2004

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SURGICAL INFECTIONS
Volume 3, Number 4, 2002

Aminoglycosides for Intra-Abdominal Infection: Equal to the Challenge?

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ABSTRACT

Background: **Aminoglycosides, combined with antianaerobic agents, have been used widely for the treatment of intra-abdominal infection. However, some prospective randomized controlled trials and other data suggested that aminoglycosides were less efficacious than newer comparators for the treatment of these infections. We therefore performed a meta-analysis of all prospective randomized controlled trials utilizing aminoglycosides to reevaluate the efficacy of these agents for the treatment of intra-abdominal infection.**

Methods: **Published English-language prospective randomized controlled trials comparing aminoglycosides with other agents for treatment of intra-abdominal infection were identified by MEDLINE search. For each study, data were collected regarding the number of patients enrolled and evaluated, their basic demographic characteristics, the sources of the intra-abdominal infections, the number of failures as determined by the study investigators, quality score, and the use of serum drug concentrations to monitor aminoglycoside therapy. These data were combined to calculate odds ratios for risk of therapeutic failure, which were assessed for significance using Chi-square analysis.**

Results: **Forty-seven prospective randomized controlled trials comparing aminoglycosides to other agents were identified. These were published between 1981 and 2000, and included a total of 5,182 evaluable patients. Analysis of all studies combined revealed an odds ratio that slightly, but significantly, favored the comparators. After excluding six trials using comparators that lacked accepted antianaerobic efficacy, the odds ratio more strongly favored comparators. Trials published since 1990 also notably favored comparators. Analyzing results by quality score or the use of aminoglycoside monitoring did not alter these findings.**

Conclusions: **In this meta-analysis, aminoglycosides were less efficacious than newer comparators for the treatment of intra-abdominal infection. Given the well-known toxicities of these agents, we conclude that they should not be used as first-line therapy for these infections.**

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Presented at the First Joint Meeting of the Surgical Infection Society and the Surgical Infection Society–Europe, Madrid, Spain, May 1–3, 2002.

AMINOGLYCOSIDES IN COMBINATION with antianaerobic agents were the first antimicrobial regimens recognized as efficacious for the treatment of patients with intra-abdominal infection. Some still consider this regimen to be the gold standard of antimicrobial therapy for these infections. However, aminoglycosides have substantial nephrotoxicity and ototoxicity. In addition, they require monitoring of serum concentrations for optimal utilization. Thus, other agents with equal efficacy that do not exhibit such toxicity or need intensive monitoring might be more desirable for the treatment of patients with intra-abdominal infections.

A large number of prospective randomized controlled trials have compared the efficacy of aminoglycosides against newer antimicrobials to identify such alternative regimens. A few of these trials actually demonstrated greater efficacy of the comparator agents, calling into question the continued use of aminoglycosides as first-line agents for the treatment of intra-abdominal infections [1]. However, nearly all trials were designed only to detect therapeutic equivalence, which allows for differences in efficacy as high as 15–20% between regimens; very few, if any, of the trials were actually powered to detect therapeutic superiority. Thus, the appropriate role of aminoglycosides in the treatment of intra-abdominal infection is difficult to ascertain on the basis of the individual study data.

Meta-analysis provides a tool with which to aggregate the results of smaller, individual trials, such that statistical analysis may be applied to answer questions that these individual studies cannot address [2–5]. In order to re-evaluate the role of aminoglycosides in the treatment of intra-abdominal infections, we performed a meta-analysis of all prospective randomized controlled trials that compared aminoglycoside-based regimens against agents from other antibiotic classes for the treatment of these infections. We hypothesized that these combined data might make it possible to more definitively answer the question as to whether or not aminoglycoside-based regimens should still be considered first-line agents for the treatment of patients with intra-abdominal infections.

MATERIALS AND METHODS

Study identification and selection

All published English-language prospective randomized controlled trials that compared an aminoglycoside in combination with an antianaerobic agent against antimicrobials from other classes for the treatment of patients with established intra-abdominal infections were selected for potential inclusion in the meta-analysis. Results available only in abstract form were not included in this analysis, because most studies on aminoglycoside use were performed more than five years ago, and it was not likely that such trials could be identified and evaluated systematically. Published trials were identified from a search of the MEDLINE database using the names of specific aminoglycosides paired with words and phrases suggesting an intra-abdominal infection (such as peritonitis, intra-abdominal abscess, appendicitis). This search strategy was supplemented by examination of the references found in various articles discussing treatment of intra-abdominal infections, and also by a search of the Cochrane database.

Published studies identified by this initial search strategy were then excluded for a variety of reasons. Studies were not considered further if the data had not been acquired prospectively, or if the subjects had not been randomized. Studies designed to evaluate prophylactic use of antimicrobials for surgical procedures not involving intra-abdominal infections were also excluded, including those involving patients undergoing elective abdominal procedures as well as those having acute intraperitoneal contamination. Trials that included subjects with infections outside the abdominal cavity were excluded unless the results were reported separately for patients with intra-abdominal infections. Finally, trials in which patients received an antimicrobial in addition to an aminoglycoside that was effective against gram-negative aerobic/facultative anaerobic bacteria were eliminated, unless that additional antibiotic was ampicillin or penicillin being provided for enterococcal coverage.

Data abstraction and assessment

The resultant trials were reviewed, and data were abstracted with regard to year of publication, total number of patients enrolled, number of evaluable patients, demographics of evaluable patients, patient diagnoses or anatomic sources of intra-abdominal infection, the specific aminoglycoside and comparator regimens used, number of treatment failures as identified by the individual study investigators, the use of serum drug levels to monitor aminoglycoside therapy, and toxicity due to antimicrobials. Quality scores were determined using the method of Jadad et al. [6]. Scores ranged from zero to five, with five representing the highest quality score that could be achieved (Table 1). All quality scores were determined independently by at least two investigators.

Statistical analysis

Risks of therapeutic failure with aminoglycoside-based therapies relative to risks of therapeutic failure with comparator therapies were expressed as odds ratios. An odds ratio less than one favored the aminoglycoside-based regimens, whereas an odds ratio greater than one favored the comparator agents. Confidence intervals were derived for these ratios, with Chi-square analysis being used to establish statistical significance. Odds ratios, *P* values, and 95% confidence intervals were determined for each individual trial, for all trials combined, and for trials grouped by year of publication, comparator class, quality score, percentage of subjects with appendiceal disease, use of aminoglycoside monitoring, and enrollment of pediatric patients [7,8].

To assess trial heterogeneity, the procedure outlined by L'Abbe et al. was utilized [4]. Predicted failure rates for aminoglycosides and comparators were determined by linear regression analysis of all trials, and 95% confidence limits about this derived relationship were determined. Individual trial results were then plotted to determine the number of trials with results outside of those confidence intervals.

Table 1. Quality Scoring System

Give one point if the study was randomized, and:
Give one additional point if the method of randomization was appropriate
Deduct one point if the method of randomization was inappropriate
Give one point if the study was double blinded, and:
Give one additional point if the method of blinding was appropriate
Deduct one point if the method of blinding was inappropriate
Give one point if there was a description of withdrawals and dropouts

From Jadad et al. [6].

RESULTS

Trial and patient characteristics

The initial search strategy identified 112 trials, of which 65 [9–73] were excluded from further analysis for the reasons given in Table 2. Data from 47 publications were included in the meta-analysis [74–120]. Two studies included three treatment arms, one of which involved an aminoglycoside-based regimen [74,76], and one other study had four separate treatment arms, two of which involved an aminoglycoside-based regimen [84]. These trials were published between 1981 and 2000. A total of 7,772 patients were enrolled in the trials, with the number of patients enrolled in individual trials ranging from 41 to 993. Of these 7,772 patients, 5,182 (66%) were clinically evaluable by individual study criteria. The number of clinically evaluable patients in these trials ranged from 28 to 341.

Study enrollment criteria included known or suspected intra-abdominal infection based on physical, laboratory, and radiographic examinations, and findings at the time of operative or other interventional procedures. Enrollment criteria usually required the patient to have undergone a source control procedure by the operative or percutaneous route. In fact, only nine clinically evaluable patients were specifically identified as having undergone medical therapy only. These patients would not have been considered to have had "complicated" intra-abdominal infection as defined by the criteria of Solomkin et al. [121].

Exclusion criteria varied from study to study.

Table 2. Reasons for Trial Exclusion

Design did not test an aminoglycoside plus an antianaerobic agent against another comparator regimen [9–26]
Included patients with infections outside the abdominal cavity, and did not separately tabulate results for patients with intra-abdominal infection [27–40]
Primarily evaluated the use of prophylactic, not therapeutic antimicrobial therapy [41–54]
Not a prospective, randomized controlled trial on detailed review [55–67]
Data available only in abstract form [68, 69]
Clinical outcomes not documented [70]
Limited number of patients with intra-abdominal infection [71]
Intraperitoneal antimicrobial therapy [72]
German language publication [73]

Most trials excluded patients outside of specific age ranges, in order to prevent enrollment of children in adult studies and vice versa. However, two trials specifically excluded patients of advanced adult age [78,102]. The most common exclusion criteria were pregnancy or lactation, previous hypersensitivity to trial antimicrobial agents, recent or concurrent treatment with antimicrobials, infection with organisms known to be resistant to study agents, and concurrent participation in other clinical trials. Many studies excluded moribund patients, those not expected to survive 48 hours, and those with terminal illnesses. Patients with high-acuity illness, immunosuppression HIV disease, granulocytopenia, and renal or hepatic dysfunction or failure were variably excluded.

Definitions of success and failure varied from study to study. Cure was generally defined as resolution of all clinical signs of infection without the need for additional antimicrobial therapy or operative intervention. Several studies also included a final outcome defined as improved, in which there was control of the primary infective process, but with some form of ongoing clinical disability. For this meta-analysis, patients classified as improved were considered to be treated successfully. Definitions of treatment failure varied somewhat more widely between studies. Patients who died as a result of their infections or who required additional antimicrobials or procedures, including drainage of wound infections, to control their infectious process were generally considered to have failed treatment. However, patients who developed adverse reactions to study medications, who developed infectious complications outside of the abdominal cavity, or who died as a result of other disease processes were variously reported as treatment failures, unevaluable, or occasionally as treated successfully.

Thirty-three of the 47 studies, including 78% of the evaluable patient population, provided demographic information. Sixty-seven percent of these patients were male. The reported age range was from 6 months to 91 years. In trials enrolling only adult patients, the mean age was 40 years. Six trials enrolled pediatric patients only [84,91,96,101,105,106], and one additional trial included a subset of pediatric patients [86]. In all, 688 of the characterized patients were in the pediatric age range. Thus, pediatric patients represented at least 13% of the total population of clinically evaluable patients.

Among the studies providing adequate information, the most prevalent source of intra-abdominal infection was the appendix. A total of 2,621 patients were described as having appendiceal disease, representing at least 51% of all clinically evaluable patients. Of these 2,621 patients, 2,126 (81%) were identified as having complicated appendicitis (gangrenous, perforated, or abscessed) and 495 were listed as having appendicitis, but not otherwise described. In all six of the studies enrolling pediatric patients exclusively, the appendix was the anatomic source of the infection. Other commonly reported diagnoses or sources of intra-abdominal infection are listed in Table 3.

Randomization of patients resulted in 2,451 being assigned to aminoglycoside-based therapy and 2,731 to comparator therapy. Aminoglycosides tested were primarily gentamicin or tobramycin, with netilmicin and amikacin being used in a few trials (Table 4). The antianaerobic agent used most commonly with the aminoglycoside was clindamycin, although metronidazole was used in several trials. In seven treatment groups, concomitant treatment with penicillin or ampicillin was required or permitted.

A variety of comparator regimens were employed (Table 5). Twenty-two treatment

TABLE 3. DIAGNOSIS OR SOURCE OF INTRA-ABDOMINAL INFECTION

Source or diagnosis	*Number of patients*
Appendix (total)	2,621
Complicated appendicitis (perforated, gangrenous, abscessed)	2,126
Appendicitis (not otherwise specified)	495
Intra-abdominal abscess	369
Hepatobiliary	354
Peritonitis (not otherwise specified)	302
Gastroduodenal perforation	290
Perforated viscus (not otherwise specified)	184
Large bowel perforation	243
Diverticular disease	100
Small bowel perforation	97
Miscellaneous (not otherwise specified)	173
Other diagnoses	208

groups received cephalosporins, with or without additional antianaerobic agents, nine received carbapenems as monotherapy, and nine received penicillins with or without beta-lactamase inhibitors. Other regimens tested included aztreonam in combination with clindamycin, the oxa-beta-lactam agent moxalactam, and the fluoroquinolone pefloxacin in combination with metronidazole.

Study quality varied widely, but tended to be low. Quality scores ranged from 0 to 5, with the mean score being two. The distribution of quality scores is indicated in Figure 1.

Outcome analysis

Efficacy. Odds ratios (OR) with 95% confidence intervals (CI) were recalculated for each trial individually. The results of this analysis are presented in Figure 2, with trials organized by date of publication. An odds ratio of less than one indicated that the trial favored the aminoglycoside-based regimen, whereas an odds ratio of greater than one favored the comparator regimen. Differences between the treatment arms were statistically significant only in those studies in which the confidence interval did not include the value one. Odds ratios could not be established in four studies in which a 100% success rate was reported for either the aminoglycoside or comparator arm [74,92,110,120]. Five studies demonstrated statistically significant differences in outcome [76,95,96,99,120], with two favoring the aminoglycoside-based regimen [76,120], and three favoring the comparator regimen [95,96,99]. One study [114] reported statistical significance in favor of the comparator regimen using logistic regression analysis, but this was not evident using simple Chi-square analysis.

TABLE 4. AMINOGLYCOSIDE-BASED REGIMENS

Agents	*Number of treatment arms*
Aminoglycosides	
Gentamicin	26
Tobramycin	15
Gentamicin or tobramycin	1
Netilmicin	4
Amikacin	2
Antianaerobic and other agents	
Clindamycin	35
Clindamycin or metronidazole	1
Metronidazole	4
Clindamycin plus ampicillin	3
Clindamycin plus penicillin	1
Metronidazole plus ampicillin	2
Metronidazole plus penicillin	1

Initial meta-analysis of data from all 5,182 patients revealed an OR of 1.194 (CI 1.014–1.407, $P = 0.04$), which slightly, but significantly, favored the comparator regimens. In reviewing the individual odds ratios, however, it appeared that trials published prior to 1990 were more likely to show therapeutic equivalence, whereas subsequent trials more consistently favored comparator regimens. Pooled data were therefore analyzed separately for trials published prior to 1990 and for those published in 1990 and later. Although no statistical difference was observed in the aggregate data published prior to 1990, the results of tri-

TABLE 5. COMPARATOR REGIMENS

Agents	*Number of treatment arms*
Cephalosporins	22
Cephalothin (monotherapy)	1
Cefamandole (monotherapy)	2
Cefoxitin (monotherapy)	4
Cefotetan (monotherapy)	2
Cefminox (monotherapy)	1
Cefotaxime (monotherapy)	1
Cefotaxime plus metronidazole	1
Cefoperazone (monotherapy)	1
Cefoperazone plus sulbactam	2
Cefoxatime plus clindamycin	1
Ceftriaxone (monotherapy)	1
Ceftriaxone plus metronidazole	1
Ceftazidime plus clindamycin	1
Cefipime plus metronidazole	1
Carbapenems:	9
Imipenem/cilastatin	6
Meropenem	3
Penicillins	9
Ampicillin/sulbactam	2
Amoxicillin/clavulanate	1
Ticarcillin/clavulanate	3
Piperacillin/tazobactam	2
Piperacillin	1
Aztreonam plus clindamycin	4
Moxalactam	3
Pefloxacin plus metronidazole	1

als published from 1990 on more strongly favored the comparator regimens (OR 1.438, n = 3,169, CI 1.165–1.775, $P = 0.001$; Fig. 3).

Six early trials [74,76,83,91,109,115] employed comparator regimens that lacked adequate anaerobic coverage according to contemporary standards [122]. These trials utilized cephalothin, cefamandole, cefotaxime, cefoperazone, or ceftriaxone as monotherapy. The data were therefore reanalyzed after excluding these six trials. A much greater risk of therapeutic failure for the aminoglycoside-based regimens was observed in this reanalysis (OR 1.296, n = 4,446, CI 1.085–1.547, $P = 0.004$; Fig. 4).

Data were also analyzed according to the class of comparator utilized (Fig. 5). Fluroquinolones were not analyzed because only one trial employed these agents. Subset analysis indicated that cephalosporins (OR 1.94, n = 1,426, CI 1.689–2.230, $P = 0.005$), carbapenems (OR 1.49, $n = 994$, CI 1.296–1.712, $P = 0.03$), and moxalactam (OR 2.24, $n = 313$, CI 1.944–2.578, $P = 0.002$) were favored over the aminoglycoside-based regimens. Azetreonam was also favored over aminoglycosides (OR 1.036, $n = 511$, CI 0.901–1.190), but this difference did not reach statistical significance. The odds ratio favored aminoglycoside-based regimens compared to regimens utilizing any type of penicillin (OR 0.91, $n = 1{,}060$, CI 0.792–1.046), but this difference was also not statistically significant. The trend in favor of aminoglycosides appeared to be due to studies utilizing ampicillin/sulbactam or amoxicillin/clavulanate; when studies using these latter agents were excluded, the odds ratio signifi-

FIG. 1. Distribution of quality scores.

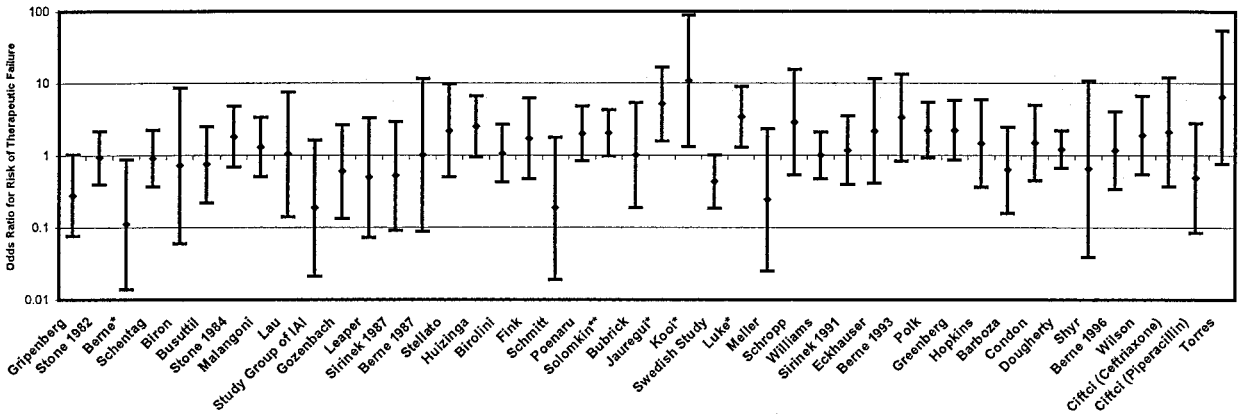

FIG. 2. Odds ratios for individual trials. Odds ratios could not be calculated for four trials [74,92,110,120] because the failure rate was zero in the aminoglycoside or comparator arm. Of these studies, that by Yellin et al. [120] demonstrated statistical significance in favor of the aminoglycoside-based regimen. *$P < 0.05$ by two-tailed test; **$P < 0.05$ by logistic regression analysis carried out in original trial, but not when recalculated by Chi square analysis.

cantly favored the remaining extended spectrum penicillins (OR 1.18, $n = 808$, CI 1.027–1.357, $P = 0.002$).

Study quality did not appear to have a major influence on the finding that comparator regimens were generally favored over aminoglycoside-based regimens. Trials were separated into two aggregates based on a quality score of less than or equal to two versus three or greater. In both subsets, the odds ratios favored the comparator agents, although this was statistically significant only for the subset with lower quality scores (quality score ≤ 2, OR 1.26, $n = 2{,}776$, CI 1.007–1.576, $P = 0.05$; quality score ≥ 3, OR 1.116, $n = 2{,}406$, CI 0.877–1.420, $P =$ ns; Fig. 6).

Since the appendix was the source of the infection in greater than 50% of patients for whom information was provided, a subset analysis was performed to determine if this influenced the results of this meta-analysis (Fig. 7). Forty trials provided sufficient information to allow separation into subsets based on the number of clinically evaluable patients who had appendiceal-related infections. Fifteen trials [76–79,84,91,93,96,97,101,105–107,110,120]

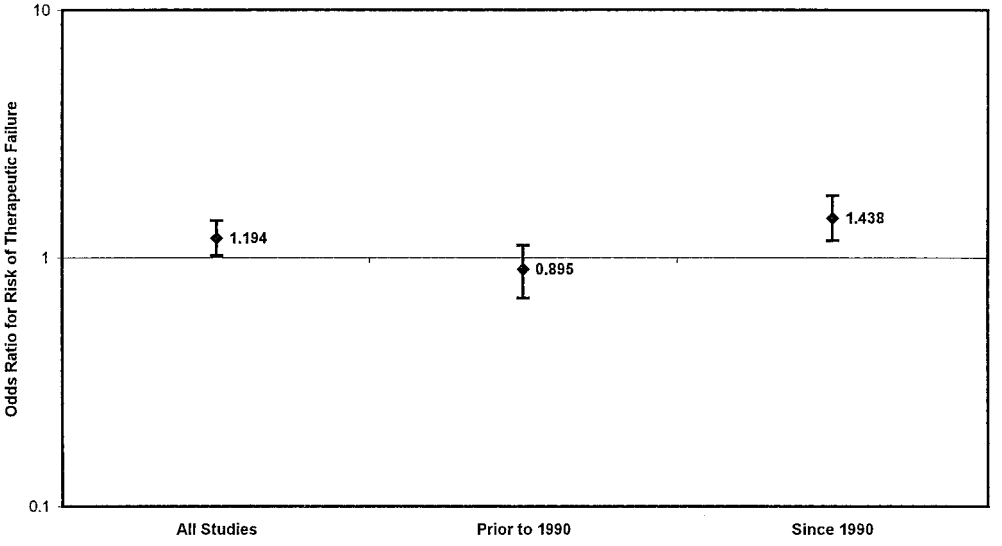

FIG. 3. Odds ratio for all studies and for studies stratified according to year of publication. For all studies $P = 0.04$; for those published prior to 1990 $P =$ ns; and for those published from since 1990 on $P = 0.001$.

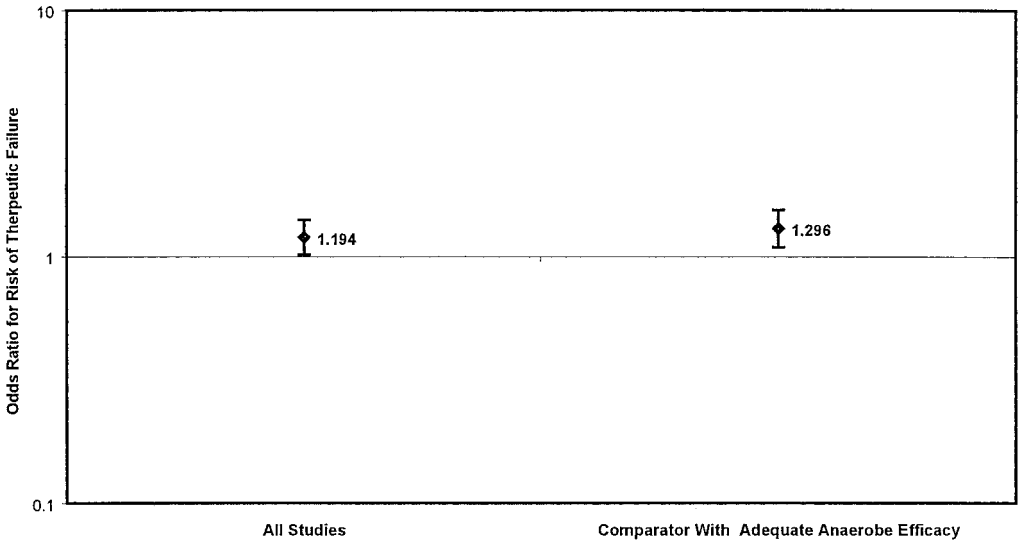

FIG. 4. Odds ratio for all studies and for studies remaining after elimination of those judged to have inadequate anaerobic coverage in the comparator arms. For all studies $P = 0.04$; for studies remaining after elimination of comparators with inadequate anaerobic efficacy $P = 0.001$.

enrolled patients with appendicitis exclusively. In these trials, the OR favored the aminoglycoside-based regimens, although this did not reach statistical significance (OR 0.83, $n =$ 1,108, CI 0.582–1.078, $P =$ ns). In a second set of seven trials [75,89,103,108,116–118], greater than 50% of the patients had the appendix as the source of their infection, although the trials were not limited to patients with appendicitis. In this subset, only a very slight advantage was observed for the comparator-based regimens (odds ratio 1.060, $n = 888$, CI 0.844–1.303, $P =$ ns). However, in the remaining studies in which fewer than 50% of the enrolled patients had the appendix as the source of their infections [81,85,87,88,90,92,94,98–100,104,109,110, 112,114,115,119], the comparator agents were significantly favored over aminoglycosides

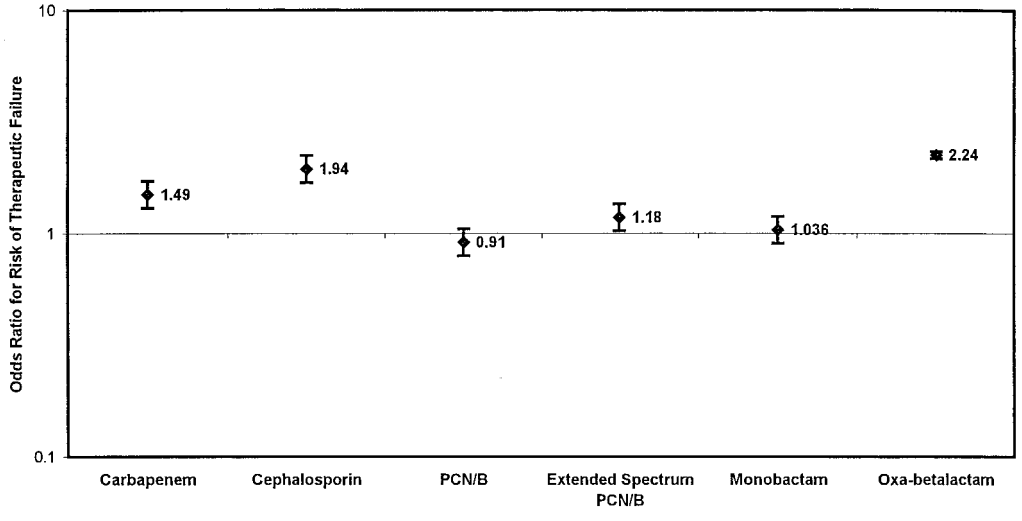

FIG. 5. Odds ratios for studies grouped according to class of comparator. For carbapenems $P = 0.03$; for cephalosporins $P = 0.005$; for any penicillins with or without beta-lactamase inhibitors (PCN/B) $P =$ ns; for penicillin/beta lactamase inhibitor combinations remaining after eliminating regimens utilizing ampicillin/sulbactam or amoxicillin/clavulanate (extended spectrum PCN/B) $P = 0.002$; for the monobactam $P =$ ns; and for the oxa-betalactam $P = 0.002$.

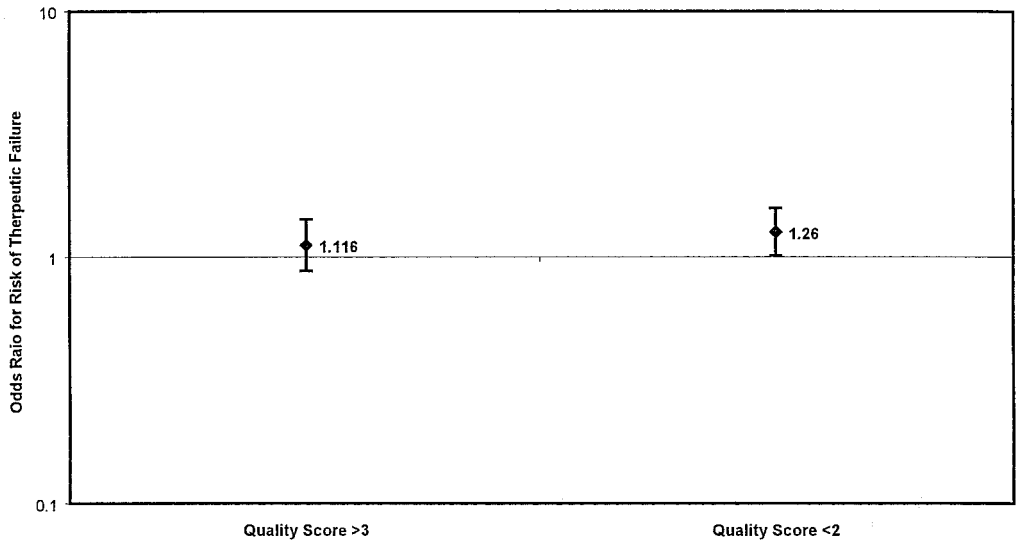

FIG. 6. Odds ratios for studies stratified by quality scores. For studies with quality scores of three or greater P = ns; for studies with quality scores of two or less $P = 0.05$.

(OR 1.399, n = 2,704, CI 1.133–1.728, $P = 0.002$). Thus, the source of the infection did appear to influence the results, with comparators being more strongly favored in trials involving larger numbers of patients with diagnoses other than appendicitis.

In 33 of the 47 studies, some monitoring of serum aminoglycoside concentrations was undertaken, although the manner in which this was used to adjust aminoglycoside dosing was not described in many articles. Trials were stratified according to whether or not serum drug monitoring was performed. Odds ratios favored comparators in both subsets, although these ratios did not reach statistical significance in either subset (group in which serum concentrations were monitored: OR 1.197, n = 3,670, CI 0.990–1.448, P = ns; group not monitored: OR 1.190, n = 1,512, CI 0.864–1.641, P = ns.).

A separate analysis was also carried out on

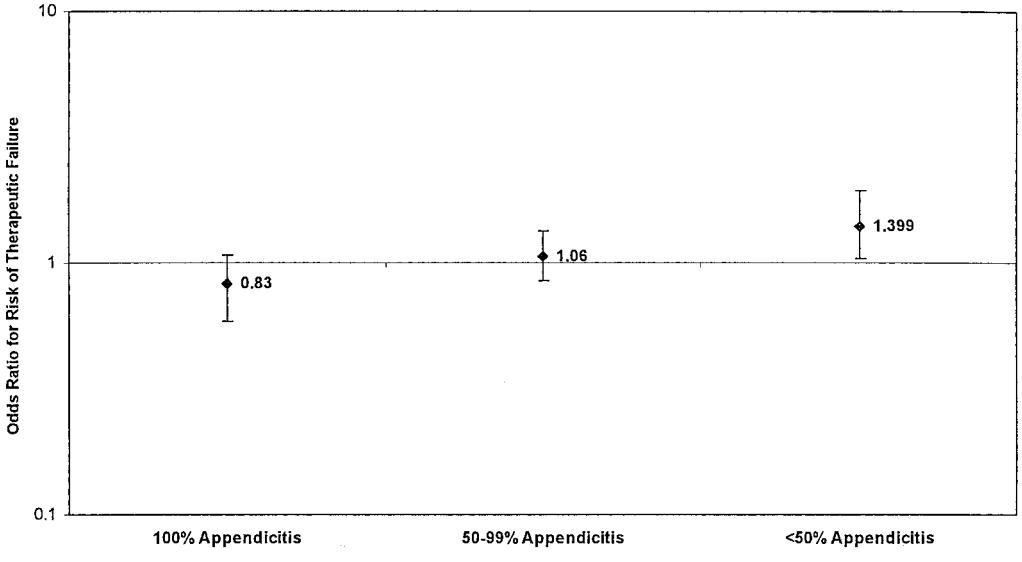

FIG. 7. Odds ratios for studies stratified according to the source of infection. For studies including only patients with appendicitis and those in which greater than 50% of the patients had appendicitis P = ns; for studies in which less than 50% of the patients had appendicitis $P = 0.002$.

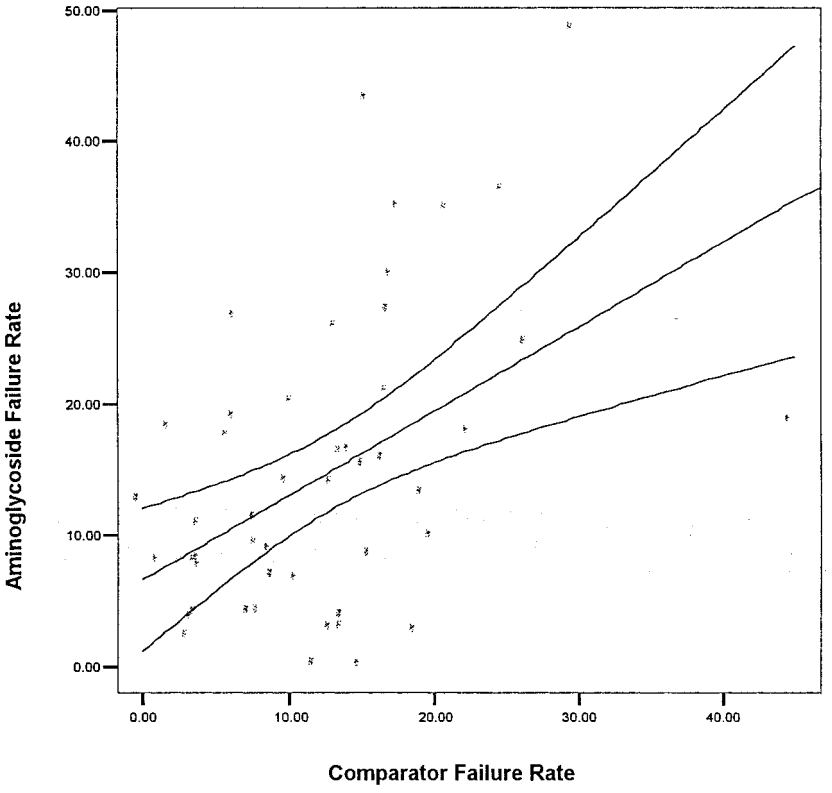

FIG. 8. Test of heterogeneity. The linear regression line for predicted rates of therapeutic failures with aminoglycoside-based regimens and comparator regimens, and the 95% confidence interval about this regression line are indicated. Data points indicate all individual studies.

the six trials that enrolled pediatric patients exclusively [84,91,96,101,105,106]. In this analysis, comparators were very slightly favored, but this difference was not significant.

Heterogeneity. Study heterogeneity was assessed by comparing actual and predicted rates of therapeutic failure for aminoglycoside-based and comparator regimens. As shown in Fig. 8, nearly two-thirds of the actual results reside outside of the predicted confidence interval, indicating significant heterogeneity of treatment effects among the various trials.

Aminoglycoside toxicity. Forty-two trials explicitly reported on nephrotoxicity, although definitions varied widely and occasionally were not described at all. Among these 42 trials, nephrotoxicity occurred in 98 patients, an incidence of 2.3%. Seventy of these patients were from trials that utilized some form of aminoglycoside monitoring, and 28 of these patients were from trials that did not report such monitoring. The incidences of nephrotoxicity in these two subsets were not statistically different by Chi square analysis.

There were only five trials involving 490 aminoglycoside-treated patients that reported explicitly on ototoxicity. Among these trials, six patients were found to have ototoxicity, an incidence of 1.2%. Five of these patients developed auditory toxicity, and one developed vestibular toxicity. Only two trials specifically described the use of some form of auditory monitoring or assessment by audiometry to detect ototoxicity. Two patients (0.9%) developed ototoxicity as a result of aminoglycoside exposure in those trials.

DISCUSSION

Effective treatment of intra-abdominal infection requires adequate drainage of peritoneal suppuration and optimally, definitive surgical control of infective foci. As adjuncts

to operative or percutaneous drainage, the role of antimicrobials is to limit the persistence of remaining infectious microorganisms. Antimicrobial therapy is given empirically, and culture results, even when obtained, rarely influence therapeutic choices or results. To be effective, antimicrobials must have activity against both the aerobic/facultative anaerobic bacteria and strictly anaerobic organisms found with intra-abdominal infections. Antimicrobial regimens that do not target both *Escherichia coli* and *Bacteroides fragilis* increase the risk of clinical treatment failure [122].

An aminoglycoside in combination with an antianaerobic agent was the first regimen generally recognized as efficacious in the treatment of intra-abdominal infection [122]. This combination is also relatively inexpensive. However, the ototoxicity and nephrotoxicity of aminoglycosides raise concerns. Routinely, serum drug concentrations are monitored to avoid toxicity and improve efficacy of these agents. However, even with careful monitoring of serum drug concentrations, aminoglycosides can still have significant toxic effects. The costs associated with pharmacokinetic surveillance as well as those associated with adverse effects may cancel out any cost savings that these agents appear to offer [123,124].

Since the first use of aminoglycosides for intra-abdominal infection, several newer antimicrobials effective against aerobic/facultative anaerobic gram-negative bacilli have become available. These agents include carbapenems, a number of second-, third- and fourth-generation cephalosporins, newer extended-spectrum penicillins (many times combined with beta-lactamase inhibitors) oxa-beta-lactams, monobactams, and fluoroquinolones. These agents have been compared to aminoglycosides for the treatment of patients with intra-abdominal infection in many prospective randomized controlled trials. Virtually all of these trials have demonstrated therapeutic equivalence of these newer comparators with aminoglycosides. A few have identified statistically significant differences in endpoints, some in favor of aminoglycosides and some in favor of comparator agents [123]. Particularly in the light of these latter studies, some have questioned the therapeutic role of aminoglycoside regimens as first-line agents for the treatment of patients with intra-abdominal infections. However, despite the large number of studies that have been carried out, the data from individual trials are inadequate to make this assessment definitively.

Meta-analysis provides a means to perform a structured and quantitative evaluation of the published literature and other studies addressing a specific clinical issue. This technique of mathematically pooling data from multiple trials may provide answers to questions when prior studies have shown conflicting or insignificant results, usually because of an inadequate sample size. In the present investigation, meta-analysis revealed a slight, but significant advantage to comparator agents compared to aminoglycoside-based regimens for the therapy of intra-abdominal infections.

Although in theory, the quantitative aspects of the meta-analytic tool may surpass the limitations of individual trials, in practice the reliability of the final product may be compromised by faulty design of the meta-analytic study itself as well as by poor quality of the individual data being pooled [1–5,125–127]. With regard to the quality of the pooled data, we sought to use the best evidence available for this analysis. This should be found in prospective randomized controlled trials published in peer-reviewed literature. In order to avoid inadvertent exclusion of relevant data, we utilized multiple overlapping search strategies to identify all publications that met our inclusion criteria, and only eliminated studies after they were reviewed fully.

For this meta-analysis, the few reports published in abstract form and unpublished data were not included as they tended to be quite old. We did not believe that this small amount of additional information was likely to be representative and unbiased, and was unlikely to influence appreciably the overall results. Due to limited resources it was not possible to review potentially useful prospective randomized controlled trials published in languages other than English, and these were excluded by our search strategy. This represents a limitation in the universal applicability of this data, which could potentially be addressed by future inquiry.

In recent years, a number of techniques have

been developed to assess the quality of prospective randomized controlled trials. External validation and evaluation of these techniques continues to evolve [6,125–127]. The primary goal of these scoring systems is to determine the likelihood of study bias. For this meta-analysis, we chose to score the component trials using the method described by Jadad et al. [6], because of its practical simplicity and familiarity to the authors. Essentially, the quality scores of the articles included in this analysis were normally distributed, with overall mean and median scores between two and three (Fig. 1). The overall low quality scores of many of the studies in this analysis is somewhat disturbing, however, raising the possibility of bias if lower quality studies favored one or the other treatment options. Therefore, we analyzed subsets that had been stratified according to their quality scores. The results in these subsets did not appear to deviate notably from the results of all studies combined, suggesting that study quality was not responsible for the observed advantage of comparators over aminoglycosides.

Some dismiss the use of meta-analyses entirely, noting that such studies are usually derived from combinations of heterogeneous data. Optimally, meta-analyses should be based on a series of homogenous studies, and the overall study results should mimic the results of the component studies. Unfortunately, such an ideal can rarely be realized. We employed one method of assessing study heterogeneity, by evaluating the variability of individual study results from the overall outcome [4]. As applied to our results, this method identified a significant degree of heterogeneity. Thus, the results of this meta-analysis need to be interpreted with some degree of caution. Nonetheless, some degree of trial heterogeneity is virtually inevitable, given the heterogeneous character of intra-abdominal infections in general, which would be further amplified by the numerous differences observed in overall study design and quality. Ultimately, future large-scale trials of aminoglycosides for the antimicrobial therapy of intra-abdominal infections are unlikely to be performed. Thus, the heterogeneous data obtained from trials published up to now will have to suffice for making recommendations with regard to the use of these agents.

In 1984, Solomkin et al. [128] provided a critical evaluation and review of study design and outcome reporting in trials of antimicrobials for intra-abdominal infection, based on the evaluation of sixteen trials published in the early 1980's. Some of the problems identified were inclusion criteria that permitted enrollment of patients with intra-abdominal contamination but not intra-abdominal infection; exclusion criteria that prevented enrollment of seriously ill patients or patients with postoperative or recurrent infections; nonuniform reporting of infectious diagnoses; and nonuniform reporting of outcomes, including the basis for designating patients as treatment failures.

Review of this larger and later collection of studies unfortunately revalidates these findings of Solomkin et al. Of the 5,182 evaluable patients, at least 1,100 (20%) had diagnoses potentially indicative of contamination but not necessarily infection. Many exclusion criteria that prevented enrollment of seriously ill patients were also encountered in this analysis. The mean adult age in this analysis of 40 years and the large number of patients with the appendix as the source of their intra-abdominal infection imply that patients enrolled in these studies were relatively younger and healthier than many with intra-abdominal infections. Thus, the applicability of these studies to an older and sicker population is problematic. Similarly, problems with regard to uniform reporting of infectious diagnosis and uniform criteria for reporting treatment outcome were evident in this analysis. With regard to this latter problem, the available data were generally insufficient to permit any attempt at revising reported success and failure rates. Ultimately, it was necessary to accept the investigator's designated outcomes at face value, although the differing definitions of success and failure likely contributed to the observed heterogeneity [121].

As indicated, the overall analysis favored the comparator agents over aminoglycosides. The difference in OR increased when evaluating only trials published since 1990. These findings could indicate that it is newer comparator agents that are more efficacious than amino-

glycosides for therapy of intra-abdominal infections. However, there exists the possibility that publication bias accounts in part for these observations. Particularly in later years, studies favoring comparator regimens might have been more likely to be published than studies favoring aminoglycosides.

The likelihood of publication bias is difficult to address without having access to the body of unpublished data collected over the years. However, the consistency of the results across a variety of different subset analyses argues against the possibility that publication bias was solely responsible for the observed findings. Perhaps some of the more interesting data came from subset analyses of different comparator classes, including those utilizing somewhat older agents. With the exception of the subset involving comparators from the penicillin class, all other regimens (carbapenem, cephalosporin, monobactam, and oxa-betalactam), were favored over aminoglycoside-based regimens. With comparators from the penicillin class, the apparent advantage of aminoglycoside-based regimens was entirely due to studies utilizing ampicillin/sulbactam and amoxicillin/clavulanate, agents that have an inferior spectrum of gram-negative coverage compared to aminoglycosides. Elimination of these studies resulted in the finding that extended-spectrum penicillin regimens were significantly more effective than aminoglycoside-based regimens. Another notable finding was that eliminating studies that employed comparator agents now considered to lack adequate antianaerobic activity also shifted the odds ratio more strongly in favor of the comparators. Thus, it appeared that comparator regimens having broad spectrum coverage of aerobic/facultative anaerobic gram-negative organisms and adequate anaerobic coverage consistently demonstrated equivalence or actual superiority compared to aminoglycoside-based regimens. These observations strengthen the hypothesis that newer comparator regimens are of potentially greater efficacy than aminoglycoside-based regimens for the therapy of intra-abdominal infections.

Failure to achieve adequate serum aminoglycoside concentrations has been cited as one possible explanation for study results favoring comparator regimens [114]. In this analysis, there was no apparent difference in outcome between those studies that reported monitoring of aminoglycoside serum concentrations and those that did not. However, the actual way in which monitoring was used to alter aminoglycoside dosing regimens was not outlined consistently. Very few studies provided any indication that prompt attainment of therapeutic aminoglycoside had been achieved, and none of the studies employed once daily dosing of aminoglycosides. Thus, the possibility that prolonged subtherapeutic concentrations of aminoglycosides contributed to increased failure rates remains a possibility.

In over 50% of the patients enrolled in these trials, the appendix was the source of the intra-abdominal infection. Although over 80% of these patients were described as having complicated appendicitis, some of those patients had gangrenous, but not perforated appendicitis. The remaining 20% of patients were only described as having appendicitis, without any other information being provided with regard to the nature of the disease process. Thus many of these patients with appendicitis may not have required greater than 24 h of antibiotics according to the Surgical Infection Society guidelines of Bohnen et al [1]. Many patients who had the appendix as their source of infection were enrolled in pediatric studies, and it is likely that many adult patients with appendicitis were also relatively young and healthy. It is notable that aminoglycosides were favored, although not significantly, in the studies in which all or a majority of the patients had the appendix as the source of their infections. Conversely, in the trials in which the majority of patients did not have the appendix as the source of infection, a significantly greater risk of therapeutic failure was observed in patients receiving aminoglycosides. Thus, the aminoglycoside-based regimens may actually have been less efficacious in patients with more serious infectious processes.

The incidence of nephrotoxicity reported with aminoglycoside use was two percent in this study population. Although this seems reassuringly low, not all studies consistently reported nephrotoxicity, and little can be said about the incidence of this complication in

older, higher-risk patients. Nonetheless, the costs of monitoring serum aminoglycoside concentrations for evidence of nephrotoxicity certainly add substantially to the burden of providing aminoglycoside therapy.

With regard to ototoxicity, only a tiny minority of studies reported any form of routine monitoring for this complication. Six patients were reported to have sustained some form of ototoxic injury associated with aminoglycoside therapy, although this was likely to have been underreported. The development of aminoglycoside-induced ototoxicity, as opposed to nephrotoxicity, is generally thought to be permanent, resulting in life-long disability. Thus, it is somewhat disturbing that routine monitoring was not employed to detect this complication in the vast majority of trials. As part of the assessment of the utility of these agents, this type of toxicity needs to be considered.

In conclusion, this meta-analysis indicates that aminoglycosides are no more efficacious, and possibly less so than newer comparator agents for the treatment of patients with intra-abdominal infections. Thus, these data refute the notion that aminoglycoside-based regimens should be considered the "gold standard" for the treatment of these infections. Although the cost of these pharmaceuticals by themselves may be low, the costs associated with monitoring add appreciably to the overall expense of these regimens, and may negate any cost advantage. In addition, these agents have a narrow therapeutic index, with well-known toxic side effects. Unfortunately, prospective evaluation of toxicity, particularly ototoxicity, has been poorly addressed in many of these clinical trials. For all these reasons, we do not believe that aminoglycosides should be utilized as first-line therapeutic agents for the treatment of intra-abdominal infection. Their use should probably be reserved for patients with severe allergic or anaphylactic reactions to most other classes of antibiotics, or to those patients who have failed treatment with other agents.

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APPENDIX: TRIAL DATABASE

Author	*N*	*N ev*	*AG agent*	*AG Combo Agent*	*Comp Agent*	*Comp Class*	*Comp Comb Agent*
Gripenberg	47	47	Tobra	Clinda	Cephalothin	Cephalosporin	Cephalexin
Stone 1982	249	155	Gent	Clinda	Cefotaxime	Cephalosporin	
Berne*	237	130	Gent	Clinda	Cefamandole or Cefperazone	Cephalosporin	
Strom	156	156	Gent	Clinda	Moxalactam	oxa-betalactam	
Baird	144	56	Gent	Clinda	Cefoperazone or Cefperazone	Cephalosporin	
Schentag	100	98	Tobra	Clinda	Moxalactam	oxa-betalactam	
Biron	42	37	Tobra	Clinda	Cefotaxime	Cephalosporin	Metronidazole
Busuttil	65	65	Gent	Clinda	Cefomandole	Cephalosporin	
Stone 1984	99	99	Gent	Clinda	Ceftriaxone	Cephalosporin	
Malangoni	170	112	Tobra	Clinda	Cefoxitin	Cephalosporin	Placebo
Yellin	197	105	Gent	Clinda	Ampicillin	PCN/B Lactam	sulbactam
Guerra	41	28	Gent	Clinda	Imipenem	Cilastatin	
Lau	122	105	Gent	Metronidazole	Cefoxitin	Cephalosporin	
Study Group of IAI	123	83	Gent	Clinda	Ampicillin	PCN/B Lactam	sulbactam
Gozenbach	93	93	Netilmicin	Clinda	Imipem	Carbapenem	Cilastatin
Leaper	45	43	Gent	Amp + Clinda	Imipem	Carbapenem	Cilastatin
Sirinek 1987	124	105	Gent	Clinda	Cefoxitin	Cephalosporin	
Berne 1987	162	84	Gent	Clinda	Azetreonam	Monobactam	Clinda
Stellato	105	59	Tobra	Clinda	Moxalactam	oxa-betalactam	
Huizinga	100	88	Gent	Amp + Metronidazole	Cefotetan	Cephalosporin	
Birolini	165	156	Tobra	Clinda	Azetreonam	Monobactam	Clinda
Fink	112	45	Gent	Clinda	Ticarcillin	PCN/B Lactam	Clavulanate
Schmitt	64	64	Netilmicin	Pen G + Metronidazole	Amoxicillin	PCN/B Lactam	Clavulanate
Poenaru	104	104	Tobra	Clinda or Metronidazole	Imipem	Carbapenem	Cilastatin
Solomkin**	290	162	Tobra	Clinda	Imipem	Carbapenem	Cilastatin
Bubrick	94	68	Tobra	Clinda	Ceftazidime	Cephalosporin	Clindamycin
Jauregui*	152	110	Gent	Clinda	Cefoperazone	Cephalosporin	sulbactam
Kooi*	100	100	Netilmicin	Metronidazole	Ceftazidime	Cephalosporin	Metronidazole
Swedish Study	271	184	Gent	Metronidazole	Pefloxacin	Quinolone	Metronidazole
Luke*	201	190	Netilmicin	Amp +Metronidazole	Ceftriaxone	Cephalosporin	Metronidazole
Meller	78	56	Gent	Clinda	Cefoxitin	Cephalosporin	
Schropp	154	97	Gent	Amp + Clinda	Cefoxatime	Cephalosporin	Clinda
Williams	316	209	Tobra	Clinda	Azetreonam	Monobactam	Clinda
Sirinek 1991	99	99	Gent	Clinda	Ticarcillin	PCN/B Lactam	Clavulanate
Eckhauser	145	117	Gent/Tobra	Clinda	Imipem	Carbapenem	Cilastatin
Berne 1993	156	96	Gent	Clinda	Cefipime	Cephalosporin	Metronidazole
Polk	331	147	Gent	Clinda	Piperacillin	PCN/B Lactam	Tazobactam
Greenberg	76	76	Gent	Clinda	Cefoperazone	Cephalosporin	sulbactam
Hopkins	114	76	Amikacin	Clinda	Cefotetan	Cephalosporin	
Barboza	67	62	Amikacin	Clinda	Azetreonam	Monobactam	Clinda
Condon	177	127	Tobra	Clinda	Meropenem	Carbapenem	
Dougherty	993	341	Gent	Clinda +/- Amp	Ticarcillin	PCN/B Lactam	Clavulanate
Shyr	77	76	Gent	Clinda	Piperacillin	PCN/B Lactam	Tazobactam
Berne 1996	228	129	Tobra	Clinda	Meropenem	Carbapenem	
Wilson	427	191	Tobra	Clinda	Meropenem	Carbapenem	
Ciftci (Ceftriaxone)	100	100	Tobra	PCN + Ornidazole	Ceftriaxone	Cephalosporin	Ornidazole
Ciftci (Piperacillin)	100	100	Tobra	PCN + Clinda	Piperacillin	PCN/B Lactam	
Torres	160	152	Gent	Metronidazole	Cefminox	Cephalosporin	

N, number of patients enrolled; N ev, number of evaluable patients; AG, aminoglycoside; AG s, number of evaluable aminoglycoside treatment successes; AG #, total number of evaluable subjects on aminoglycoside arm; C s, number of evaluable comparator treatment successes; C #, total number of evaluable subjects on comparator arm; Q, quality score; N Appy, number of evaluable pediatric patients; PK 1 = y, AG pharmacokinetic monitoring was reported; Year, year of study publication; 1 C/Ana, comparator regimen with accepted anti-anaerobe efficacy; ORRF, odds ratio; CI, confidence interval; Clinda, clindamycin; PCN, penicillin; Gent, gentamycin; Tobra, tobramycin; Amp, ampicillin.

AG S	*AG #*	*C S*	*C #*	*Q*	*N Appy*	*N Peds*	*PK 1 = y*	*Year*	*1 = C/Ana*	*ORRF*	*Lower CI*	*Upper CI*
22	27	11	20	0	47	47	0	1981	0	0.278	0.075	1.031
65	77	65	78	1	26	0	0	1981	0	0.923	0.392	2.174
39	40	73	90	3	130	0	1	1982	0	0.11	0.014	0.859
45	79	65	77	0	37	0	0	1982				
16	16	34	40	3	NR	NR	0	1983	0		0	0
37	49	36	49	2	13	0	1	1983	1	0.898	0.362	2.229
14	15	20	22	2	15	NR	0	1984	1	0.714	0.059	8.665
28	34	24	31	1	NR	NR	0	1984	0	0.735	0.217	2.486
38	52	39	47	2	20	0	0	1984	0	1.796	0.676	4.77
42	53	49	59	3	22	0	1	1985	1	1.283	0.496	3.32
38	38	59	67	4	105	0	1	1985	1		0	0
14	16	12	12	2	7	0	1	1985				
50	52	51	53	3	105	NR	1	1986	1	1.02	0.138	7.525
36	37	40	46	3	NR	0	1	1986	1	0.185	0.021	1.613
43	46	42	47	2	53	0	1	1987	1	0.586	0.132	2.609
22	24	16	19	2	5	0	1	1987	1	0.485	0.072	3.247
49	51	50	54	3	105	NR	1	1987	1	0.51	0.089	2.914
27	28	54	56	2	84	0	1	1987	1	1	0.087	11.525
24	30	26	29	3	15	NR	1	1988	1	2.167	0.487	9.641
28	43	37	45	3	27	0	1	1989	1	2.478	0.922	6.659
69	80	66	76	2	78	NR	0	1989	1	1.052	0.419	2.641
16	25	15	20	3	10	0	1	1989	1	1.688	0.46	6.195
34	35	25	29	1	64	64	0	1989	1	0.184	0.019	1.746
34	52	41	52	1	NR	0	1	1990	1	1.973	0.821	4.744
57	81	67	81	2	39	0	1	1990	1	2.015	0.954	4.256
31	34	31	34	2	NR	0	1	1990	1	1	0.187	5.344
25	34	71	76	3	NR	0	1	1990	1	5.112	1.564	16.71
41	50	49	50	1	100	100	0	1990	1	10.756	1.308	88.473
94	104	64	80	3	115	0	1	1990	1	0.426	0.182	0.997
78	96	88	94	2	76	NR	0	1991	1	3.385	1.279	8.954
26	27	25	29	1	56	56	1	1991	1	0.24	0.025	2.301
42	47	48	50	5	97	97	0	1991	1	2.857	0.527	15.504
89	105	88	104	3	96	0	1	1991	1	0.989	0.466	2.099
36	43	48	56	1	99	NR	1	1991	1	1.167	0.387	3.514
59	64	51	53	2	18	NR	1	1992	1	2.161	0.402	11.619
38	46	47	50	3	96	0	1	1993	1	3.298	0.818	13.296
32	43	90	104	3	79	0	1	1993	1	2.21	0.91	5.364
15	29	33	47	3	24	0	1	1994	1	2.2	0.843	5.745
31	36	36	40	3	76	NR	1	1994	1	1.452	0.358	5.885
27	31	25	31	2	36	0	0	1994	1	0.617	0.156	2.447
56	63	59	64	4	46	0	1	1995	1	1.475	0.442	4.919
115	137	176	204	2	NR	124	1	1995	1	1.202	0.656	2.204
45	46	29	30	3	21	0	1	1995	1	0.644	0.039	10.713
60	66	58	63	5	129	0	1	1996	1	1.16	0.336	4.01
87	94	93	97	5	141	0	1	1997	1	1.871	0.529	6.613
46	50	48	50	2	100	100	0	1997	1	2.087	0.365	11.948
48	50	46	50	2	100	100	0	1997	1	0.479	0.084	2.743
70	76	75	76	2	95	0	1	2000	1	6.429	0.755	54.744