Antibiotic Prophylaxis in Pulmonary Surgery

A Double-Blind Study of Penicillin Versus Placebo

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A prospective, randomized double-blind study comparing high-dose short-term penicillin-G prophylaxis with placebo was conducted on patients referred for elective pulmonary surgery. The major advantages of penicillin prophylaxis over placebo were observed for wound infections (2/45 vs 9/47, respectively, p = 0.03), postoperative antibiotic use (13/45 vs 23/47, respectively, p = 0.049), and postoperative hospital stay (median 10 days vs 13 days, respectively, p = 0.02). The prophylactic penicillin regimen had no effect on the incidence of empyema or lower respiratory tract infections. *Staphylococcus aureus* and Haemophilus were identified as the major pathogens in postoperative infections. Penicillin significantly reduced the incidence of *S. aureus* in spite of resistance to penicillin in most isolated strains, while the frequency of Haemophilus was similar in the two treatment groups. Colonization with Enterobacteriaceae and *Pseudomonas aeruginosa* was pronounced in the penicillin group. Few side-effects of penicillin treatment were recorded. Short-term penicillin prophylaxis is recommended, but the ideal prophylactic regimen in pulmonary surgery has not yet been found.

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POSTOPERATIVE INFECTIONS in pulmonary surgery are usually serious and may be fatal. Despite the severity of the infectious complications involved, few studies have been published concerning antibiotic prophylaxis in noncardiac thoracic surgery. Furthermore, present day application of the results from the earlier studies is difficult due to different patterns of morbidity, *e.g.*, the decreasing importance of tuberculosis.

The first double-blind, controlled studies of antimicrobial prophylaxis in pulmonary surgery have only recently been published.[1,2] Cefalosporins were used in both studies, but the conclusions were contradictory. In the first study, a five-day course of cefalosporin prophylaxis significantly reduced postoperative infections as related to the placebo group, and no side effects were encountered.[1] In the other study, a two-day regimen of the same antibiotics failed to influence the infection rates, while a high degree of side effects to the cefalosporins was reported.[2]

In the early 1950s, Eriksen et al.[3,4] proposed penicillin-G as an effective prophylactic antibiotic in pulmonary surgery. This drug has a broad spectrum when administered in high doses, active even against penicillinase-producing *Staphylococcus aureus*, and is largely nontoxic. Later, a controlled, prospective, but not double-blind study evaluated penicillin prophylaxis in pulmonary surgery, but the penicillin treatment was extended for 14 days.[5] There is general agreement today that antibiotic prophylaxis for surgical procedures should start before operation and be as short as possible.[6,7]

To study the effect of a high-dose short-term penicillin-G prophylactic regimen in pulmonary surgery, we conducted a double-blind prospective study incorporating a nontreated control group.

Materials and Methods

A double-blind, randomized, controlled prospective study on patients referred for elective thoracotomy with possible pulmonary resection was conducted at the Department of Thoracic Surgery of the Copenhagen County Hospital in Gentofte from January 1 to December 31, 1980. Eligible for the study were patients who were above the age of 18 years and had no known allergy to penicillins, who had not received antibiotics within three days prior to operation, and who gave informed consent to the study. Once enrolled in the study, patients were excluded for the following reasons: if a suppurative process within the chest was found during

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operation, if other antibiotic therapy was started during prophylactic treatment, if one or more doses of the study drugs was omitted, and if allergic reactions emerged during prophylactic treatment.

The prophylactic regimen consisted of six doses of penicillin-G 5 million IU or placebo, intravenously. The first dose was administered immediately before surgery, and the five remaining doses every six hours thereafter. The antibiotic or the placebo of identical appearance was supplied in precoded, randomly numbered packets, so that each patient enrolled in the study was assigned one packet.

The day before operation the thorax and upper extremities of all patients were washed four times with 2% hexachlorophene. Immediately before surgery the skin of the surgical field was disinfected with a solution containing euflavine 0.1%, hibitane 5%, and ethanol 96%.

For all thoracotomies except pneumonectomies, pleural drainage was standard. Regular chest physiotherapy was given after surgery in all patients. Continuous positive airway pressure was prescribed postoperatively if considered necessary.

Clinical assessment of the patients was done by the thoracic surgical team at least twice daily after operation. Chest roentgenograms were obtained routinely every day during the first seven days postoperatively, and again shortly before discharge. Additional chest roentgenograms were taken whenever indicated by a change in the clinical status of the patients.

Preoperative baseline studies included chest roentgenograms, pulmonary function studies, bronchoscopy, complete blood cell counts, and renal and liver function studies.

In the postoperative period protocol-assigned data included complete blood cell counts on days 3 and 7 after surgery, as well as renal and liver function studies on the seventh postoperative day. An allergic reaction to the penicillin was considered if an urticarial rash, laryngeal edema, or other anaphylactic reaction developed during or immediately after prophylaxis.

The observation period for the study incorporated the whole postoperative hospital stay, usually ten days, and any further relevant information provided during the three-month period of follow-up in the out-patient clinic was also included in the study. Effectiveness of prophylaxis was measured by the incidence of postoperative infections, the duration of postoperative hospitalization, and nonprophylactic postoperative use of antibiotics during hospitalization. Infectious complications were diagnosed according to the following criteria:

1. Empyema—recovery of pus from the pleural space with or without positive culture.

TABLE 1. *Reasons for Exclusion of Patients from Study*

	Placebo	Penicillin
One or more doses of study drug omitted	3*	3
Suppurative process found at operation	1	1
Nausea and dizziness at first injection	—	1
Evaluable	47	45

* Number of patients.

2. Lower respiratory tract infection—rectal temperature above 38.0 C, with a chest roentgenogram showing signs of a new infiltrate.

A positive sputum culture was not considered necessary for the diagnosis of infection.

Realizing the difficulty in obtaining an exact diagnosis of pneumonia, we deliberately avoided the term. Our definition may have included some cases of minor atelectasis, intrapulmonary hemorrhage, or pulmonary infarction, which could not be differentiated from pneumonia by the ordinary routine methods used.

3. Wound infection—erythema, induration, and tenderness along with suppuration.
4. Bacteremia—at least one positive blood culture with bacteria not considerred contaminants, such as *Staphylococcus epidermidis.*
5. Other—rectal temperature above 38.5 C of unknown origin for at least three days.

Urinary tract infection, here defined as significant bacteriuria [*i.e.*, $\geq 10^5$ colony-forming units (CFU)/ml of urine], was recorded but not included as a target infection in the evaluation of the prophylactic regimen.

All patients were evaluated before the code was broken at the end of the study. The study was done in accord with the Helsinki Declaration of 1975 and approved by the Danish National Health Service (Sundhedsstyrelsen).

Bacteriology

Cultures for investigation of aerobic and anaerobic bacteria were obtained from 1) sputum preoperatively, if coughed secretions were present; 2) tracheal aspirates at the beginning and at the end of surgery; 3) the main bronchus immediately after resection; 4) the pleura prior to closure of the thorax; 5) sputum, daily for the first seven postoperative days and thereafter whenever indicated by the clinical condition of the patient; 6) the pleural drains at time of removal; 7) the pleural fluid whenever thoracocentesis was performed; 8) the wound if discharge was present; 9) venous blood, if septicemia was suspected; and 10) urine, if symptoms of urinary tract infection were present.

All cultures were immediately referred to the micro-

TABLE 2. *Diagnoses*

	Placebo n = 47	Penicillin n = 45
Primary bronchial carcinoma	29*	30
Bronchial adenoma	—	3
Benign solitary nodule	6	4
Bullous emphysema	7	2
Metastatic carcinoma	1	4
Other†	4	2

* Number of patients.
† Placebo: Fibromyosarcoma,[1] thymoma,[1] pleuritis sequela,[1] diaphragmatic hernia.[1] Penicillin: Neurinoma,[1] mesothelioma.[1]

biology department. Diagnostic bacteriology was conducted according to laboratory routine. Gram's stains were prepared from all cultures, directly from the sputum or swabs, as a control for the culture results. Antibiotic sensitivity testing was performed by disc diffusion (Biodisk). Phage-typing of *S. aureus* was performed at Statens Seruminstitut, Copenhagen. Alfahaemolytic streptococci, Neisseria species other than meningitidis and gonorrhoea, coryneformic rods, Candida species, *S. epidermidis*, and anaerobic bacteria were considered normal commensals of the upper respiratory tract.

Statistical analysis

Populations are in the text described by the medians and the tenth and 90th percentiles. Comparative statistical analysis included the Fisher exact test, or chi-square test, depending upon the size of the study population, and the Mann-Whitney test;[8,9] $p < 0.05$ was considered significant.

TABLE 3. *Preoperative Clinical Status of the Patients in the Two Treatment Groups*

	Placebo n = 47	Penicillin n = 45
Age, years	60* (40.8-68)	59 (36.4-69)
Sex		
Female	17†	16
Male	30	29
Smokers	36	38
Preoperative pulmonary function		
Normal	33	32
Decreased	12	12
Not tested	2	1
Complicating diseases		
Bronchial asthma	1	—
Chronic bronchitis	4	4
Cardiovascular disease	6	3
Chronic renal disease	—	3
Extrapulmonary cancer	2	4
Other‡	3	2

* Median (10th and 90th percentiles).
† n, number of patients.
‡ Placebo: Myxoedema,[1] liver cirrhosis,[1] hemiparesis.[1] Penicillin: Mb. Recklinghausen,[1] ulcerative colitis.[1]

TABLE 4. *Details of Operations*

	Placebo n = 47	Penicillin n = 45
Exploratory thoracotomy	14*	9
Pneumonectomy	2	9†
Lobectomy	19	20
Segmental resection	10	5
Other‡	2	2

* Number of patients.
† $p = 0.03$.
‡ Placebo: Pleural decortication,[1] repair of diaphragmatic hernia.[1] Penicillin: Biopsy of pleura,[1] excision of neurinoma.[1]

Results

The study included 101 patients. Of these, nine patients, five in the penicillin group and four in the placebo group, were excluded for the reasons shown in Table 1. Of the 92 patients left for evaluation, 45 belonged to the penicillin group and 47 to the placebo group. The two groups were comparable with regard to diagnoses and various clinical parameters, as shown in Tables 2 and 3. The two groups were also similar with regard to the types of operative procedures (Table 4), except for pneumonectomies, of which in spite of randomization fewer were performed in the placebo group than in the penicillin group ($p = 0.03$).

Table 5 shows the rates of postoperative infections in the two groups. The high frequency of postoperative infections in both groups combined (48.9%) was mainly due to lower respiratory tract infections (37%), and there was no difference between the two groups concerning this complication. Pneumonectomies and lobectomies carried infection rates of 73% and 51%, respectively, while 47% occurred after segmental resection and 39% after exploratory thoracotomies. These differences were not significant ($p > 0.30$).

TABLE 5. *Postoperative Infections*

	Placebo n = 47	Penicillin n = 45	Total (%)	p
Empyema	2*	2	4 (4.3)	NS†
Lower respiratory tract infections	19	15	34 (37.0)	NS
Wound infections	9	2	11 (12.0)	0.03
Fever of unknown origin	2	—	2 (2.2)	NS
Number of patients with infections	28	17	45 (48.9)	0.04

* Number of patients; some patients had more than one infection.
† NS, not significant.

TABLE 6. *Diagnoses and Bacteriological Data of Patients with Empyema and Wound Infections in the Two Treatment Groups*

	n	Diagnosis		Bacteriology				
		Malignant	Benign	*S. aureus*	*S. epidermidis*	*Enterobacter Klebsiella*	*P. aeruginosa*	No Pathogens
Placebo								
Empyema	2*	2	—	2	—	—	—	—
Wound infection	9	5	4	3	3	2	1	2
Penicillin								
Empyema	2	2	—	1	—	1	1	—
Wound infection	2	2	—	1	—	—	—	1

* Number of patients; some patients had more than one pathogen.

The significant difference between the two groups in the number of patients with postoperative infections was mainly due to a significantly higher incidence of wound infections in the placebo group than in the penicillin group. All 11 cases of wound infections showed some degree of suppuration from the wound, and all were treated by reopening the wound (Table 6).

Empyemas occurred in two patients in each group (Table 6). In one patient in each group, the empyema was preceded by a lower respiratory tract infection. All four patients with empyema were treated with drainage and rigorous antimicrobial therapy. Three of the patients died within three months after the operation, while one patient, in the placebo group, survived.

Table 7 gives detailed clinical and bacteriological information concerning the patients with lower respiratory tract infections (LRTI) in the two treatment groups. Patients with primary cancer of the lung or metastases to the lungs were more prone to develop LRTI than patients without malignant disease ($p = 0.03$). We could not demonstrate any significant correlation between LRTI and type of operation. Haemophilus was the pathogen most frequently isolated from sputum in patients with LRTI, and the emergence of this pathogen significantly correlated with LRTI (23 of 34 cases of LRTI vs 22 of 58 cases without LRTI, $p = 0.006$). Haemophilus appeared either alone or in mixed infections with one or two other pathogens (Table 7). We could not detect any difference as to the severity of LRTI in the patients from the two groups, *i.e.*, antibiotic treatment was instituted in 18 of 19 patients in the placebo group versus 12 of 15 patients in the penicillin group ($p > 0.05$). LRTI without empyema possibly contributed to the fatal outcome in one patient in each of the two treatment groups. No septicemias occurred.

Fewer patients in the penicillin group than in the

TABLE 7. *Clinical and Bacteriological Data Concerning Patients with Lower Respiratory Tract Infections after Pulmonary Surgery in the Two Treatment Groups*

	Placebo n = 19	Penicillin n = 15
Sex		
Female	5*	3
Male	14	12
Diagnosis		
Malignant	14	14
Benign	5	1
Operation		
Thoracotomy	7	2
Pneumonectomy	—	6
Lobectomy	10	6
Segmental resection	2	1
Pathogens isolated from sputum		
Haemophilus alone	8	4
Haemophilus and *S. pneumoniae*	2	—
Haemophilus and *S. pneumoniae* and *S. aureus*	3	—
Haemophilus and Enterobacteriaceae†	1	5
Enterobacteriaceae† alone	4	5
No pathogens	1	1

* Number of patients.
† Klebsiella sp., *E. coli*, and/or *E. cloacae*.

TABLE 8. *Complications and Clinical Parameters in Connection with Pulmonary Surgery in the Two Treatment Groups*

	Placebo n = 47	Penicillin n = 45	p
Death*	2†	3	NS‡
Atelectasis	8	12	NS
Cardiac dysrhythmias	6	5	NS
Therapeutic bronchoscopy	3	5	NS
Antibiotic use postoperatively	23	13	0.049
Duration of operation (hours)	2½§ (1¼–3¾)	2½ (1–4½)	NS
Duration of pleural drainage days	4‖ (2.5–9)	5 (3–7)	NS
Postoperative hospital stay (days)	13 (9–21)	10 (8–27)	0.02

* Within three months after surgery.
† Number of patients.
‡ NS, not significant.
§ Median, (10th and 90th percentiles). Duration of operation: Placebo: n = 45, Penicillin: n = 44.
‖ Placebo: n = 34, Penicillin: n = 31.

TABLE 9. *Distribution of Pathogens* Isolated during or after Surgery from Sputum, Operation Sites, Pleural Drains, and Thoracic Wounds of Patients in the Two Treatment Groups*

	Placebo		Penicillin		
	Infected	Not Infected	Infected	Not Infected	Total
n	28†	19	17	28	92
S. aureus	13	5	5	1	24
S. epidermidis‡	3	2	3	—	8
S. pneumoniae	7	2	—	2	11
S. beta-haemolytic	1	1	1	3	6
S. faecalis	—	—	2	1	3
Haemophilus	15	11	10	10	46
E. coli	7	3	7	6	23
Citrobacter	—	—	2	1	3
Enterobacter	6	3	8	6	23
Klebsiella	8	—	5	6	19
Other Enterobacteriaceae§	1	1	2	2	6
P. aeruginosa	2	—	4	3	9

* Figures in table include only aerobic/facultative pathogens. For distribution of anaerobes, see text.
† Number of patients; most patients had more than one pathogen.
‡ *S. epidermidis* was recorded only when present in pure culture.
§ Proteus, Hafnia, or Serratia.

placebo group needed antibiotic treatment during the postoperative hospital stay (Table 8). Antibiotics most frequently used were ampicillin, gentamicin, and cefalothin. Not included in this comparison were two patients in the placebo group who received sulfonamide treatment for urinary tract infections, of which only one was confirmed by culture.

Postoperative stay was significantly longer for patients in the placebo group than in the penicillin group (Table 8). Patients with postoperative infections stayed significantly longer in the hospital than patients without infectious complications [14 (9–34) days vs 11 (8–16) days, respectively, p = 0.007].

The duration of operation was significantly longer for patients with subsequent postoperative infections than for the rest of the study population (infected, 3 (1½–4¼) hours vs noninfected, 2½ (1–4) hours, p = 0.03). Similarly, duration of pleural drainage was significantly more protracted in patients with LRTI than in patients not suffering from this complication [5 (3–9) days vs 4 (2–6) days, respectively, p = 0.02]. Factors with no correlation to postoperative infection were age, pulmonary function, and smoking history.

Table 9 shows details about the pathogens isolated from the patients in the two treatment groups. There were no differences between the two groups as to the numbers of sputum cultures or swabs obtained during the study. Anaerobic bacteria were almost always present in sputum cultures, usually *Bacteroides melaninogenicus* and anaerobic streptococci. No anaerobes were isolated from pleural or wound cultures. Haemophilus was the pathogen most frequently isolated overall, with no difference in isolation rates between the two groups. *S. aureus* and *Streptococcus pneumoniae* were encountered significantly more often in the placebo group than in the penicillin group (p = 0.006 and p = 0.03, respectively, Table 9). Seventeen of 25 *S. aureus* strains were isolated from pleural drains. Penicillin-sensitive *S. aureus* was found in four patients in the placebo group and in two patients in the penicillin group. The rest of these pathogens were resistant to penicillin, but methicillin sensitive. Phage-typing of *S. aureus* revealed a prevalence of hospital-acquired strains. In contrast to the gram-positive organisms, gram-negative bacteria of the Enterobacteriaceae group together with *Pseudomonas aeruginosa* were isolated significantly more often in the penicillin group relative to the placebo group. This is illustrated in Fig. 1, which shows that sputum from approximately 50% of the patients in the penicillin group had gram-negatives from the first postoperative day, in contrast to that of only 25% of the patients in the placebo group. This divergence was apparent until day 7 after surgery (p = 0.0001). The white blood cell (WBC) counts were significantly increased at the seventh postoperative day relative to the preoperative values (preoperative total, both groups combined, was 9.9 (6.9 -12.2) × 10^9/l vs postoperative total, 11.0 (8.2–17.1) × 10^9/l, p = 0.04). Apart from this, WBC counts did not differ significantly between infected and noninfected patients in either treatment group and were thus not helpful in the diagnosis of infectious complications.

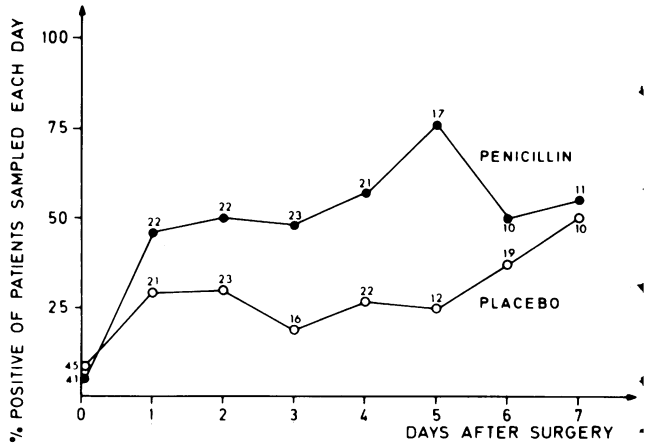

FIG. 1. Occurrence of gram-negative organisms (Enterobacteriaceae and Pseudomonas aeruginosa) in sputum during the first seven postoperative days from patients in the two groups. Ordinate, number of patients with gram negative cultures in sputum in per cent of total number of patients sampled on each day. Numbers along the curves indicate the total number of patients sampled in each group on each day.

No variation in liver or renal function parameters relative to penicillin administration was observed. Very few side effects of penicillin treatment were recorded. Apart from the patient excluded due to suspected anaphylactic reaction, one patient suffered a rash that possibly had connection with penicillin treatment.

Discussion

A malignant disease, primarily bronchial carcinoma, rendered the patients less resistant to postoperative infections. Apart from this, we found no preoperative risk factor that assisted in predicting the outcome of pulmonary surgery in these patients. The variation in the types of operations between the two groups probably does not influence our results, since we could not demonstrate significant differences in the postoperative infection rates among the various surgical procedures. Duration of operation and duration of pleural drainage significantly correlated with the incidence of postoperative infections. Both treatment groups were comparable with regard to these as well as all other parameters tested (Tables 2, 3, and 4).

Infection rates depend on the definition of the infections expected. Empyemas and wound infections are fairly easy to diagnose, and the frequencies of these infections in our study, 4.3% and 12%, respectively, corresponded with results from other studies.[3,4,7,10] In contrast, pneumonias or lower respiratory tract infections are difficult to distinguish from other postoperative pulmonary complications. With definitions of pneumonia similar to our definition of lower respiratory tract infections, other investigators found incidences of these complications corresponding with those in the present study.[1,11]

The low incidence of empyemas in the two treatment groups provides no clue as to the effect of penicillin prophylaxis against this complication. The rate of wound infections was significantly lower in the penicillin group, as compared with the placebo group. Since the short penicillin regimen had an effect on the wound infections, it is apparent that the wounds must have been seeded with the pathogens during or immediately after surgery.

Concerning the other parameters for measuring the effect of prophylaxis, we found a significant reduction in postoperative hospitalization as well as in postoperative use of antibiotics in the penicillin group relative to the placebo group. Further, in favor of penicillin were the few side effects experienced from its use.

While cefalosporin prophylaxis in thoracic surgery can reduce the incidence of postoperative pneumonia,[1,11] such an effect could not be demonstrated with penicillin in this study. This lack of effect may be explained by the bacteriology of the lower respiratory tract infections. Haemophilus, identified here as the major pathogen in these infections, is relatively resistant to penicillin but sensitive to most cefalosporins.

Pleural drains apparently were important ports of invasion for *S. aureus*, but further investigation into the origin of these pathogens was not a part of this study. Identification of nasal carriage of *S. aureus* with subsequent local treatment has been shown of value in prevention of infection after surgery.[12] A possible drawback of penicillin prophylaxis, as shown in this study, was the colonization of the respiratory tract with gram-negative bacteria of the Enterobacteriaceae group and *P. aeruginosa*. We could demonstrate a distinct effect, in spite of the short duration of therapy, for up to one week after surgery. Infection does not necessarily follow from such colonization, but the pathogenicity of the gram-negative bacteria was illustrated by their role in both empyemas and in wound infections. Colonization with Enterobacteriaceae has been shown to occur soon after admission to the hospital.[13] Furthermore, other studies have shown that predisposing factors include antibiotic therapy, old age, assistant ventilation, coma, and anemia.[13-16] Also, the size of the penicillin dose has been reported to correlate to subsequent colonization.[13,17] A reduction of the penicillin dose might diminish the extent of colonization but could also impair the effect on *S. aureus*.[18]

Cost-benefit analysis of penicillin prophylaxis in pulmonary surgery based on our data would clearly show a benefit from penicillin, if we incorporated only such parameters as hospital stay and cost of penicillin and other antibiotics used postoperatively. Hospital stay was reduced by a mean of three days by penicillin prophylaxis, and the cost of a hospital day in this country far exceeds the cost of the antibiotics used. The consequences with regard to cost of the penicillin-induced colonization with gram-negative organisms are difficult if not impossible to evaluate. In conclusion, our study demonstrated a significant effect of high-dose short-term penicillin prophylaxis in pulmonary surgery, since penicillin significantly reduced the incidence of wound infections, the duration of hospital stay, and the postoperative use of antibiotics, as compared with placebo. We identified Haemophilus and *S. aureus* as the main pathogens against which antibiotic prophylaxis should be directed. While penicillin had little effect on Haemophilus, its activity against *S. aureus* and other gram-positive pathogens was evident. Considering the low cost and low toxicity of penicillin, it is still an excellent choice for prophylactic use. Further investigation is warranted, however, of a possible reduction in dosage and the addition of an anti-Haemophilus antibiotic.

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