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Calculated Empiric Antimicrobial Therapy for Mixed Surgical Infections*

Summary: In acute life-threatening surgical infections requiring immediate institution of antimicrobial therapy before bacteriological results are available, antibiotic treatment must be empiric. For best efficacy a more sophisticated form of empiric therapy is offered, termed calculated antibiotic therapy (CAT). Calculated antibiotic therapy requires consideration of a) typical bacterial spectrum; b) bacterial pathogenicity and synergism; c) antibacterial concentrations at the site of infection; d) toxicity and adverse effects; e) interaction with immune response; and f) results of properly conducted trials. Intraabdominal infections are used as an example here to assess the efficacy of clinically used cephalosporins and penicillins for determination of calculated antibiotic therapy. CAT identifies *Escherichia coli* and *Bacteroides fragilis* as the most important pathogens for intraabdominal infections and determines the most effective antibiotics at the tissue breakpoint, which is defined as the minimal concentration maintained for more than 90% of the dosage interval period at the infected tissues. At the tissue breakpoint calculated antibiotic therapy identifies cefotaxime-generation cephalosporins to be fully (100%) active against the most important aerobic pathogen *E. coli* and metronidazole as fully active against the important obligate anaerobe *B. fragilis*. Calculated antibiotic therapy becomes relatively important, since impeccably controlled clinical therapeutic trials as a foundation for therapy are rarely published.

Zusammenfassung: *Kalkulierte empirische antimikrobielle Therapie für Mischinfektionen in der Chirurgie.* Die Therapie akuter lebensbedrohlicher chirurgischer Infektionen erfordert eine empirische initiale antimikrobielle Chemotherapie. Die kalkulierte antimikrobielle Chemotherapie (CAT) kann als eine Verbesserung der rein empirischen Therapie betrachtet werden. Sie erfordert, daß folgende Kriterien berücksichtigt werden: 1. Typisches Spektrum der Infektionserreger, 2. Pathogenität der Bakterien und deren infektiogener Synergismus, 3. Konzentrationen des Antibiotikums am Ort der Infektion, 4. Nebenwirkungen, 5. Störungen der Immunabwehr, 6. Ergebnisse sauberer kontrollierter klinischer Studien. Am Beispiel der intraabdomionalen Infektionen wird die Leistungsfähigkeit der CAT mit klinisch wichtigen Penicillinen und Cephalosporinen untersucht. Die CAT identifiziert *Escherichia coli* und *Bacteroides fragilis* als die wichtigsten Infektionserreger der bakteriellen Peritonitis. nach CAT wird ein Tissue-Breakpoint als die Konzentration definiert, die während 90% des Dosisintervals am Ort der Infektion realisiert bleibt. Die effektivsten Antibiotika nach CAT sind Cefotaxim-Generation Cephaloporine, durch die 100% aller *E. coli* Bakterien (n = 10 413) am Gewebe-Breakpoint erfaßt werden und Metronidazol, durch das 100% aller obligaten Anaerobier der Spezies *B. fragilis* (n = 2345) bei Gewebe-Breakpoint Konzentrationen erfaßt werden. CAT gewinnt an Bedeutung, weil sich gezeigt hat, daß kontrollierte Studien mit Antibiotika nur selten qualitativ ausreichende Informationen enthalten, um als Therapiegrundlage verwertet werden zu können.

Introduction

Surgical infections are primarily treated by incision and drainage according to the classical principle, *"ubi pus, ibi evacua."* This reduces bacterial inoculum and enhances the host's ability to perform bacterial killing and to phagocytose necrotic and toxic material. Many surgical infections are definitively treated without antimicrobial agents. The most highly lethal and invasive surgical infections require the addition of antibiotic therapy, since bacteria in these situations have often spread systemically and are thus beyond the scope of operative management. In the pre-antibiotic era, gram-positive cocci were the major pathogens responsible for much morbidity and mortality due to surgical infections. *William Altemeier,* commenting about surgical infections before 1930, stated, "Staphylococcal, streptococcal and pneumococcal infections were commonly seen, and frequently became invasive. Recovery was infrequent, and mortality was approximately 90%" [1].

The discovery of penicillin in 1929 [2] led to a dramatic improvement of therapeutic results in streptococcal and staphylococcal infections. A remarkable reduction in the death rate was achieved, and today death from a streptococcal infection is extremely rare. This extraordinary success is due to the fact that from the very beginning penicillin killed 100% of group A streptococci at concentrations easily achieved in tissue. Penicillin

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* See also *Aprahamian, C.* and *Wittmann, D. H.:* Operative management of intraabdominal infection. Infection 19 (1991) 453–455.

retains its absolute effectiveness on these streptococci to this day. Staphylococci and other bacteria, however, have enzymes such as β-lactamases that destroy penicillin's β-lactam ring and thus its antibacterial potency. Consequently, penicillin-resistant strains have been selected through therapy and have become a therapeutic challenge [3]. The development of semisynthetic penicillins resistant to penicillinases has allowed further progress in the control of staphylococci.

In spite of the success seen in gram-positive surgical infections after the availability of penicillin, gram-negative infections originating from the gastrointestinal tract, for example, remained a tenacious problem. These infections are usually of mixed anaerobic/aerobic type with a predominance of gram-negative bacteria. Penicillin has little effect against gram-negative bacteria, and infections due to these organisms remain a therapeutic problem. The development of semisynthetic penicillins did not substantially improve the outcome.

Many other factors contribute to this therapeutic dilemma. Most importantly, the bacteria involved are difficult to isolate. Consequently, the true etiologic agents often remain obscure, making specific or directed treatment impossible. Most surgical infections, including but not limited to intraabdominal infections, present as an acute illness, and antibiotics must be given without confirmation of the target microorganisms and their susceptibility. Furthermore, in polymicrobial infections it may be difficult to identify the true pathogenic microorganisms and to differentiate such organisms from mere contaminants.

Bacteriological culturing and sensitivity testing are time-consuming processes and results are clinically available only after days, which is too late for initiating an effective directed treatment in a timely fashion; thus empiric therapy is usually initiated. To further structurally improve empiric antibiotic therapy, the concept of calculated chemotherapy was developed. It is based on the knowledge gained in previous studies and allows selection of those antimicrobial agents yielding the highest likelihood of success with empiric therapy. Calculated antibiotic therapy is presented using intraabdominal infections as an example.

Calculated Antibiotic Therapy

Selection of the ideal antimicrobial agent for calculated antibiotic therapy requires several pieces of information:
a) The spectrum of pathogens typical for the disease at hand.
b) The quality of each infectious organism, i. e., the virulence, and the potential for synergism or antagonism between bacterial species.
c) The ultimate concentration of the antimicrobial agent at the site of infection (tissue breakpoint), and the proportion of the pathogens killed at this concentration.
d) The potential for adverse effects resulting from antibiotics.
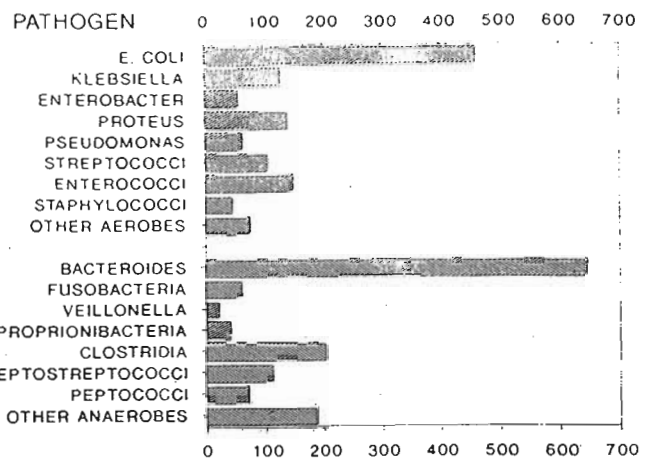

Figure 1: Bacteriology of intraabdominal infections: isolates from a total of 900 cases from six independent studies.

e) The possibility of interactions of antimicrobial agents with host defense mechanisms and wound healing.
f) Results of impeccably controlled clinical trials.
This information should be obtained from controlled clinical trials. The results of such trials, however, have been shown to be of little help when critically assessed to determine their applications to the problem in the immediate clinical situation [4]. This emphasizes the need for a more sophisticated empiric treatment with foundations other than manipulated controlled trials. Calculated antibiotic therapy may be such an alternative.

Typical Spectrum of Pathogens

Results from clinical isolates in previous studies of intraabdominal infection can provide a typical spectrum of pathogens likely to be encountered in the majority of cases. While intraabdominal infections are polymicrobial, there is a clear predominance of certain organisms in all studies with good bacteriological technique [5–10]. Among aerobes, gram-negative bacilli are most common, with *Escherichia coli* being most prevalent. Among the anaerobes, *Bacteroides* species clearly predominate, followed by clostridia and peptococci (Figure 1). These findings clearly point to *E. coli* and *Bacteroides fragilis* as main targets for antimicrobial chemotherapy.

Pathogenicity and Synergism

The virulence of different bacteria can be demonstrated utilizing well known animal models [6]. Intraabdominal infection is a biphasic disease and may be replicated by implantation of feces in experimental animals. The first stage, known as the peritonitis stage, occurs during the first week. Mortality is high, and most animals have blood cultures poisitve for *E. coli*. Peritoneal exudate, when cultured, also grows primarily *E. coli*. In the second week, known as the abscess stage, mortality is low to nil and blood cultures are negative. During this phase,

intraperitoneal abscesses often form and, when cultured, produce a predominance of obligate anaerobes.

Synergistic activity of the bacteria in intraabdominal infection may be demonstrated by intraperitoneal challenge with pure cultures of various bacteria. *E. coli*, when injected at concentrations greater than $10^{7.1}$, results in high mortality but no abscess formation in survivors. The same results were obtained when endotoxin only was used. Gram-negative obligate anaerobes (e. g., *B. fragilis* or *Fusobacterium varium*), when injected alone in concentrations four times greater, cause no mortality and no abscess. The same is true for enterococci. However, the combination of low concentrations of *E. coli* and *B. fragilis* mimics the full picture of intraabdominal infection seen following fecal challenge and results in the typical mortality with abscesses in all survivors. Enterococci did not cause disease when implanted alone, and when combined with *B. fragilis*, were able to induce abscesses but no mortality.

These examples demonstrate that not only must the quantity of bacteria be studied but also the pathogenic interrelationships between bacteria. Clearly, the key to management of intraabdominal infection is elimination of *E. coli*. In addition, obligate anaerobes must be killed because of the potential for synergism with otherwise non-pathogenic organisms such as enteroccoci. The pathogenicity of clostridia and anaerobic cocci is also remarkable but will not be discussed here. Gram-positive anaerobes, however, appear to rank next in importantce as organisms to be respected.

Antibacterial Activity at the Site of Infection

The bacterial location for the site of pathology in intraabdominal infections is the peritoneal cavity, i. e. tissue rather than blood. Therefore, bactericidal activity must be concentrated within the infected tissue, i. e. the peritoneal cavity for peritonitis. Consequently, it is important to select antibiotics capable of reaching the infected tissues in concentrations sufficient to kill the pathogenic bacteria. This can be verified by determining tissue fluid concentrations of antimicrobial agents. Agents capable of reaching levels in excess of the minimal inhibitory concentration (MIC) or the minimal bactericidal concentration (MBC) for the likely pathogens should be selected.

Peritoneal fluid concentrations of clinically used cephalosporins and penicillins were reported previously [11, 12]. Their minimal concentration maintained for more than 90% of the dosage interval period at the infected tissues may be regarded as the tissue breakpoint (Figure 2). This concentration may be compared to the MICs of antimicrobial agents for the respective pathogens. Information about the MICs of most antibiotics has been published from studies utilizing standardized techniques and an inoculum of 10^6. The data from 104 such publications has been used to determine the proportion of pathogens for which the MIC is less than the tissue breakpoint [12–14].
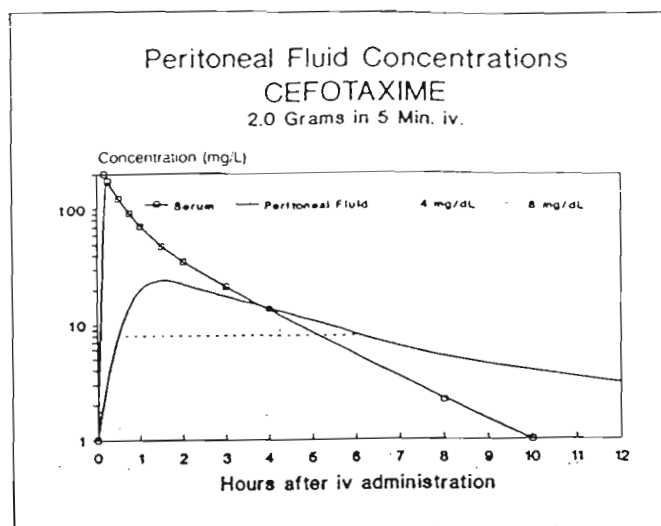

Figure 2: Serum and peritoneal fluid concentrations following intravenous bolus injection of 2 g of cefotaxime – sodium. A concentration of 8 mg/l is maintained for about 6 h (dotted line). A concentration of 4 mg/l is maintained for about 11 h at the site of infection. (Curves based on NONLIN pharmacokinetic calculations of 92 serum samples and 63 peritoneal fluid samples from 8 patients, and assayed microbiologically.)

These studies showed that the MICs of all third-generation cephalosporins such as cefotaxime, ceftazidime and moxalactam were less than the tissue breakpoints for 10,413 strains of *E. coli* tested (Figure 3). It is surprising that of the extended-spectrum penicillins, piperacillin and mezlocillin yielded tissue breakpoints greater than the MICs for only 62% of strains of *E. coli*. Second-generation cephalosporins were able to inhibit bacterial growth of *E. coli* at percentages of 81% for cefoxitin, 76% for cefuroxime and 87% for cefoperazone.
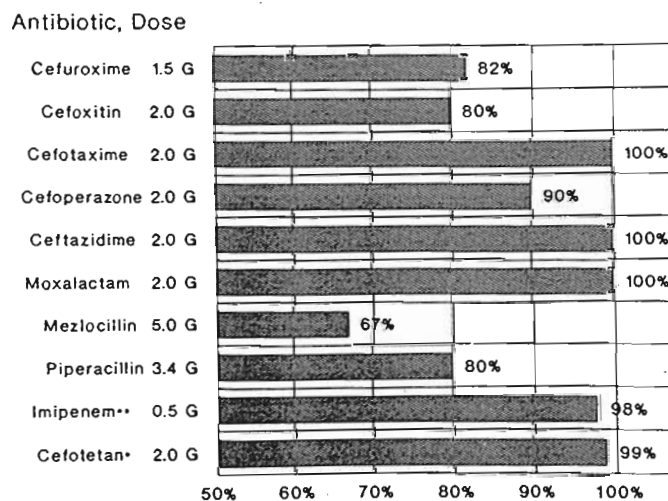

Figure 3: Percent of MICs of 10,413 *Escherichia coli* which are inferior to the tissue fluid concentrations (tissue breakpoint) measured following administration of various antibiotics.

Antibiotic, Dose

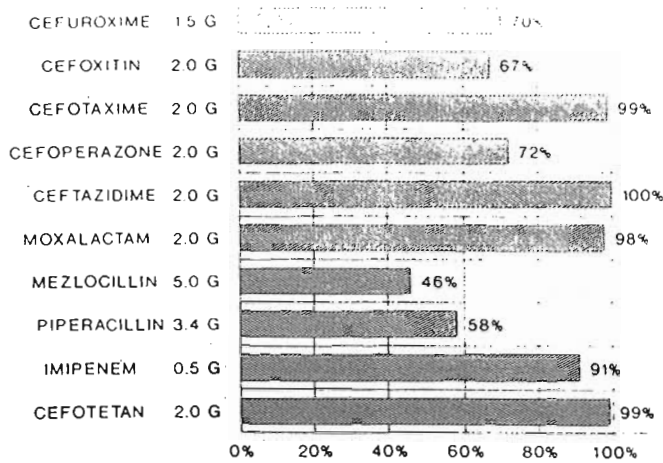| Antibiotic	Dose	Percent
CEFUROXIME	1.5 G	70%
CEFOXITIN	2.0 G	67%
CEFOTAXIME	2.0 G	99%
CEFOPERAZONE	2.0 G	72%
CEFTAZIDIME	2.0 G	100%
MOXALACTAM	2.0 G	98%
MEZLOCILLIN	5.0 G	46%
PIPERACILLIN	3.4 G	58%
IMIPENEM	0.5 G	91%
CEFOTETAN	2.0 G	99%

0% 20% 40% 60% 80% 100%

Figure 4: Percent of MICs of 5,279 *Klebsiella* spp. which are inferior to the tissue fluid concentrations (tissue breakpoint) measured following administration of various antibiotics.

Antibiotic, Dose

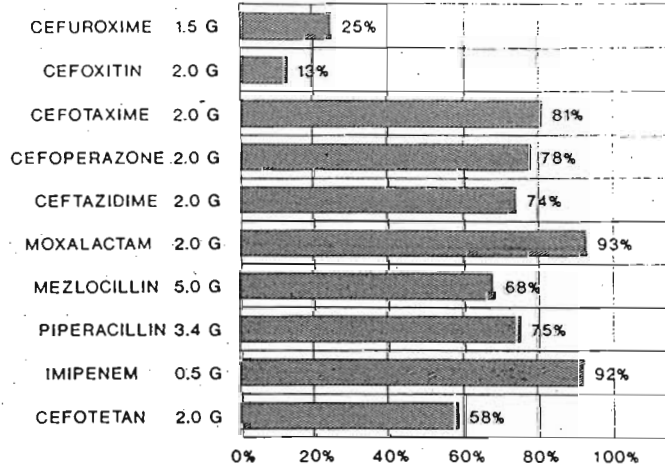| Antibiotic	Dose	Percent
CEFUROXIME	1.5 G	25%
CEFOXITIN	2.0 G	13%
CEFOTAXIME	2.0 G	81%
CEFOPERAZONE	2.0 G	78%
CEFTAZIDIME	2.0 G	74%
MOXALACTAM	2.0 G	93%
MEZLOCILLIN	5.0 G	68%
PIPERACILLIN	3.4 G	75%
IMIPENEM	0.5 G	92%
CEFOTETAN	2.0 G	58%

0% 20% 40% 60% 80% 100%

Figure 5: Percent of MICs of 3,180 *Enterobacter* spp. which are inferior to the tissue fluid concentrations (tissue breakpoint) measured following administration of various antibiotics.

Antibiotic, Dose

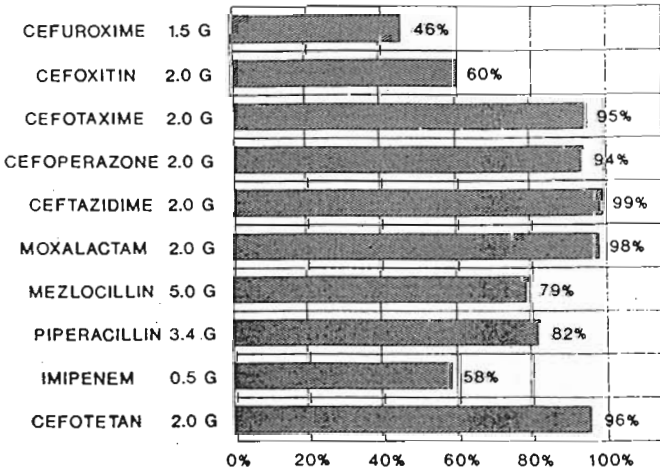| Antibiotic	Dose	Percent
CEFUROXIME	1.5 G	46%
CEFOXITIN	2.0 G	60%
CEFOTAXIME	2.0 G	95%
CEFOPERAZONE	2.0 G	94%
CEFTAZIDIME	2.0 G	99%
MOXALACTAM	2.0 G	98%
MEZLOCILLIN	5.0 G	79%
PIPERACILLIN	3.4 G	82%
IMIPENEM	0.5 G	58%
CEFOTETAN	2.0 G	96%

0% 20% 40% 60% 80% 100%

Figure 6: Percent of MICs of 6,566 *Proteus* spp. which are inferior to the tissue fluid concentrations (tissue breakpoint) measured following administration of various antibiotics.

Antibiotic, Dose

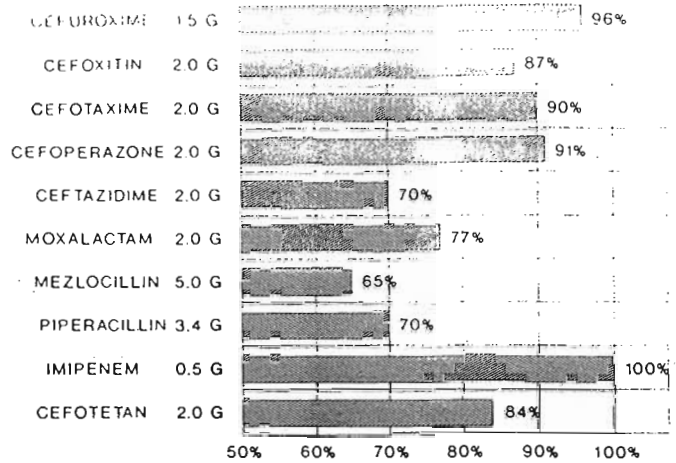| Antibiotic	Dose	Percent
CEFUROXIME	1.5 G	96%
CEFOXITIN	2.0 G	87%
CEFOTAXIME	2.0 G	90%
CEFOPERAZONE	2.0 G	91%
CEFTAZIDIME	2.0 G	70%
MOXALACTAM	2.0 G	77%
MEZLOCILLIN	5.0 G	65%
PIPERACILLIN	3.4 G	70%
IMIPENEM	0.5 G	100%
CEFOTETAN	2.0 G	84%

50% 60% 70% 80% 90% 100%

Figure 7: Percent of MICs of 4,270 strains of *Staphylococcus aureus* which are inferior to the tissue fluid concentrations of various antibiotics.

Antibiotic, Dose

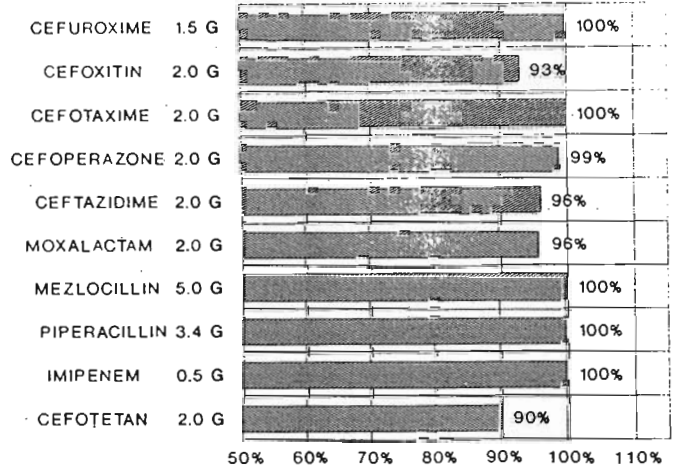| Antibiotic	Dose	Percent
CEFUROXIME	1.5 G	100%
CEFOXITIN	2.0 G	93%
CEFOTAXIME	2.0 G	100%
CEFOPERAZONE	2.0 G	99%
CEFTAZIDIME	2.0 G	96%
MOXALACTAM	2.0 G	96%
MEZLOCILLIN	5.0 G	100%
PIPERACILLIN	3.4 G	100%
IMIPENEM	0.5 G	100%
CEFOTETAN	2.0 G	90%

50% 60% 70% 80% 90% 100% 110%

Figure 8: Percent of MICs of 1,049 streptococci which are inferior to the tissue fluid concentrations (tissue breakpoint) measured following administration of various antibiotics.

Antibiotic, Dose

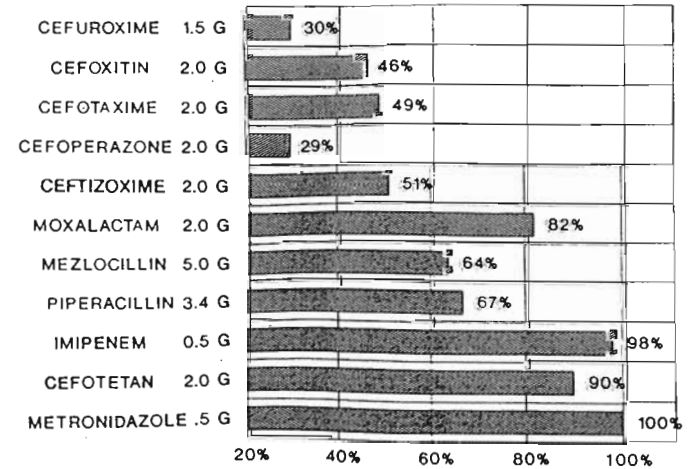| Antibiotic	Dose	Percent
CEFUROXIME	1.5 G	30%
CEFOXITIN	2.0 G	46%
CEFOTAXIME	2.0 G	49%
CEFOPERAZONE	2.0 G	29%
CEFTIZOXIME	2.0 G	51%
MOXALACTAM	2.0 G	82%
MEZLOCILLIN	5.0 G	64%
PIPERACILLIN	3.4 G	67%
IMIPENEM	0.5 G	98%
CEFOTETAN	2.0 G	90%
METRONIDAZOLE	.5 G	100%

20% 40% 60% 80% 100%

Figure 9: Percent of MICs of 2,345 *Bacteroides fragilis* strains which are inferior to the tissue fluid concentrations (tissue breakpoint) measured following administration of various antibiotics.

Similar results were obtained with 5,279 strains of *Klebsiella* spp. (Figure 4), with tissue breakpoints found to be higher than 55% of the MICs of mezlocillin, 67% of cefoxitin, 70% of cefuroxime, 72% of cefoperazone, 78% of piperacillin, and more than 99% of those of the third-generation cephalosporins. None of the antimicrobials agents was able to inhibit growth of all 3,180 strains of *Enterobacter* spp. (Figure 5), of all 6,566 strains of *Proteus* spp. (Figure 6), or of all 4,270 *Staphylococcus aureus* strains (Figure 7), but most could inhibit the 1,049 streptococci tested (Figure 8). Against anaerobes, especially the β-lactamase-producing strain of the bacteroides, the cephalosporins are less active (Figure 9).

These studies clearly indicate that antibiotic therapy of intraabdominal infection requires a combination of a cefotaxime-generation cephalosporin with an antimicrobial agent specific for anaerobes. The most active and reliable compound against anaerobes is metronidazole. It has a half-life of 8 h, requiring dosage intervals of not less than 12 h [15]. With such a combination of antimicrobial agents, all important pathogens of intraabdominal infections are likely to be eliminated.

While cefotaxime totally covers the pathogenically most important aerobe *E. coli* at the site of infection, metronidazole is 100% active against the most important obligate anaerobe, *B. fragilis*. This full activity is comparable to the full activity of penicillin against streptococci mentioned earlier. Development of resistance, therefore, is unlikely to occur. Remarkably, ten years after its introduction, cefotaxime retains 100% activity against *E. coli* without emergence of clinically significant resistant strains. In this sense cefotaxime represents a real innovation in antibacterial chemotherapy analogous to the discovery of penicillin and its continued absolute effectiveness against group A streptococci.

Adverse Effects of Antimicrobial Agents

Because patients with intraabdominal infection are potentially dehydrated due to fluid shift into the peritoneum and because of endotoxemia, their renal function may be impaired early in the course of the disease. In these circumstances, additional insult caused by the antibacterial agents themselves cannot be tolerated unless there is no alternative. Aminoglycosides are no longer favored because of their potential nephrotoxicity, which became evident in clinical trials with intraabdominal infections in which significantly higher incidences of renal impairment where found in the aminoglycoside groups as compared to treatment groups who received other antimicrobial agents [16, 17]. Clindamycin's activity against anaerobes is good but inferior to that of metronidazole. It might be used in combination with the third-generation cephalosporins when staphylococci are of concern. Clindamycin, however,

has been associated with frequent occurrence of pseudomembranous colitis in association with the overgrowth of *Clostridium difficile*.

Interaction with Host Defense

Certain antimicrobial agents which have been used in intraabdominal infection may have adverse effects on host defense mechanisms and wound healing [18–20]. This includes chloramphenicol, which causes dose-related bone marrow suppression and the occasional occurrence of aplastic anemia. Some of the cephalosporins, notably moxalactam and cefoperazone (both of which have the methylthiotetrazole side chain structure), may contribute to coagulopathy and post-operative hemorrhage. Almost all antimicrobial agents interfere with cellular and humoral host defense, a fact which is critical in surgical infections where healing of a large wound requires these processes [15–17].

Truth in Controlled Clinical Trials

Much of the information dicussed in the preceding sections is based on deductive experiments and clinical observation rather than randomized controlled clincial trials. Unfortunately, there are only a few relevant trials in intraabdominal infections reported to date. In a critical review of antibiotic trials and intraabdominal infections, *J. S. Solomkin* et al. [4] commented that, "Exclusionary criteria employed generally prevented enrollment of seriously ill patients or infections with a high failure rate." They noted that the mortality rates in these studies was only 3.5% on average, while mortality rates in non-antibiotic related studies is generally in the 25 to 35% range. This suggests that the available controlled clinical trials of antibiotics are applicable only to the least ill of the patients with intraabdominal infections.

Recommendations for Therapy of Intraabdominal Infections

It is clear that to achieve cure of intraabdominal infection, *E. coli* and gram-negative anaerobes must be eliminated by means of adequate surgery and appropriate chemotherapy. The third-generation cephalosporins are capable of killing 100% of *E. coli* without the development of unacceptable side effects. These agents are still considered first-choice therapy for intraabdominal infections, always in combination with metronidazole for coverage of anaerobes. Aminoglycosides are no longer indicated for primary therapy of gram-negative surgical infections, with the exception of those proven to be caused by resistant organisms (notably *Pseudomonas aeruginosa*). The alternative to metronidazole is clindamycin, particularly if staphylococcal or clostridial infection is suspected or proven.

References

1. Altemeier, W. A.: Perspectives in surgical infections. Surg. Clin. North. Am. 60 (1980) 5–13.
2. Fleming, A.: On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. Br. J. Exp. Path. 10 (1929) 226–236.
3. Wittmann, D. H.: Staphylococci, a problem in surgical infections? (Staphylokokken, ein Infektionsproblem in der Chirurgie?). Fortschr. antimikrob. antineoplast. Chemother. 5 (1986) 1333–1339.
4. Solomkin, J. S., Meakins, J. L., Dellinger, E. P.: Antibiotic trials in intra-abdominal infections: a critical evaluation of study design and outcome reporting. Ann. Surg. 181 (1984) 29–39.
5. Arbeitsgemeinschaft Peritonitis PEG: Bacteriological findings in peritonitis of different origins (Bakteriologische Befunde bei verschiedenen Peritonistisformen). In: *Wittmann, D. H.* (ed.): Intra-abdominelle Infektionen. Futuramed Verlag, München 1983, pp. 432–492.
6. Bartlett, J. G., Onderdonk, A. B., Louie, T., Kaspar, D. I.: A review. Lessons from an animal model of intraabdominal sepsis. Arch. Surg. 113 (1978) 853–857.
7. Gonzenbach, H. R., Sonnabend, W.: Moxalactam – ein neues β-Lactam Antibiotikum in Monotherapie bei schweren Infektionskrankheiten in der Chirurgie. Schweiz. Med. Wochenschr. 31/32 (1981) 1–15.
8. Finegold, S. M., Bartlett, J. G., Chow, A. W., Flora, D. J., Gorbach, S. L., Harder, E. J., Tally, F. P.: Management of anaerobic infection. Ann. Intern. Med. 83 (1975) 375–389.
9. Swenson, L.B.: The bacteriology of intraabdominal infections. Surg. Clin. North Am. 55 (1975) 1349–1354.
10. Stone, H. H., Kolb, L. D., Geheber, C. E.: Incidence and significance of intraperitoneal anaerobic bacteria. Ann. Surg. 181 (1985) 705–715.
11. Wittmann, D. H., Schassan, H.-H.: Penetration of eight beta-lactam antibiotics into peritoneal fluid. Arch. Surg. 112 (1983) 205–212.
12. Wittmann, D. H.: Treatment of peritonitis. Habilitation, Hamburg University Medical School, Hamburg, FRG 1984.
13. Wittmann, D. H.: Directed and calculated therapy of surgical infections with imipenem/cilastatin. Arzneimittelpraxis 15 (1985) 661–670.
14. Wittmann, D. H., Mueller, M.: Patient stratification in intraabdominal infection. Chemioterapia 6 (Suppl. 1) (1987) S1–8.
15. Wittmann, D. H.: Clinics and pharmacokinetics of metronidazole (German). In: *Werner, H., Wittmann, D. H., Riemann, J. F.* (eds.): Metronidazole. Futuramed Verlag, München 1983, pp. 757–782.
16. Schoentag, J. J., Plat, M. E., Cerra, F. B., Wels, P. B., Walzak, P., Bucklay, R.: Aminoglycoside nephrotoxicity in critically ill surgical patients. J. Surg. Res. 26 (1979) 270–279.
17. Strom, P., Fabian, T., Dunlop, W. E., Stone, H. H.: The third generation cephalosporins in polymicrobial surgical infections. Arch. Surg. 118 (1983) 193–200.
18. Dittrich, H.: Adverse effects in wound healing (Wundheilungsstörungen). Chirurg. 42 (1971) 289–285.
19. Pulverer, G., Roszkowski, W., Ko, H. L., Roskowski, K., Jeljaszewicz, J.: Animal experiment studies on the modification of the immune system by ofloxacin. Infection 14 (Suppl. 3) (1986) S42–44.
20. Gemmel, G. C.: Potentiation of phagocytosis of pathogenic bacteria by exposure to low concentrations of antibiotics. J. Antimicrob. Chemother. 23 (1984) 407–409.