Antibiotic Trials in Intra-abdominal Infections

A Critical Evaluation of Study Design and Outcome Reporting

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The introduction of several new antibiotics, including cephalosporins and ureido-penicillins, has been a stimulus for clinical trials with these agents for intra-abdominal infection. Despite marked differences in antibacterial spectra, substantial differences in treatment results have not been documented. We reviewed published trials of antibiotic therapy for intra-abdominal infection to determine factors in study design that might impair identification of clinically important differences between regimens. Sixteen articles were identified that provided sufficient numbers of cases and data for analysis. Eight were prospective comparative trials, the remainder "single-armed" studies. The mortality rate was 3.5%, and the overall success rate was 84% for aminoglycoside plus clindamycin (range 52%–96%), 89% (range 83%–93%) for aminoglycoside plus metronidazole, and 93% (range 61%–95%) for cephalosporin-based regimens. Several defects in study design were identified. (1) Exclusionary criteria employed generally prevented enrollment of seriously ill patients or infections associated with high failure rates: Patients were excluded if even mild renal impairment was present or if antibiotic therapy had been recently administered, thereby excluding patients with postoperative or recurrent infections. Several studies allowed entry of contaminated but not infected patients. (2) Criteria used for reporting infectious diagnosis, premorbid health status, severity of infection, and outcome were nonuniform, and few studies provided such information. (3) Despite the small number of treatment failures, data reported did not allow determination of the basis for failure. For example, only four studies provided information on the operations performed upon treatment failures. Whether treatment failures were due to inadequate antibiotic therapy could therefore not be determined. Enrollment of a variety of low mortality infections precluded demonstration of any differences in regimens. Use of stratified randomization, stratifying for site of infection and severity of infection, and inclusion of greater numbers of patients would increase the likelihood of identifying differences between regimens. Such study design would likely require a multicenter trial to enroll sufficient numbers of cases for statistical analysis.

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SURGICAL MANAGEMENT of intra-abdominal infection is founded upon drainage of abscesses, debridement of devitalized tissue, and removal of sources of contamination. However, several elements of perioperative therapy for patients with intra-abdominal infection remain controversial, including peritoneal debridement, postoperative peritoneal irrigation, techniques of drainage, and abdominal wound closure.[1-3]

The question of optimal antibiotic therapy continues to elicit the most controversy. Most investigators, however, have become convinced of the utility of treating the anaerobic copathogens invariably isolated from such infections.[4,5] "Standard" antibiotic therapy for intra-abdominal infection has therefore generally come to be a combination of an aminoglycoside and clindamycin.

The introduction of several parenteral antibiotics including metronidazole, "second" and "third generation" cephalosporins, and ureido-penicillins has reawakened interest in less toxic alternatives in the treatment of intra-abdominal infection. To examine the value of the newer antibiotics regimens in the management of intra-abdominal infection, numerous clinical trials have been conducted.[6-35] Study design has ranged from open (noncomparative) to randomized comparisons of investigational antibiotics with "standard therapy," generally defined as an aminoglycoside plus clindamycin. These studies have not demonstrated substantial differences between the compared regimens, often despite marked differences in antibacterial spectrum of the various agents. Because of this fact, we have undertaken a review of published trials of antibiotic therapy for intra-abdominal infection in an attempt to determine those factors in study design that might impair the identification of clinically important differences between antibiotic regimens.

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Methods

A list of studies evaluating various antibiotic regimens published since 1975 was compiled by review of MEDLARS (National Library of Medicine) searches for English language articles reporting results of prospective trials of antibiotics in intra-abdominal infections. Additional articles were identified through review of personal files and correspondence with pharmaceutical manufacturers. From this list studies were chosen that had been prospective and that included 20 or more patients with intra-abdominal infection.[6–21] Several studies reported larger number of infected patients but enrolled relatively few with intra-abdominal infection.[22–26] Only articles that appeared in peer-reviewed journals are detailed.[27,28] In those cases where data from a single study were published in two or more articles, the original article was reviewed.[29–31] Additional articles were excluded if insufficient data were provided to characterize the infections treated and/or results of treatment.[32–35]

Results

Sixteen articles met the above criteria. These are overviewed in Table 1 and represent references 6 to 21. Eight were prospective comparative trials.[6–13] Four of the eight noncomparative studies evaluated treatment results of "standard therapy."[14–16,19] The other four noncomparative studies evaluated the antibiotics cefamandole, metronidazole, and cefoperazone for intra-abdominal infection.[17,18,20,21]

Criteria for Patient Eligibility

Criteria for patient eligibility for the reported studies were quite similar. Thirteen accepted clinical evidence of infection. Only three studies required either operative or microbiologic confirmation of an infective process.[12,15,17] The major point of variation was eligibility of patients at risk of infection because of soiling by enteric contents. Two studies specified this as an allowed entry criterion,[13,20] while in three others "bowel perforation" was given as a diagnostic classification.[6,7,9] In these latter studies, the settings in which visceral perforation occurred were not detailed.

In all 16 studies, exclusionary criteria were stated. Patients who were pregnant or lactating were excluded in the comparative trials. Two studies stated that patients were excluded if renal impairment was present,[9,21] and one study excluded patients with infections "subjectively judged . . . severe enough to demand an immediate antibiotic regimen with multiple agents."[17]

Patient Allocation

The eight comparative trials employed several different methods of allocation. In five, random assignment was made after informed consent was obtained. In these studies random number tables or other accepted randomization devices were used.[6,7,10,11,13] In one study, the process was not described.[9] In two studies, assignment was based on hospital number.[8,12]

The methods of patient selection in the noncomparative studies were not expressed. In five, the impression was given that every patient admitted with the clinical characteristics of intra-abdominal infection were entered into the study.[15–17,19,20] In the other noncomparative trials, the impression was given that certain patients eligible for the study were placed on alternative therapy not under the investigators' control. This would represent a major biasing factor in evaluating an antibiotic regimen for intra-abdominal infection.

This form of bias was likely to be operative in all of the reviewed studies; none provided data on the number of patients admitted to the institution who met eligibility criteria but were not placed on study.

Documentation of Infections Treated

Characteristics of Noninfectious Background Diseases

Since the underlying health status of the host has been shown to be an important determinant of the outcome of antibiotic therapy for acute infection,[36] we reviewed methods employed to evaluate the premorbid health status of the enrolled patients. Eight of the 16 studies provided no information on premorbid condition.[9,10,14,15,17,18,20,21] Three studies mentioned the McCabe–Jackson system for describing underlying diseases (nonfatal/ultimately fatal/rapidly fatal underlying disease).[6,11,13,36] One report cited "clinical judgment,"[7] and four provided data on the incidence of several chronic conditions believed to affect outcome such as diabetes, alcoholism, malignancy, or obesity.[8,12,16,19]

Documentation of Severity of Treated Infections

Only four studies provided information on the severity of the infections treated.[7,11,17,19] Methods employed varied from "clinical judgment" to reporting the number of patients with temperature and leukocyte count greater than some specific number. No study reported on the number of patients requiring support within an intensive care unit, and only three provided the number of bacteremic patients.[6,13,21]

Identification of Diseases Treated

Information on the variety of diseases treated is presented in Table 2. There was essentially no uniformity in diagnostic classifications used; four studies classified all patients into "abscess' or "peritonitis" although clarification of the illnesses treated was provided.[11,15–16,21]

In certain cases, the data presented in the table represent

TABLE 1. *Overview of Antibiotic Trials Reviewed*

Reference	Date of Publication	Regimens Employed		Total Number of Infections Treated*
Comparative				
6	1980	Clindamycin plus gentamicin Chloramphenicol plus gentamicin Ticarcillin plus gentamicin		134 (134)
7	1980	Metronidazole plus tobramycin Clindamycin plus tobramycin		58 (58)
8	1980	Erythromycin plus cefamandole Metronidazole plus gentamicin Clindamycin plus gentamicin		188 (188)
9	1981	Clindamycin plus any agent Metronidazole plus any agent		170 (170)
10	1981	Cefoxitin plus/minus amikacin Clindamycin plus amikacin		74 (45)
11	1982	Cefoxitin Clindamycin plus aminoglycoside		47 (47)
12	1982	Cefotaxime Clindamycin plus gentamicin		112 (85)
13	1983	Metronidazole plus tobramycin Clindamycin plus tobramycin		141 (141)
			Subtotal	924 (868)
Noncomparative				
14	1977	Clindamycin plus gentamicin		107 (57)
15	1977	Clindamycin plus gentamicin		144 (64)†
16	1978	Clindamycin plus gentamicin		59 (50)
17	1978	Cefamandole		113 (113)
18	1978	Metronidazole		30 (20)
19	1981	Clindamycin plus tobramycin		20 (20)
20	1982	Metronidazole plus tobramycin		48 (48)
21	1983	Cefaperazone		35 (35)
			Subtotal	556 (407)
			Total	1480 (1275)

* Numbers in parentheses indicate number of intra-abdominal infections.

† Twelve patients with intra-abdominal infection treated with carbenicillin plus gentamicin are included.

our interpretation of the published data. Appendicitis was the most common (24%, 322/1275).

Operations Performed

The timing and nature of operative therapy are thought to be of primary importance in determining outcome from an episode of intra-abdominal infection. In eight studies, neither the number of patients undergoing operation nor the operations performed were reported.[6–8,11,14,15,20,21] Only two studies categorized the operations performed more precisely than as "excision," "drainage," "debridement," or "intestinal vent."[10,16]

Antibiotic Dosing Regimens Employed

The search for a nontoxic alternative to aminoglycoside therapy was a motivation for many of the reported studies. Aminoglycosides have a narrow therapeutic ratio requiring determinations of serum levels and, often, dose and dosing interval adjustments must be made to achieve therapeutic but nontoxic levels.[37,38] Six of the 14 studies using gentamicin and/or tobramycin employed a standard dose of 1.5 mg/kg every 8 hours.[6,7,13–16] Two studies used 1 mg/kg every 8 hours[8,12] and in one instance, dosing information was not provided.[9] Only three studies adjusted the dose and dosing interval to achieve generally

TABLE 2. *Incidence of Specific Sites of Origin of Infections in Trials of Antibiotic Therapy for Intra-abdominal Infection*

Reference	Total Cases	Esophagogastric Junction to Ligament of Treitz	Biliary Tract	Ligament of Treitz to the Ileocecal Valve	Appendicitis	Ileocecal Valve to the Peritoneal Reflection	Intra-abdominal Infection Following Operation	Distal to Peritoneal Reflection	Pancreatic Abscess	Liver Abscess	Gynecologic Infections	Surgical Wound Infection	Specified Only As Abscess	Specified Only As Peritonitis	Miscellaneous or Not Specified
Comparative															
6	134	14		15	45	38				2		20			
7	58			20*	24	6									8†
8	188	9	20	12	35	7		29	2	1	4	7	27	9	26
9	170			18	72	36							12		32
10	45		5		7	6					2	4	19	2	
11	47							7					29	4	7
12	85	13	6	9	11	6		14			2		19		5
13	141			21‡	43	36§									41‖
Total	868	36	31	95	237	135		50	2	3	8	31	106	15	154
% of total:		4%	3%	10%	26%	15%		5%	—	—		3%	11%	2%	17%
Noncomparative															
14	57		1			8						10	26	10	2
15	64									10		8	17	28	1
16	50		2		8			3	1	3		3	22	8	
17	113	11	24	15	39	3					5		7	3	6
18	20			1	8	11									
19	20	4	3		6		1								6
20	48	2		8¶	21	6	2						1		8**
21	35		6		3	1		4				6	10	4	1
Total	407	17	36	24	85	29	3	7	1	13	5	27	83	53	24
% of total:		4%	9%	6%	21%	7%	—	2%	—	3%	1%	7%	20%	13%	6%
Grand Totals (Including Comparative and Noncomparative trials):															
	1275	53	67	119	322	164	3	57	3	16	13	58	189	68	178
% of total:		4%	5%	9%	24%	12%	—	4%	—	1%	1%	4%	14%	5%	13%

* Includes 16 "bowel perforations."
† Includes seven "inflammatory bowel disease."
‡ Includes 21 "bowel perforations."
§ Includes 19 "bowel resections," 17 "diverticulitis."
‖ Includes 16 "unknown and miscellaneous," 12 "inflamed viscera," 13 "at risk."
¶ Includes four traumatic perforation of small intestine.
** Includes five inflammatory bowel disease, two colostomy closures.
NS = Not Stated.

TABLE 3. *Overview of Reported Treatment Results for Comparative Antibiotic Trials**

Reference	Authors' Classification	Regimen	Reported Results 1-Cured	2-Improved	3-Failed	Deaths	Comments
6	Cure†/failure‡	Clindamycin/gentamicin	33/42 (79)	—	9/42 (21)	1	
		Chloramphenicol/gentamicin	43/53 (81)	—	10/53 (19)	4	
		Ticarcillin/gentamicin	35/39 (90)	—	4/39 (10)	3	
7	Good†/fair§/poor‡/died‡	Clindamycin/tobramycin	20/23 (87)	—	3/23 (13)		
		Metronidazole/tobramycin	32/35 (91)	—	3/35 (9)		
8	Effective†/failed‡	Clindamycin/gentamicin	65/68 (96)	—	2/68 (4)	2	1 indeterminate
		Metronidazole/gentamicin	56/60 (93)	—	1/60 (7)	2	3 indeterminate
		Erythromycin/cefamandole	57/60 (95)	—	2/60 (3)	2	1 indeterminate
9	Patients showing no signs of infection on day 7	Clindamycin + any agent	—Not specified—			7	
		Metronidazole + any agent				2	
10	Cure†/improvement§/failure‡	Cefoxitin +/− amikacin	24/37 (65)	10/37 (27)	3/37 (8)		Results include 29 patients with extraperitoneal infections
		Clindamycin/amikacin	29/37 (78)		8/37 (22)		
11	Cure†/failure‡	Cefoxitin +/− gentamicin or tobramycin	16/26 (66)	—	9/26 (34)		
		Clindamycin + gentamicin or tobramycin	11/21 (52)	—	9/21 (43)		
12	Cure†/recurrent§/failure‡	Cefotaxime	46/56 (82)	3/56 (5)	7/56 (13)	2	1 indeterminate
		Clindamycin/gentamicin	46/56 (82)	6/56 (11)	3/56 (5)	4	Results include 31 cases of extraperitoneal infection
13	Cure†/improvement§/failure‡	Clindamycin/gentamicin	58/69 (84)	8/69 (12)	3/69 (4)	3	
		Metronidazole/gentamicin	60/72 (83)	8/72 (11)	4/72 (6)	2	
						34 (4%)	

The average cure rate for control arms (aminoglycoside + clindamycin) was 84% (262/313)

* Numbers in parentheses are per cents.
† Outcome category given by authors considered as "cured."
‡ Outcome category given by authors considered as "failed."
§ Outcome category given by authors considered as "improved."

accepted peak and trough serum levels for the aminoglycosides employed.[10,11,19] Other antibiotic doses were generally in accord with the recommendations of the Medical Letter.[39] Two studies, however, employed clindamycin at subtherapeutic doses (5 mg/kg every 8 hours).[8,12]

Outcome Evaluation

Criteria stated for scoring outcome therapy varied markedly from study to study. Each provided a two- to four-tiered scheme based upon resolution of clinical signs of infection including fever, leukocytosis, wound appearance, and drainage. In two studies rapidity of response was also included in outcome evaluation,[7,15] and in one study a fever index was utilized to attempt to define differences between antibiotic regimens.[9,40]

The outcome results are provided in Tables 3 and 4. The aggregate data from the comparative studies show a cure rate of 84% (range 52%–96%) for aminoglycoside plus clindamycin, 89% (range 83%–93%) for aminoglycoside plus metronidazole, and 93% (range 61%–95%) for cephalosporin-based regimens.

Seven studies provided outcome data in relation to infection treated. The outcome data from these reports are detailed in Table 5. These data support the contention that patients with relatively less severe infections were

TABLE 4. *Overview of Reported Treatment Results for Noncomparative Trials**

Reference	Author's Classification	Regimen	Reported Results 1-Cured	2-Improved	3-Failed	Deaths	Comments
14	Cure†/failure‡	Clindamycin/gentamicin	51/57 (89)	—	5/57 (9)	5	1 indeterminate
15	Excellent†/good†/fair§/poor‡	Clindamycin/gentamicin	51/64 (79)	9/64 (14)	4/64 (6)	1	
16	Cured†/partial§	Clindamycin/gentamicin	36/50 (72)	5/50 (10)		0	9 indeterminate
17	Cured†/improved§/no change‡	Cefamandole	95/113 (84)	12/113 (11)	6/113 (5)		
18	Cured†/improved§/poor response‡	Metronidazole	22/30 (73)	7/30 (23)	2/30 (7)	2	
19	NS	Clindamycin/ tobramycin	17/20 (85)	—	1/20 (5)	1	2 not evaluable
20	Good/fair§/poor‡/died‡	Metronidazole/ tobramycin	38/48 (79)	8/48 (17)	3/48 (6)	2	
21	Cured†/improved§/failed‡	Cefaperazone	25/35 (71)	7/35 (20)	3/35 (9)	NS	
		Totals	335/417 (80%)	48/417 (12%)	24/417 (6%)	11 (3%)	

* Numbers in parentheses are per cents.
† Outcome category given by authors considered as "cured."
‡ Outcome category given by authors considered as "failed."
§ Outcome category given by authors considered as "improved."
NS = Not specified.

selected. This contention is illustrated by the finding that the failure rates for appendicitis (23%) were greater than for conditions generally considered to be of higher risk, notably colon-derived infections (0% failure rate) and intra-abdominal abscess (12%).

Based on review of the studies, an outcome evaluation system was devised (Table 6) and the original data retabulated (Table 7). The major effect of applying such a system was to decrease the number of "not evaluable" cases and transfer these to "treatment failures." The cure rate remained 84%.

Reporting of Treatment Failures

In abdominal infection many factors unaffected by antibiotic therapy may effect outcome. For this reason the details of treatment failures are of considerable importance in allowing the reader to determine the potential contribution of antibiotic choice to the poor result. This is particularly true for those treatment failures due to recurrent or uncontrolled infections since failure due to adverse reaction often can be judged quite objectively. In addition, because "treatment failure" under the outcome evaluation schemes provided was an uncommon event, considerable detail could have been given. We, therefore, scored the number of studies providing information on background disease, severity of infection, type of infection treated, susceptibility of associated organisms, and operations performed. Two reports detailed background diseases[6,7]; one reported severity of infection.[19] Only four studies provided data on the susceptibility of the organisms associated with treatment failure.[7,11,19,21] Nine reported infections treated[7,10,13,16–21] and four reported operations performed.[7,10,13,19]

Discussion

A variety of host- and disease-specific factors affect the response of intra-abdominal infection to treatment. These factors include the premorbid health status of the host (associated chronic diseases, age, sex), the particular site of infection and the severity of the infection.[41–49] In addition, the operative procedure performed (or not performed) and its timing are frequently major determinants of outcome.[50,51] The relative importance of a therapeutic adjunct such as antibiotic therapy may therefore not be easily discernible in series reporting results of treatment for intra-abdominal infection.

A commonly stated rationale for antibiotic selection in the treatment of intra-abdominal infection has been that agents active against *all* organisms likely to be encountered should be employed. This has generally implied the use of an aminoglycoside (gentamicin, tobramycin, or amikacin) in combination with an agent effective against almost all enteric anaerobes (clindamycin or metronidazole). The evidence to support this approach has not, however, been derived from controlled therapeutic trials of intra-abdominal infection. Rather, this conclusion is an extrapolation of data from a surprisingly small number of prospective comparative studies using mixed flora contamination of the peritoneal cavity or gynecologic infection as "disease models."[52–55]

The accuracy of using a "disease model" to predict effective antibiotic regimens for the wide variety of diseases

TABLE 5. *Successful Results Expressed by Disease Treated*

Reference	Esophagogastric Junction to Ligament of Treitz	Biliary Tract	Jejunum to Ileum	Ileocecal Valve* to Peritoneal Reflection	Distal to Peritoneal Reflection	Appendicitis	Gynecologic Infections	Wound Infection	Specified as Abscess	Specified as Peritonitis
12	12/13	5/6	5/9	6/6	13/14	7/11	2/2	—	18/19	—
15	—	—	—	—	—	—	—	7/8	13/14	21/28
16	—	1/1	—	1/1	—	—	—	9/9	14/15	7/7
17	8/11	24/24	11/13	3/3	3/3	31/39	4/5	—	6/7	—
19	—	—	—	—	—	—	—	—	5/6	12/14
20	—	—	—	—	—	—	—	—	19/22	—
21	—	4/5	—	1/1	3/4	3/3	—	3/6	7/10	2/4
Totals	20/23 (83%)	34/36 (94%)	16/22 (73%)	11/11 (100%)	19/21 (90%)	41/53 (77%)	6/7 (86%)	19/23 (83%)	82/93 (88%)	42/53 (79%)

* All cases were specified as diverticulitis.

TABLE 6. *Proposed Clinical Outcome Reporting Scheme*

Successful:
Resolution of signs and symptoms of infection without requirement for additional antibiotics, whether or not agent(s) changed to a less toxic or organism specific oral or parenteral antimicrobial after an initial favorable response.

Failed:
1. Lack of objective response to therapy requiring change in antimicrobial agents or additional operation.
2. Recurrence of infection posttherapy at a site related to the initial infection.*
3. Change of antimicrobial agent(s) necessitated by:
   A) adverse reaction
   B) delayed response
   C) *in vitro* resistance of an isolate from the infected site.
4. Death (while on antimicrobial therapy) with infection a contributing factor or death due to an adverse drug reaction.

Indeterminate:
1. Inadequate surgical procedure
2. Death with infection not a contributing factor†
3. Death within 72 hours of initiation of therapy;
4. Superinfection at initial site of infection by organisms not identified at initiation of therapy.

* These can be divided into intra-abdominal recurrences and extra-abdominal infections such as wound or drain tract infections.

† Death occurring following end of therapy with resolution of signs and symptoms of infection, ideally with autopsy confirmation of absence of infection.

subsumed under the heading of intra-abdominal infection has not been established. The use of any particular regimen as the standard or control regimen in antibiotic trials of intra-abdominal infection is therefore more a function of prejudice than established fact. Similarly, the validity of comparing treatment results derived from a wide variety of infections (often both intra-abdominal and extra-abdominal) has not been established. It is apparent that comparative clinical trials of antibiotic therapy are required to define optimal therapy for intra-abdominal infection.

Our review showed that infections entered into the comparative trials were generally those that have low mortality and low recurrence rates. Of the 1275 patients included in the studies reviewed, there were only 45 deaths, a mortality rate of 3.5%. This low mortality experience was clearly due to enrollment of low-mortality infections. Of the 1275 infections studied, 322 (25%) were acute appendicitis. Recent series of acute appendicitis in adults have reported mortality figures ranging from 0% to 2%.[45,56] Five studies appeared to enroll patients if contamination by enteric contents occurred, even if there were no pathologic or clinical evidence of infection.[6,7,9,13,20] Another deliberately excluded patients with severe infections.[17]

Conversely, conditions known to be associated with a high mortality rate were rarely enrolled in either the comparative or noncomparative trials; several studies appeared to include no such high-risk infections. Examples of such

TABLE 7. *A Revised Outcome Evaluation Based on the Proposed Outcome Evaluation System*

Reference	Number Treated	Number Cured	Number Failed	Treatment Failure					Not Evaluable				
				Dead of Infection	Lack of Objective Response	Developed Abscess/ Peritonitis	Relapse Post Treatment	Adverse Reaction	Inadequate Operation	Super-infection	Dead <72 hours	With Initial Infection Not Contributing	Undetermined
6	134	111	29	8	5		2	5	2				
7	58	52	5	5		8						1	
8	188*	136	40	6			24	10	2	2		3	5
10	74†	64	8	1		4	2	1		2			
11	47	26	21			19		2					
12	112‡	76	19	4			9	6		2		4	1
13	141	117	12	5	1	1		5		12			
Totals	754	582 (84%)	133 (16%)	29	6	32 133 (23%)	37	29	4	18	36 (5%)	8	6

* Includes results of 26 patients with extra-abdominal infections.
† Includes results of 29 patients with extra-abdominal infections.
‡ Includes results of 31 patients with extra-abdominal infections.
In some reports, insufficient data were provided to score individual patients.

infections are those arising from the colon (perforated diverticulitis) or pancreas, and those occurring after intra-abdominal operation.[44–49] While infections derived from the colon constituted 12% of the cases reported (Table 2), the cure rate was 100% in those series reporting outcome by disease (Table 5), and these were all specified as diverticulitis. Further, it was unclear from the material presented how many of these patients (if any) required operative intervention. Only three pancreatic infections and only three postoperative infections were described in the 1275 infections reported. In the selection of such infections for study, one would not expect that any single variable (other than operation) would demonstrably affect outcome.

In view of the low treatment failure rates to be expected with the infections treated, the statistical underpinnings of these studies becomes of considerable importance. Statistical analysis in randomized clinical trials is based upon assumptions of α and β values: α refers to the probability that a false-positive conclusion will be reached; β refers to the probability that a false-negative conclusion will be reached. It is customary to make determinations of sample size based on an α of 0.05; that is, to accept a probability of 0.05 that a false-positive conclusion will be reached. Similarly, a probability of 0.10 that a false-negative conclusion will be reached is generally used since false-negative conclusions are likely to be of lesser clinical significance. Only one study provided a discussion of α and β values assumed and discussed determination of sample size.[13] With reported failure rates of 10% to 15%, an enormous sample size would be required to detect a difference in therapeutic efficacy. For example, using an α of 0.05 and β of 0.10, approximately 270 patients would be required if one regimen lowered the failure rate to 5%.[57] The largest two-armed study reported 170 infections, and four of the seven other comparative trials enrolled fewer than 80 patients (Table 1). It is apparent that statistical evaluation of the study results was precluded.

It is apparent that it will be practically impossible to distinguish clinical efficacy between antimicrobial regimens with similar spectra and toxicity utilizing clinical endpoints such as recurrent infection, death or adverse reaction within the study design most commonly employed (single center randomized comparative trial with a mixed group of infectious etiologies). Two multicenter studies also failed to show differences between antibiotic regimens.[9,13] This conclusion seems to be confirmed by those studies employing exceedingly low doses of "standard therapy" (aminoglycoside plus clindamycin), doses so low as to be considered placebo-controlled studies.[8,12] Similar treatment results were seen even when two bacteriologically inappropriate agents were used, as, for example, with use of either cefamandole or metronidazole as single agent therapy.[17,18] (Cefamandole is effective

against aerobic gram-negative and gram-positive organisms but has little activity against *Bacteroides fragilis;* metronidazole is highly effective against *Bacteroides fragilis* but has no aerobic activity.) Studies evaluating the use of each as single agent therapy failed to reveal any difference between these markedly disparate regimens.

The conclusion to be drawn from the studies reviewed is not that the various regimens are of equal efficacy, but rather that the studies were designed in such a way to guarantee failure to distinguish between either regimen.

Review of the data from the noncomparative trials provided little additional insight into the efficacy of individual regimens. These studies suffered the same flaws as the comparative trials. Results of noncomparative trials become impossible to evaluate given the inherent lack of control for operative technique, severity of infection, host factors, and use of ancillary support measures provided at the individual study center. While such studies establish normative treatment results, the routine use of noncomparative trials as the basis for therapeutic decision making cannot be accepted.

The use of randomized, prospective studies has definitely added to our knowledge of therapeutics. However, use of this study design depends upon several characteristics of the problem under study and the population encountered. The most prominent lessons from those antibiotic studies (both surgical and nonsurgical) that have shown significant differences in antibiotic regimens include use of a single disease entity in which nonbacterial factors affecting outcome are balanced in a standardized fashion (*e.g.,* fixed operative technique for dealing with perforated appendicitis). Only diseases that have a substantial failure rate with standard therapy should be studied. Finally, sufficient numbers of patients must be studied to permit recognition of relatively slight differences in outcome (on the order of 10%).

One example of studies showing significant differences between antibiotic regimens is the comparison of single agent *versus* combination therapy with synergistic agents for gram-negative infections in leukopenic patients.[58] The recently reported trials of antibiotic therapy for perforated appendicitis comparing regimens with agents effective against anaerobes with agents not effective against anaerobes are other examples of infections with control failure rates sufficiently high to show significant differences between antibiotic regimens without extraordinary numbers of patients.[59,60]

Other criteria have been employed to examine differences between antibiotic regimens. These include cost-effectiveness and biochemical evidence of clinically inapparent toxicity.[61,62] The comparative effects of antibiotics on endogenous flora is another factor that could be used to base selection of antibiotic therapy.[63]

However, clinical outcome criteria and toxicity do seem to be the most appropriate evaluators of efficacy. It seems possible that a study design for the comparative evaluation of antibiotic regimens for a mixture of intra-abdominal infectious diseases can be achieved. One possible approach would be to only allow entry of infections if the infection is known to have a poor outcome. An alternative approach would be the use of a stratified randomization process, stratifying for both disease to be treated and severity of infection.[64,65] This approach would allow evaluation of toxicity of the compared drug regimens in a large number of patients, while allowing use of clinical outcome criteria in the higher risk infections. It is most likely that a multicenter trial would be necessary with either approach because of the relative infrequency of high mortality infections (*e.g.,* peritonitis from perforated diverticulitis or postoperative peritonitis).

An additional value of stratified randomization by disease and severity would be to isolate and evaluate host factors associated with drug toxicity. It is becoming apparent that the newer antibiotics have considerably different toxicities than do the "standard" of aminoglycoside plus clindamycin. Several recent reports have described superinfection with *enterococcus* in patients treated with "third-generation" cephalosporins, and the ability of these agents to produce coagulation disturbances related both to vitamin K deficiency and platelet dysfunction has been appreciated only recently.[66,67] From a microbiologic standpoint, there is considerable concern for the induction of resistance in initially sensitive gram-negative organisms, despite a relative paucity of data on this point.[68] These studies have primarily described critically ill patients, implying that the frequency of toxic effects is higher in critically ill patients. Concerns regarding toxicity (rather than efficacy) would be most promptly evaluated using a stratified study design.

It seems apparent, however, that standardization of reporting schemes for infections treated, background health, and severity of infection are required. This subject has been recently discussed at length by Meakins et al. (in press) who recommended a surgical infections stratification (SIS) scheme based on both pathologic criteria (*i.e.,* the site of origin of the pathogens being treated) and use of the Acute Physiologic Scoring System reported and extensively evaluated by Knauss and colleagues[69,70] to stratify for physiologic stress. A standardized reporting scheme for outcome evaluation, clearly not provided in the studies reviewed, would also be of considerable value in allowing comparisons of one study with another and in confirming the authors' conclusions.

Conclusions

Based on our review of antibiotic trails, adequate design of studies evaluating therapy for intra-abdominal infection

are: (1) inclusion of infections with high failure rates and sufficient numbers of patients to adequately compare the therapeutic regimen(s) in mixed-flora intra-abdominal infections; (2) use of randomization techniques effective in eliminating bias in patient assignment; (3) stratification for other variables affecting outcome, including premorbid health status, severity of illness, and type of infection; (4) outcome evaluation criteria precise enough to allow differentiation of antibiotic regimens; and (5) provision of sufficient data to support the outcome evaluation reported.

The studies reviewed in this article enrolled the spectrum of infections in which combination antibiotic therapy is commonly recommended and employed. It is apparent, however, that other selection criteria need be employed if efficacy of antibiotic therapy (as opposed to efficacy of operative therapy in intact hosts) is to be evaluated. Use of stratified randomization would possibly allow the use of currently employed entry criteria for studies of new antibiotics with broad *in vivo* activity against aerobic and anaerobic organisms. Continued use of recurrent infection (the primary cause of treatment failure in the studies reviewed) as an endpoint of therapy is desirable because of our less than complete ability to define the clinical relevance of pharmacokinetic and *in vitro* antibacterial data.

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