MEDICAL GRAND ROUNDS

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Prophylaxis with antimicrobial drugs

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PROPHYLAXIS WITH ANTIMICROBIAL DRUGS

This discussion is planned as a general review of information on the use of antimicrobial drugs in the prevention of infections. It is probably safe to say that the prevailing opinion among physicians holds that there is really not much of a role for antimicrobial drugs in prophylaxis. Certainly most internists appear to have strong convictions along these lines, and they receive considerable reinforcement from the infectious disease specialists. Surgeons have divergent views, but even those who use the drugs prophylactically appear to do so apologetically. There are obvious reasons for these attitudes. In the first place many of the early studies on chemoprophylaxis were poorly conceived and poorly executed. Many were carried out with drugs having a very limited spectrum of activity. In some the drugs were given at what now would be considered inappropriate times. Finally, expectations may often have been too high. There is little question, for example, that even optimal antimicrobial drug prophylaxis is unlikely to be as efficient in specific situations as certain biologic products, for example poliomyelitis vaccine.

Despite many reservations about individual studies, and despite the fact that chemoprophylaxis with antimicrobial drugs is imperfect at best, I would like to review the subject today and to present the view that there is indeed a reasonably wide field of usefulness for these drugs in the prevention of infection. Only a few examples can be cited in which the use of antimicrobials may have a major public health impact, but I believe the data indicate that in some specific patient problems we can do better than we have been doing.

The conventional attitude about prophylaxis referred to previously is well expressed in a quotation from the 1974 Medical Letter Handbook of

Antimicrobial Therapy, a source very widely respected.

ANTIMICROBIAL PROPHYLAXIS

> Antimicrobial drugs are often used prophylactically. Often such use subjects the patient to the risk of superinfection and other adverse effects of the drugs with little prospect of success in preventing infection. In relatively few circumstances is antimicrobial prophylaxis unquestionably useful; in some its usefulness is controversial.
>
> Handbook on Antimicrobial Therapy. The Medical Letter. Ref. Ed. 1974

Most textbooks of medicine make little mention of chemoprophylaxis. For example, the subject has not appeared as a separate topic in Beeson and McDermott's Textbook of Medicine until the 14th edition, published in 1975. The entire section in this edition is as follows:

Beeson and McDermott - Textbook of Medicine
14th ed. 1975 (R.B.Roberts)

CHEMOPROPHYLAXIS

Antimicrobial agents are often administered to individuals who are believed to be at some increased risk of acquiring a bacterial infection.

Prophylaxis is usually successful only when a single drug is given for a specific organism. The antimicrobial drugs and their clinical indications which are considered to be of value are summarized in Table 3. Antimicrobial prophylaxis is not effective in viral respiratory diseases, viral exanthems, clean abdominal surgery, and congestive heart failure. Unlike the therapeutic situation in which the identity of the offending microbe might be in doubt and there is urgency in selecting therapy, with chemoprophylaxis there is usually no urgency, and the microbe in question is known. Consequently, the use of antimicrobial drugs in chemoprophylaxis should be more rational than in therapy. Unfortunately, this is not always the case, and in many instances the prophylactic use of antimicrobial agents is unwarranted, ineffective, and often dangerous because of toxic reactions, superinfection, and emergent resistance. The matter of drug toxicity requires comment. Selection of a drug is a matter of weighing offsetting risks. It is easy to forget that a degree of drug toxicity that is acceptable when weighed against an instance of a particular disease may be unacceptable when weighed against the chance that someone *might* acquire that disease. Finally, although one must emphasize the need for caution in chemoprophylaxis, it is fitting to remember that in terms of the number of people benefited, the use of the drugs in this way represents one of the greatest achievements of modern biomedical science and technology.

TABLE 3. Recommendations for Antimicrobial Prophylaxis

Disease or Clinical Setting	Etiologic Agent	Antimicrobial Drug
Acute rheumatic fever (recurrent)	Group A streptococcus	Penicillin, erythromycin, sulfonamide
Meningococcal infections	*Neisseria meningitidis*	
	Sulfonamide-susceptible	Sulfisoxazole
	Sulfonamide-resistant	Minocycline
Microbial endocarditis		
Oral cavity instrumentation	Viridans streptococcus	Penicillin, cephalosporin
Urogenital and gastrointestinal instrumentation	Enterococcus	Penicillin or vancomycin plus streptomycin
Open heart surgery	*Staphylococcus aureus* and *epidermidis*	Penicillinase-resistant penicillin, cephalosporin
Newborn nursery epidemics	Enteropathic *E. coli*	Neomycin, Colistin
	Staphylococcus aureus	Penicillinase-resistant penicillin
	Group A streptococci	Penicillin
Tuberculin reactors of certain sorts	*Mycobacterium tuberculosis*	Isoniazid
Malaria	Plasmodia	
	Chloroquine-susceptible	Chloroquine followed by primaquine
	Chloroquine-resistant (*P. falciparum*)	Chloroguanide and sulfone
Ophthalmia neonatorum	*Neisseria gonorrhoeae*	Silver nitrate, penicillin
Burns		Silver sulfadiazine, silver nitrate
Bronchitis (chronic)	Pneumococcus or *Hemophilus influenzae*	Ampicillin, tetracycline

This is a considerably more positive statement than the previous one, and although the cautionary note is still apparent, the closing sentence of this text is a remarkably optimistic statement.

In general terms, as we review the data to be presented several aspects of each individual situation need to be considered.

Considerations in the evaluation of prophylaxis with antimicrobial drugs.

1) The number of species of microorganisms.
2) The biologic state of the microorganisms.
3) The nature of the disease
   Frequency, duration of risk, recognition of risk, morbidity and/or mortality, economic consequences.
4) The drug
   Potency, bactericidal vs. bacteriostatic, cost, ease of administration, side effects.
5) Attitudes of public toward disease.

First, we need to consider how many different microorganisms are involved in the particular situation. It is quite clear that where there is one organism involved and one effective drug, the results tend to be considerably better. Next, one needs to consider the biologic state of the organisms, for the reason that some of the antimicrobial drugs are relatively inactive on organisms which are not in a position to multiply. One needs to consider the nature of the disease. What is its frequency? What is the duration of risk? What are the morbidity and the mortality? A serious consideration is the economic consequence both of what we are trying to prevent and the potential of the drugs we are using. How much do the drugs cost? How much is it going to cost the patient in money or in disability if he gets sick either from the disease or from the drug? How effective is the drug? Finally the attitude of the public toward the disease is sometimes very important as we will point out later.

With all of these qualifying considerations, I would like now simply to review the present state of chemoprophylaxis. In the main, I will be selective and will report only on those areas in which in my own opinion there is substantial evidence for effectiveness. I recognize that one could probably find some fault with many of the studies to be reported but it is hoped that even critical analysis would not significantly alter the conclusions. I will review also a few of the studies which suggest that prophylaxis is not valuable in an effort to point out their positive findings as well as certain weaknesses. The bulk of this presentation however will purposefully be directed to the positive aspects of the question which I feel require emphasis. In addition to the usual bibliography I have appended a subject outline which gives references both pro and con on prophylaxis.

Rheumatic fever

Penicillin

- Primary prophylaxis
- Secondary prophylaxis

Problems:

- Continuing need for injections
- Prolonged need
- Reactions to penicillin
- Unexplained failures

It is well established that in rheumatic fever penicillin is an effective drug both as primary and secondary prophylaxis. If one adequately treats an acute Group A streptococcal infection, it is effective in the prevention of rheumatic fever. In most patients who have had rheumatic fever it is effective as secondary prophylaxis in preventing relapses. There are problems, however, even in this very good example. There is a need for continuing injections. We don't know when we can stop it. There

are many reactions to penicillin and there are unexplained failures. But all in all, this is an effective use of an antimicrobial for prophylaxis.

Meningococcal infections

Effectiveness of prophylaxis demonstrated in closed populations.

Drugs: Sulfonamide
Minocycline
Rifampin

Problems: Limited usefulness
Drug resistance
Toxicity
Failures

Prophylaxis against meningococcal infections is a good example of one of the problems with chemoprophylaxis. A few years ago, effective prophylaxis existed with the use of sulfonamides. This is still true if we happen to be dealing with a strain which is sulfonamide sensitive, but many of the strains causing epidemics now are insensitive to sulfonamides and therefore the usefulness of sulfonamides is very limited. The other two drugs, minocycline and rifampin, are probably not as good as sulfonamides and they have some drawbacks. The major drawback to minocycline is its toxicity, which is a frequent problem. The major drawback to rifampin is the fact that resistance to rifampin develops very rapidly. It thus appears inevitable that if rifampin is extensively used in the prophylaxis of meningococcal infections its usefulness will rapidly diminish.

Venereal disease

Gonorrhea) Penicillin
Syphilis)

Chancroid - Sulfonamide

Prophylaxis probably effective if
given in proper dosages at proper time.

Problems:
1) Drug reactions
2) Risk uncertain
3) Poor compliance
4) Multiple drugs
5) Drug resistance

Another example in which the potential of prophylaxis has been demonstrated is in venereal disease. One can, with the proper dosage at the proper time, prevent gonorrhea and syphilis with the use of penicillin. One can prevent chancroid with the use of sulfonamides. The problems are easily visualized, and although technically feasible it seems unlikely to be adopted as a good public health measure. There are many drug reactions. The risk of infection is, of course, uncertain. The compliance in taking the drugs is likely to be poor under the best of circumstances, and multiple drugs are required. Thus, this becomes a potential but relatively impractical example of chemoprophylaxis.

Tuberculosis - (Isoniazid)

Priorities

1) Household and other close contacts of active cases.
2) Recent converters (any age).
3) Tuberculin positive person with pulmonary lesion compatible with tuberculosis.
4) Inactive tuberculosis with inadequate or no prior therapy.
5) Positive tuberculin reactors with diabetes, silicosis, gastrectomy, immunosuppression.
6) Positive reactors under 20.
7) Other identified positive reactors.

The next example is of considerably greater importance. Isoniazid

has been clearly demonstrated to be a highly effective chemoprophylactic agent in the prevention of tuberculosis. Details of the extensive background data about this are given in reference 51. Consideration of these data have led to the development of a set of priorities for the use of isoniazid in the prevention of tuberculosis. In any household or other close contact, any known recent converters, a tuberculin positive person with a pulmonary lesion compatible with tuberculosis, inactive tuberculosis with no prior therapy or with inadequate prior therapy, positive tuberculin reactive with diabetes, silicosis, gastrectomy, and immunosuppression, positive reactors under the age of 20, and other identified positive reactors. Whether or not to administer isoniazid becomes a judgmental matter in which several factors need to be considered, namely: 1) drug cost, 2) medical costs for supervision of drug administration, 3) drug toxicity, 4) magnitude of savings in health care costs as opposed to cost of treating, (for example, is it more costly to give isoniazid to 250 people for a year to prevent one case of tuberculosis than it is to treat that case) and finally 5) the impossible question of how much it is worth from a social and humane standpoint to prevent one case. My own judgment would be to use isoniazid in the first six categories. The seventh priority does not seem justifiable because the risk is very low and the hepatic toxicity of isoniazid sufficiently great to make its administration unwarranted. As will be readily apparent the first six priorities constitute a very important group and there isoniazid is highly effective.

Malaria

Chloroquine

Pyrimethamine — Pl. falciparum

Dapsone
Sulfonamide

Chloroquine

Primaquine, etc. — Pl. vivax and Pl. ovale

Problems:

Compliance; drug toxicity; multiple organisms; "prophylaxis" vs "suppressive treatment."

Prophylaxis of malaria is an example which is well known. The drugs are highly effective and of a low order of toxicity. When administered on a compulsory basis, compliance is a small problem.

Less familiar, perhaps, is the matter of prophylaxis against smallpox. There have been two excellent studies on the prevention of smallpox and alastrim with methisazone. These are summarized below.

Smallpox and variola minor (alastrim)

Highly effective = methisazone
(N. methylisatin-3 thiosemicarbazone)

Methisazone trials

Study	Controls/cases	Treated/cases
Madras 1963	2997/128	2283/6*
Brazil 1965	267/42	215/8**

Significance = * < 0.001 ** < 0.01

The first study was done in Madras. The control cases who did not receive the methisazone prophylaxis numbered about 3,000 and there were 128 cases of smallpox. In the treated group, there were 6 cases in almost 2300 exposed. A similar study was conducted in Brazil with similar findings. The results of both studies are statistically significant and there is little

question that this drug, although it has some undesirable side effects, could be used if we found ourselves involved in an outbreak of smallpox in a nonimmune population. This is particularly important at present because of the prevailing attitude of public health officials, namely that smallpox is a well contained disease, that it is going to be eradicated from the world very shortly and that in a very few years we will not be using smallpox vaccination at all. In the transition period or in the event that this opinion happens to be wrong, methisazone could be of great importance.

Influenza

Controlled trials in human volunteers demonstrated effectiveness of

Amantadine Hcl vs Influenza A-2

a) Decreased frequency of infection
b) Decreased severity of illness

Problems: Rapidity of diagnosis
Cost
Drug reactions

Under special circumstances amantadine is effective in preventing influenza. It has not yet been of wide usefulness. Speed of diagnosis, the generally mild nature of recent outbreaks, cost, and drug reactions have limited its use but it serves as a well documented example of antimicrobial drug prophylaxis.

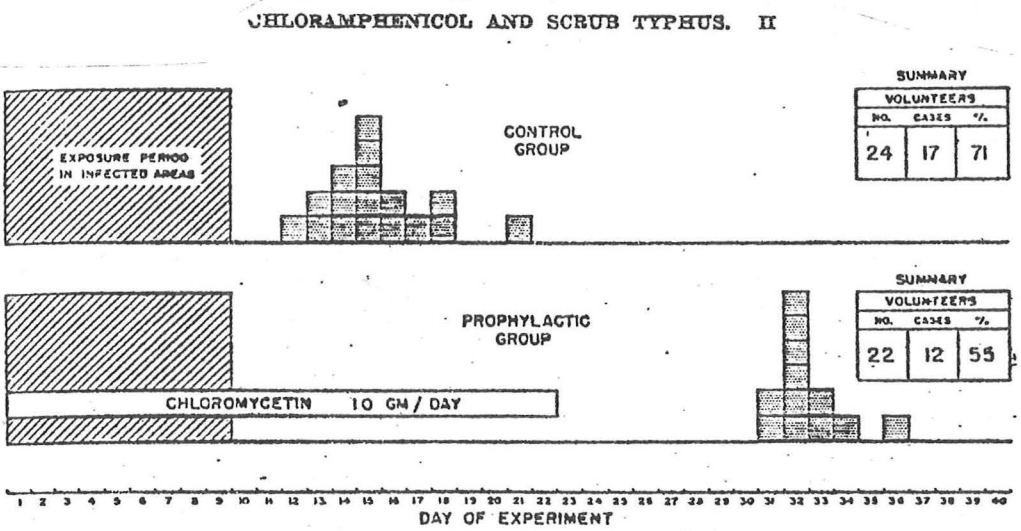

FIGURE 1. Chemoprophylactic effect of chloromycetin against scrub typhus in volunteers, test no. 1, Kuala Lumpur, 1948.

The next is a remote example but one of earliest and historically important ones. After World War II it was demonstrated that chloramphenicol could serve as effective prophylaxis against scrub typhus in the military. It will be noted in the figure however, that when chloramphenicol was given, the soldiers remained well while they were on the drug, but then many became ill when the drug was stopped. Although that seems highly undesirable the subsequent attacks were very quickly terminated without recurrence by additional administration of chloramphenicol. Thus, when used as a part of a tactical manoeuver in the military this might be very significant. At present one would obviously not use chloramphenicol, but would use tetracycline, which would presumably do the same thing.

You are familiar with the utilization of locally applied antimicrobial drugs in burns.

Burns

Sulfamylon
Silver Sulfadiazine
Gentamicin
Various antibiotics administered
by subeschar clysis

I will not go into detail about this, but I believe it is fair to say that antimicrobial drugs used locally and in some instances, systemically, have made substantial differences in recovery from burns. Of special interest are the studies of Baxter, Curreri and Marvin carried out in this institution on the control of burn wound sepsis with quantitative bacteriologic studies and subeschar clysis of antibiotics.

I will turn now to consider various areas of the use of antimicrobial drugs in surgery. It is here that most of the conflict has arisen. Before considering the individual situations I want to review with you the classification of surgical wounds. This is a standard classification in the surgical literature, which we want to refer to later.

Classification of surgical wounds
Ann. Surg. 1964

1) Clean wounds.

Non-traumatic, uninfected. No opening of bronchi, GI or GU tract. Includes "non-inflammatory" cholecystectomy, appendectomy, hysterectomy and urinary tract operations.

2) Clean contaminated.

Opening of viscera made but <u>without unusual</u> contamination.

3) Contaminated

4) Dirty

Old traumatic wounds, those involving abscesses or perforated viscera.

This classification incidentally was set up originally by a study group consisting of representatives of a number of surgical societies who were attempting to study the use of ultra violet light in the operating rooms. This was the basis for the classification of wounds in that study and it has been maintained in the surgical literature since that time. The first are clean wounds, non-traumatic, uninfected, with no opening into bronchi,

gastrointestinal or genitourinary tract. It includes so called non-inflammatory cholecystectomy, appendectomy, hysterectomy and urinary tract operations. The second is the clean contaminated wound in which an opening of one of these viscera was made without unusual contamination. The third is a contaminated wound, and the fourth is a dirty wound which is old, traumatic or involving abscesses, or perforated viscera.

First let us consider some examples of studies which have received considerable attention and which have helped give chemoprophylaxis a bad name. The next table summarizes one which has been widely quoted.

Prophylaxis in general surgery
Johnstone. Surg., Gyn-Obst. 1963

401 patients given antibiotics - Infections 24.9%
619 patients "controls" (i.e. no antibiotics) - Infections 8.7%

Problems: Cases not randomized
No description of type of cases included
"Prophylactic" drugs given post-operatively

Johnstone in 1963 reported a study of chemoprophylaxis. He included 401 general surgical patients given antibiotics. The infection rate was almost 25%. There were 619 so-called controls to whom no antibiotics were given and their infection rate was 8.7%. The obvious conclusion from this was that chemoprophylaxis was detrimental. There are some problems about this study though which are obvious now. In the first place, the cases were not randomized. There is no description of the type of case involved, but the cases are simply listed as "general surgical cases". Finally the so-called "prophylactic drugs" were given post-operatively. In subsequent experiments I believe it has been clear that this is not the optimum time to start the drugs.

Prophylaxis in general surgery

(Karl et al NEJM 1966)

Used 2 Gm methicillin and 0.5 Gm Chloramphenicol before (IM), during (IV) and after (IV) surgery.

Randomized study.

Drug	65 patients	Wound infections 18.5%
Placebo	70 patients	Wound infections 12.9%

Problems:
1) Choice of drugs
2) ? IM Chloramphenicol
3) Type of case (i.e. of "specified" cases relatively few with high risk, yet infection rate high)

Karl and his associates have published one of the early, well designed studies. I can find no real criticism of this study except for one factor which was dictated not by the study itself, but by the time at which it was conducted. It was a randomized study and the patients were followed very carefully. The patients receiving antibiotics had an 18% wound infection rate and those on placebo, 12.9%. This is not statistically significant in indicating an adverse effect of the drugs but obviously there was no benefit. The choice of drugs in this situation might be questioned retrospectively, especially the choice of methicillin. During the operation these investigators gave chloramphenicol intramuscularly and afterwards intravenously. In searching for faults in this study, one can suspect at least two possibilities. One is that staphylococcal disease is notably periodic in wound infections in hospitals. There may be times when the rate is low and other times when it is high. Thus the potential value of methicillin might be quite variable. The second thing is that intramuscular chloramphenicol probably was an ineffective drug. This was not known at that time, but it has been found subsequently to be the case. In spite of possible criticism, this was an

excellent study and does not show any advantage of chemoprophylaxis.

Next I would like to list a number of studies which I judge to be well

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Bernard and Cole Surgery 1964

Randomized study of operations on stomach, intestine, pancreaticobiliary system.

Penicillin, methicillin and chloramphenicol given preop., during and 4 hours post op.

	No. pts/infections
Controls	55/3
Antibiotics	63/16

$P < 0.01$

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controlled and well documented. Bernard and Cole in 1964 reported an excellent randomized study of operations on the stomach, intestine, pancreatic and biliary system. They used intravenous chloramphenicol, methicillin and penicillin. In their controls, there were 63 patients with 16 infections, and in those on antibiotics, 55 patients with 3 infections. These figures prove to be significant statistically. Polk and Lopez-Mayor in 1969 started the present trend of surgical studies. Their studies were simply, carefully constructed and have served as a model for a number of other studies.

Polk and Lopez-Mayor 1969 (1)

Design of study:

1) Consecutive elective operations on G.I. tract excluding elective biliary tract surgery.

2) Double-blind randomization of cases.

3) Monitored - blood and tissue drug levels, wound cultures at operation.

4) Drug = cephaloridine 1.0 Gm IM on call to OR, and 5 and 12 hours thereafter.

5) No other preop. or intraop. antimicrobials

They chose consecutive elective operations on the gastrointestinal tract, excluding biliary tract surgery. They did double-blind randomization of the cases. They monitored blood and tissue levels of drug, and wound cultures. As an aside here, it should be noted that they did cultures all the way through these operations, starting with the time they were about to close the peritoneum. They found that the cultures of the wound prior to the cutaneous closure proved to be the most significant cultures, that is, organisms found at that level correlated well with the organisms appearing later if clinical signs of infection developed. They chose cephaloridine, at that time representing the only cephalosporin compound which could be given intramuscularly and which achieved high tissue and blood levels. They gave 1 gram on call to the operating room and 5 and 12 hours thereafter and nothing else. No other drug or bowel preparation was given.

Polk and Lopez-Mayor 1969 (2)

Table I. *Frequency of wound and intra-abdominal infection among study groups.*

	Cephaloridine	*Placebo*	*P (treated-placebo)*
Double blind patients	101	98	< 0.001
Wound/intra-abdominal infections	6	29	
Determinate double blind patients	91	90	< 0.001
Wound/intra-abdominal infections	5	26	
All determinate patients	161	90	< 0.001
Wound/intra-abdominal infections	12	26	
Gastroduodenal operations*	32	36	0.001
Wound/intra-abdominal infections	0	11	
Colorectal operations*	54	50	0.001
Wound/intra-abdominal infections	4	15	

*Determinate double blinded cases.

It is worthwhile to examine these data in detail. There were 101 cases in the cephaloridine group, 98 in the placebo group which were completely within the double-blind framework. Out of those 101 treated patients there were 10 in whom all the data were not entirely complete. These are referred to as the "determinate" group, 91 in all. A similar group of 8 incomplete

cases were identified in the placebo group. There were then 90 double-blind determinate cases in the placebo group. An additional 60 cases were subsequently treated without controls, making a total of 161 treated cases. All of these data related to wound infections reveal highly significant differences between the two groups. You will note 101 treated cases with six infections compare with 98 placebo cases and 28 infections. The other groups are likewise significant. All determinate cases, as well as the individual types of surgery, i.e. gastroduodenal,and colorectal operations - in all there were significant differences in the wound infection rates.

A similar study was carried out by Brown, Cooper and Rambo in 1969.

Brown, Cooper and Rambo 1969

Controlled, prospective double-blind study. Employed cephaloridine 1.0 Gm preop. and q8h for 5-10 doses.

		No. of infections			
Treatment group	No. of patients	Wound	Pulm	GU.	Total
Placebo	92	9	6	6	21*
Cephaloridine	90	4	2	0	6*

*Significant $P < 0.01$
(Note: includes many patients with low risk)

This was a double-blind, prospective, controlled study. Cephaloridine again was the drug chosen and in this instance the drug was given slightly longer than in the previous study, that is for 48-72 hours after surgery.

The details of this group of patients are given in the Table. The difference between the two groups is significant, and an important feature of this study, in contrast with the previous one, is that this one included a large number of patients with relatively low risk. It is surprising to find major differences here, but indeed these investigators did find a statistically significant difference in infections in the two groups.

Bernard, Clark, Leather, Gray 1969

Compared IV penicillin (1 million units) and IV Cephalothin (1.0 Gm) before, during and 4 hours after surgery in potentially contaminated operations.

"Major preventable wound Sepsis"

No. pts.	Drug	Result
78	Penicillin	6
79	Cephalothin	1

Bernard and his associates have carried out a more recent study comparing penicillin to cephalothin. As a result of prior work these investigators apparently were convinced that some type of prophylaxis was at least an ethical requirement. Thus they compared penicillin with cephalothin, giving only 3 doses of each drug, one before, one during and one 4 hours after surgery. All cases were potentially contaminated operations. Many more details are given in the reference but I have listed here only what they referred to as major preventable wound sepsis. The difference is statistically significant at the 0.01 level.

An additional mode of prophylaxis needs also to be considered, namely the use of local antibiotics in surgical wounds. Certainly, local antibiotics as irrigating fluids have been utilized considerably but their effectiveness has been difficult to assess. Less common has been the local application of antibiotics in the wound itself during surgery. Hopson and his associates have published an interesting set of animal experiments related to this.

Hopson, et al.

Table 3. Results—Staphylococcus aureus *Group*

Solution	Number of Guinea Pigs with Control Infection	Number of Treated Incisions Clinically Infected	Number of Treated Incisions Bacteriologically Contaminated
Saline	25	24 (96%)	23 (92%)
Cephalothin	25	18 (72%)	12 (48%)[a]
Kanamycin	20[b]	8 (40%)[b] (31%)[c]	7 (35%)[b] (28%)[c]

[a]Two additional pigs were contaminated with *Proteus,* but no *S. aureus* was present.
[b]Results after discarding the five noninfected controls.
[c]Results if the five noninfected controls are included.

The figure refers to operations in guinea pigs in which operative incisions were infected with cultures of staphylococci. The controls developed a high rate of infection. Local cephalothin in staphylococcal infections was not effective. The local kanamycin effect was significant. More impressive are the results in a group infected with E.coli.

Table 4. Results—Escherichia coli *Group*

Solution	Number of Guinea Pigs with Control Infection	Number of Treated Incisions Clinically Infected	Number of Treated Incisions Bacteriologically Contaminated
Saline	25	18 (72%)	18 (72%)
Cephalothin	25	10 (40%)	10 (40%)
Kanamycin	19[a]	2 (11%)[a] (8%)[b]	2 (11%)[a] (8%)[b]

[a]Results after discarding the six noninfected controls.
[b]Results if the six noninfected controls are included.

Hopson, et al. J.Surg.Res. 8, 1968

The controls again have a high rate of infection, 72%. Note that both the cephalothin and kanamycin were significantly active when locally applied in the wounds, whether one judges by clinical infection or culture positivity.

There are many clinical studies in the literature related to prophylaxis with local antibiotics and it is difficult to decide in reading these

which are the best. I will present just a few.

The report of Ryan is a most remarkable study done between 1951 and 1960.

Topical penicillin for wound prophylaxis

Ryan 1967 (Study 1951-1960)

All operations were for external hernia. All performed by same surgeon. Penicillin injected deep to external oblique and in subcutaneous tissue just before skin closure. (500,000 u in adults, 200,000 in children)

	Cases	Infections	%
Control	5439	84	1.54
Test	1310	2	0.15

$P = < 0.0001$

All of these external hernia operations were done by one surgeon who used topical penicillin applied in the operative wound just before closure. This is of course a type of operation where the infection rate is usually low. Here it was 1.5% in the control group. As indicated, the infection rate was 0.15% in the treated group. Despite the fact that this is not a truly controlled randomized study, the results are interesting and impressive by virtue of the sheer numbers involved.

The report of Evans et al is of a more detailed study of local drug use in a variety of types of surgery including arterial surgery. This study was concerned with the use of cephaloridine, one gram of which was put into the subcutaneous layer of the wound before closure.

Evans et al 1974

Topical cephaloridine

	Cephaloridine		No Cephaloridine		
Wounds	No.	% infections	No.	% infections	P
Clean	79	3.8%	107	5.6%	NS
Contaminated	109	12.8%	106	38.7%	<0.001

If one examines the clean cases first, it may be seen that in them no benefit was derived from the drug. In the contaminated cases, however, there is a different picture, with a highly significant difference in the rate of wound infections.

Stoker and Ellis have compared topical ampicillin with topical penicillin and a sulfonamide in patients with operations involving opening the alimentary tract or biliary tract.

Topical ampicillin Stoker and Ellis 1972

Surgery on patients in whom alimentary or biliary tract was to be opened were randomized. Antimicrobial applied as a powder after closure of peritoneum.

Total pts/ No. infections

Ampicillin	Pen. + Sulfa.
59/4	53/11

P - < 0.01

The patients were randomized. The antimicrobial drug was applied as a powder at the closure of the peritoneum. They used ampicillin in 59 patients, and there were 4 infections. Fifty-three received penicillin and sulfonamide and were considered controls. Eleven became infected. The difference between these groups is statistically significant.

On the basis of his own experience and his review of the surgical literature, the distinguished Canadian surgeon Dr. Lloyd MacLean has summarized his views editorially.

Guidelines for use of prophylactic antibiotics and wound closure.

Editorial: Lloyd D. MacLean Canad. J. Surg. 1973

Type of operation	Antibiotic	Closure
1) Clean	0	Primary
2) Clean contaminated	+	Primary
3) Contaminated	+	Delayed primary(?)
4) Dirty	+	Delayed primary or secondary

Dr. MacLean feels that clean wounds should require no antibiotic prophylaxis and should have primary closure. He suggests that clean contaminated wounds should have antibiotics with primary closure. In contaminated wounds he recommends antibiotic prophylaxis with delayed primary closure. For dirty wounds he suggest antibiotic prophylaxis with delayed primary or secondary closure. (A subsequent contrary editorial in the same journal was published by Wright, in reference 134.)

I should like next to review a few studies of more restricted areas of surgery. Surgery on the colon and rectum always is attended by a high infection rate. Bridoux has recently published a study on "prophylaxis" which has been quoted as providing evidence against its value.

Preoperative antibiotics in Colon Surgery harmful
Bridoux, Dis Col & Rect July-Aug 1974

"A retrospective study of 100 cases of elective colonic surgery . . . once more it appeared that the use of an antibiotic was detrimental."

This review recorded a retrospective study of 100 cases of elective forms of surgery on the bowel. The conclusion was that once more it appeared that the use of an antibiotic was detrimental.

TABLE 3. *Preoperative Preparation*

	Number of Patients
Mechanical (98)	
Restrictive diet only	2
Laxatives only	0
Enemas only	3
Diet and enemas	16
All three	77
Antibiotic (80)	
Oral only	72
Systemic only	3
Both routes	5
Single drug	50
Sulfasuxidine	14
Neomycin	13
Kanamycin	14
Cephalothin	6
Tetracycline	3
Combination of drugs	30

Bridoux 1974

This table lists the different types of prophylaxis used and I believe the very number of variations in 100 patients make analysis of these colon and rectal cases virtually impossible.

TABLE 7. *Effects of Preoperative Preparation on Complications*

	Per Cent with Complications
Mechanical preparation (20 cases)	5
Mechanical and antibiotic preparation (80 cases)	22
Sulfasuxidine	28
Kanamycin	35
Neomycin	23
Cephalothin	0
Tetracycline	33
Sulfasuxidine and neomycin	23

Bridoux 1974

This table is a listing of the percentage of complications. As you will see, of the 20 patients who had mechanical preparations, 5% had complications. The infection rates were high in the other groups, (22% to 35%) except for the cephalothin group which was too small to permit analysis. I believe that even a casual analysis of this study points up the problems in interpreting the results.

The next table is from another study which raises a very important question about prophylaxis.

Herter and Slanetz
Surgery, Gynecology & Obstetrics · July 1968

TABLE I.—INCIDENCE OF SUTURE LINE RECURRENCE IN RELATION TO THE TYPE OF INTESTINAL PREPARATION

Group	No.	Suture line recurrences	
		No.	Per cent
Ileocolectomy			
Prepared	143	2	1.4
Unprepared	75	0	0
Colectomy			
Prepared	257	5	1.9
Unprepared	93	2	2.2
Anterior Resection			
Prepared	158	15	9.5
Unprepared	64	1	1.6
Total	790	25	3.2

Herter and Slanetz reported on the frequency of recurrence in operations on cancer of the colon. These authors compared those patients receiving mechanical bowel preparation with a group receiving both mechanical preparation and antimicrobials, usually a non-absorbed sulfonamide or neomycin. These are data on the incidence of suture line recurrence in relation to the type of preparation used. The most important figure here is that in anterior resection. Those patients who were prepared with antibiotics had a 9.5% suture line recurrence and those unprepared 1.6%. This is a result difficult to interpret. It is supported by at least two studies in experimental animals but to my knowledge has not been reported in other

human studies. It does raise a disturbing question, however, in this particular type of surgery.

There are other studies on colon preparation which relate directly to rates of infection.

Rosenberg et al Brit. J. Surg. 1971

Bowel prep. in patients undergoing major bowel surgery, mainly for neoplasms.

Treatment	No. pts.	No. Sepsis	% Sepsis
Mechanical prep.	45	29	64.4%
Mechanical prep. plus drug*	83	31	37.3%

*phthalylsulfathiazole with or without neomycin.

Rosenberg and associates compared mechanical versus mechanical and drug bowel preparations in patients undergoing major bowel surgery, mainly for neoplasms. There were significant differences in the rates of sepsis, although the rates are high in both groups.

In connection with bowel surgery, I should like to report in some detail one study which I feel is extremely important. Nichols and his co-workers elected the type of preparation for bowel surgery detailed here.

TABLE 1. *Neomycin-Erythromycin Base Colon Preparation*

Day 1:	Low residue diet
	Bisacodyl, 1 capsule orally at 6 p.m.
Day 2:	Continue low residue diet
	Magnesium sulfate, 30 ml. 50% solution (15 Gm.) orally at 10:00 a.m., 2:00 p.m. and 6:00 p.m.
	Saline enemas in evening until return clear
Day 3:	Clear liquid diet; supplemental IV fluids as needed.
	Magnesium sulfate, in dose above, at 10:00 a.m. and 2:00 p.m.
	No enemas
	Neomycin 1 Gm. } p.o. at 1:00 p.m.,
	Erythromycin base 1 Gm. } 2:00 p.m. and 11:00 p.m.
Day 4:	Operation scheduled at 8:00 a.m.

Nichols, et al. Ann.Surg. 1973

They started out with a low-residue diet and a laxative on Day 1. They continued on day two with the diet and another laxative, together with saline enemas. On the third day a clear liquid diet was given with three doses of neomycin and erythromycin. Neomycin incidentally has been used many times and has not been regarded as very effective by itself. A major difference between this and other regimens is the use of erythromycin, which it was hoped would reduce the number of anaerobes in the bowel. These results show what happened to the bacterial flora in the 10 patients who were studied in detail.

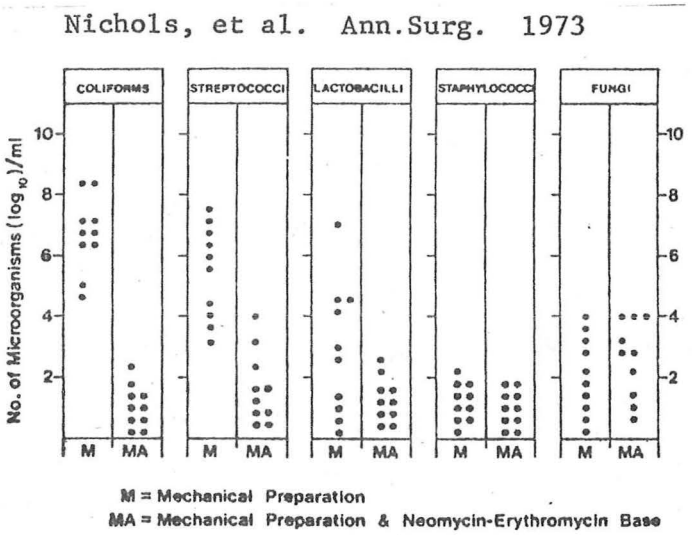

FIG. 1. Effect of neomycin-erythromycin on the aerobic colonic microflora. Cultures showing no growth are below the limit of sensitivity of our bacteriologic methods and are indicated in the shaded area (< 2 logs).

Ten controls and 10 patients received antibiotics. The coliforms were markedly reduced in numbers. Streptococci were markedly reduced. Lactobacilli were also reduced. Staphylococci were usually not detectable. Fungi were unchanged.

Nichols,et al. Ann.Surg 1973

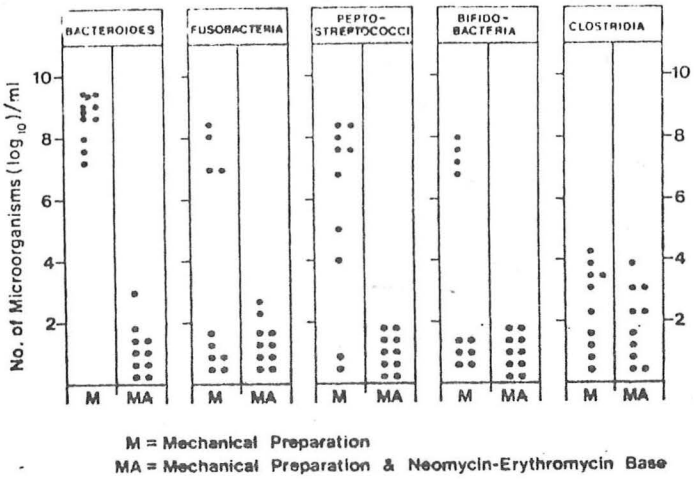

FIG. 2. Effect of neomycin-erythromycin on the anaerobic colonic microflora. Cultures showing no growth are below the limit of sensitivity of our bacteriologic methods and are indicated in the shaded area (< 2 logs).

The various anaerobes were conspicuously changed. Bacteroides, considered the most important species, were markedly reduced. Fusobacteria were also reduced. Streptococci were markedly reduced as were bifidobacteria. Clostridia remained unchanged.

These investigators initially studied 10 treated and 10 control patients. They had no infections in the first 10 who had the preparation described. They had 3 serious infections in the 10 who were not prepared. They decided at that time to conclude the controlled study. They went on however, to study this preparation in a larger series of patients, although they did not include controls.

TABLE 3. *Types of Preoperative Bowel Preparations and Related Infections*

Preoperative Preparation	Number of Cases	No. of Wound Infections
Neomycin-Erythromycin base	69	0
Mechanical preparation only	16	3
Neomycin	8	1
Neomycin-Sulfathalidine	2	1
Kanamycin	2	0
Kanamycin-Sulfathalidine	1	0
	98	5

Nichols, et al. Ann. Surg. 1973

Despite the lack of controls, considering the usual very high rate of infection in such patients, these results are very important to consider. It will be noted in the table that the infection rate in 98 patients who got this type of prophylaxis was very low.

Washington et al. Ann. Surg. 1974

Prospective, randomized, double-blind study on preoperative antibiotics.
(all patients had mechanical prep)

Drug	No. Pts.	Wound infections
1) Placebo	63	27 (41%)
2) Neomycin	68	28 (40%)
3) Neomycin/Tetracycline	65	3 (4.6%)

Differences: 3 vs 1, 3 vs 2 = $P < 0.01$

Washington and his associates have reported a similar study with neomycin and tetracycline. All of the patients had mechanical bowel preparation. As may be seen, neomycin was ineffectual in itself. The two drugs together had a highly significant effect, presumably a major portion of which was related to the effect of tetracycline on anaerobes.

In this area also, various topical antibiotics have been studied.

Topical ampicillin in appendectomy
Rickett and Jackson. Brit. Med. J. 1969

Double-blind study. Included all appendectomies except patients hypersensitive to penicillin.

	Number of Cases/Infections
Placebo	66/16
Ampicillin	64/2
	$P = < 0.01$

This table is a double-blind study of appendectomies as reported by Rickett

and Jackson using just topical ampicillin as prophylaxis. Again the infection rate was significantly reduced.

Turning now to a second special area, that of cesarean section, Gibbs et al reported in 1973 on the use of penicillin and kanamycin in prevention of wound infection and endometritis.

Prophylaxis in Cesarean Section
Gibbs et al. Am. J. Obst. Gyn. 1973

Ampicillin and kanamycin immediately pre-op., and 2 and 8 hours post-op.

	Total	Wound Infec.	Endometritis
Placebo	62	10	28
Drug	67	0*	13**

Significance *P = < 0.001
**P = < 0.01

As may be seen there was a significant difference between the two groups, both in wound infections and in the occurrence of endometritis.

Another recent study on cesarean section is reported by Moro and Andrews.

Prophylaxis in Cesarean Section
Moro and Andrews, Obst. & Gyn. 1974

Cephalothin followed by Cephalexin for 5 days. (Double-blind study)

Morbidity = temp. > 100^4 F. twice after 48 hours.

	Total/Febrile
Placebo	74/20
Antibiotic	74/6

Their patients received cephalothin pre-operatively followed by cephalexin by mouth for 5 days post-operatively. This again was a double-blind study.

They recorded morbidity as a temperature over 100.4 twice after the first 48 hours. As may be seen, there were twenty instances of morbidity in the control group and 6 in the treated group. This is a statistically significant difference.

Allen et al have reported on the use of cephalothin prophylaxis in a technique similar to that described previously.

Allen, et al Obstet. & Gyn. 1972

Cephalothin just before, during and 72 hours after surgery.

Cases	Total Abd. Hysterectomy		Total Vaginal Hysterectomy	
	Drug	Placebo	Drug	Placebo
Total	85	83	48	50
% morbid	14.1*	41	4.1**	50

* $P < 0.001$
** $P < 0.001$

They reported on total abdominal hysterectomy and on total vaginal hysterectomy. In this study, the morbidity was recorded essentially the same as in the previous study mentioned. The prophylactic antibiotic again appeared highly effective in both groups. In abdominal hysterectomy the rates were 14% and 41% respectively in the treated and in the placebo group. With vaginal hysterectomy the rate was 4% in those who received drugs, and 50% in the placebo group.

Another excellent study was reported by Ledger and his associates. This study employed cephaloridine on the day of surgery in vaginal hysterectomy in premenopausal women.

Ledger, et al Am. J. Obstet. & Gyn. 1973

Prophylactic cephaloridine (3.0 Gm on day of surgery) in vaginal hysterectomy in premenopausal women.

Postoperative morbidity

	Antibiotic	Placebo
Total	50	50
Urinary tract infection	9	14
Other	6	4
Pelvic infection	4	17

Total = P = < 0.025
Pelvic = P = < 0.005

Although the infection rates here were not as high in the control cases as in some of the prior studies, the results were significant.

Another area of special interest is in orthopedic surgery. In this particular group of patients, there is normally a low infection rate, but despite this fact, the situation is such that infection is a particularly catastrophic event, especially when prostheses are involved.

Prophylactic antibiotics in clean orthopedic surgery.
Pavel et al. J.Bone & Joint Surg. 1974

Cephaloridine 1.0 Gm I.M. preop and 1.0 Gm IV over 4 hour period during and after surgery.

	Total Cases/infections
Placebo	704/35 (5%)
Antibiotic	887/25 (3.0%)

p = 0.025

The study of Pavel et al suggests that even a low infection rate may be reduced by a prophylactic antibiotic. In this instance the rate was

reduced from 5% to 3%.

There are a number of other situations which I will not discuss in detail.

Miscellaneous uses of antimicrobial drug prophylaxis of varying effectiveness and utility.

Prevention of infective endocarditis
Cardiac surgery
Pacemakers
Scribner shunts
Ventricular shunts

Bacillary dysentery
Chronic bronchitis

Cystic fibrosis
CSF rhinorrhea

Post-coital urinary tract infections.

Some of these are listed in this table and references are given in the bibliography. Antibiotics are routinely used in an attempt to prevent infective endocarditis in patients with certain congenital or acquired heart diseases. Unfortunately it is true that now 35 years after the introduction of penicillin, we are uncertain of its value. It would be considered poor practice not to use it, however, as it is so well established.

The studies in cardiac surgery have varied considerably in their approach and it is difficult to assess them. One study which started out as a truly controlled study is of special interest. This was a very carefully designed study by a group of investigators at Vanderbilt, reported by Goodman and his associates. (1968) Before the study was very well underway two patients in their control group not receiving any antibiotics developed pneumococcal endocarditis. They felt they could no

longer continue the control study. The rate of infection with various regimens studied was not apparently influenced by the drugs. Prophylaxis of one type or another is routinely practiced in cardiac surgery but the studies remain difficult to assess.

Prophylaxis has been demonstrated to be of value in certain special situations such as the use of temporary pacemakers. Prophylaxis has been used considerably in Scribner shunts and is probably effective at least in preventing staphylococcal disease. In ventriculoatrial or ventriculoperitoneal shunts the value of prophylaxis is very questionable. In bacillary dysentery there are few opportunities to use prophylaxis, but it is apparently effective.

Prophylaxis in chronic bronchitis during winter months has also been considered to be helpful. Prophylaxis in cystic fibrosis is of minimal if any value. In patients with cerebrospinal fluid leaks, prophylaxis may have some effect, but again it is not highly effective.

Another recent study reports on a small group of women who persistently had urinary tract infections after sexual intercourse. (Vosti 1975) I think the evidence presented is good that with various antimicrobials one can prevent this type of infection.

In conclusion, it may be said that in spite of the many problems attendant on the use of antimicrobial drugs for prophylaxis and despite the fact that they are very imperfect, the evidence at present suggests that we need to reevaluate our more or less conventional opinions as to just where we should use them and where we shouldn't. There are a number of areas in which prophylaxis has been clearly demonstrated to be effective. There are a number where it is clearly not effective. There is also a large

intermediate group where we need considerably more information, especially in those cases involving contaminated and potentially contaminated surgical wounds, where I believe the evidence is accumulating that chemoprophylaxis of one sort or another is of value. Cephalosporin compounds certainly appear worthy of careful examination in this respect. Cephaloridine has been studied most extensively but because of toxicity should not be used. Only one of the cephalosporins, namely cephradine,can be used by the intravenous, intramuscular and oral routes, and thus may have certain theoretical advantages, although experience with it is limited.

It is to be hoped that controlled studies of prophylaxis will be pursued to help clarify the many remaining questions.

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