1987

Formulary status of cephalosporins

Agnes J. Renault
University of the Pacific

UNIVERISTY OF THE PACIFIC

STOCKTON, CALIFORNIA

FINAL EXAMINATION

OF

AGNES RENAULT

FOR THE DEGREE OF

MASTER OF SCIENCE

Friday, August 29, 1986

Room D-102, School of Pharmacy

1:15 P.M.

COMMITTEE FOR DISSERTATION

Dr. David P. Lipson, Chairman

Dr. Michael Mergener

Dr. James Blankenship

Dr. Robert Gehres

This thesis, written and submitted by

Agnes Kennedy

is approved for recommendation to the Committee on Graduate Studies, University of the Pacific.

Department Chairman or Dean:

Thesis Committee:

Chairman

Dated 12/5/86

FORMULARY STATUS OF CEPHALOSPORINS

Agnes J. Renault, Doctor of Pharmacy

University Paris XI, France. 1984

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE, MASTER OF SCIENCE IN CLINICAL PHARMACY AT THE UNIVERSITY OF THE PACIFIC

AUGUST 29, 1986

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

Hospital drug expenditures have increased dramatically over the last fifteen years. In 1972, hospitals allocated one billion dollars for drugs. That figure had risen to three billion dollars by 1982, a 300% increase (1). Part of this inflation in drug expenditures has been due to a number of factors, including increased number of hospital patient days, increased average drug expenditure per patient and increased cost of drugs. At the same time, innovations in the various antibiotic therapeutic categories have resulted in new and relatively expensive antibiotics being introduced into the market almost every year (2). This has resulted in an increase in antibiotic use which adds to drug expenditures.

The increased use of antibiotic therapy over the last few decades has led to a number of problems for the health care delivery system. These include bacterial resistance to the current antibiotics with a concomitant increase in the cost of health care. Attempts have been made to contain the use and cost of antibiotic therapy through drug utilization review and the implementation of closed formulary systems (3). There have also been attempts made to contain the overall cost of health care through innovative financing mechanisms which offer an incentive

to optimize quality while minimizing the cost. Included among these financing mechanisms is a system of Diagnosis Related Groups (DRG's), currently being utilized by Medicare. The rationale behind DRG's is to offer a fixed level of reimbursement based on the patient's primary diagnosis as well as a number of other patient variables. It is incumbent upon the hospital to keep the cost of treating these Medicare patients below this fixed level, dictated by DRG's, in order to earn a profit (or to avoid a loss). This system of reimbursement is vastly different from the fee-for-service method which tends to encourage over-utilization of health services. In order to cope with the DRG system of reimbursement, a number of different strategies have been considered by pharmacy departments. Among these are competitive bidding, strict enforcement of drug formularies and physician education regarding the cost-benefit aspects of drug therapy. The process of accepting a drug onto a hospital formulary has shifted from marketing and promotion to rationalization on the basis of its efficacy, safety and cost. The advent of computerized systems within the hospital pharmacy allows the pharmacist to evaluate expensive drug products in terms of their efficacy.

Among the major therapeutic categories within the general classification of antibiotics, cephalosporins have had a

significant impact on health care costs. Since the cephalosporins were first introduced, they have accounted for an increasing proportion of the hospital drug budget. Presently, about 50% of the average drug budget in hospitals is allocated to cephalosporins (4,5). In 1983, Cefoxitin and Cefamandole ranked first and second, respectively, among all cephalosporins in terms of dollars spent (6).

The primary purpose of this study is to analyze the formulary status of cephalosporins among a representative sample of hospitals in the United States. In addition, the research design attempts to determine the ranking of cephalosporins in terms of acceptance to the hospitals' formulary and actual stocking of the cephalosporin products. The study will attempt to ascertain the reasons for these rankings and the influence of DRG implementation, teaching status and hospital bedsize on number of cephalosporins on formulary and in stock. This may yield insight into the strategies that hospitals are currently using to contain a significant proportion of their budget for pharmaceutical products.

PHARMACY ECONOMICS, DRGS AND INFECTIOUS DISEASES

The hospital pharmacy budget is generally comprised of two parts: salaries (approximatively 30%) and drugs (approximatively 60%). Antibiotics are the major component of the hospital drug budget (7). As many as 35% of all in-patients receive an antibiotic during their hospital stay (8). Eight cephalosporins were among the top twenty hospital products in terms of dollar sales in 1983 (see Table 1) making cephalosporins the largest therapeutic category within the antibiotic budget. Oral and parenteral cephalosporins account for approximately half of the antibiotic pharmacy budget. With the ongoing development of new antibiotics, a number of problems have emerged. Among these are the escalation of health care expenditures and the frequency of superinfections. As a result of the increase in health care expenditures, the pharmacy profession is confronted with new challenges. It is incumbent upon pharmacists to decrease the overall cost of drug therapy while maintaining the quality of care.

TABLE 1
TOP-SELLING CEPHALOSPORINS PRODUCTS IN HOSPITALS
FOR 1983

GENERIC NAME	TRADE NAME	RANKING
CEFOXITIN	MEFOXIN	1
CEFAMANDOLE	MANDOL	2
CEFAZOLIN	ANCEF	6
CEFOTAXIME	CLAFORAN	7

TABLE 1 (CONT.)
TOP-SELLING CEPHALOSPORINS PRODUCTS IN HOSPITALS FOR 1983

MOXALACTAM	MOXAM	11	
CEFAZOLIN	KEFZOL	12	
CEFOPERAZONE	CEFOBID	13	
CEPHALOTHIN	KEFLIN	15	

source: BARRIERE S.L.-Cost-Containment of Antimicrobial Therapy-Drug Intelligence and Clinical Pharmacy,19,1985, pp.278-281.

With increases in health expenditures, third-party programs have become engaged in innovative mechanisms to control the cost of health care. Diagnosis-Related Groups (DRGs) are indicative of this new attitude. Inglehart reviewed the different steps prior to the implementation of DRG's (9). Attempts by the Carter Administration to impose hospital cost control in 1977 did not meet with success. Section 223, enacted originally as part of the Social Security Amendment in 1972, was initially directed to limit the per diem payment for hospital costs. The Omnibus Budget Reconciliation Act of 1981 tightened section 223 amendments but was still limited to routine costs. In 1983, the Congress voted the system of prospective reimbursement (called Diagnosis Related Groups) and it was decided that this amendment should be implemented over the fiscal years 1984-1987 (10).

TABLE 2
IMPLEMENTATION OF DRGS

FISCAL YEAR	REGIONAL RATE	HISTORICAL COSTS	NATIONAL RATE
1984	25% DRG	75% DRG	0% DRG
1985	37.5% DRG	50% DRG	12.5% DRG
1986	37.5% DRG	25% DRG	37.5% DRG
1987	0% DRG	0% DRG	100% DRG

*Historical costs: drawn from the target rate provisions outlined in the Tax Equity and Fiscal Responsability Act (TEFRA) 1972.

source: ENRIGHT S.M. Understanding Prospective Pricing and DRG's. American Journal of Hospital Pharmacy. 4:1493-1494, 1983.

The new section 223 extends the limits to special care, operating costs and ancillary services (e.g. pharmacy services). The limits are on the basis of cost per discharge. These limits are not applicable to children's hospitals, long-term care hospitals, and rural hospitals with fewer than 50 beds.

The prospective payment system involves prepayment for services according to that patient's DRG. A patient may be placed in one of 467 existing DRGs which are defined by 6 different variables (11).

These are:

1) primary diagnosis,

2) secondary diagnosis (comorbidity),

3) age,

4) sex,

5) discharge status,

6) operating room procedures.

Hospitals may keep the difference between the fixed DRG payment rate and their actual costs for treating Medicare patients. Therefore, the financial incentive is to minimize the use of ancillary services. This cost containment system was not developed to decrease the quality of care but rather to stimulate the reevaluation of ancillary services . The influence of DRG's forces health care professionals to reevaluate the average cost of drugs used per DRG as well as to stimulate competitive bidding in hospitals. Curtis reviewed the different management strategies developed in order to cope with the new reimbursement system (12). These strategies focus on the drug product, cost of storage and the prescriber. Economies in the pharmacy department may be achieved through volume purchasing, cash payment and group purchasing. Bid contracts have the potential of significantly reducing the hospital's overall pharmaceutical budget. Antibiotics are many times subject to bid contracts. This is particularly true of first generation cephalosporins. Bid contracts may be signed for

one product marketed by two different companies (e.g. Cefazolin) or two products which are considered to be therapeutic equivalents (e.g. Cephalothin and Cefazolin). The implementation of a closed formulary may facilitate the objective of decreased drug inventory through periodic reevaluation of each drug based upon its efficacy and cost. The restriction of open prescribing has been shown to be both cost effective and to improve the quality of care (13-16). A number of strategies are available for restricting the prescribing patterns of physicians. These include written request and control of antibiotic release by the infectious disease service and/or pharmacy department.

The advent of DRG's has prompted hospital pharmacies to restrict their formularies in order to control inventory costs. Antibiotics are the primary focus of the Pharmacy and Therapeutic (P&T) Committees due to their wide utilization, high costs and misuses (17-19). In 1970, Scheckler and Bennett reported that no clear indication was found in 60% of patients receiving antimicrobial therapy (20). Approximatively 35% of all infants and children admitted to hospitals receive antibiotics some time during their hospital stay (21). The rationale for their use is not always clear and the duration of therapy

is oftentimes excessive. Durbin et al., studied the impact of a new system incorporating the rationale for each antibiotic prescribed in a general hospital (22). They reported that the most important effect of this system was on prophylactic surgery where the mean duration for surgical prophylaxis dropped from 4.9 days to 2.9 days. In addition, the percentage of patients receiving surgical prophylaxis for more than 2 days was reduced by half. Hayman and Sbravati reported on the effectiveness of controlling usage of cephalosporins and aminoglycosides. Second generation cephalosporin utilization was reduced by 52% while first generation usage increased by 48%. The average cephalosporin cost per dose decreased from $5.85 to $4.94. The shift towards an increased use of first generation cephalosporins and the restriction on the prescribing of aminoglycosides resulted in the savings of $200,000. Little change was reported in the total number of antibiotic doses dispensed during the study period (23).

Programs of formulary control have been implemented in many hospitals (24,25). Infectious disease specialists frequently achieve their goal of rational drug therapy through control of the approval process. However, in the case of community hospitals, physicians are normally office-based and, therefore, have a difficult time

allowing another health professional to control their prescribing patterns.(26)

Information is necessary to ensure that therapeutic agents are used appropriately by physicians. There are numerous ways of providing this information. These include newsletters and drug utilization reviews. Norwell and Lyon demonstrated that a newsletter can be an effective tool in altering prescribing habits over a period of three months while inservice education was judged relatively ineffective. They concluded that deletion from the formulary was still the most appropriate method for controlling the use of antibiotics (27).

Drug utilization review employs a different approach to dosage, length of treatment and alternative therapy of antibiotic usage. Hetaway and Barriere found that DUR mostly involves aminoglycosides (38%), cephalosporins (35%) and penicillins (10%). Drug utilization reviews are generally divided into three different approaches; retrospective, concurrent and prospective. A retrospective DUR helps to define areas where education is needed while concurrent DUR is helpful in avoiding drug interactions and iatrogenic disease. Prospective DUR studies alternate therapy by taking into account cost factors and evaluating ancillary services such as drug assays (28).

FORMULARY ACCEPTANCE OF ANTIBIOTICS/CEPHALOSPORINS

A formulary attempts to establish a compilation of drugs for the medical staff without therapeutic duplication at the lowest possible cost(29). The American Society of Hospital Pharmacists (A.S.H.P.) has set guidelines for establishing a formulary. The formulary system must first be approved by the medical staff and then the Pharmacy and Therapeutics Committee is organized. The minimum membership of this committee is three physicians, a nurse, a pharmacist and an administrator. Their responsibilities include evaluation of new drugs and educational activities. Drugs are typically considered according to their chemical (versus trade) name during the acceptance process. Non-formulary drugs normally have explicit procedures indicating how to obtain them for unique situations. Because of the large number of drugs available, both effectiveness and cost of therapy are considered. It is this committee which decides whether drug are admitted or deleted from the hospital formulary (30).

Once a drug product is accepted, selection of a specific vendor is conducted by the Pharmacy Department. Criteria for drug procurement are summarized in Table 3. These criteria may be used to optimize the hospital's formulary.

TABLE 3
CRITERIA FOR DRUG PROCUREMENT

Bioavailibility	Availibity on a reliable basis
Cost	Demand / Usage
Stability	Service
Manufacturer's past record of producing quality products	

source: KELLY W.N., BENDER F.H.-Implementing and Maintaining a Viable Formulary, Hospital Formulary, Volume 18,1983,pp.976-987.

Antibiotics (particularly cephalosporins) are frequently reviewed because of their high cost and potential misuses which have have been reported to be as much as 87% (31). Furthermore, new cephalosporin antibiotics are constantly being marketed. The admission criteria for cephalosporins and other antimicrobials traditionally have been based upon spectrum of activity. Because of the availability of numerous therapeutic equivalents as well as the implementation of new reimbursement systems, a number of other issues have recently arisen. Among these issues are host-bacteria interaction, pharmacokinetics and the overall cost of antibiotic therapy (32).

Criteria for admission onto the formulary may depend on the type of institution considered as well as the drug itself. The mix of drug products appears to be dependent upon the type of institution. For example, the formulary of a maternity hospital will likely be different than that of a psychiatric hospital (33). Teaching hospitals may also differ from their non-teaching counterparts in terms of the makeup of their formularies. There are a number of attitudes that may predominate in the case of teaching hospitals. These include the need to provide a broad exposure of drug therapy to medical residents and the need to teach rational drug prescribing habits.

There are specific factors which need to be addressed prior to a drug's acceptance onto a formulary(34,35). They are as follows:

Specific Indications:

The main indications for which the drug has been F.D.A. approved need to be mentioned in view of its formulary acceptance.

Spectrum of Action (see Table 4):

In the case of antibiotics, the MIC-90 (concentration of antibiotic required to inhibit growth of 90% of a pool of clinical isolates of a particular bacterial species) must be indicated for the major organisms encountered in the

clinical setting. The notion of generation for cephalosporins has been defined on the basis of activity against gram negative organisms. Tables 5, 6 and 7 list cephalosporin antibiotics by generation.

The first generation cephalosporins are mainly active against gram positive organisms. The chief shortcoming is a lack of activity against most gram negative bacilli and the anaerobic rod Bacteroides fragilis (35).

The classical pattern of second generation cephalosporins has been a more extended spectrum against gram negative species including Haemophilus influenzae, Enterobacter aerogenes, Proteus mirabilis, Proteus sp. and Neisseria sp. Cefuroxime has a similar spectrum of activity as does Cefamandole against gram negative bacilli but is less active against gram positive organisms (36). The newer second generation Cefonicid and Ceforanide, have been shown to have an irregular activity against gram positive organisms (37,38). Cefoxitin must be considered apart from the other second generation cephalosporins. It possesses the highest activity against Bacteroides fragilis and is considered the drug of choice in cases of anaerobic infections (39).

The third generation cephalosporins exhibit their best activity against gram negative bacilli including Escherichia coli, Klebsiella pneumoniae, Enterobacter sp., Proteus

mirabilis, Providencia sp. (40). The anti-pseudomonal activity of the third generation cephalosporins differs according to the drug considered. Cefoperazone, Ceftazidime and Moxalactam have been reported to be effective against Pseudomonas aeruginosa(41). However, these products are not considered the drug of choice for pseudomonal infections.

Enterococci (Streptoccus faecalis), Listeria sp. and Legionella sp. (42) are not adequately covered by cephalosporins (all three generations considered). Open trials are extremely difficult to interpret because of variation of pathogens and severity of illness. Any review of the primary literature should include controlled trials.

Pharmacokinetics:

The pharmacokinetic information for each drug must include half-life, protein binding, and pathway of excretion. The importance of half-life allied with MIC-90 is increasingly emphasized with the newer cephalosporins. Ceforanide has a half-life of 3 hours, Cefonicid has a half-life of 4.5 hours and Ceftriaxone has a half-life of 7 hours (43-45). These long half-lives in combination with effective MIC90's at 12 hours for Cefonicid and 24 hours for Ceforanide and Ceftriaxone influence the dosing interval.

A biliary excretion pathway is a parameter to consider in cases of patients with impaired renal function or infections of the biliary tract. Only Ceftriaxone and Cefoperazone have significant biliary excretion among the cephalosporins (46).

Adverse drug reactions:

It is necessary to evaluate therapeutic advantages over adverse drug reactions. The safety profile of cephalosporins is oftentimes such that formulary decisions cannot be based upon this issue. In the case of Ceftriaxone therapy , the frequency of diarrhea has been reported as high as 40% (47). Coagulopathies have been reported with Moxalactam and less frequently with Cefoperazone and Cefamandole (48).

Contraindications and precautions:

Because of high levels of toxicity, drugs might be restricted to certain types of patients. Classically, cephalosporins are considered to be drugs with a low level of toxicity. In cases of renal impairment, the only recommendation for cephalosporins is a dosage adjustment with respect to the creatinine clearance in cases of renal impairment. This restriction is applicable to cephalosporins whose major route of excretion is via the

kidneys .

Major drug interaction(s):

Significant interactions with the most frequently used drugs might be a limitation of the usefulness of the new drugs. In the case of cephalosporins, this limitation does not generally apply.

Recommended dosages :

Frequency of administration is an important factor to consider for the evaluation of the cost of a particular drug's therapy. The recommended dosages should be specified for children, adults, cases of renal and hepatic insufficiency, and life threatening situations.

First generation cephalosporins are considered therapeutically equivalent. Only their dosing intervals differ. Cefazolin is the only first generation cephalosporin which can be given every 8 hours.

The second generation cephalosporins are very heterogeneous. The newer second generation cephalosporins with their long dosing intervals (every 12 to 24 hours) have been demonstrated to be useful in surgical prophylaxis and may be competitive with Cefazolin for position on the hospital formulary. Some of the newer second generation cephalosporins have suffered from reports regarding poor coverage of Staphylococcus aureus

(50,51).

Cefamandole and Cefuroxime have identical spectrum with the exception of activity on gram positive organisms. Cefuroxime has a better pharmacokinetic profile (penetration in the cerebrospinal fluid and long half-life), with a dosing interval of 8 hours rather than 6 hours. With the recent marketing of Cefotetan, Cefoxitin may also be subject to further scrutiny because both drugs have the same spectrum of activity with different dosing intervals. Cefotetan can be administered every 12 hours whereas Cefoxitin should be administered every 6 hours (52).

Cefotaxime has been promoted on the basis of an 8 or 12 hour dosing interval. However, because of its pharmacokinetic properties, Cefotaxime is now used mostly at a dosage level of 2 grams every 6 hours. On the other hand, Ceftizoxime with an identical spectrum of coverage and better pharmacokinetic profile, allows an 8-hour dosing regimen even in cases of life threatening situations. Cefoperazone and Ceftriaxone with interval dosing of 12 hours and 24 hours, respectively, make them attractive cephalosporins for many hospitals' formularies (49).

Availability of the product:

At some institutions, packaging of the products is an important attribute. A unit dose distribution system may provide a good system of quality control as well as a high level of safety. Baxter-Travenol has recently introduced a premixed frozen antibiotic system which has the potential to save labor cost. The time that is saved by this type of system may be used to provide an improved level of clinical services (53).

Cost:

Cost-benefit analyses are needed to include new drugs onto formularies (54). Antibiotic costs can be reduced if the number of doses per day can be safely reduced. This has prompted F.D.A. approval for cephalosporins with long half-lives.

TABLE 4
COST OF THERAPY FOR THE FIRST GENERATION CEPHALOSPORINS

NAME	$/GM	TOTAL COST PER DAY USUAL DOSES	TOTAL COST PER DAY MAX.DOSES
CEPHALOTHIN	$2.88	$51.52/ 1GM Q6H.	$94.56 2GM Q4H
CEPHAPIRIN	$3.55	$54.20/ 1GM Q6H	$102.60 2GM Q4H
CEFAZOLIN	$6.55	$49.65 1GM Q8H.	$92.40 2GM Q6H.

TABLE 5

COST OF THERAPY FOR SECOND GENERATION CEPHALOSPORINS

NAME	$/GM	TOTAL COST PER DAY USUAL DOSES	TOTAL COST PER DAY MAX.DOSES
CEFAMANDOLE	$7.15	$61.45/ 1GM Q6H.	$145.80/ 2GM Q4H
CEFUROXIME	$7.85	$47.67/ 0.75GM Q8H	$87.12/ 1.5GM Q6H
CEFONICID	$15.20	$25.20/ 1GM Q24H	$50.40/ 2GM Q24H
CEFORANIDE	$9.95	$29.90/ 0.5GM 12H	$39.90/ 1GM Q12H
CEFOXITIN	$8.49	$73.96/ 1GM Q6H	$161.88/ 2GM Q4H

TABLE 6

COST OF THERAPY FOR THIRD GENERATION CEPHALOSPORINS

NAME	$/GM	TOTAL COST PER DAY USUAL DOSES	TOTAL COST PER DAY MAX.DOSES
CEFOTAXIME	$11.45	$85.80/ 1GM Q6H.	$197.40/ 2GM Q4H.
CEFTIZOXIME	$11.18	$63.54/ 1GM Q8H	$129.44/ 2GM Q6H.
CEFOPERAZONE	$12.20	$66.60/ 1GM Q8H	$175.36/ 3GM Q6H.
CEFTRIAXONE	$25.12	$25.12/ 1GM Q24H	$125.36/ 2GM Q12H.
MOXALACTAM	$12.20	$66.60/ 1GM Q8H	$186.40/ 3GM Q6H.

1984-1985 American Druggist Blue Book Average Wholesale Price.

According to Barriere, open formularies are not appropriate in today's health care environment. The trend is to limit duplication for the purpose of minimizing cost. Due to the cost of I.V. preparation, the concept of single dose therapy is attractive from a cost standpoint. I.V. preparation can range from 35-75% of the total cost of the drug therapy (54).

Previously, teaching status and bedsize have been used to explain differences in hospital costs. The implementation of DRG's creates a method to evaluate the quality of care and utilization of services in most hospitals. Three areas will be influenced by the implementation of DRG's (54):

1. Length of stay: great variability exists from one hospital to another in the duration of antimicrobial therapy (e.g. endocarditis antimicrobial therapy ranges from 2 to 6 weeks)

2. Ancillary services: restricting the use of expensive drugs and increased use of generic equivalents will be considered. A more homogeneous attitude towards drugs will be achieved only if estimated duration of antimicrobial therapy is assessed.

3. Capital purchases: manufacturers will concentrate on areas which seek to decrease the total cost of therapy.

Sophisticated technologies will probably be modulated in their development.

Already, formulary revaluations have taken place and will help in the control of hospital drug budgets. Crane et al. reported savings projected for 1985-86 for cephalosporin antibiotics due to formulary changes. Expenditures were decreased by 5.24% for first generation cephalosporins, 11.31% for second generation cephalosporins and 39.4% for third generation cephalosporins (56).

RESEARCH OBJECTIVES

The objectives of the study are to determine the formulary status of cephalosporins, the reasons for their status and their levels of stocking in hospitals in the United States. These objectives will be accomplished by evaluating the following:

1. The cephalosporins will be analyzed in terms of the levels of formulary approval.

2. The non-formulary status of cephalosporins will be analyzed in terms of those:

- not included on formulary through formal rejection
- not included on formulary with a planned review
- not included on formulary with no plans to review

3. The stocking of cephalosporins in hospitals.

DEFINITION OF TERMS

1. Full Approval Status - the drug is not submitted to any kind of formulary restrictions

2. Restricted Approval Status - the physician does not have full power over the choice of drug therapy; for example, a specific drug may not be used without prior infectious disease or clinical pharmacist consultation; further restrictions may be due to trial use of a particular drug or the limitation of use to a specific diagnosis or infection.

3. Not on Formulary Due to Formal Rejection - the drug is not admitted to the formulary as a result of deliberations of the Pharmacy and Therapeutics Committee.

4. Not on Formulary With Plans to Review - the drug has not yet been accepted on the formulary; however, evaluation of the drug for formulary review is scheduled.

5. Not on Formulary With No Plans to Review - the drug has not been accepted on the formulary; there are no plans to review.

6. Therapeutic Equivalent - a drug product that is considered to be equal or superior to other drugs within the same therapeutic category.

HYPOTHESES

The following research hypotheses guide this investigation. The first six hypotheses relate to the first objective, to determine the formulary approval status of cephalosporins.

Hypothesis 1:

There is a significant difference in the formulary approval rate among the three generations of cephalosporins.

Hypothesis 2:

There is a significant difference in the restricted approval rate among the three generations of cephalosporins.

Hypothesis 3:

The reasons for restricting cephalosporins are dependent upon the generation considered.

Hypothesis 4:

Cephalosporins admitted on formulary are dependent upon whether DRG's are in effect.

Hypothesis 5

Cephalosporins admitted on formulary are dependent upon the hospital's teaching status.

Hypothesis 6

Cephalosporins admitted on formulary are dependent upon the hospital's bedsize.

Hypotheses 7 through 13 relate to the second objective. These hypotheses will determine whether non-formulary status of cephalosporins and the concomitant reason(s) are the same for each of the three generations.

Hypothesis 7:

There is a correlation between the date in which a cephalosporin enters the market and its formulary status.

Hypothesis 8:

There is a significant difference in the rate of formal rejection among the three generations of cephalosporins.

Hypothesis 9:

The reasons why cephalosporins are formally rejected vary based upon their generation.

Hypothesis 10

There is a significant difference among the three generations of cephalosporins regarding the hospital's plans to review the cephalosporins for formulary status.

Hypothesis 11

The expected outcome of non-formulary cephalosporins which are scheduled for review is dependent upon the generation of cephalosporins considered.

Hypothesis 12

There is a significant difference based upon generation in the rate of cephalosporins that are non-formulary without any plans to review.

Hypothesis 13

There is a significant difference based upon generation for the reasons that cephalosporins are not accepted onto the formulary and why they do not have a planned review.

The last five hypotheses relate to the third research objective which is to evaluate the stocking of cephalosporins in hospitals.

Hypothesis 14

There is a significant difference in the stocking status among the three generations of cephalosporins.

Hypothesis 15

There is a significant difference in the stocking status of the three generations of cephalosporins.

Hypothesis 16

The total number of cephalosporins stocked is dependent upon the implementation date of DRG's.

Hypothesis 17

The total number of cephalosporins stocked is dependent upon the teaching status of the hospital.

Hypothesis 18

The total number of cephalosporins stocked is dependent upon the bedsize of the hospital.

METHODOLOGY

This study utilizes data collected from hospitals in all nine census regions of the United States. A questionnaire (see Appendix 1) was sent to 100 hospitals in January of 1985. The response rate was 86%. One hospital was dropped from the study because its formulary system was in the process of being developed. Table 1 describes the sample of the study.

TABLE 1
DESCRIPTION OF THE SAMPLE

TEACHING HOSPITAL STATUS	DRG IMPLEMENTATION	HOSPITAL BEDSIZE
55 teaching hospitals	53 hospitals with DRGs	44 hospitals <250 beds
28 non teaching hospitals	32 hospitals with no DRG	23 hospitals 250--500 beds
2 undetermined		13 hospitals >500 beds

GEOGRAPHICAL DISTRIBUTION OF THE SAMPLE		
7 hospitals in New England	2 hospitals in Mideast	14 hospitals in South Atlantic
10 hospitals in Great Lakes	2 hospitals in Midsouth	14 hospitals in Plain
7 hospitals in Southwest	13 hospitals in Rocky Mountain	14 hospitals in Farwest

Cephalosporins Studied

Thirteen cephalosporins were incorporated in the study. Of the cephalosporins, fourteen brand name products were considered:

GENERATION	CHEMICAL NAME	BRAND NAME
1	CEFAZOLIN	ANCEF,KEFZOL
1	CEPHALOTHIN	KEFLIN
1	CEPHAPIRIN	CEFADYL
2	CEFAMANDOLE	MANDOL
2	CEFOXITIN	MEFOXIN
2	CEFONICID	MONOCID
2	CEFORANID	PRECEF
2	CEFUROXIME	ZINACEF
3	CEFOTAXIME	CLAFORAN
3	MOXALACTAM	MOXAM
3	CEFOPERAZONE	CEFOBID
3	CEFTIZOXIME	CEFIZOX
3	CEFTRIAXONE	ROCEPHIN

Statistical Tests

Hypotheses (with the exception of hypothesis 6) were tested by using chi-square statistical tests (at alpha level of 0.05). When the overall chi-square was found to be significant, follow-up procedures were performed (57). In these cases, generations of cephalosporins were compared. Hypothesis 6 was tested by using Spearman's rank order correlation test in order to determine whether there was a relationship between formulary rejection and year of marketing.

FINDINGS

The findings relative to each hypothesis are presented in this chapter.

HYPOTHESES 1 THROUGH 5:

These five hypotheses are concerned with the formulary approval status of cephalosporins.

Testing Hypothesis 1

Hypothesis 1 was designed to study the formulary approval status of cephalosporins . To test this hypothesis, full approval and restricted approval status were combined to indicate that a drug was on formulary. Formal rejection, planned review and no plans to review were combined to indicate that a drug was not on formulary. The results of this analysis are summarized in Table 2.

TABLE 2
FORMULARY STATUS OF CEPHALOSPORINS
BY GENERATION

	1ST GEN.	2ND GEN.	3RD GEN.
ON FORMULARY	137	192	177
NOT ON FORMULARY	119	233	248
TOTAL	256	425	425

df=2 Chi-square=9.16 alpha=0.05 $p<0.02$

Table 2 demonstrates that there are significant differences in the rate of formulary approval among the three generations of cephalosporins. Follow-up tests were conducted to determine which generations were the cause of the significance.

Post hoc procedures for chi-square test indicate that there is a significant difference between first and third generation cephalosporins in the rate of formulary approval (respectively 53% and 41.6%). On the other hand, the second and third generation cephalosporins rate of approval as well as the first and second generation cephalosporins rate of approval do not differ significantly.

When the rate of formulary approval was examined by looking at each drug independently, among all three generations, four drugs were responsible for more than half of the total number of cephalosporins that received formulary approval. These products are cefazolin (86), cefoxitin (82), cefotaxime (57) and cefoperazone (53). Table 3 indicates the number of instances as well as the rate of formulary approval for each drug in our 85 hospital sample.

TABLE 3
FORMULARY APPROVAL OF CEPHALOSPORINS

DRUG	FORMULARY APPROVAL		NOT ON FORMULARY	
	#	%	#	%
CEFAZOLIN*	86	(100%)	0	(100%)
CEPHALOTHIN	31	(36.5%)	54	(63.5%)
CEPHAPIRIN	20	(23.5%)	65	(76.5%)
CEFAMANDOLE	48	(56.5%)	37	(43.5%)
CEFOXITIN	82	(96.5%)	3	(3.5%)
CEFONICID	27	(31.7%)	58	(69.4%)
CEFORANIDE	10	(11.7%)	75	(88.2%)
CEFUROXIME	25	(29.5%)	60	(70.5%)
CEFOTAXIME	57	(67%)	28	(32.9%)
MOXALACTAM	26	(30.6%)	59	(69.4%)
CEFOPERAZONE	53	(62.3%)	32	(37.6%)
CEFTIZOXIME	34	(40%)	51	(60%)
CEFTRIAXONE	7	(8%)	78	(92%)
TOTAL	506		600	

* In one case, cefazolin was on formulary under Ancef and Kefzol. Ancef was full approval status and Kefzol was restricted approval status.

Testing of Hypothesis 2

Formulary approval status was further divided into full approval and restricted approval. The results are summarized in Table 4.

TABLE 4
APPROVAL STATUS BY GENERATION

FORMULARY APPROVAL	1ST.GEN.	2ND.GEN.	3RD.GEN.
FULL APPROVAL	124	163	125
RESTRICTED APPROVAL	13	29	52
TOTAL	137	192	177

df=2 X2=22.66 alpha=0.05 p<0.001

These figures show that there is a significant difference in the rate of full approval versus restricted approval among the three generations of cephalosporins. Follow-up procedures were conducted to determine which generations contributed to the significant difference. The results of the post hoc procedures indicate a significant difference due to the rate of restricted approval of third generation cephalosporins. Third generation cephalosporins were shown to have a superior number of restricted formulary status ($p<0.001$). This is expected because third generation cephalosporins have a high potential to induce bacterial resistance and are generally more expensive than their first and second generation counterparts. Therefore, third generation cephalosporins are considered to be second-line agents in antibiotic therapy. Restricted formulary status oftentimes is implemented to limit their usage. First and second generation cephalosporins do not

differ significantly with regards to their rate of restricted formulary status.

When the restricted formulary status is studied for individual cephalosporins, the rate of full approval formulary status rate is greater than restricted formulary status with the exception of ceforanide, ceftriaxone and moxalactam.

All cephalosporins have a percentage of restricted approval less than 20% of the overall approval rate. Third generation cephalosporins have the highest percentage of restricted approval status. Ceftriaxone is the exception among third generation cephalosporins. Its full approval status is only 2.35%. This can be explained by the recent marketing of this product at the time of the study (January - March, 1985).

First and second generation cephalosporins are rarely restricted with a percentage of restricted approval status constantly below 10%. These results are summarized in Table 5.

TABLE 5
FULL APPROVAL STATUS VS. RESTRICTED APPROVAL STATUS OF CEPHALOSPORINS

	FULL APPROVAL	RESTRICTED APPROVAL	RATIO FA*/RA*
CEFAZOLIN	85 (100%)	1 (1%)	99%/1%
CEPHALOTHIN	23 (27%)	8 (9.5%)	74.2%/25.8%
CEPHAPIRIN	16 (18.8%)	4 (4.7%)	80%/20%
CEFAMANDOLE	44 (51.7%)	4 (4.7%)	91.6%/8.3%
CEFOXITIN	76 (89.4%)	6 (7%)	92.6%/7.4%
CEFONICID	20 (23.5%)	7 (8.2%)	74%/26%
CEFORANIDE	5 (5.8%)	5 (5.8%)	50%/50%
CEFUROXIME	18 (21%)	7 (8.2%)	72%/28%
CEFOTAXIME	43 (50.6%)	14 (16.5%)	75.4%/24.6%
MOXALACTAM	16 (18.8%)	10 (11.7)	61.5%/38.5%
CEFOPERAZONE	41 (48,2%)	12 (14.1%)	77.4%/22.6%
CEFTIZOXIME	23 (27%)	11 (13%)	67.6%/32.4%
CEFTRIAXONE	2 (2.3%)	5 (5.8%)	28.6%/71.4%
TOTAL	412	94	

FA= FULL APPROVAL
RA= RESTRICTED APPROVAL
FA*= NUMBER OF FA / TOTAL NUMBER OF FORMULARY APPROVAL FOR EACH DRUG
RA*= NUMBER OF RA/TOTAL NUMBER OF FORMULARY APPROVAL FOR EACH DRUG

Testing Hypothesis 3

First generation cephalosporins were not considered in testing Hypothesis 3 because of their low incidence of restricted approval on the hospital formularies. Consequently, it was not possible to include that generation of cephalosporins in the chi-square statistical

test. The reasons why second and third generation cephalosporins were formulary restricted are analyzed in Table 6.

TABLE 6
REASONS FOR 2ND GENERATION AND 3RD GENERATION CEPHALOSPORINS RESTRICTED APPROVAL STATUS

	2ND GEN.R.A.	3RD GEN.R.A.
SPECIFIC DIAGNOSIS	10	16
ID. CONSULTATION	8	24
OTHERS*	9	8

df=2 X2=3.87 alpha = 0.05 N.S.

OTHERS: special request, pharmacy intervention, trial use, P&T Committee intervention.

Second and third generation cephalosporins did not show any significant difference regarding reasons for their formulary restriction. Specific diagnosis and ID consultation are the most frequently selected reasons for the restriction of these two generations of cephalosporins.

A number of second and third generation cephalosporins (ceftizoxime and ceftriaxone) were listed as restricted approval due to trial use. Among those on trial use, ceforanide and cefonicid were currently being investigated for surgical prophylaxis and cefuroxime was on

trial for infant meningitis. With respect to those cephalosporins listed under restricted approval, specific diagnosis was recorded for cefoxitin, cefonicid, cefamandole, cefuroxime. Surgical prophylaxis, pulmonary and pediatric infections were the major indications for these second generation cephalosporins.

All third generation cephalosporins were restricted with regard to formulary acceptance. This emphasizes that these products are normally considered to be second-line agents. The restricted formulary status was indicated when aminoglycoside therapy was not adequate or when microorganisms were only sensitive to these products (e.g. Pseudomonas infections, bacterial meningitis, and cholecystitis). In one case, moxalactam was restricted because of its potential bleeding problems. Formulary restriction appeared to be used to draw the physician's attention to the possible side effects of the drug.

Testing Hypotheses 4, 5 and 6

Hypotheses 4, 5 and 6 are concerned with the relationship between the number of cephalosporins accepted on formulary and specific parameters. These parameters include the implementation of DRGs, hospital teaching status, and hospital bedsize.

First, the different combinations among each generation of cephalosporins admitted on formulary were studied as well as the number of cephalosporins admitted on formulary. The results are indicated in Tables 7 through 10.

TABLE 7
NUMBER OF CEPHALOSPORINS ADMITTED ON FORMULARY

NUMBER OF CEPHALOSPORINS ON FORMULARY	RESPONDENTS	PERCENTAGE
2	3	3.5%
3	5	5.9%
4	20	23.5%
5	17	20
6	13	15.3%
7	9	10.6%
8	7	8.2%
9	7	8.2%
10	3	3.5%
12	1	1.1%
TOTAL	85	100.0%

As seen by these data, the most frequent number of cephalosporins admitted on formulary was four (23.5% of the hospitals in the sample). Hospitals with four, five,

and six cephalosporins admitted to their formulary represent 58.8% of the total. When considering only first generation cephalosporins, one is the most frequent number admitted to formularies (58.8% of all respondents). In this case, cefazolin was always the sole first generation cephalosporin selected. When two first generation of cephalosporins were selected, cefazolin and cephalothin was the most frequently chosen combination. Only seven hospitals had all three first generation cephalosporins on their formulary. This appears to confirm the trend to eliminate therapeutic duplication from the formulary. These results are summarized in Table 8.

TABLE 8
COMBINATIONS OF FIRST GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 1ST GEN. ON FORMULARY	COMBINATIONS	RESPONDENTS #	RESPONDENTS %	% OF TOTAL
ONE	CEFAZOLIN	50	100%	58.7%
TWO	CEFAZOLIN + CEPHALOTHIN	21	75%	24.7%
	CEFAZOLIN + CEPHAPIRIN	7	25%	8.3%
THREE	CEFAZOLIN + CEPHALOTHIN + CEPHAPIRIN +	7	100%	8.3%

Two second generation cephalosporins is the most frequently selected number in terms of formulary acceptance. The top three (out of five) second generation cephalosporins represent 86% of all second generation cephalosporins admitted to the formularies of our sample. Three hospitals had no second generation cephalosporins admitted on their formulary while two hospitals had all five products admitted on their formulary. Cefoxitin was the most popular second generation cephalosporin in terms of formulary acceptance. This drug was present in every combination of second generation cephalosporins.

Table 9 lists the top three combinations of second generation cephalosporins in our 85 hospital sample.

TABLE 9
COMBINATIONS OF SECOND GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 2ND.GEN. ON FORMULARY	COMBINATIONS	RESPONDENTS #	RESPONDENTS %	% OF TOTAL
TWO	CEFOXITIN + CEFAMANDOLE	19	54.3%	22.3%
	CEFOXITIN + CEFUROXIME	9	25.7%	10.5%
	CEFOXITIN + CEFONICID	7	22%	8.2%

TABLE 9 (CONT.)
COMBINATIONS OF SECOND GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

	CEFOXITIN + CEFAMANDOLE + CEFONICID	8	40%	9.4%
	CEFOXITIN + CEFAMANDOLE + CEFUROXIME	8	40%	9.4%
THREE	CEFOXITIN + CEFAMANDOLE + CEFORANID	3	15%	3.5%
	CEFOXITIN + CEFONICID + CEFORANID	1	5%	1.1%
ONE	CEFOXITIN	17	100%	20%

Eighty percent of the hospitals in our sample had either one, two or three third generation cephalosporins admitted onto their formularies. Two is the most frequent number of third generation of cephalosporins admitted on formulary (31.8% of all respondents). Six hospitals had admitted no third generation cephalosporins to their formularies. No hospitals admitted all five third generation cephalosporins to their formulary.

When compared with the other generations, third generation cephalosporins have more combinations of products selected for formulary approval. This may reflect the fact that there are more specific indications listed for this

generation of cephalosporins. Cefotaxime was the most frequently selected third generation cephalosporin for formulary acceptance. However, this product among third generation cephalosporins was less predominant than cefazolin and cefoxitin in their respective generations.

Table 10 summarizes the different possible combinations for the top three choices of third generation cephalosporins admitted on formulary.

TABLE 10
COMBINATIONS OF THIRD GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 3RD GEN ON FORMULARY	COMBINATIONS	RESPONDENTS #	RESPONDENTS %	% OF TOTAL
TWO	CEFOTAXIME + CEFOPERAZONE	12	44.4%	14.1%
	CEFOPERAZONE + CEFTIZOXIME	6	22.2%	7.05%
	CEFOTAXIME + CEFTIZOXIME	4	14.8%	4.7%
	CEFOTAXIME + MOXALACTAM	4	14.8%	4.7%
	CEFOPERAZONE+ MOXALACTAM	1	3.7%	1.1%
ONE	CEFOTAXIME	11	44%	12.9%
	CEFOPERAZONE	7	28%	8.2%
	CEFTIZOXIME	6	24%	7.05%

TABLE 10 (CONT.)
COMBINATIONS OF THIRD GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

	MOXALACTAM	1	4%	1.1%
	CEFOTAXIME + MOXALACTAM + CEFOPERAZONE	8	47%	9.4%
	CEFOTAXIME + CEFOPERAZONE + CEFTIZOXIME	4	23.5%	4.7%
THREE	CEFOTAXIME + CEFOPERAZONE + CEFTRIAXONE	2	11.7%	2.3%
	MOXALACTAM + CEFOPERAZONE + CEFTIZOXIME	2	11.7%	2.3%
	CEFOTAXIME + MOXALACTAM + CEFTIZOXIME	1	5.8%	1.1%

Chi-square tests were conducted to analyze hypotheses 4, 5 and 6. These hypotheses examine the influence of DRG implementation, hospital teaching status and hospital bedsize on the number of cephalosporins admitted on formulary . The results are indicated in Tables 11 through 21.

It was not possible to test the influence of DRGs on the total number of cephalosporins admitted on formulary because of the low response rate (2 cells with expected

values less than 5).

TABLE 11
INFLUENCE OF DRG IMPLEMENTATION
ON NUMBER OF FIRST GENERATION
CEPHALOSPORINS ADMITTED ON FORMULARY

NUMBER OF 1ST GEN. ON FORMULARY	DRGS	NO DRGS
ONE	31	19
TWO	20	8
THREE	4	3

df=2 X2=0.89 alpha=0.05 N.S.

The figures in Table 11 demonstrate that there are no significant differences in the number of first generation cephalosporins admitted on formulary in regard to DRG implementation.

TABLE 12
INFLUENCE OF DRG IMPLEMENTATION
ON NUMBER OF 2ND GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 2ND GEN. ON FORMULARY	DRGS	NO DRGS
TWO	23	12
THREE	13	8
ONE	11	6

df=2 X2=0.08 alpha=0.05 N.S.

The figures in Table 12 demonstrate that there are no significant differences in the number of second generation cephalosporins admitted on formulary in regard to DRG implementation.

TABLE 13
INFLUENCE OF DRG IMPLEMENTATION
ON THE NUMBER OF THIRD GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 3RD GEN. ON FORMULARY	DRGS	NO DRGS
TWO	22	5
ONE	14	11
THREE	8	8

df=2 X2=5.67 alpha=0.05 N.S.

The figures in table 13 demonstrate that there are no significant differences in the number of third generation cephalosporins admitted on formulary and DRGs implementation.

DRG implementation has no influence on the number of cephalosporins admitted on formulary when cephalosporins are considered by generations. However, at an alpha level of 0.1, the number of third generation cephalosporins admitted on formulary is significantly less in those hospitals in which DRG's are implemented. In this case,

the implementation of DRG appears to prioritize the focus on the formulary acceptance of third generation cephalosporins which is an area of high expenses.

TABLE 14
INFLUENCE OF HOSPITAL TEACHING STATUS
ON NUMBER OF CEPHALOSPORINS ADMITTED ON FORMULARY

NUMBER OF CEPHALOSPORINS ON FORMULARY	TEACHING	NON TEACHING	TOTAL
FOUR	10	10	20
FIVE	1	16	17
SIX	3	10	13

df=2 X2=9.08 2 cells<5.0 alpha=0.05 p<0.02
df=1 X2=8.56 alpha=0.05 p<0.01

It was not possible to perform a chi-square test on the first three choices of cephalosporins admitted on formulary. This is due to the number of cells being less than 5.0. However, when the test is performed on the first two rows, the figures in table 14 demonstrate a significant difference in the number of cephalosporins admitted on formulary according to the hospital teaching status. There are less cephalosporins admitted onto formulary in teaching hospitals. This may be the result of most teaching hospitals having an infectious disease service. This department normally assists the P&T

committee in, among other things, preventing therapeutic duplications.

TABLE 15
INFLUENCE OF HOSPITAL TEACHING STATUS
ON THE NUMBER OF FIRST GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 1ST GEN. ON FORMULARY	TEACHING	NON TEACHING
ONE	15	35
TWO	8	20
THREE	2	3

df=2 X2=0.26 alpha=0.05 N.S.

The figures in Table 15 demonstrate that there are no significant differences in the number of first generation cephalosporins admitted on formulary due to the hospital's teaching status.

TABLE 16
INFLUENCE OF HOSPITAL TEACHING STATUS
ON THE NUMBER OF 2ND GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 2ND GEN. ON FORMULARY	TEACHING	NON TEACHING
TWO	10	24
THREE	6	14
ONE	7	10

df=2 X2=0.79 alpha=0.05 N.S.

The figures in Table 16 demonstrate that there are no significant differences in the number of second generation cephalosporins admitted on formulary due to the hospital's teaching status.

TABLE 17
INFLUENCE OF HOSPITAL TEACHING STATUS
ON THE NUMBER OF THIRD GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 3RD GEN. ON FORMULARY	TEACHING	NON TEACHING
TWO	6	21
ONE	6	19
THREE	7	7

df=2 X2=3.92 alpha=0.05 N.S.

The figures in Table 17 demonstrate that there are no significant differences in the number of third generation cephalosporins admitted on formulary due to the hospital's teaching status.

Hospital teaching status has a significant influence on the overall number of cephalosporins admitted on formulary. Non-teaching hospitals tend to admit a larger number of cephalosporins on their formulary ($p<0.02$). This phenomenon might be related to the absence of an

infectious disease specialist or a clinical pharmacist on the medical staff assisting the P&T Committee. On the other hand, when the total number of cephalosporins is broken down by generation, the hospital teaching status was not found to have any influence.

Hospital bedsize was divided into two categories (<250 beds and >250 beds. Medium and large hospitals were considered together in order to be able to perform the chi-square test. The results of these analyses are presented in Tables 18 through 21.

TABLE 18
INFLUENCE OF HOSPITAL BEDSIZE
ON NUMBER OF CEPHALOSPORINS ACCEPTED ON FORMULARY

NUMBER OF CEPHALOSPORINS ON FORMULARY	SMALL <250	MEDIUM + LARGE >250	TOTAL
FOUR	8	11	19
FIVE	13	4	17
SIX	7	6	13

df=2 X2=4.41 alpha=0.05 N.S.

The figures in Table 18 demonstrate that there are no significant differences in the total number of cephalosporins admitted on formulary due to the hospital's bedsize.

TABLE 19
INFLUENCE OF HOSPITAL BEDSIZE
ON NUMBER OF 1ST GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 1ST GEN. ON FORMULARY	SMALL <250	MEDIUM+ LARGE >250
ONE	25	29
TWO	17	11
THREE	2	4

df=2 X2=1.68 alpha=0.05 N.S.

The figures in Table 19 demonstrate that there are no significant differences in the number of first generation cephalosporins admitted on formulary due to the hospital's bedsize.

TABLE 20
INFLUENCE OF HOSPITAL BEDSIZE
ON NUMBER OF SECOND GENERATION
ADMITTED ON FORMULARY

NUMBER OF 2ND GEN. ON FORMULARY	SMALL <250	MEDIUM+ LARGE >250
TWO	21	14
THREE	12	8
ONE	6	10

df=2 X2=2.53 alpha=0.05 N.S.

The figures in Table 20 demonstrate that there are no significant differences in the number of second generation cephalosporins admitted on formulary due to the hospital's bedsize.

TABLE 21
INFLUENCE OF HOSPITAL BEDSIZE
ON MUBER OF THIRD GENERATION CEPHALOSPORINS
ADMITTED ON FORMULARY

NUMBER OF 3RD GEN. ON FORMULARY	SMALL <250	MEDIUM LARGE >250
TWO	14	12
ONE	17	8
THR E	7	8

df=2 X2=1.99 alpha=0.05 N.S.

The figures in Table 21 demonstrate that there are no significant differences in the number of third generation cephalosporins admitted on formulary due to the hospital's bedsize.

Hospital bedsize was shown to have no influence on the total number of cephalosporins admitted on formulary when cephalosporins are considered overall or divided into generations. The type of medical and surgical services available in the hospital may influence the selection of cephalosporins more than hospital bedsize. Although data

on the number and type of services were not available in this study, future research may include these independent variables as a possible influence on the number of cephalosporins admitted on hospital formularies.

Testing Hypotheses 7 Through 13

Hypothesis 7 is concerned with the possible relationship of the marketing year of the drug and the formulary status. The results are presented in Table 22.

TABLE 22
RELATIONSHIP
BETWEEN FORMULARY STATUS OF CEPHALOSPORINS
AND YEAR OF MARKETING

CEPHALOSPORINS	FORMULARY REJECTION	MARKETING YEAR	RANK
CEFTRIAXONE	78 (93%)	1984	13
CEFORANIDE	75 (89.4%)	1984	12
CEPHAPIRIN	65 (77.6%)	1974	3
CEFUROXIME	60 (71.7%)	1983	10
MOXALACTAM	59 (70.6%)	1981	7
CEFONICID	58 (69.4%)	1984	11
CEPHALOTHIN	54 (64.7%)	1964	1
CEFTIZOXIME	51 (61.2%)	1983	9
CEFAMANDOLE	37 (44.7%)	1978	4
CEFOPERAZONE	32 (38.8%)	1982	8

TABLE 22 (CONT.)
RELATIONSHIP
BETWEEN FORMULARY STATUS OF CEPHALOSPORINS
AND YEAR OF MARKETING

CEFOTAXIME	26 (31.8%)	1981	6
CEFOXITIN	3 (4.7%)	1979	5
CEFAZOLIN	0 (0%)	1974	2

Spearman coefficient = -.56 $p<0.05$ alpha=0.05

The relationship between the year that the drug was marketed and the formulary status was tested using a Spearman rank correlation test. The correlation coefficient was -0.56, indicating a moderately negative correlation between the marketing year and the formulary status. The newer cephalosporins are more likely to be rejected from the formulary by the P&T Committee. This may due to the lack of originality in the spectrum of activity, therapeutic indications of these new drugs allied with a poor cost-benefit ratio.

Hypotheses 8 through 13 are concerned with the non-formulary status of cephalosporins. Prior to testing, the non-formulary status of cephalosporins was divided into formulary rejection, non-formulary status with planned review and non-formulary status without planned review. In some cases, respondents checked two answers. When

respondents selected formulary rejection and planned review status, planned review status was chosen. When respondents selected formulary rejection and non-formulary status with no plans to review, no plans to review status was chosen. The results relating to the non-formulary status of cephalosporins are presented in Table 23.

TABLE 23
NON FORMULARY STATUS OF CEPHALOSPORINS
BY GENERATION

	1ST GEN.	2ND GEN.	3RD GEN.
FORMULARY REJECTION	79	110	104
NON-FORMULARY WITH PLANS TO REVIEW	2	40	63
NON FORMULARY WITH NO PLANS TO REVIEW	38	79	80

df=4 X2=35.8 alpha=0.05 p<0.001

The figures in Table 23 demonstrate that there is a significant difference in the formulary rejection status among the three generations of cephalosporins. Follow-up procedures were conducted to determine which generation was responsible for these differences.

From the first hypothesis, third generation cephalosporins were found to have the greatest frequency of formulary rejection(247). First and second generation of

cephalosporins had a total of 119 and 233 formulary rejections respectively. First generation cephalosporins differ significantly from the other two generations.

Of those first generation cephalosporins that are not on formulary, most of them are formally rejected. Planned review status was rarely selected in the first generation when compared to the other generations and is responsible for the significant difference when the chi-square test was performed. This low rate might be explained by the length of time that first generation cephalosporins have been in use. Cephalothin and cephapirin are the two first generation cephalosporins that are responsible for the non-formulary status of the first generation cephalosporins.

Similar to the the first generation, formulary rejection was found to be the most frequent formulary status for the second generation of cephalosporins ($p<0.001$) with the exception of cefoxitin. This was expected because cefoxitin was found to be the one of the most widely accepted of all cephalosporins.

Unlike the other generations of cephalosporins, third generation cephalosporins are usually rejected from the formulary. However, in the case of the third generation,

planned formulary review is more frequently selected. Ceftriaxone and ceftizoxime, both newly marketed drugs, were mainly responsible for the planned review status. The large number of newly marketed products in this generation as well as their relatively high cost may be responsible for the high level of planned review status of the third generation cephalosporins.

Hypothesis 9 is concerned with the reasons why cephalosporins are rejected. The major reasons for rejecting cephalosporins were:

1. No advantage:47.2%
2. No advantage/high cost: 29.9%
3. High cost :12.3%:
4. No advantage/side-effect:5%
5. Misuse:1.5%

Despite precited literature references concerning the frequent misuse of antibiotics, misuse is rarely selected as a reason for rejecting cephalosporins from hospital's formulary(1.5%). The reasons for cephalosporin formulary rejection are indicated in Table 24.

TABLE 24
REASONS FOR
CEPHALOSPORIN FORMULARY REJECTION

	1ST GEN.	2ND GEN.	3RD GEN.
NO ADVANTAGE*	56	65	32
NO ADVANTAGE* AND HIGH COST	39	38	20
HIGH COST *	23	4	13
NO ADVANTAGE+ SIDE EFFECTS	0	3	15
SIDE EFFECTS	0	0	11
MISUSE	0	3	2

df=4 X^2=14.79 alpha = 0.05 $p<0.01$
* indicates which rows are tested

The first three reasons for rejecting cephalosporins were tested. The overall chi-square was found statistically significant ($p<0.01$). Follow-up tests were conducted to determine which generations were the cause of the significance. The second generation cephalosporins were found to be the cause of the significant difference. For this generation, cost alone was rarely selected (4). Misuse was selected three times for cefonicid. This drug has a different dosing schedule from the other cephalosporins.

The first generation of cephalosporins are mostly rejected for reasons of cost and/or the availability of therapeutic

equivalents.

With the third generation cephalosporins, cost and the availability of therapeutic equivalents are the major reasons for formulary rejection. However, there is a shift towards side effects as the major reason for rejection of drugs within this generation. This is mostly due to bleeding problems reported for moxalactam.

Hypothesis 10 is concerned with the outcome of cephalosporins with planned review status. First generation cephalosporins were not included in the testing of hypothesis 10 for reasons of cells being less than 5. This made it impossible to perform a chi-square test. The outcome of second and third generation cephalosporins when a planned review was indicated are analyzed in Table 25.

TABLE 25
OUTCOME OF 2ND AND 3RD GENERATION CEPHALOSPORINS WHEN PLANNED REVIEW

	2ND GEN.	3RD GEN.
APPROVAL	9	12
UNCERTAIN	11	20
REJECTED	5	16

df=2 X2=1.73 alpha= 0.05 N.S.

The figures in Table 25 demonstrate that there is no significant difference in the expected outcomes of second and third generation cephalosporins when there is a planned review. In the cases of both second and third generation cephalosporins, 'uncertain' outcome is most frequently selected. This may be explained by the drug review being conducted by the P&T committee which plays a determinant role in the addition or deletion of drugs from the formulary.

Next, the expected outcomes for each drug was studied. The outcome of the first generation cephalosporins (cephalothin, cephapirin) was always rejection from the formulary. The hospitals in the sample seemed to adopt the trend of one first generation cephalosporin on formulary. Newly marketed agents (cefonicid, ceforanide and cefuroxime) are responsible for most of the planned review status in our sample. In the case of ceforanide, the expected outcome of its planned reviews was rejection in 5 out of the 10 responses. This drug does not seem to stimulate the interest of health professionals despite a single daily dosing.

Among the third generation cephalosporins, ceftriaxone had the highest rate of planned review status. Rejection was

rarely projected (4 out of 28). Moxalactam, because of its side-effects, was expected to be rejected after its planned review in four out of five cases. This probably confirms the disfavor of this product among health professionnals.

Hypothesis 12 is concerned with the reasons why cephalosporins are not reviewed. The reasons listed were:

1. Adequate equivalent already available:32%
2. Adequate equivalent and minimal M.D. interest:28%
3. Minimal M.D. interest:31%

The results are summarized in Table 26.

TABLE 26
REASONS WHY CEPHALOSPORINS
ARE NOT PLANNED FOR REVIEW

	1ST GEN.	2ND GEN.	3RD GEN.
ADEQUATE EQUIVALENT	21	17	16
ADEQ.EQUIV + MIN. M.D.INT.	14	18	18
MIN. M.D.INT.	5	34	34

df=4 X^2=19.4 alpha= 0.05 p<0.001

The figures in Table 26 indicate that there is a significant difference in the reasons why cephalosporins are not reviewed. Follow-up tests were conducted to

determine which generations were the cause of the significance.

The post hoc test demonstrates that the first generation of cephalosporins differs from the other two generations of cephalosporins. Availability of an adequate equivalent is the primary reason why first generation cephalosporins are not reviewed. In four instances, bid contracts were used to decide between cephapirin and cephalothin.

M.D. interest is rarely selected as a reason for a lack of planned review because these products have been available on the market for many years. Therefore, physicians likely judge these drugs more on a therapeutic equivalent basis.

When second and third generation cephalosporins are analyzed, minimal M.D interest is the most frequently selected reason. Physicians are many times satisfied with the antibiotics that are already available. Therefore, P&T committees may not be willing to evaluate those cephalosporins that are not already on formulary.

Among the second generation cephalosporins, cefuroxime (25) and ceforanide (25) have the highest score for not being reviewed. Physicians do not seem to be interested by

the potential pharmacokinetic advantages offered by these two drugs.

Among third generation cephalosporins, ceftriaxone (33) and ceftizoxime (16) have the highest number of no planned review responses. Ceftriaxone also had the highest number of planned review responses. Ceftriaxone appears to divide health professionnals into two categories; those that are interested in the drug and those that have no interest.

Testing Hypotheses 13 through 18

Hypotheses 13 through 18 are concerned with cephalosporin stocking. The ranking order for formulary acceptance follows the order for cephalosporin stocking as determined by a Spearman Rank Order correlation test. The results are indicated in Table 27.

TABLE 27
COMPARISON
BETWEEN FORMULARY STATUS AND STOCKING STATUS

CEPHALOSPORIN	STOCKED #	STOCKED RK	ON FORMULARY #	ON FORMULARY RK
CEFAZOLIN	85	1	96	1
CEFOXITIN	82	2	82	2
CEFOTAXIME	62	3	57	3
CEFOPERAZONE	56	4	53	4

TABLE 27 (CONT.)
COMPARISON
BETWEEN FORMULARY STATUS AND STOCKING STATUS

CEFAMANDOLE	50	5	48	5
CEFTIZOXIME	35	6	34	6
CEFUROXIME	34	7	25	10
CEFONICID	33	8	27	8
CEPHALOTHIN	29	9	31	7
MOXALACTAM	28	10	26	9
CEPHAPIRIN	16	11	20	11
CEFORANIDE	13	12	10	12
CEFTRIAXONE	10	13	7	13

Spearman coefficient = 0.96 alpha=0.05

The Spearman coefficient indicates a high correlation between stocking and formulary acceptance (0.96). Cefuroxime, moxalactam and cephalothin have a different stock ranking compared to their formulary acceptance ranking. Special uses (e.g.specific diagnosis, trial use) and restrictions of the drug utilization for only one service may explain the difference between the two rankings for these drugs.

Next, the stocking status of cephalosporins was considered. The results are summarized in Table 28.

TABLE 28
STOCKING STATUS OF CEPHALOSPORINS
BY GENERATION

	1ST GEN.	2ND GEN.	3RD GEN.
STOCKED	130 (51%)	212(49.9%)	191 (45%)
NON STOCKED	125 (49%)	213(50.1%)	234 (55%)
ON FORMULARY	137	213	177

df=2 X2=3.08 alpha=0.05 N.S.

The figures in Table 28 demonstrate that there is no significant difference in the stocking of cephalosporins considered by generation. Half of all first generation cephalosporins are stocked in our hospital sample. Cephalothin and cephapirin are stocked a lower level than their formulary acceptance. This is due to the bid contracts generally indicative of two drugs. Cefazolin is in stock in each hospital of our sample.

Half of all second generation cephalosporins are stocked in our hospital sample. Cefoxitin is the second generation cephalosporin most frequently stocked and has the same rate of formulary approval. On the other hand, cefamandole, cefonicid, ceforanide, and cefuroxime are stocked at a greater rate than their rate of formulary approval although the difference was shown not statistically significant. This difference might be

explained by the restriction of some cephalosporins to one hospital. Therefore, it is not necessary to admit these drugs onto the formulary. Trial use may also explain this phenomenon. When a drug is being used experimentally, it may be stocked prior to its formulary review.

Of the third generation cephalosporins, cefotaxime was the most frequently stocked third generation cephalosporin. Although cefotaxime and ceftizoxime are considered therapeutic equivalents, the latter is not frequently stocked (41.2% vs 73%). As with the second generation, third generation cephalosporins have a higher rate of stocking than formulary acceptance (although not statistically significant). The reasons for this discrepancy is probably the same as those of the second generation cephalosporins.

When the total stocking of cephalosporins was determined by hospitals, five cephalosporins is the most frequent number stocked. Six cephalosporins ranked second with only one less hospital. The results are summarized in Table 29.

TABLE 29
NUMBER OF CEPHALOSPORINS STOCKED

NUMBER OF CEPHALOSPORINS IN STOCK	RESPONDENTS	PERCENTAGE
5	17	20%
6	16	18.8%
7	14	16.5%
4	12	14.1%
9	9	10.6%
8	6	7%
10	3	3.5%
3	3	3.5%
11	2	2.3%
12	1	1.2%

One is the most frequent number of first generation cephalosporins stocked representing 55.3% of the answers. Cefazolin is included in every combination of first generation cephalosporins. When two first generation cephalosporins are stocked, cefazolin and cephalothin is the favorite combination. Table 30 summarizes the results of first generation cephalosporin combinations.

TABLE 30
1ST GENERATION CEPHALOSPORIN
COMBINATIONS IN STOCK

NUMBER OF 1ST GEN. IN STOCK	CHOICE	PERCENTAGE #	PERCENTAGE %	% OF TOTAL
1 (47)	CEFAZOLIN	47	100%	55.3%
2 (30)	CEFAZOLIN + CEPHALOTHIN	21	70%	24.7%
	CEFAZOLIN + CEPHAPIRIN	9	30%	10.6%
3 (8)	CEFAZOLIN + CEPHALOTHIN+ CEPHAPIRIN	8	10 %	9.4%

Two, three and one represent the top three choices of second generation cephalosporins stocked with 77.4% of the total hospitals. Cefoxitin is the most frequently stocked second generation cephalosporin. In seven cases, cefamandole and cefuroxime were stocked together although these products are considered therapeutically equivalents. Cefoxitin and cefamandole are the most frequent combinations despite articles about bacterial resistance due to cefamandole use. The different combinations of second generation cephalosporins are summarized in Table 31.

TABLE 31
COMBINATIONS OF 2ND GENERATION CEPHALOSPORINS
IN STOCK

NUMBER OF 2ND GEN. IN STOCK	CHOICE	PERCENTAGE #	PERCENTAGE #	% OF TOTAL
TWO	CEFOXITIN + CEFAMANDOLE	19	57.6%	23.3%
	CEFOXITIN + CEFUROXIME	9	27.3%	10.6%
	CEFOXITIN + CEFONICID	5	15.1%	5.9%

Combinations of two, one and three third generation cephalosporins represent 847% of all hospitals in our sample. Like the second generation cephalosporins, the stocking of third generation cephalosporins is less than formulary acceptance. The diversity of the single third generation cephalosporin reflects the heterogeneity of the

class as well as the hospitals in our sample. At that period of time(January-March, 1985), ceftriaxone was never selected as the sole third generation cephalosporin. However, this product had only been out on the market for a few months at that time. The results of third generation cephalosporin combinations stocked in our hospital sample are summarized in Table 32.

TABLE 32
COMBINATIONS OF 3RD GENERATION CEPHALOSPORINS IN STOCK

NUMBER OF 3RD GEN. CEPHALOSPORINS	CHOICE	PERCENTAGE #	PERCENTAGE %	% OF TOTAL
TWO	CEFOTAXIME+ CEFOPERAZONE	12	42.8%	14.1%
	CEFOPERAZONE+ CEFTIZOXIME	6	21.4%	7.05%
	CEFOTAXINE + MOXALACTAM	6	21.4%	7.05%
	CEFOTAXIME + CEFTIZOXIME	2	7.1%	2.35%
	MOXALACTAM + CEFOPERAZONE	1	3.6%	1.1%
	CEFTIZOXIME+ CEFTRIAXONE	1	3.6%	1.1%
ONE	CEFOTAXIME	10	45.5%	11.76%
	CEFTIZOXIME	6	27.3%	7.05%
	CEFOPERAZONE	5	22.7%	5.88%
	MOXALACTAM	1	4.5%	1.1%

TABLE 32 (CONT.)
COMBINATIONS OF 3RD GENERATION CEPHALOSPORINS IN STOCK

	CEFOTAXIME + MOXALACTAM + CEFOPERAZONE	9	42.8%	10.6%
	CEFOTAXIME + CEFOPERAZONE+ CEFTIZOXIME	6	27.3%	7.05%
THREE	CEFOTAXIME + CEFOPERAZONE+ CEFTRIAXONE	4	19%	4.7%
	MOXALACTAM + CEFOPERAZONE+ CEFTIZOXIME	2	9.5%	2.35%

Hypotheses 15 through 18 were concerned with the influence of certain parameters on the stocking of cephalosporins. As in previous analyses, the parameters selected were implementation of DRGs , the hospital teaching status and the hospital bedsize. The results are summarized in Tables 33 through 45.

TABLE 33
INFLUENCE OF DRG IMPLEMENTATION
ON NUMBER OF CEPHALOSPORINS IN STOCK

NUMBER OF CEPHALOSPORINS IN STOCK	DRGS	NO DRGS
FIVE	14	3
SIX	10	6
SEVEN	9	5

df=2 X2=1.89 alpha=0.05 N.S

The figures in Table 33 demonstrate that there is no significant difference in the number of cephalosporins in stock due to the implementation of DRGs.

TABLE 34
INFLUENCE OF DRG IMPLEMENTATION
ON NUMBER OF IST GENERATION CEPHALOSPORINS
IN STOCK

NUMBER OF 1ST GENERATION IN STOCK	DRGS	NO DRGS
ONE	30	17
TWO	20	10
THREE	4	4

df=2 X2=0.76 alpha=0.05 N.S

The figures in Table 34 demonstrate that there is no significant difference in the number of first generation

cephalosporins in stock due to the implementation of DRGs.

TABLE 35
INFLUENCE OF DRG IMPLEMENTATION
ON NUMBER OF 2ND GENERATION CEPHALOSPORINS
IN STOCK

NUMBER OF 2ND GENERATION IN STOCK	DRGS	NO DRGS
TWO	21	13
THREE	10	9
ONE	10	4

df=2 X2=1.27 alpha=0.05 N.S

The figures in Table 35 demonstrate that there is no significant difference in the number of second generation cephalosporins in stock due to the implementation of DRGs.

TABLE 36
INFLUENCE OF DRG IMPLEMENTATION
ON NUMBER OF 3RD GENERATION CEPHALOSPORINS
IN STOCK

NUMBER OF 3RD GENERATION IN STOCK	DRGS	NO DRGS
TWO	21	8
ONE	13	9
THREE	7	4

df=2 X2=1.55 alpha=0.05 N.S.

The figures in Table 36 demonstrate that there is no significant difference in the number of third generation cephalosporins in stock due to the implementation of DRG's.

The chi-square test conducted to determine the influence of DRG implementation on the stocking of all cephalosporins examined collectively as well as broken down into generations did not demonstrate statistical significance. This might be due to the fact that the number of cephalosporins in stock is not representative of the quantity in terms of dollar percentage of overall inventory. Hospitals that have a large number of cephalosporins on stock may be highly concentrated in only several products while retaining the other products at a low inventory level for the purpose of special uses (e.g. trial use). Therefore, if DRG's were implemented, deletion of a few units of cephalosporin would have little or no effect on the hospital's overa l cost containment measures.

TABLE 37
INFLUENCE OF HOSPITAL BEDSIZE
ON NUMBER OF CEPHALOSPORINS IN STOCK

NUMBER OF CEPHALOSPORINS IN STOCK	SMALL <250	MEDIUM LARGE >250
FIVE	12	5
SIX	9	7
SEVEN	5	9
FOUR	5	6

df=3 X2=4.11 alpha=0.05 N.S

The figures in Table 37 demonstrate that there is no significant difference in the number of cephalosporins in stock due to hospital bedsize.

TABLE 38
INFLUENCE OF HOSPITAL BEDSIZE
ON NUMBER OF IST GENERATION CEPHALOSPORINS IN STOCK

NUMBER OF 1ST GENERATION IN STOCK	SMALL <250	MEDIUM LARGE >250
ONE	22	24
TWO	18	12
THREE	3	4

df=2 X2=1.32 alpha=0.05 2 CELLS<5.0 N.S
df=1 X2=1.08 alpha=0.05 N.S.

The figures in Table 38 demonstrate that there is no significant difference in the number of first generation

cephalosporins in stock due to hospital bedsize.

TABLE 39
INFLUENCE OF HOSPITAL BEDSIZE
ON NUMBER OF 2ND GENERATION CEPHALOSPORINS IN STOCK

NUMBER OF 2ND GENERATION IN STOCK	SMALL <250	MEDIUM LARGE >250
TWO	21	12
THREE	11	7
ONE	5	8
FOUR	4	8

df=3 X2=4.93 alpha=0.05 N.S.

The figures in Table 39 demonstrate that there is no significant difference in the number of second generation cephalosporins in stock due to hospital bedsize.

TABLE 40
INFLUENCE OF HOSPITAL BEDSIZE
ON NUMBER OF 3RD GENERATION CEPHALOSPORINS IN STOCK

NUMBER OF 3RD GENERATION IN STOCK	SMALL <250	MEDIUM LARGE >250
TWO	17	11
ONE	13	9
THREE	8	12
FOUR	3	8

df=3 X2=5.07 alpha=0.05 N.S

The figures in Table 40 demonstrate that there is no significant difference in the number of third generation cephalosporins in stock due to hospital bedsize.

Hospital bedsize does not seem to influence the number of cephalosporins in stock. The reasons are probably similar to those related to DRG status. The type of service available in the hospitals of our sample is likely a more relevant parameter concerning the number of cephalosporins in stock. Those hospitals with a wide variety of services available (i.e. ob./gyn., orthopedic surgery) are likely to have more varied requests for different cephalosporins. Again, this may not be indicative of the level of cephalosporins as a percentage of the total drug budget.

TABLE 41
INFLUENCE OF TEACHING STATUS
ON NUMBER OF CEPHALOSPORINS IN STOCK

NUMBER OF CEPHALOSPORINS IN STOCK	TEACHING	NON TEACHING
FIVE	3	14
SIX	5	11
SEVEN	6	8
FOUR	4	8

df=3 X2=2.38 alpha=0.05 N.S.

The figures in Table 41 demonstrate that there is no significant difference in the number of cephalosporins in stock due to hospital teaching status.

TABLE 42
INFLUENCE OF TEACHING STATUS
ON NUMBER OF 1ST GENERATION CEPHALOSPORINS IN STOCK

NUMBER OF 1ST GENERATION IN STOCK	TEACHING	NON TEACHING
ONE	15	32
TWO	8	22
THREE	2	3

df=2 X2=0.47 alpha=0.05 2 Cells <5.0 N.S.
df=1 X2=0.24 alpha=0.05 N.S.

The figures in Table 42 demonstrate that there is no significant difference in the number of first generation cephalosporins in stock due to hospital teaching status.

TABLE 43
INFLUENCE OF TEACHING STATUS
ON NUMBER OF 2ND GENERATION CEPHALOSPORINS IN STOCK

NUMBER OF SECOND GENERATION IN STOCK	TEACHING	NON TEACHING
TWO	8	25
THREE	7	10
ONE	5	9

df=2 X2=1.66 alpha=0.05 N.S.

The figures in Table 43 demonstrate that there is no significant difference in the number of second generation cephalosporins in stock due to hospital teaching status.

TABLE 44
INFLUENCE OF TEACHING STATUS
ON NUMBER OF 3RD GENERATION CEPHALOSPORINS IN STOCK

NUMBER OF 3RD GENERATION IN STOCK	TEACHING	NON TEACHING
TWO	8	21
ONE	5	17
THREE	8	11
FOUR	4	6

df=3 X2=2.32 alpha=0.05 1 cell<5.0 N.S.

The figures in Table 44 demonstrate that there is no significant difference in the number of third generation cephalosporins in stock due to hospital teaching status.

Contrary to the results concerning formulary acceptance of cephalosporins, the number of cephalosporins in stock was not influenced by the hospital teaching status. This may be explained by the fact that in teaching hospitals the P&T Committees have access to a wider variety of experts(e.g. I.D. specialist) than their non-teaching counterparts. This would lead to a more rigorous

procedure in getting a new drug approved to the hospital formulary. On the other hand, teaching hospitals are probably involved in experimentation leading to a higher level of stocking as compared to the drugs that have been accepted on formulary.

RESULTS AND DISCUSSION

Hypotheses 1 through 3 were designed to study the formulary approval of cephalosporins. The analysis revealed that the first generation of cephalosporins is more frequently accepted onto hospital formularies than the second and third generation cephalosporins. Despite the fact that the current literature describes the restricted formulary status as a useful tool to control the use of antibiotics, the full approval status was the most common status once a drug was accepted onto the formulary. Third generation cephalosporin demonstrated a higher rate of restricted approval status for the identical reasons (ID. consultation and specific diagnosis) as the second generation cephalosporins.

Four cephalosporins (cefazolin, cefoxitin, cefotaxime and cefoperazone) represented over half of the total number of cephalosporins that received formulary acceptance in our

sample. Cefazolin was admitted on each formulary of the 85 hospitals considered. In terms of the number of cephalosporins accepted onto hospital formularies, four, five and six cephalosporins are the most frequent number of cephalosporins admitted. These three numbers represented 58% of our hospital sample. When cephalosporins were considered by generation, one first generation, two second generation and two third generation cephalosporins were the most frequent numbers of cephalosporin products admitted on formulary. This confirms the trend to limit the formulary acceptance of cephalosporins particularly in the first generation.

The reasons for the non-formulary status of cephalosporins was of interest in testing hypotheses 7 through 12. The date of marketing was shown to be moderately correlated to the formulary status. After a product enters the market, formulary acceptance follows as a function of time. Frequently, the product is tested by physicians within a hospital and, through an acculturation process, becomes accepted as being efficacious. The advantages of new products (e.g. pharmacokinetics, dosing schedule) did not seem to stimulate the formulary acceptance of cephalosporins. When the non-formulary status was analyzed, the first generation cephalosporins had the

lowest frequency of planned review status. This appears to be due to the fact that these drugs have been available for a long time and that no new products have been recently marketed. The main reasons for formulary rejection of cephalosporins were due to high cost and the availability of therapeutic equivalents. High cost alone was a more predominant factor among the first generation cephalosporins. Side-effects was a significant cause of formulary rejection in the case of the third generation cephalosporins. This was mostly due to the bleeding problems reported with moxalactam therapy. The main reasons for not reviewing a drug was different according to the generation considered. The availability of therapeutic equivalent was the major reason for the first generation cephalosporins. This confirms that the notion of interchangeability that has been reported in the literature. Second and third generation cephalosporins were not reviewed for formulary acceptance primarily because of minimal M.D. interest.

Hypotheses 13 through 18 were concerned with the stocking of cephalosporins. Cefazolin, cefoxitin, cefotaxime and cefoperazone were the most frequently products in stock. The formulary ranking correlates with the stocking. This demonstrates that the formulary acceptance of a drug may

imply the stocking of this drug. Five, six and seven cephalosporins were the most frequent numbers of cephalosporins in stock. When the cephalosporins are divided into generations, one first generation, 2 second and two third generation were the most common numbers of cephalosporins in stock. This distribution is similar to the number of cephalosporins admitted on formulary. However, when the relationship between the number of cephalosporins in stock was compared to the number of cephalosporins admitted on formulary, the two variables demonstrated only moderate correlation. This may be due to the stocking of drugs reserved for trial use or restricted to one service. When the total number of cephalosporins in stock was analyzed relative to DRG implementation, hospital teaching status and hospital bedsize, no significant differences were identified. The number of cephalosporins in stock may not be directly related to the proportion of the drug budget devoted to cephalosporins. Future research might include inventory cost as a variable to be tested against the three aforementioned parameters.

This study was conducted during the first quarter of 1985. Further research may focus on the changes in formulary status of the drugs studied in this project as well as new cephalosporins that have entered the marketplace since

early 1985. In 1987, DRG's will be fully implented across the United States. This situation may eventually have a profound effect on the process of accepting expensive antibiotics to hospital formularies. Even if these products are accepted, their availability will likely be subject to tight restrictions due to cost containment incentives that have become prevalent throughout our health care system.

BIBLIOGRAPHY

1- Mehl B. Indicators to Control Drug Costs in Hospitals. Am.J.Med.41:667-675,1984.

2- Hendeles L. Need for 'Counter-Detailing' Antibiotics. Am.J.Hosp.Pharm.33:918-924,1976.

3- American Society of Hospital Pharmacists. A.S.H.P. Statement on the Formulary System. Am.J.Hosp.Pharm. 40:1384, 1983.

4- Kunin C.M., Tupasi T., Craig W.A. Use of Antibiotics: A Brief Exposition of the Problem and Some Tentative Solutions. Ann.Intern.Med.79:555-560,1973.

5- Craig W.A., Uman S.J., Shaw W.R. et al. Hospital Use of Antimicrobial Drugs.Ann.Intern.Med.89:793-795,1978.

6- Barriere S.L. Cost-Containment of Antimicrobial Therapy. Drug Intell.Clin.Pharm.19:278-281,1985.

7- Mc Gowan J.E.,Finland M. Usage of Antibiotics in a General Hospital:Effect of Requiring Justification. J.Infect.Dis.30:165-168,1974.

8- Castle M., Willert C.M., Cate T.R. et al. Antibiotic Use at Duke University Center. J.A.M.A.237:2819-2822,1977.

9- Iglehart J.K. The new Era of Prospective Payment for Hospitals. N.Eng.J.Med. 309:1288-1292,1982.

10- Enright S.M. Understanding Prospective Pricing and DRG's. Am.J.Hosp.Pharm.4:1493-1494,1983.

11- Curtiss F.R., Pharmacy Managment Strategies for Responding to Hospital Reimbursement Changes. Am.J.Hosp.Pharm.40:1489-1496,1983.

12- Ibid. p.2

13- Seligman S.J. Reduction in Antibiotic Costs by Restricting Use of an Oral Cephalosporin. Am.J.Med. 71:941-944,1981

14- Craig W.A., Uman S.J., Shaw W.R., Rambopai V.et al. Hospital Use of Antimicrobial Drugs: Survey at 19 Hospitals and Results of Antimicrobial Control Program. Ann.Int.Med. 89:793-795,1978.

15- Hayman J.N. and Sbravati E.C. Controlling Cephalosporin and Aminoglycoside Costs through Pharmacy and Therapeutic Restrictions. Am.J.Hosp.Pharm. 42:1343-1341 ,1985.
16- Hateway G.J., Barriere S.L. Areawide Survey of Antimicrobial Restrictions Policies and the Role of Hospital Pharmacists. Hosp.Form. 17:1095-1105,1982.

17- Coppa G.F. Antimicrobial Therapy in Abdominal Surgery: Factors to Consider in Antibiotic Selection. Hosp.Form. 21:36-43,1986.

18- Talley J.M. Cephalosporin Selection:View from a Beleaguered P&T Committee Member. Hosp.Form. 21:76-84,1986.

19- Roberts A.W., Visconti J.A. The Rational Use and Irrational Use of Systemic Antimicrobial Drugs. Am. J. Hosp. Pharm. 29:828-34,1972.

20- Scheckler W.E, Bennett J.V. Antibiotic Usage in Seven Community Hospitals. J.A.M.A. 213:264-267,1970.

21- Durbin W.A., Lapidai B., Goldmann D.A. Improved Antibiotic Usage Following Introduction of a Novel Prescription System. J.A.M.A. 246:1796-1800, 1981.

22- Hayman J.N. and Sbravati E.C. Controlling Cephalosporin and Aminoglycoside Costs through Pharmacy and Therapeutic Restrictions. Am. J. Hosp. Pharm. 42:1343-1341, 1985.

23- Ibid. p.19

24- Ibid. p.19

25- Brooks G.F., Barriere S.L. Clinical Use of the New Beta- Lactam Antimicrobial Drugs: Practical Considerations for Physicians, Microbiology Laboratories, Pharmacists and Formulary Committee. Ann.Int.Med. 98:530-535, 1983.

26- Lyon R.A., Norvell M.J. Effect of a P&T Committee Newsletter on Anti-Infective Prescribing Habits. Hosp. Form. 20:742-744, 1985.

27- Ibid. p.19

28- Kelly W.N. Implementing and Maintaining a Viable Formulary. Hosp.Form.18:976-987,1983.

29- Ibid. p.1

30- Roberts A.W., Visconti J.A. The Rational Use and Irrational Use of Systemic Antimicrobial Drugs. Am. J. Hosp. Pharm. 29:828-834, 1972.

31- Ibid. p.20

32- Ibid. p.21

33- Weintraub M.,Guttmacher L. P&T Committee Formualry Requests: Criteria for Admission. Hosp. Form. 19:975-980, 1984.

34- Alford R.H. New Cephalosporins: How Much of a Good Thing? Hosp.Formul.17:1339-1352,1982.

35- Barza M., Miao P.V. Antimicrobial Spectrum, Pharmacology and Therapeutic Use of Antibiotic. Part 3:Cephalosporins. Am.J. Hosp.Pharm.34:621-629,1977.

36- Murray B.E., Mollering, R.C., Cephalosporins. Ann. Rev.Med. 32:559-581,1981.

37- Karney W., Correa-Coronas R., Zajtchuk R. et al. Ceforanide versus Cephalothin prophylaxis in Cardiac Surgery. In:Program and Abstracts of the Twenty-Second Interscience Conference on Antimicrobial Agents and Chemotherapy. Miami Beach,Fla, American Society for Microbiology,Abstract 764,1982.

38- Lea A.S., Gould P.S., Merrill K.D., et al.: A Comparative Trial of Cefonicid versus Cefazolin for the Treatment of Skin and Soft Tissue Infections Caused by Gram Positive Cocci. In: Program and Abstracts of the Twenty-Second Interscience Conference on Antimicrobial Agents and Chemotherapy, Miami Beach,Fla, American Society for Microbiology, Abstract 794,1982.

39- Neu H.C. Structure-Activity Relations of New Beta-Lactam Compounds and in Vitro Activity against Common Bacteria. Rev.Inf.Dis.5(suppl.2):319-336,1983.

40- Barriere S.L. and Flaherty J.F. Third Generation Cephalosporins: A Critical Evaluation. Clin.Pharm.3:351-373,1984.

41- Wise R. Penicillins and Cephalosporins Antimicrobial and Pharmacological Properties. Lancet,2:140-141,1982.

42- Neu H.C. The Pharmacokinetics of New Cephalosporins: Significance in Clinical Practice. Bull. N.Y. Acad. Med. 60:380-393,1984.

43- Cefonicid Sodium (Monocid). Med.Lett.26:71-72,1984.

44- Ceforanide (Precef). Med.Lett.26:91-92,1984.

45- Ceftriaxone Sodium (Rocephin).Med.Lett.27:37-38,1985.

46- Harding S.M. Pharmacokinetics of the Third Generation Cephalosporins. Am.J.Med.79:21-24,1985.

47- Lin T.Y. et al. Seven days of Ceftriaxone Therapy is as Effective as Ten Day's Treatment for Bacterial Meningitis. J.A.M.A. 253: 3559-3563, 1985.

48- Parry M.F. Toxic and Adverse Reactions Encountered with New Beta-Lactam Antibiotics. Bull. N.Y. Acad. Med. 60:358-368,1984.

49- Cunha B.A.- Third Generation Cephalosporins. In:A Rational Basis for Selection, Health Communication Press, p.29, 1985.

50- Ibid p.12

51- Ibid p.12

52- Poindexter A., Sweet R., Ritter M. Cefotetan in the Treatment of Obstetric and Gynecologic infections. Am. J. Obstet. Gynecol. 154:946-950,1986.

53- Crane V.S.,Morgan R.,Caffey B. Changing Antibiotic Prescribing Habits Through a Multi-disciplinary Team Approach.Proceeding of the 6th International Conference on Pharmacy Economics/Third Party,Lee R. Strandberg Ed., Sept.1-2, 1985,Montreal,Quebec,Canada.

54- V.A. Pharmacy Service Study Group. Variable Cost per Dose of Preparing and Administering Small Volume Cephalosporin Admixture. Am.J.Hosp.Pharm.41:2624-2634,1984.

55- Turck M., Smith J. Prospective Pricing System and Its Effect on the Principles and Practice of Infectious Diseases. Am.J.Med.78:23-28,1985.

56- Ibid p.16

57- Morascuilo L. Statistical Methods for Behavorial Science Research. Mc Gawhill Book Co, 1971, New York.