence interval from 7 to 11%). Wttewaall-Evelaar included 39 trials in her meta-analysis of randomized controlled trials of antibiotic prophylaxis in abdominal hysterectomy[10]. The 4.6% overall difference in wound infection rates (95% confidence interval from 2.7 to 6.5%) is comparable with our result. The meta-analysis of Velanovich[11] revealed a difference of 43.7% in favour of the use of antibiotics *versus* placebo. In this analysis only three prospective studies were included and the rate of infections ranged from 36 to 87%, while in the antibiotic arms, the rates were from 0 to 36%. Therefore, the relative difference had a rather wide 95% confidence interval of between 14.9 to 72.5%[11].

In a review DiPiro *et al.* (1984) could not demonstrate a significant difference between various cephalosporins used in the prophylaxis of surgical infection[12]. However, many studies compared groups of patients that were too small to rule out significant differences. Also in our meta-analysis the comparison of wound infection rates in patients treated with first generation *versus* second or third generation cephalosporins revealed no significant effect. From the 95% confidence interval (−1.5 to +2.5%) we concluded that trials which have as primary objective the comparison of first *versus* newer generation cephalosporins will almost certainly fail to detect any clinically or statistically significant difference in wound infection rates.

With respect to the methodology, the usual procedure for event data is the Mantel-

Haenszel test[13,14]. This fixed-effect method was used in the meta-analysis of antibiotic prophylaxis in abdominal hysterectomy, performed by Wttewaall-Evelaar[10]. From another review of 26 trials evaluating the efficacy of antibiotic prophylaxis in colonic surgery[15] it was demonstrated that not only is homogeneity within trials essential but also homogeneity of treatment effects between individual trials. DerSimonian and Laird introduced a method that incorporates the heterogeneity of effects in the analysis of the overall treatment efficacy[16]. We have adopted this random-effects method, as did Velanovich in his meta-analysis of randomized trials of antibiotic prophylaxis in head and neck surgery[11]. Clinical heterogeneity between individual trials, however, remains a problem in meta-analysis[17]. One of the drawbacks of meta-analysis is a lack of expert agreement concerning the most appropriate form of statistical analysis[18]. A variety of statistical techniques have been developed for combining the results of separate studies.

Publication bias is another problem in pooling data. Because of the tendency of a publication bias towards positive trials in clinical research[19], we tried to include all available trials, whether published or not. As reported by others, the search for unpublished data is unsatisfactory and, in fact, a registration of all clinical trials is essential[20]. In the UK a directory of registries of clinical trials has recently been developed[21]. This is an example that should be followed in other countries. Although the approach of meta-analysis has its limitations[17], it is the best available approach to making sense of a large number of individually inadequate trials[22]. Moreover, it might help in planning a new major trial.

Eventually, we conducted a trial of single-dose *versus* three doses of cefuroxime in the prophylaxis of biliary tract operations (*Chapter 5*). It proved very complicated to specify the minimum difference between treatment responses to conclude that one treatment has a clinically important advantage over the other. Information about side effects, complications, and costs against the benefits of the two treatment modalities are necessary to judge the size of the smallest clinically important difference[23]. We have judged a 5 per cent difference in major wound infection rate between treatment arms as clinically important. Although the planned number of 2348 patients could not be attained, the final result of 1044 patients has a statistical power of 80 per cent. The use of group sequential analyses has been advocated to allow the trial to be terminated at the earliest point at which statistically valid conclusions can be drawn[24]. We have performed only one interim analysis, because the decision to stop the trial was mainly dependent on practical aspects as time and costs. The interim analysis revealed no statistically significant difference between the two study groups.

The results of the present trial show an estimated 0.8% difference in major wound infection rate between the two study groups (95% confidence interval from −1.7 to +3.3%). These results can best be compared with another multicentre study of antibiotic

prophylaxis in 1451 patients with infection risk factors who underwent gastroduodenal and biliary surgery[31]. Single-dose cefotaxime was compared with four doses of cefoxitin. Cefotaxime is also a short-acting agent with a serum half-life of 1.2 hours. The frequency of wound infections was 3.3% in the cefotaxime group and 7.6% in the cefoxitin group. The 95% confidence interval of the estimated difference was from 1.9 to 6.7%. Our results broadly corroborate the results of this study. With an estimated 0.8% difference we feel that conclusions from the present multicentre trial have a representive base to allow extrapolation to the entire population of biliary surgery patients.

In recently published trials of antibiotic prophylaxis in primarily gallbladder surgery a variety of antimicrobial agents were investigated: single-dose cefonicid *versus* single-dose mezlocillin[25], multiple-dose cefmetazole *versus* multiple-dose cefoxitin[26], single-dose *versus* multiple-dose cefotaxime[27], single-dose aztreonam *versus* multiple-dose gentamicin[28], single-dose ceftizoxime *versus* single-dose cephradine[29] and single-dose piperacillin *versus* single-dose tobramycin[30]. The largest group of patients in these trials comprised 99 patients[29]. Wound infection rates varied between 0 and 19.5 per cent. Rodilico *et al.*[27] concluded from only 44 patients that aztreonam is safe and effective for the prevention of infections following biliary surgery. Lewis *et al.*[28] validated from a total of 26 patients the efficacy of single-dose cefotaxime prophylaxis in high risk patients undergoing gastroduodenal surgery. Perhaps superfluous to point out that the sample sizes of all the above-mentioned trials were too small to detect small differences with sufficient statistical power. The conclusions drawn from these studies are premature.

We did not perform a formal cost-benefit analysis, because differentiated hospital charges and costs were not available due to the cost structure of hospitals in The Netherlands (*Chapter 6*). Moreover, the cost effects of single-dose and multiple-dose cefuroxime prophylaxis can hardly be compared with other cost analyses of antibiotic prophylaxis. First, the literature is scarce. Secondly, hospital costs and the hospital cost structure are different in other countries. Thirdly, the value of money and percentage of inflation are not taken into account. Nevertheless, the method to estimate the excess cost/patient of a wound infection (C + PW) is similar to the method used by Garcia-Rodrigues *et al* [31]. In our cost calculations (one U.S.dollar = 1.9 Dutch guilders) the excess cost/patient was $31.18 in case of single-dose cefuroxime prophylaxis and $43.27 in case of three doses of cefuroxime. Because the excess cost/patient without prophylaxis was estimated at $64.04, we concluded that both single-dose and multiple-dose cefuroxime prophylaxis are cost-effective compared with no prophylaxis, while single dosage is less expensive. Garcia-Rodrigues *et al.*[31] estimated the cost of a wound infection to be 3.4 (days) × 144.43 U.S.dollar (hospitalization cost/day) = $491. This

amount was increased by the average cost of therapeutic antibiotics ($186.15). Consequently, the overall cost of a wound infection was $677.15. The excess cost/patient was calculated at $104.43 in case of cefoxitin prophylaxis and $28.64 in case of cefotaxime prophylaxis. Savings related to the use of cefotaxime instead of cefoxitin averaged $75.65 per patient in whom antibiotic prophylaxis was needed[31].

We have pointed out the effect of septic complications other than wound infection on costs. As a consequence, the initial favourable effect of single-dose cefuroxime prophylaxis has changed into a final benefit in favour of the multiple-dose regimen. Based on 500 treated patients, an overall cost-difference of Dfl. 16,865 was calculated. In an excellent study on perioperative antibiotic prophylaxis for herniorrhaphy and breast surgery (single-dose cefonicid *versus* placebo) a similar effect was noted[32]. The authors concluded from their study that the difference between the two treatment groups in their need for postoperative interventions, including antibiotic therapy, extra visits to a physician and re-admissions, supported a clinically as well as biologically important effect of prophylaxis. The cost effect of septic complications other than wound infections can also be deduced from a study of antibiotic prophylaxis in vaginal and abdominal hysterectomies[33]. In this analysis the total excess cost/patient increased significantly: $1,777 for vaginal and $716 for abdominal hysterectomies, compared to $104.43 per patient when only the excess cost of wound infections was included in the analysis[31].

In the Dutch system of hospital budgetting, profits of modern pharmacotherapy in the hospitals are earned outside the hospital[34]. We should realize that these profits must be re-invested to ensure a healthy health-care system in the future. A true saving based on efficacious and cost-effective prophylaxis should be reflected in fewer staff positions for nurses and pharmacists in hospitals but this, probably, will not occur - at least not in The Netherlands.

7.2 Future directions

The development of laparoscopic cholecystectomy has enabled to minimize the problems of major wound infection in gallbladder surgery. Therefore, future trials in antibiotic prophylaxis are better directed to surgical procedures with higher wound infection rates, such as colorectal surgery.

Since the quality of medical care is related to its cost-effectiveness, it is a matter of concern to physicians. Our classic responsibility to our patients threatens to change in an economic marketplace. Therefore, cost analyses are essential and should be performed in all comparative clinical trials of antibiotic prophylaxis.

A sensitivity analysis should be considered in further economic evaluations. Uncertain or controversial estimates include hospitalization costs, discount rates, and effectiveness of new drugs.

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SUMMARY

The topic of this thesis "Antibiotic prophylaxis in biliary tract surgery" has been approached in several ways. An introduction to the subject, including some historical aspects, is presented in *Chapter 1*.

First, the current practice of antibiotic prophylaxis in biliary surgery in The Netherlands has been investigated (*Chapter 2*). A questionnaire was sent to the Chairmen of the Departments of Surgery of 175 hospitals in The Netherlands. The surgical clinics are classified into three categories depending on the type of residency in general surgery: A, B, or C clinic. Overall, 80% replied. Antibiotic prophylaxis in elective cholecystectomy is given in 76% of the clinics (100/132), and single-dose prophylaxis is employed in 28% of these clinics (28/100). In patients with acute cholecystitis, emergency surgery is the treatment of choice in 108 hospitals (82%). Differences in antibiotic prophylaxis between the three categories of hospitals include the absence of prophylaxis in elective cholecystectomy in 31% of the C-clinics (*versus* 10% of the A-clinics and 16 per cent of the B-clinics), and the use of single-dose prophylaxis in 13% of the B-clinics (*versus* 30% of the A-clinics and 31% of the C-clinics).

Conclusion: Since prophylaxis for more than 24 hours has no additional effect and peri-operative prophylaxis in acute cholecystitis is mandatory, antibiotic prophylaxis in biliary tract surgery is inappropriate in at least 31 hospitals in The Netherlands (23%).

An overview of all cholecystectomies performed in The Netherlands from 1987-1989 is presented with details of frequency, mortality and morbidity (*Chapter 3*). Compared to the period 1979-1981 the number of cholecystectomies decreased by 25.5%, whereas the number of cholecystectomies with common bile duct exploration decreased by 43.8%. The mortality rate reduced from 1.9 to 1.4%. In the period 1987-1989 the frequency of postoperative complications, including wound infection was low: 4.3 and 1.5%, respectively. Acute cholecystitis, age 70 years and over, and common bile duct exploration appeared to be risk factors with significantly higher mortality and morbidity rates.

Conclusions: - The frequency of cholecystectomies in The Netherlands showed a 25%

decrease within a period of eight years (1981-1989).
- In the same period the number of common bile duct explorations decreased by 43.8%.
- Mortality and morbidity rates are low: 1.4 and 4.3%, respectively.

The literature study comprises a meta-analysis (*Chapter 4*). In this study all available clinical trials of antibiotic prophylaxis in biliary tract surgery, published from 1965 to 1988, were examined. Results of 42 randomized controlled trials (4129 patients), in which a group of patients treated with antibiotics was compared with a group of patients not treated with antibiotics, were pooled. Wound infection rates in the control groups range from 3 to 47% and are 15% overall. The overall difference in infection rates is 9% in favour of antibiotic treatment (95% confidence interval 7% - 11%), while the common odds ratio is 0.30 (95% confidence interval 0.23-0.38). Subgroup meta-analysis showed a significant stronger protective effect in high risk patients, while early (in hospital) or late (follow-up) wound inspection markedly influenced the treatment effect reported. Comparison of wound infection rates in patients treated with first generation cephalosporins *versus* second or third generation (11 trials, 1128 patients), as well as single *versus* multiple-dose regimens (15 trials, 1226 patients) did not reveal any significant effect ($p > 0.05$) in each trial separately, as well as in the overall comparison.

Conclusions:
- The overall difference in wound infection rates is 9% in favour of antibiotic prophylaxis compared with no prophylaxis (95% confidence interval from 7% to 11%).
- Subgroup analysis showed a stronger protective effect in high risk patients.
- No significant difference in wound infection rates was found in patients treated with first generation *versus* newer generation cephalosporins, as well as single-dose *versus* multiple-dose regimens.
- A major trial comparing single *versus* multiple dosage of the same, short-acting antibiotic is worthwhile, provided that a sufficient number of patients can be included.

A randomized, controlled double-blind multicentre trial (so-called Galant-Trial) was conducted (*Chapter 5*). One-dose cefuroxime (1.5 g intravenously) was compared with a three-dose regimen as control (1.5 g cefuroxime preoperatively and two doses of 0.75 g postoperatively). The study group comprised 1004 patients with infection risk factors. All patients were followed up for four to six weeks after surgery. The characteristics of both groups were comparable. No statistically significant difference was found between

the two antibiotic regimens in preventing postoperative wound infections: 6.6 *versus* 6.2% minor wound infections (p=0.78) and 4.6 *versus* 3.8% major wound infections (p = 0.52). The estimated difference in major wound infection rates between the two groups was 0.8% (95% confidence interval from −1.7% to +3.3%). However, the frequency of deep wound dehiscence, additional postoperative antibiotic therapy and mean postoperative hospital stay showed significant differences in favour of the multiple-dose regimen ($p < 0.05$). In a multivariate analysis three factors appeared to have a high prognostic value for the development of major wound infections: (a) previous gastric surgery; (b) local tenderness in the right upper abdomen; and (c) gallbladder perforation.

Conclusions:
- In terms of major wound infections no statistically significant difference was found between single-dose and multiple-dose cefuroxime in the prophylaxis of biliary tract surgery.
- Previous gastric surgery, local tenderness in the right upper abdomen and gallbladder perforation at operation have a high prognostic value for the development of a postoperative major wound infections.
- Prophylactic antibiotics should be effective against endogenous as well as exogenous wound contaminants.

Results of the randomized controlled trial of cefuroxime prophylaxis in biliary tract surgery were adapted to estimate the effect of different antibiotic regimens on costs. The total excess costs of 500 treated patients were Dfl. 60,840 in case of no prophylaxis, Dfl. 29,625 in case of single-dose cefuroxime prophylaxis, and Dfl. 41,110 in case of a three-dose cefuroxime prophylaxis. If the effects of septic complications other than wound infection were taken into account, the difference in total excess cost between the two study groups was estimated at Dfl. 16,865 in favour of multiple-dose cefuroxime prophylaxis. In The Netherlands, potential savings up to Dfl. 400,000 per year can be achieved using a more cost-effective antibiotic prophylaxis in biliary surgery nationwide.

Conclusions:
- The hospital per diem costs of a nursing-day overshadow most other expenses.
- Both single- and multiple-dose cefuroxime prophylaxis are cost-effective compared with no prophylaxis, whereas single-dose cefuroxime prophylaxis is less expensive than multiple doses.
- If cost effects of septic complications, other than wound infection, are taken into account in the analysis, the outcome is in favour of multiple-dose cefuroxime prophylaxis.
- Further analysis is mandatory to test the sensitivity of the results.

The thesis is concluded with a general discussion and conclusions drawn from the study (*Chapter 7*).

SAMENVATTING

Het thema van dit proefschrift "Antibiotica-profylaxe in de galwegchirurgie" werd van verschillende kanten benaderd. Als eerste is een inleiding gegeven over het onderwerp, waarbij verscheidene historische aspecten zijn belicht (*Hoofdstuk 1*).

Vervolgens werd het huidige antibiotica-beleid bij galwegoperaties in Nederland nagegaan (*Hoofdstuk 2*). Een vragenformulier werd opgestuurd naar de hoofden van de chirurgische afdelingen van 175 Nederlandse ziekenhuizen. Deze ziekenhuizen zijn onderverdeeld in drie categorieën (A-, B-, of C-kliniek), afhankelijk van het type opleiding in de algemene heelkunde. In totaal beantwoordde 80% het vragenformulier. In 76% van de onderzochte klinieken (100/132) werd antibiotica-profylaxe gebruikt bij electieve galblaasextirpaties. Een éénmalige profylaxe werd toegepast in 28% van deze klinieken (28/100). Bij patiënten met een acute cholecystitis werd in 108 ziekenhuizen bij voorkeur een spoedoperatie verricht (82%). Wat betreft de verschillende opleidingscategorieën bleek er in 31% van de C-klinieken geen profylaxe gegeven te worden bij electieve galblaasextirpaties (*versus* 10% in A-klinieken en 16% in B-klinieken). Een éénmalige profylaxe werd gebruikt in 13% van de B-klinieken (*versus* 30% van de A-klinieken en 31% van de C-klinieken).

Conclusie: - Aangezien antibiotica-profylaxe langer dan 24 uur geen extra voordelen biedt en het nut van profylaxe bij patiënten met een acute cholecystitis bewezen is, moet het gebruik van antibiotica-profylaxe in de galwegchirurgie in minstens 31 Nederlandse ziekenhuizen (23%) als ontoereikend worden beschouwd.

Een overzicht van alle galblaasoperaties in Nederland in de periode 1987-1989 wordt gegeven in *Hoofdstuk 3*. Aan de hand van SIG-gegevens werden de frequentie, operatie-mortaliteit en postoperatieve complicaties (specifiek van wondinfecties en -dehiscenties) bepaald. Ten opzichte van de periode 1979-1981 is er een daling van het aantal galblaasextirpaties van 25,5%. Het aantal galblaasextirpaties met choledochusexploratie is verminderd met 43,8%. De operatieve sterfte is gedaald van 1,9% in de periode 1979-1981 tot 1,4% in de periode 1987-1989. Postoperatieve complicaties, waaronder wondinfecties, kwamen relatief weinig voor, respectievelijk in

4,3 en 1,5% van de gevallen. Acute cholecystitis, leeftijd ouder of gelijk aan 70 jaar en choledochusexploratie blijken risicofaktoren te zijn met een significant hogere operatie-mortaliteit en postoperatieve morbiditeit.

Conclusies:
- De frequentie van galblaasextirpaties in Nederland is met 25% gedaald in een periode van 8 jaar (1981-1989).
- In dezelfde periode daalde het aantal choledochotomieën met ruim 43%.
- De operatieve sterfte is laag (1,4%) en postoperatieve complicaties komen relatief weinig voor (4,3%).

De literatuurstudie omvat een meta-analyse (*Hoofdstuk 4*). In deze studie werden alle beschikbare gerandomiseerde klinische trials over antibiotica-profylaxe in de galwegchirugie, gepubliceerd tussen 1965 en 1988, geanalyseerd. De resultaten van 42 gerandomiseerde trials (4129 patiënten), waarin patiënten behandeld met antibiotica werden vergeleken met patiënten die geen antibiotica kregen, werden gecombineerd. In de contrôle-groepen variëerde de wondinfectie percentages van 3 tot 47%, met een totaal gemiddelde van 15%. Het totale verschil in wondinfectie percentage bedroeg 9% ten gunste van de patiënten die profylaxe hadden gekregen (95% betrouwbaarheids-interval van 7-11%). Meta-analyse van subgroepen toonde aan, dat het beschermend effect groter is bij patiënten met een "hoog risico", terwijl het moment van wondinspectie (ten tijde van de opname of bij een vervolgonderzoek na 4-6 weken) een duidelijke invloed op het behandelingsresultaat had. Bij vergelijking van wondinfectie percentages tussen patiënten, behandeld met een eerste generatie cefalosporine *versus* patiënten, behandeld met een tweede of derde generatie cefalosporine (11 trials, 1128 patiënten), werd geen significant verschil gevonden ($p>0,05$). Evenmin werd een significant verschil aangetoond tussen een éénmalige gift en meerdere giften van profylactische antibiotica (15 trials, 1226 patiënten).

Conclusies:
- Het totale verschil in wondinfectie percentage tussen wel of geen antibiotica profylaxe is 9% ten gunste van profylaxe (95% betrouwbaarheids-interval van 7 tot 11%).
- In een subgroep-analyse werd een sterker beschermend effect gevonden bij patiënten met een verhoogd risico voor infecties.
- Geen significant verschil in wondinfectie percentage werd gevonden tussen patiënten, behandeld met een eerste generatie *versus* een nieuwere generatie cefalosporine, en tussen patiënten, behandeld met een éénmalige dosis antibiotica *versus* een meervoudige gift.
- Een nieuwe trial, waarin een éénmalige gift van een kortwerkend antibioticum wordt vergeleken met meerdere giften van hetzelfde

middel, lijkt zinvol op voorwaarde dat het aantal deelnemende patiënten groot genoeg is.

De uitvoering en resultaten van een gerandomiseerde, dubbelblinde, multicentrische studie (Galant-trial) worden besproken in *Hoofdstuk 5*. Een éénmalige dosis cefuroxim (1,5 g intraveneus) werd vergeleken met een driemalige dosis als contrôle (1,5 g cefuroxim preoperatief en tweemaal 0,75 g postoperatief). De studiegroep bestond uit 1004 patiënten, allen met 1 of meer risico faktoren voor het ontwikkelen van een wondinfectie. Alle patiënten werden 4-6 weken na de operatie vervolgd. De kenmerken van beide studie-groepen waren vergelijkbaar. Tussen de twee groepen werd geen statistisch significant verschil gevonden wat betreft het percentage wondinfecties: 6.6 *versus* 6,2% graad I wondinfecties ($p = 0,78$) en 4,6 *versus* 3,8% graad II wondinfecties ($p = 0,52$). Het geschatte verschil in percentage graad II wondinfecties bedroeg 0.8 (95% betrouwbaarheids-interval van −1,7% tot +3,3%). Echter, de gemiddelde postoperatieve opnameduur, het aantal patiënten dat postoperatief met antibiotica werd behandeld en de frequentie van wondehiscenties vertoonden significante verschillen ten gunste van de behandeling met de driemalige profylaxe ($p<0,05$). In een multivariant analyse bleken drie factoren een grote voorspellende waarde te hebben voor de ontwikkeling van graad II wondinfecties: (a) een vroegere maagoperatie; (b) locale drukpijn in de rechter bovenbuik; en (c) galblaas-perforatie.

Conclusies:
- Er is geen statistisch significant verschil tussen een éénmalige en een driemalige dosis cefuroxim in de profylaxe van galwegoperaties.
- Een vroegere maagoperatie, locale drukpijn in de rechter bovenbuik en een galblaasperforatie durante operationem zijn prognostische factoren met een grote voorspellende waarde voor de ontwikkeling van een wondinfectie.
- Profylactische antibiotica moeten werkzaam zijn tegen zowel endogene als exogene wondcontaminanten.

De resultaten van de gerandomiseerde multicentrische trial werden gebruikt om het effect van verschillende antibiotica regimes op de kosten te bestuderen (*Hoofdstuk 6*). De extra kosten van antibiotica en eventuele wondinfecties per 500 geopereerde patiënten bedragen *f* 60.840,- indien geen antibiotica-profylaxe wordt gegeven, *f* 29.625,- bij éénmalige cefuroxim profylaxe en *f* 41.110,- bij een driemalige cefuroxim profylaxe. Indien de gevolgen van andere septische complicaties worden meegerekend, dan is het verschil in extra kosten tussen de twee studiegroepen *f* 16.865,- ten gunste van de driemalige cefuroxim profylaxe. Besparingen tot een bedrag van *f* 400.000,- per jaar zijn mogelijk, indien in alle Nederlandse ziekenhuizen

een effectiever beleid gevoerd zou worden ten aanzien van de kosten van antibiotica-profylaxe in de galwegchirurgie.

Conclusies:
- De kosten van een verpleegdag zijn zo hoog, dat de meeste andere kosten hierbij in het niet vallen.
- Zowel een éénmalige als een driemalige cefuroxim profylaxe zijn kosteneffectief vergeleken bij het achterwege laten van profylaxe, waarbij éénmalig goedkoper is dan driemalig.
- Indien de effecten van andere septische complicaties naast wondinfecties worden betrokken in de kosten-analyse, dan is de uitkomst in het voordeel van de driemalige cefuroxim profylaxe.
- Nader onderzoek is nodig om de sensitiviteit van de resultaten te testen.

Het proefschrift wordt afgesloten met een algemene discussie, conclusies en aanwijzingen voor toekomstig onderzoek (*Hoofdstuk 7*).

APPENDIX A *Questionnaire sent to the Chairmen of the Surgical Departments of 175 hospitals in The Netherlands*

1. How do you use antibiotic prophylaxis in elective cholecystectomy?
   a. Never
   b. Routinely
   c. Selectively

2. If selectively, which high risk factors are an indication for antibiotic prophylaxis?
   a. Patients over ... years of age
   b. Rigors within 1 week before operation
   c. Attack of acute cholecystitis within 1 month before operation
   d. Jaundice
   e. Common duct stone(s) or planned common bile duct exploration
   f. Previous biliary tract surgery
   g. Diabetes mellitus
   h. Morbid obesity
   j. Immuno-suppressive therapy
   k. Other reasons

3. If you do use antibiotic prophylaxis, which agent(s) in which dosis ?

4. How long is the total duration of your antibiotic prophylaxis?
   a. Single-dose
   b. ... hours
   c. ... days

5. How is the management of acute cholecystitis at your department usually?
   a. Emergency operation with peri-operative antibiotic prophylaxis (less than 48 hours)
   b. Emergency operation with "therapeutic" antibiotics (beyond 48 hours)
   c. Elective operation as soon as possible with peri-operative antibiotic prophylaxis
   d. Elective operation as soon as possible, starting antibiotic treatment immediately after admission
   e. Initial conservative treatment and delayed cholecystectomy

APPENDIX B

The Galant-trial Study Group (14 Dutch hospitals):

P.J.Breslau, M.D., Ph.D., Rode Kruis Hospital, Den Haag;
W.A.H.Gelderman, M.D., Ph.D., Groot Ziekengasthuis, Den Bosch;
J.M.Heslinga, M.D., Ph.D., Bronovo Hospital, Den Haag;
C.M.Hoogenboom, M.D., Van Weel-Bethesda Hospital, Dirksland;
C.L.Koppert, M.D., Eudokia Hospital, Rotterdam;
H.Kuiken, M.D., Schieland Hospital, Schiedam;
A.C.van der Ham, M.D., Sint Clara Hospital, Rotterdam;
J.K.S.Nuytinck, M.D., Ph.D., Sint Ignatius Hospital, Breda;
K.H.Ong, M.D., Hospital Rivierenland, Tiel;
C.H.Ruseler, M.D., Sint Franciscus Gasthuis, Rotterdam;
M.K.M.Salu, M.D.,Ph.D., Zuiderziekenhuis, Rotterdam;
P.F.Verhagen, M.D., Ph.D., Sint Maartens Gasthuis, Venlo;
W.F.Weidema, M.D., Ph.D., Reinier de Graaf Gasthuis, Delft;
O.J.van West, M.D., Sint Joseph Hospital, Oosterhout.

APPENDIX C

GALANT-TRIAL

Plak hier sticker
met ampul/pat.nr.

(via apotheek)

Algemene registratie

achternaam patiënt ☐☐ (eerste 2 letters)

geb. datum ☐☐ dag ☐☐ mnd ☐☐ jaar

☐ man / ☐ vrouw

ZIEKENHUIS: _____

Inclusie Eén of meer van deze vragen moet met ja beantwoord worden

	ja	neen
1. leeftijd ≥60 jaar	☐	☐
2. icterus (bilirubine ≥50 µmol/l)	☐	☐
3. acute aanval van cholecystitis <1 maand voor de operatie	☐	☐
4. choledocholithiasis	☐	☐
5. anamnestisch reeds een galwegoperatie ondergaan	☐	☐
6. koude rilling(en) <1 week voor operatie	☐	☐

Exclusie Bij deelname aan de trial moeten deze vragen met **neen** beantwoord zijn

Datum: ☐☐ dag ☐☐ mnd ☐☐ jaar

	ja	neen
1. bekende overgevoeligheid voor cefalosporinen	☐	☐
2. indien tegelijkertijd een andere intra-abdominale ingreep wordt verricht (bv appendectomie of maagresectie)	☐	☐
3. haemodynamisch instabiele patiënt	☐	☐
4. ernstige nierfunctiestoornis (kreatinine >300 µmol/l)	☐	☐
5. zwangerschap	☐	☐
6. gebruik van antibiotica binnen 7 dagen voor operatie	☐	☐
7. choledochusresectie (b.v. Whipple operatie)	☐	☐
8. gebruik van immuno-suppressiva, zoals Prednison	☐	☐

Algemene patiëntgegevens

Opname-datum ☐☐ dag ☐☐ mnd ☐☐ jaar

Opname: – electief ☐

– acuut ☐

Verwijzing naar chirurg:

– via huisarts ☐

– via internist ☐

– via ander specialisme ☐

Zo ja, welk? _____

Anamnestische gegevens

Aard van de klachten	ja	neen
kolieken	☐	☐
koorts	☐	☐
koude rilling	☐	☐
misselijk/braken	☐	☐
icterus	☐	☐

Duur van de klachten

Aantal uren ☐☐
dagen ☐☐
weken ☐☐
maanden ☐☐
jaren ☐☐

Vroegere abdominale operaties/ziekten

	ja	neen
– pancreatitis	☐	☐
– diverticulosis/itis	☐	☐
– appendectomie	☐	☐
– cholecystectomie	☐	☐
– colonoperatie	☐	☐
– maagoperatie	☐	☐
– uterusextirpatie	☐	☐
– overige	☐	☐

Zo ja, beschrijf_____

Bijkomende aandoeningen/ziekten

	ja	neen
– hernia diafragmatica	☐	☐
– ulcus pepticum	☐	☐
– cardio-vasculair	☐	☐
– CARA	☐	☐
– overige	☐	☐

Zo ja, beschrijf_____

Geneesmiddelen gedurende de afgelopen twee weken

	ja	neen
– antidiabetica	☐	☐
– antistolling	☐	☐
– diuretica	☐	☐
– anticonceptiva	☐	☐
– antirheumatica	☐	☐
– corticosteroiden	☐	☐
– cardiale middelen	☐	☐
– overige	☐	☐

Zo ja, beschrijf_____

Onderzoek

Lichamelijk onderzoek

– temperatuur bij opname in °C ☐☐,☐
rectaal ☐ axillair ☐ oraal ☐
– lengte in cm ☐☐☐
– gewicht in kg ☐☐☐

	ja	neen
– (sub)icterus	☐	☐
– abdomen: lokale drukpijn	☐	☐
percussiepijn	☐	☐
defense musculaire: – lokaal	☐	☐
– gegeneraliseerd	☐	☐
palpabele galblaas	☐	☐
bovenbuikslitteken	☐	☐
– overige essentiële bevindingen	☐	☐

Zo ja, beschrijf_____

(VERVOLG ONDERZOEK)

Röntgenologisch onderzoek

	ja	neen
a. echografie	☐	☐
b. orale cholecystografie	☐	☐
c. intraveneuze cholangiografie	☐	☐
d. percutane cholangiografie (PTC)	☐	☐
e. ERCP	☐	☐
f. hepatobida-scan	☐	☐
g. CT-scan	☐	☐

Geef chronologische volgorde van de onderzoeken aan:

1. ☐
2. ☐
3. ☐

Gevonden afwijkingen

	ja	neen	n.v.t.
– cholelithiasis	☐	☐	☐
– niet opkomende galblaas	☐	☐	☐
– verdikte galblaaswand	☐	☐	☐
– choledocholithiasis	☐	☐	☐
– verwijde intrahepatische galwegen	☐	☐	☐
– verwijde extrahepatische galwegen	☐	☐	☐
– choledochusstenose/strictuur	☐	☐	☐
– RIP in galblaas/leverhilus/pancreas	☐	☐	☐
– overige	☐	☐	☐

Zo ja, beschrijf _____

_____

Klinisch-chemisch onderzoek (pre-operatief)

	Hb	☐☐,☐	mmol/l
	BSE	☐☐☐	mm/uur
	leuco's	☐☐	g/l
*	eo	☐☐	%
*	baso	☐☐	%
*	st	☐☐	%
*	segm	☐☐	%
*	lymfo	☐☐	%
*	mono	☐☐	%
		ja ☐ neen ☐	
*	toxisch		
	bilirubine	☐☐☐	umol/l
	alk. fosf.	☐☐☐	U/l
	SGOT	☐☐☐	U/l
	SGPT	☐☐☐	U/l
**	gamma GT	☐☐☐	U/l
	kreatinine	☐☐☐	umol/l
**	amylase	☐☐☐☐	U/l
**	albumine	☐☐☐	g/l

* In geval van acute cholecystitis
** facultatief

Acute cholecystitis

ja ☐ neen ☐

Definitie van acute cholecystitis:

a. acute buikpijn >24 uur en <7 dagen;
b. drukpijn in rechter hypochondrium en/of palpabele galblaas;
c. leucocytose >10.000 × 10^6/l en/of koorts >38°C rectaal, of >37,5°C axillair gemeten; en eventueel
d. aangetoonde galstenen.

Voorbereiding operatiegebied:

– scheren met mes	☐
– scheren met tondeuse	☐
– ontharingsmiddel	☐
– géén ontharing	☐

Tijdstip van ontharing:

– dag voor operatie	☐
– vlak voor operatie	☐
– niet van toepassing	☐

Operatiegegevens

Operatie-datum ☐☐ dag ☐☐ mnd ☐☐ jaar

Algemene gegevens

		ja	neen
operateur: – chirurg	☐		
– chir. assistent	☐		
assistentie: – chirurg		☐	☐
– chir. assistent		☐	☐
– co-assistent(e)		☐	☐
– operatie-assistent(e)		☐	☐

Duur van de ingreep: ☐☐☐ minuten

Tijd tussen toedienen antibiotica en incisie: ☐☐☐ minuten

Incisie

– techniek	huid	subcutis	fascie
scalpel	☐	☐	☐
diathermisch	☐	☐	☐
– localisatie:		subcostaal	☐
		mediaal	☐
		paramediaan	☐
		overige	☐

Zo ja, beschrijf _____

Aard van de ingreep

	ja	neen
– cholecystectomie		
– antegraad (= vanaf fundus)	☐	☐
– retrograad	☐	☐
– peroperatieve cholangiografie	☐	☐
– choledochotomie	☐	☐
– choledochoscopie	☐	☐
– choledocho-enterostomie	☐	☐

Toestand van de galblaas

	ja	neen
– normaal aspect	☐	☐
– palpabele galstenen	☐	☐
– ontsteking (vaatinjectie en/of oedeem)	☐	☐
– hydrops/witte gal	☐	☐
– empyeem	☐	☐
– gangreen	☐	☐
– infiltraat	☐	☐
– perforatie – spontaan	☐	☐
– iatrogeen	☐	☐
– overige	☐	☐

Zo ja, beschrijf _____

Toestand van de choledochus

	geen exploratie	ja	neen
– normaal	☐	☐	☐
– indien **niet** normaal:			
– verwijd (☐☐ mm)		☐	☐
– verdikte wand		☐	☐
– obstructie – steen		☐	☐
– tumor		☐	☐

Spill van gal in het operatiegebied (contaminatie)

geen ☐

gering ☐

ernstig ☐

(VERVOLG OPERATIEGEGEVENS)

Galstenen:

	ja	neen
– zijn er bij het openen van de galblaas stenen gevonden?	☐	☐
– indien choledochotomie/scopie verricht is, zijn er choledochusstenen gevonden?	☐	☐

Buikholte

Gespoeld:

- neen ☐
- ja, met fys. zout/Ringers ☐
- ja, met andere vloeistof ☐

Zo ja, beschrijf_____

Type drainage:

- gesloten drainage ☐
- gesloten zuigdrainage ☐
- sump-drainage ☐
- geen drainage ☐

Drain uitgeleid:

- via aparte steekopening ☐
- via wond ☐

Wond

	ja	neen
– **peritoneum** gesloten	☐	☐
– **fascie** gesloten met dexon		☐
met vicryl		☐
met PDS		☐

	ja	neen
Huid: atraumatisch gesloten	☐	☐

Subcutis:

- niet gesloten ☐
- gesloten met catgut ☐
- met dexon ☐
- met vicryl ☐

Protocol-violation

DRAINAGE :

- abdominale drain niet geplaatst ☐
- drainage subcutane redondrain wel geplaatst ☐

WOND :

- fascie niet doorlopend gesloten ☐
- wond gespoeld met fys. zout/Ringers ☐
- wond gespoeld met andere vloeistof ☐

beschrijf _____

PA-uitslag

	ja	neen
– tekenen van acute ontsteking	☐	☐
– tekenen van chronische ontsteking	☐	☐
– géén tekenen van ontsteking	☐	☐

Plak hier sticker met ampul/pat.nr.

(via apotheek)

_____

Post-operatieve gegevens

Drains

	ja	neen	
– abdominale drain binnen 48 uur na operatie verwijderd	☐	☐	zoniet, wanneer wel? na ☐☐ dagen
– T-drain (indien geplaatst):			
– post-operatief cholangiogram	☐	☐	
– restconcrementen	☐	☐	
– T-drain verwijderd op dag ☐☐ post-operatief			
– therapie van evt. rest-concrement(en):			
– percutane transhepatische extractie	☐	☐	
– choledochoscopie via kanaal van T-drain	☐	☐	
– ERCP + papillotomie	☐	☐	
– spoeling via T-drain	☐	☐	
– re-operatie	☐	☐	zo ja, datum ☐☐ dag ☐☐ mnd ☐☐ jaar

Antibiotica

– heeft patiënt ná de profylaxe nog antibiotica gekregen	☐	☐

Zo ja, welke? 1. _____ gedurende ☐☐ dagen

2. _____ gedurende ☐☐ dagen

3. _____ gedurende ☐☐ dagen

Wondinspecties

	DAG 5		DAG 10 (of dag ontslag ziekenhuis)		WEEK 4-6	
	ja	neen	ja	neen	ja	neen
– **Wondinfectie**	☐	☐	☐	☐	☐	☐
zo ja, klasse	I	II	I	II	I	II
	☐	☐	☐	☐	☐	☐
– Intra-abdominaal	ja	neen	ja	neen	ja	neen
– infiltraat	☐	☐	☐	☐	☐	☐
– abces	☐	☐	☐	☐	☐	☐
– aangetoond met echografie, CT-scan en/of punctie	☐	☐	☐	☐	☐	☐
– **Sepsis**	☐	☐	☐	☐	☐	☐

Op de hoeveelste dag postoperatief trad bovengenoemde septische complicatie op? Dag ☐☐

Complicaties

	ja	neen
– temperatuur >39°C rectaal, of 38,5°C axillair	☐	☐
– heeft patiënt binnen 24 uur bloedtransfusie gehad	☐	☐
– temperatuur >38°C rectaal, of 37,5°C axillair langer dan 4 dagen achtereen	☐	☐

Interventie bij wondinfectie

	ja	neen
– punctie	☐	☐
– wond geopend	☐	☐
– wond defect (spontaan)	☐	☐

Overige complicaties

	ja	neen
– wonddehiscentie	☐	☐
– buikwanddehiscentie	☐	☐
– ileus mechanisch	☐	☐
paralytisch	☐	☐
– re-operatie?	☐	☐

Zo ja, beschrijf _____

– wondhaematoom	☐	☐
ontlast	☐	☐
– luchtweginfectie	☐	☐
– urineweginfectie	☐	☐
– thrombose/embolie	☐	☐
– thrombophlebitis	☐	☐
– decompensatio cordis	☐	☐
– overige	☐	☐

Zo ja, beschrijf _____

_____

Op de hoeveelste dag postoperatief trad bovengenoemde complicatie op? Dag ☐☐

Mortaliteit tgv het volgende lijden

	ja	neen
– cardiaal	☐	☐
– sepsis	☐	☐
– bloeding	☐	☐
– longembolie	☐	☐
– pneumonie	☐	☐
– overige	☐	☐

Zo ja, beschrijf _____

_____

– obductie	☐	☐

Datum ontslag/overlijden:

☐☐ dag ☐☐ mnd ☐☐ jaar

Kweekuitslagen

Grampreparaat van de gal:

gr + coccen ☐ gr + staven ☐

gr − coccen ☐ gr − staven ☐

		Hoeveelheid van de geïsoleerde bacterie (groeidichtheid) + = laag + + = matig + + + = hoog		Gevoeligheid voor cefuroxim + of −	
MATERIAAL	DATUM AFNAME	GEÏSOLEERDE MICROORGANISME(N)	NIET INVULLEN	GROEIDICHTHEID	GEVOELIGHEID CEFUROXIM
1. Gal	peroperatief				
2. Wond	peroperatief				
3.					
4.					
5.					
6.					

Naam onderzoeker: ..... **Paraaf:**

CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren in 1947 te 's-Gravenhage. Hij behaalde zijn eindexamen HBS-B aan het Baarns Lyceum te Baarn in 1964. In dat zelfde jaar werd de medische studie aangevangen aan de Rijksuniversiteit te Leiden. Na het behalen van het candidaatsexamen was hij gedurende twee jaar werkzaam als student-assistent op de afdeling Anatomie van de Leidse Universiteit. In 1974 werd het artsexamen afgelegd. Hierna werkte hij als arts-assistent op de afdelingen Interne Geneeskunde en Chirurgie van het Ziekenhuis Antoniushove te Leidschendam (Dr.J.Blankespoor en H.Hollander). In 1975 begon hij de opleiding algemene heelkunde in het Sint Clara Ziekenhuis te Rotterdam (Opleider A.A.van Puyvelde). In 1981 werd hij ingeschreven in het specialisten register. In 1982 was hij werkzaam als Surgical Research Fellow in het Memorial Sloan-Kettering Cancer Center te New York (Dr.D.M.Kinne, Head of the Department of Breast Surgery and Dr.M.P.Osborne, Consultant Surgeon). Sinds 1983 is hij als algemeen chirurg verbonden aan het Sint Clara Ziekenhuis te Rotterdam.