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Review

ANTIBIOTIC THERAPY IN INTRA-ABDOMINAL INFECTIONS A REVIEW ON RANDOMISED CLINICAL TRIALS

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Abstract: There have been 79 randomised antibiotic studies in intra-abdominal infections retrieved. The overall success rate of the studied antibiotics ranges from 70-100%. Unfortunately only about one fourth of the studies have used a disease severity classification, e.g., APACHE II score, despite clear recommendations by the Surgical Infections Society of North America. The mortality rate in the published antibiotic studies is still rather low (approximately 4%) and does not correspond to the average mortality in peritonitis (30-40%). Failure analysis is not uniform and only performed in about 1/5 of retrieved studies. Failure analysis included data on diagnosis, type of operation, pathogen isolated at first operation, susceptibility and persistence of pathogen, re-operation or change of antibiotic regimen, and follow-up (ICU duration, death or survival, hospitalisation). Only one study has performed an analysis of the adequacy of the surgical treatment (source control). The clinical success rate of the antibiotics studied in a larger population is comparable for gentamicin + clindamycin (80%), tobramycin + clindamycin (83%), meropenem (89%), imipenem (85%), aztreonam + clindamycin (89%), cefoxitin (88%), cefotetan (92%), moxalactam (83%), cefotaxime + metronidazole (87%), ampicillin/sulbactam (87%). Piperacillin/tazobactam has in most studies a success rate of approximately 90%. The aggregated data on adverse events and clinical failure rate do not show a major advantage for any of these antibiotics. It is striking that the adverse event rate reported for ticarcillin/clavulanic acid is low when compared to all other antibiotics, which is in contrast to severe adverse events reported for clavulanic acid. The data of quinolone studies in intra-abdominal infections do not yet allow a recommendation, even when it is acknowledged that two studies were performed with good results and a good study plan. In conclusion, the comparability of antibiotic studies in intra-abdominal infections is limited due to a lack of disease severity stratification and a relatively small study population for most antibiotics. The clinical success rate of the best-studied antibiotics is similar and the choice which antibiotic is used depends on the expected pathogens and the resistance rate in a clinical setting.

Key words: Intra-abdominal infections, antibiotic therapy; peritonitis; intra-abdominal abscess; adverse events; cephalosporin; carbapenem quinolone; sorce control; aminoglycoside

INTRODUCTION

The treatment of intra-abdominal infection is based on surgical treatment, the use of potent antibiotics and when necessary intensive care treatment. Solomkin has reviewed antibiotic studies of intra-abdominal infection in 1984 and criticized the heterogeneity of the study population, the lack of stratification and the failure to define the severity of illness. In many studies intra- and extra-abdominal infections were grouped together, and reporting of bacteraemia, verification of disease, and outcome measures were inconsistent. (Solomkin et al. 1984) Up to 1984 the mortality rate in most studies was rather low (3.5%) and the authors reported an overall success rate of 84% for aminoglycoside plus clindamycin, 89% for aminoglycoside plus metronidazole, and 93% for cephalosporin-based regimens. Exclusionary criteria did not allow enrollment of seriously ill patients or infections associated with high failure rates. (Solomkin et al. 1984). Most studies did not allow the evaluation of the clinical failures. There was no information on source control available. It was therefore concluded that it could not be decided whether treatment failures were due to inadequate antibiotic therapy. (Solomkin et al. 1984). With regard to single operation and single antibiotic treatment different success rates were reported: the overall mortality was 24% and the rate of treatment success with a single operation and single course of antibiotics was 48%. (Dellinger et al. 1985). The comparability of antibiotic studies may be better since Meakins proposed a classification of intra-abdominal infections based on ten etiologic classifications of intra-abdominal infection combined with an acute physiology score (APS). (Meakins et al. 1984).

The purpose of this study was to evaluate the randomised clinical antibiotic trials in intra-abdominal infections and/or peritonitis for their information on surgical therapy (source control), stratification, mortality, clinical and bacteriological success rates, and adverse events to develop a recommendation for the appropriate use of antibiotics in clinical practice.

MATERIAL AND METHODS

We focussed this investigation on randomised, controlled antibiotic studies in intra-abdominal infections and peritonitis. A medline search for randomised clinical antibiotic trials in intra-

abdominal infection and peritonitis was performed. Studies were included for evaluation if the majority of study patients had intra-abdominal infection. Several studies were excluded when only few patients had intra-abdominal infections (Levine et al. 1989).

Stratification was positive when the trial reported information on the APS, APACHE II score or the sepsis score. The mortality is indicated as the overall mortality of the study. Clinical and bacteriological failures were included when indicated by authors or whenever it could be calculated from the available data. Adverse events were recorded as the percentage of adverse events per study population. We screened the publications for analysis of the adequacy of the surgical procedure (source control) and whether an analysis of treatment failures was done.

Results

We retrieved 79 studies including 9890 evaluable patients, which investigated the clinical efficacy of antibiotics in intra-abdominal infections since 1972. The average study population of evaluable patients consists of 125 patients (range 5 – 460). Since 1984 there are 30/67 (44.8%) studies with less than 100 evaluable patients per study and since 1990 16/42 (38.1%) studies in which less than 100 patients were evaluable. The mortality rate is 4.8% for all studies. Most studies concentrated on intra-abdominal infections (88.9%). Nine of 79 studies investigated patients with different surgical infections.

Stratification

21/79 (26%) studies have indicated a comparable stratification system, e.g., APACHE II, SAPS; there are 43/67 (64.2%) studies since 1984 without disease severity stratification.

22 (28%) studies investigated "severe", "serious" or "complicated" intra-abdominal infections. 13 (59%) of these reports did include a disease severity stratification system. Four (22%) studies reported mean APACHE II scores of above 10 (de Marie 1998; Colardyn 1996; Cakmakci 1993; Jaspers 1998). The Canadian Metronidazole Study Group enrolled patients with a mortality rate of 17.7%. The mean APACHE II scores were less than 10 in 2 studies (Zanetti 1999; Barie 1997). In one study more than 65% of the enrolled patients had an APACHE II score 10 or less (Kempf 1996), in another study 94% of patients had an APACHE II score of 1-10 and only 6% had an APACHE II score of 11-20 (Brismar 1996). In one study the SAPS score was applied (Dupont 2000). The mean mortality in these studies on severe, complicated or serious intra-abdominal infections was 4.3 % (range 0-17.7) (Table 1).

Clinical and Bacteriological Outcome

71 of 79 studies (89.9%) rated the clinical outcome as success or failure, 28/79 studies (35.6%) evaluated the bacteriological outcome as success or failure. The overall clinical success rate was 84.58%; the overall bacteriological success rate was 83.75%.

18 different *aminoglycoside* combinations were investigated in intra-abdominal infections. Most patients were enrolled in 21 studies with clindamycin/gentamicin (n = 1517) followed by 12 studies using tobramycin/clindamycin (n = 561) and 4 studies using gentamicin/metronidazole (n = 241). Triple combinations were investigated in seven studies. Studies indicated a clinical success rate of 52% to 100%. The combination gentamicin/clindamycin had a mean clinical failure rate of 19.4 ± 21.5 (0-48), tobramycin/clindamycin 17.37 ± 2.7 (6.6-29.6) (Table 2).

19 *cephalosporin* antibiotics were investigated in intra-abdominal infections. Cefotetan (n = 395 patients) was used in 5 studies, cefoxitin (n = 389) in 6 studies, moxalactam (n = 316 patients) in 5 studies, and cefotaxime/metronidazole (n = 236 patients) in 4 studies. The overall clinical success rate ranges from 56.9% to 97%. Cefoxitin is associated with a mean failure rate of 12.31 ± 0.56, cefotetan with 8.4 ± 2.8, moxalactam with 16.5 ± 10.6 and cefotaxime/metronidazole with 13.25 ± 11.32 (Table 3).

Four *carbapenem/monobactam* products (alone or in combination) were investigated in intra-abdominal infections. Most patients were enrolled in imipenem studies (n=1637) in 23 studies, followed by meropenem (n = 657) in 10 studies, and aztreonam/ clindamycin (n = 241) in 5 studies. The clinical success rate ranges from 57% to 100%. Meropenem is associated with a mean failure rate of 10.7 ± 5.93, imipenem with 14.4 ± 3, aztreonam/clindamycin with 10.6 ± 5.93 and biapenem with 34.9 (Table 4).

4 different quinolones (alone or in combination) were examined in intra-abdominal infections. Ciprofloxacin, alone or with metronidazole, was used in 4 studies (n = 196 patients). Trovafloxacin (n = 156) and clinafloxacin (n = 150) were examined each in one study only. The clinical success rate ranges from 82% to 95%. The clinical failure rate for trovafloxacin was 18% and for clinafloxacin 17% (Table 5).

7 *Penicillin and penicillin/β-lactam inhibitors* regimens were examined in intra-abdominal infections. Most patients were enrolled in 5 piperacillin/tazobactam studies (n = 430), followed by 3 ticarcillin/clavulanic acid studies (n = 280), and 2 studies with ampicillin/sulbactam (n = 163). One study was performed with amoxycillin/clavulanic acid (n = 40). The clinical success rate ranges from 48% to 93.3%. Piperacillin/tazobactam is associated with a mean failure rate of 34.35 ± 39.1, ticarcillin/clavulanic acid with 20.06 ± 2.6, ampicillin/sulbactam with 13 ± 1.41 (Table 6).

Clinical Failure Rates in Imipenem/Cilastatin Studies in Intra-abdominal Infections

Imipenem/cilastatin was tested in 23 randomised studies (n = 1637 patients) in intra-abdominal infections. In 8/23 studies other surgical infections, e.g., soft tissue infection, pneumonia, were investigated. 16/23 studies enrolled less than 100 evaluable patients in the imipenem/cilastatin study arm. The mean clinical failure rate was 14.4 ± 3 ranging from

Table 1. Studies investigating the effect of antibiotic treatment in "severe", "serious", "complicated" intra-abdominal infections.

Author	Year	APACHE II score	Mortality
Canadian Study Group	1983	-	17.7
Henning	1984	-	0
Tally	1986	-	3
Christen	1987	-	0
Scott	1987	-	6
Huizinga	1988	-	3
Leal del Rosal	1989	-	0
Fink	1989	-	0
Swedish Study Group	1990	-	1
Eckhauser	1992	-	5.1
Kreter	1992	-	5.1
Walker	1993	-	0
Cakmakci	1993	11.8 (4-29) I/C 10.3 (0-27) C	0
Piperacillin/Tazobactam Study Group	1994	-	8.1
Kempf	1996	1-10 > 65% 11-20 30%	1.2
Colardyn	1996	14.1 ± 6.9	14.6
Brismar	1996	1-10 94% 11-20 6%	6
Barie	1997	9.3 ± 8 (median)	4.3
De Marie	1998	17	0
Jaspers	1998	18 (10-29) 20 (6-41)	2.8
Zanetti	1999	6.4	3.7
Dupont	2000	SAPS score 30 ± 11 31 ± 11	12.2

I/C = Imipenem/cilastatin; C = Comparator

Table 2. Aminoglycoside antibiotics and combinations – clinical failure rate.

Antibiotic	Patients	Studies	Clinical Failure
Gentamicin + clindamycin	1517	21	19.4 ± 21.5 (0-48)
Gentamicin + clindamycin + ampicillin	22	1	18
Tobramycin + clindamycin	561	12	17.37 ± 2.7 (6.6-29.6)
Amikacin + clindamycin	31	1	6.3
Aminoglycoside + clindamycin + amoxycillin	28	2	23 (overall) includes also pneumonia
Gentamicin + ampicillin + metronidazole	49	1	35
Tobramycin + metronidazole	68	2	17
Gentamicin + metronidazole	241	4	5.7 ± 4.59 (3-10.3)
Aminoglycoside + ornidazole	55	1	9
Aminoglycoside + clindamycin	153	3	9.25 ± 2.05
Gentamicin + cefuroxime (± metronidazole)	33	1	33
Gentamicin	51	1	9.9
Tobramycin	52	1	7.7
Gentamicin + Penicillin G + Metronidazole	24	1	25
Gentamicin + chloramphenicol	124	1	48.7
Netilmicin + ampicillin + metronidazole	96	1	18.7
Netilmicin + tinidazole	20	1	5
Netilmicin + clindamycin	67	2	5.45 ± 7.7 (0-10.9)

Table 3. Cephalosporin antibiotics and combinations – clinical failure rate.

Antibiotic	Patients	Studies	Clinical Failure
Cefuroxime + metronidazole	108	2	26.75 ± 13.08
Cefotaxime + metronidazole	236	4	13.25 ± 11.32 (3-25)
Cefotaxime + metronidazole + topical cefotaxime	87	1	17
Cefoperazone + sulbactam	123	2	18.3 ± 6.5
Ceftazidime + clindamycin	41	1	9
Cefepime + metronidazole	145	2	6
Cefotaxime	201	2	18
Cefotetan	395	5	8.4 ± 2.8 (2-18)
Cefoxitin	389	6	12.31 ± 0.56
Cefoxitin ± Tobramycin	33	1	9
Moxalactam	316	5	16.5 ± 10.6 (9-24)
Cephalothin	44	1	43.1
Ceftriaxone + metronidazole	94	1	6.3
Cefuroxime	59	1	22
Ceftriaxone	94	1	17.1
Cefoperazone	141	1	Not evaluated
Cefamandole + erythromycin	60	1	Not evaluated
Cephradine + metronidazole	28	1	25
Ceftazidime	40	1	12.5

Table 4. Carbapenem-, Monobactam-, Quinolone-, Penicillin-antibiotics – clinical failure rate.

Antibiotic	Patients	Studies	Clinical Failure
Meropenem	657	10	10.7 ± 5.93 (0-43)
Imipenem/cilastatin	1637	23	14.4 ± 3 (0-37.5)
Biapenem	43	1	34.9
Aztreonam + clindamycin	241	5	10.6 ± 5.93
Trovafloxacin	156	1	17
Clinafloxacin	150	1	18
Ciprofloxacin + metronidazole	111	1	10 ± 8.4
Ciprofloxacin	85	3	5
Pefloxacin + metronidazole	104	1	6.3
Piperacillin	91	2	19.2 ± 13.8
Amoxycillin + clavulanic acid + metronidazole	40	1	10
Piperacillin + tazobactam	430	5	34.35(39.1 (6.7-62)
Piperacillin + tazobactam + amikacin	105	1	53
Amoxycillin + clindamycin	29	1	23
Ticarcillin + clavulanic acid	280	3	20.06 ± 2.6 (14.2-25)
Ampicillin + sulbactam	163	2	13 ± 1.41
Clindamycin	17	1	12.8 ± 6.7
Chloramphenicol	50	1	Not evaluated
Ornidazole	12	1	8.3
Aspoxicillin	52	1	9.6

Table 5. Clinical failure rate and severity of illness in case of imipenem.

Year	Author	Patients per study arm	Clinical failure rate %	APACHE II score
1985	Solomkin#	24	24.3 (overall)	0 – 9 21.6% 10 – 19 67.6% 20 – 30 11.8
1987	Christen#	8	37.5	-
1987	Gonzenbach	47	12.8	-
1988	Danziger#	3	0 (overall)	-
1990	Geroulanos#	8	13 (overall)	-
1990	Solomkin	83	17.2	13 (median)
1992	Eckhauser	53	3.8	-
1992	Kreter#	170	0	-
1993	Cakmakci#	16	14.6 (overall)	11.8 (overall)
1993	De Groot	38	24	7 (1-8)
1993	Karrellakopoulou	32	3.2	-
1993	Niinikoski	39	11.5	-
1995	Geroulanos	88	6	-
1996	Christou	104	12.2	8.9 ± 5.3
1996	Colardyn#	87	23	14.1 ± 6.9
1996	Brismar	40	32.5	0-10 92.5% 11-20 7.5%
1996	Solomkin	113	19	10.5 ± 6.3
1997	Barie	122	24	9.3 ± 8 (median)
1997	Basoli	101	6.4	-
1998	Donahue	152	16	7
1998	Jaccard#	83	5	7.3 ± 4.9
1999	Zanetti	64	6.2	6.4 (overall)
2001	Solomkin	162	20	7.8 ± 5.1
Total n = 23		1637	14.4	

study includes other types of infections (pneumonia, soft tissue infection)

Table 6. Failure analysis in antibiotic studies in intra-abdominal infection.

Author	Infection	Pathogen	Susceptibility	Elimination of pathogen	Adequacy of surgical intervention	Clinical cause of treatment failure	Follow-up
Solomkin 2001	X	X	X	X	X	X	X
Donahue 1998	X	X	X	X	-	-	X
Jaspers 1998	X	X	X	-	-	-	X
Solomkin 1996	X	X	X	X	-	X	X
Christou 1996	X	X	X	X	-	X	X
Kempf 1996	X	X	X	X	-	-	X
Doughtery 1995	X	X	X	-	-	X	-
Greenberg 1994	X	X	-	-	-	-	X
Berne 1993	X	X	X	X	-	X	-
Solomkin 1990	X	X	X	X	-	X	X
Fink 1989	X	X	X	X	-	X	-
Tally 1986	X	X	X	X	-	X	X
Birolini 1985	X	X	X	X	-	X	-

Table 7. Adverse reactions in antibiotic studies in intra-abdominal infections.

Author	Year	Antibiotics	Adverse reactions %
Rambo	1972	Cephalothin	-
Stone	1975	Tobramycin vs Gentamicin	9.6 vs 11.8
Stone	1980	Gentamicin + clindamycin vs gentamicin + metronidazole vs cefamandole + erythromycin	25.4 (overall)
Smith	1980	Tobramycin + metronidazole vs clindamycin + tobramycin	4 vs 5.8
Collier	1981	Metronidazole vs clindamycin	28.6 vs 38
Stone	1982	Cefotaxime vs gentamicin + clindamycin	15.8 vs 30.7
Kirkpatrick	1983	Gentamicin + clindamycin vs gentamicin + metronidazole	0 - 18
Giamarellou	1982	Ornidazole vs clindamycin	Unclear
Schentag	1983	Moxalactam vs tobramycin + clindamycin	55 vs 43
Smith	1983	Metronidazole	Not reported
Canadian study group	1983	Gentamicin + metronidazole vs gentamicin + clindamycin	10 vs 10
Stone	1983	Gentamicin + clindamycin vs gentamicin + metronidazole	Not indicated
Stone	1983	Third Generation cephalosporins vs gentamicin + clindamycin	9.9 vs 13.2
Biron	1984	Cefotaxime + metronidazole vs clindamycin + tobramycin	Not indicated
Henning	1984	Netilmicin tinidazole vs netilmicin + clindamycin	Not indicated
Stone	1984	Gentamicin + clindamycin vs ceftriaxone	12.2 vs 0
Solomkin	1985	Imipenem/cilastatin vs gentamicin + clindamycin	10.8 vs 27
Yellin	1985	Ampicillin/sulbactam vs clindamycin + gentamicin	21 vs 13
Malangoni	1985	Cefoxitin vs tobramycin + clindamycin	20.3 vs 17
Birolini	1985	Aztreonam + clindamycin vs tobramycin + clindamycin	8.3 vs 10
Törnqvist	1985	Cefuroxime vs cefuroxime + metronidazole	Not indicated
Lennard	1985	Clindamycin + gentamicin vs gentamicin + chloramphenicol	3.8 vs 0
Heseltine	1986	Cefoxitin vs clindamycin + gentamicin	9 vs 15
Tally	1986	Moxalactam vs cefoxitin ± tobramycin	33 vs 41
Nomikos	1986	Chloramphenicol	Not indicated
Gonzenbach	1987	Imipenem/cilastatin vs netilmicin + clindamycin	8.5 vs 8.7
Berne	1987	Aztreonam + clindamycin vs gentamicin + clindamycin	Unclear
Christen	1987	Imipenem/cilastatin vs aminoglycoside + amoxycillin + clindamycin	0
Scott	1987	Cefotetan vs gentamicin + penicillin G + metronidazole	Unclear
Lewis	1988	Cefotetan vs cefoxitin	27.3 vs 16.7
Huizinga	1988	Cefotetan vs ampicillin + gentamicin + metronidazole	2-31 vs 5-26 (different laboratory values)
Stellato	1988	Moxalactam vs tobramycin + clindamycin	24.1 vs 33.3
Wilson	1988	Cefotetan vs moxalactam Cefotetan vs cefoxitin	17 vs 16 27 vs 17
Danziger	1988	Imipenem/cilastatin vs clindamycin + gentamicin	45-72.7 vs 44.4 (no exact data available)
Birolini	1989	Aztreonam vs tobramycin	18.4 vs 16.2
Leal del Rosal	1989	Ciprofloxacin	Not indicated
Fink	1989	Gentamicin + clindamycin vs ticarcillin + clavulanic acid	3.3 vs 2.7
Bubrick	1990	Ceftazidime + clindamycin vs tobramycin + clindamycin	0 vs 6.4
Geroulanos	1990	Imipenem/cilastatin vs aminoglycoside + amoxycillin + clindamycin	0
Swedish Study Group	1990	Pefloxacin + metronidazole vs gentamicin + metronidazole	10.6 vs 8.8
Solomkin	1990	Tobramycin + clindamycin vs imipenem/cilastatin	12.5 vs 7.1
Jauregui	1990	Cefoperazone + sulbactam vs gentamicin + clindamycin	3-10 vs 1.9 –13 (no overall result available)

Author	Year	Antibiotics	Adverse reactions %
Luke	1991	Ceftriaxone + metronidazole vs ampicillin + netilmicin + metronidazole	Not indicated
Paakkonen	1991	Piperacillin vs cefuroxime + metronidazole	0
Yoshioka	1991	Ciprofloxacin + metronidazole vs amoxycillin + clavulanic acid + metronidazole	2.6 vs 0
Sirinek	1991	Ticarcillin + clavulanic acid vs gentamicin + clindamycin	Unclear
Kreter	1992	Imipenem/cilastatin vs clindamycin + aminoglycoside	12 vs 13
Eckhauser	1992	Imipenem/cilastatin vs clindamycin + aminoglycoside	7.5 vs 6.2
Berne	1993	Cefepime + metronidazole vs gentamicin + clindamycin	40 vs 19.6
Cakmakci	1993	Imipenem/cilastatin vs aminoglycoside + amoxycillin + clindamycin	0
Walker	1993	Ampicillin + sulbactam vs cefoxitin	34.3 vs 31.7
de Groot	1993	Imipenem/cilastatin vs aztreonam + clindamycin	17 vs 17 (only for phlebitis a clear% indicated)
Niinikoski	1993	Piperacillin + tazobactam vs imipenem/cilastatin	14.9 vs 2.6
Kanella-kopoulou	1993	Meropenem vs imipenem/cilastatin	No exact data available
Yellin	1993	Clindamycin (900 every 8h) vs clindamycin (600 every 6h)	15 vs 15
Polk	1993	Piperacillin + tazobactam vs clindamycin + gentamicin	2 vs 4
Barboza	1994	Clindamycin + amikacin vs clindamycin + aztreonam	29.4 vs 15.1
Scheinin	1994	Aspoxicillin vs piperacillin	1.9 vs 0
Piperacillin/ Tazobactam Study Group	1994	Piperacillin + tazobactam vs clindamycin + gentamicin	29 vs 27.2
Greenberg	1994	Cefoperazone + sulbactam vs clindamycin + gentamicin	2-60 vs 3.4-52 (different side effects – no overall rate available)
Dougherty	1995	Ticarcillin + clavulanic acid vs clindamycin + gentamicin ± ampicillin	0.2-2.3 vs 0.6-1.4 (different side effects – no overall rate available)
Huizinga	1995	Meropenem vs cefotaxime + metronidazole	15.6 vs 12
Geroulanos	1995	Meropenem vs imipenem/cilastatin	38.8 vs 36.2
Condon	1995	Meropenem vs tobramycin + clindamycin	No overall rate available
Kempf	1996	Meropenem vs cefotaxime + metronidazole	25 vs 28.3
Colardyn	1996	Meropenem vs imipenem/cilastatin	9 vs 12
Christou	1996	Cefoxitin vs imipenem/cilastatin	1.3 vs 4
Brismar	1996	Biapenem vs imipenem/cilastatin	19 vs 20
Solomkin	1996	Ciprofloxacin + metronidazole vs imipenem/cilastatin	Unclear
Berne	1996	Meropenem vs tobramycin + clindamycin	9.5 vs 3
Barie	1997	Cefepime + metronidazole vs imipenem/cilastatin	13-24 vs 13-24 (different side effects – no overall rate available)
Basoli	1997	Imipenem/cilastatin vs meropenem	0.7 vs 2.7
Jaspers	1998	Meropenem vs cefuroxime + gentamicin	48.7 vs 45
De Marie	1998	Ciprofloxacin	Not indicated
Donahue	1998	Trovafloxacin vs imipenem/cilastatin	Unclear
Jaccard	1998	Imipenem/cilastatin vs piperacillin + tazobactam	13.6 vs 15.9
Zanetti	1999	Meropenem vs imipenem/cilastatin	16.9 vs 20.3
Dupont	2000	Piperacillin + tazobactam vs piperacillin + tazobactam + amikacin	52 vs 57
Solomkin	2001	Clinafloxacin vs imipenem/cilastatin	34 vs 26

0% to 37.5%. 13 studies (56.5%) were performed with disease stratification. In 8/13 studies with disease stratification the average APACHE II score was 10 or less. 5 studies included patients with an average APACHE II score of more than 10 (Table 7).

Evaluation of Surgical Therapy (Source Control)

Treatment, according to the methods section in most studies, was considered successful if resolution of signs and symptoms of infection was achieved with a single course of antibiotics and if only one operation was required to control the infectious process. The treatment was considered a failure if antimicrobial therapy was changed because of lack of response, if additional operations were required to control the local infectious process, or if any adverse reaction occurred requiring a change of antibiotic therapy. (Solomkin et al. 1985). Failure analysis is presented in studies by Birolini 1985, Tally 1986, Fink 1989, Solomkin 1990, Berne 1993, Greenberg 1994, Dougherty 1995, Kempf 1996, Christou 1996, Solomkin 1996, Jaspers 1998, Donahue 1998. These studies contain information on the type of infection, the pathogen, the susceptibility, elimination of the pathogen, clinical reasons for treatment failure, and the follow-up (Table 7).

However, with the exception of one study (Solomkin 2001), there was no information available that the study intended from the beginning to evaluate the adequacy of the surgical procedure. For surgical procedure adequacy was defined by drainage of all purulent collections identified on preoperative radiographic examination, and by removal of the source of infection. However, no further firm criteria for evaluation of the adequacy of the procedure have been indicated.

Adverse Events

70/79 (88%) include data on adverse events. 7/79 (8.6%) studies did not provide exact data on adverse events. The rate of adverse events reported for the antibiotics with the largest overall study population is comparable. The mean adverse event rate is 17.2% for gentamicin and clindamycin, 16.35% for tobramycin and clindamycin. Meropenem was associated with a mean adverse event rate of 20.8%, imipenem 11%, and aztreonam plus clindamycin with 13.5%. Cefoxitin had 16% adverse events on an average, cefotaxime plus metronidazole 20.2%, cefotetan 23.8% and moxalactam 24.4%. Piperacillin/tazobactam was reported to have 22.8% adverse events, ampicillin/sulbactam 27.7% and for ticarcillin/clavulanic acid the range was 0.2% to 27% (Table 7).

Clinical failure rate and adverse events rate of the best-investigated antibiotics are indicated in Table 8. The carbapenems are associated with adverse event rate ranging from 11 to 20.8 and a clinical failure rate ranging from 10.6 to 15.32 on an average. The adverse event rates of cephalosporin have a range from 16 to 24.4 and an average clinical failure rate from 8.4 to 16.5. Penicillin/Beta-lactam combinations have a mean adverse event rate ranging from 2.7 to 27.7 and a mean clinical failure rate ranging from 13 to 34.

Discussion

The treatment of intra-abdominal infections and peritonitis is based on sound surgical technique and source control, potent antibiotics with a spectrum that ensures the killing of anaerobic and aerobic pathogens, and adjuvant intensive care treatment. Solomkin et al. have reviewed 16 articles in 1984 on antibiotic trials in intra-abdominal infections. These studies were criticized for a low overall mortality rate of 3.5%, using non-uniform criteria for reporting infectious diagnosis, premorbid health status, severity of infection and outcome. Whether treatment failures were due to inadequate antibiotic therapy could not be determined due to a lack of failure analysis. (Solomkin 1984). Since the publication of this article further clinical trials with antibiotic agents have been published. We wanted to investigate the outcome of

Table 8. Adverse events and clinical failure in the best studied antibiotics.

Antibiotic	Adverse event rate (% mean)	Range (% mean)	Clinical failure (% mean ± SD)	Range (% mean)
Gentamicin + clindamycin	17.2	3.3 – 44.4	19.4 ± 21.5	0-48
Tobramycin + clindamycin	16.35	3 – 43	17.37 ± 2.7	6.6-29.6
Meropenem	20.8	2.7-48.7	10.7 ± 5.93	0-43
Imipenem	11	0-36.2	15.32 ± 12.37	0-37
Aztreonam + clindamycin	13.5	8.3-17	10.6 ± 5.93	0-29
Cefoxitin	16	1.3-31.7	12.31 ± 0.56	5-22
Cefotetan	23.8	17-27.3	8.4 ± 2.8	2-18
Moxalactam	24.4	16-33	16.5 ± 10.6	9-24
Cefotaxime + metronidazole	20.2	12-28.3	13.25 ± 11.32	3-25
Piperacillin/tazobactam	22.8	2-52	34.35 ± 39.1	6.7-62
Ticarcillin/clavulanic acid		0.2-2.7	20.66 ± 2.8	14.2-25
Ampicillin/sulbactam	27.7	21-34.3	13 ±1.41	12-14

the antibiotic studies with regard to mortality, number of evaluable patients, severity of disease stratification, clinical and bacteriological outcome, failure analysis and adverse events. Almost 10.000 patients were enrolled in randomised, controlled clinical antibiotic trials in intra-abdominal infections. The average evaluable study population consists of 125 patients. Of the retrieved studies published since 1984 44.8% of the studies had actually less than 100 evaluable patients enrolled. 50% of the comparative studies in the report by Solomkin (Solomkin 1984) had less than 100 patients treated which has lead Solomkin to ask for the inclusion of greater number of patients to increase the likelihood of identifying differences between regimens.

The overall mortality rate of 4.8% of the 79 retrieved studies is low. In a recent review on clinical peritonitis studies the average mortality rate in peritonitis/intra-abdominal infection studies was shown to range between 30 and 40%. (Holzheimer and Dralle 2001). In most studies patients are excluded when renal impairment is present or if antibiotics have been previously administered excluding postoperative or recurrent intra-abdominal infections. (Fink 1989, Luke 1991, Paakkonen 1991) In some studies the inclusion or exclusion criteria a rather vague. (Christen 1987; Gonzenbach 1987; Geroulanos 1990). Many of these patients seem to have a localized inflammation or contamination of the abdominal cavity rather than peritonitis or intra-abdominal infection. 55.6% of the evaluated patients had cholecystitis, cholangitis, perforated appendicitis, or perforated peptic ulcer (Fink 1989). Appendicitis may be present in 62% of patients remaining for analysis (Swedish Study Group 1990). However, intra-abdominal infection from appendicitis is known to be associated with a low mortality rate. (Christou 1993) Mortality rate in generalized peritonitis was 38%. Mortalities were 10% in appendicitis and perforated duodenal ulcer, 50% in causes of intraperitoneal origin other than appendix or duodenum, and 60% in postoperative peritonitis. Organ failure was a risk factor with 76% mortality and was associated with late operation. (Bohnen 1983).

There are several studies, which have investigated the effect of antibiotics in different types of surgical infections, including intra-abdominal infections (Stone 1975; Stone 1980; Giamarellou 1982; Stone 1983; Stone 1984; Solomkin 1985; Christen 1987; Danziger 1988; Geroulanos 1990; Kreter 1992; Cakmakci 1993; Colardyn 1996; Jaspers 1998; Jaccard 1998). Although most of these studies allowed a subanalysis of the outcome of antibiotic treatment in intra-abdominal infections, it should be noted that the study design might be criticized. The mortality rate for pneumonia (7.6% and 9.3%) was higher when compared to the mortality for peritonitis (1.3% and 2.%) in one study, which was associated with higher APACHE II scores in the pneumonia group (14.6/14.9 mean) than in the peritonitis group (7.3/8.3). (Jaccard 1998). It is doubtful to compare results obtained in different diseases pneumonia and peritonitis, even when stratification of disease severity has been performed. With regard to comparability studies should focus on a single disease, either peritonitis or pneumonia or soft tissue infection.

26% of 79 retrieved studies included a stratification of disease severity in their protocol. Solomkin has emphasized the necessity of disease stratification for study design and outcome reporting (1984). Since Meakins proposed a classification of intra-abdominal infections (1984) and Christou has published the evaluation of management techniques and outcome (1993) the disease severity stratification, preferably APACHE II score should have been implemented in every antibiotic study in intra-abdominal infections.

22 of 79 studies have investigated the effect of antibiotics in "severe", "serious", or "complicated" intra-abdominal infections. Unfortunately 59% of these studies are not comparable due to missing disease stratification. In two studies, which indicated an average APACHE II score, the index was less than 10 (Barie 1997; Zanetti 1999). Two further studies enrolled patients which had in the majority an APACHE II score or less than 10 (Kempf 1996; Brismar 1996). The average mortality rate of all patients was 4.3% (range 0-17.7). Only the Canadian Metronidazole Study Group had a mortality rate of 17.7%, which compares to the mortality of severe intra-abdominal infection, and fulfils the postulate that diseases that have a substantial failure rate with standard therapy should be studied (Solomkin 1984).

However, this author has adopted his policy 17 years later; it seems appropriate to enrol 40% to 60% of the patients in a trial with appendicitis (Solomkin 2001).

Clinical and Bacteriological Failure

89.9% of retrieved studies have reported the results of clinical outcome and 35.6% of the retrieved studies the bacteriological response, e.g., eradication of the pathogen. Although a comparability of the different antibiotics is hampered by the lack of disease severity stratification, low mortality in some studies and higher mortality in others, the overall clinical success rate of the antibiotics, which were tested in several studies and a relatively sufficient large patient population, ranges from 65% (piperacillin/tazobactam) to 92% (tobramycin + clindamycin; cefotetan). Ticarcillin/ clavulanic acid (79%), gentamicin + clindamycin (81%), moxalactam (84%), imipenem (86%), cefotaxime + metronidazole (87%), ampicillin/sulbactam (87%), cefoxitin (88%), meropenem (89%), and aztreonam + clindamycin (90%) have comparable clinical success rates. The relatively low success rate for piperacillin/tazobactam is due to 62% failure rate in a study reported by Dupont in 2000. (Dupont 2000). The failure rate reported by Niinikiski was 6.7%, by Polk 11%, and by the Piperacillin/Tazobactam Study Group 11% (Niinikoski 1993; Polk 1993; Piperacillin/Tazobactam Study Group 1994). The characteristics of clinical failure in antibiotic studies have been disputed for their relevance for daily clinical practice. Regardless of which antibiotics are used initially, change or addition of other antibiotic agents is likely in a large proportion of patients. In clinical practice

changing an antibiotic regimen is not a failure. Reoperation whether scheduled or dictated by the clinical course is a success if it results in a living, healthy patient. (Dellinger 1991) The rate of treatment success with a single operation and single course of antibiotics may be as low as 48%. (Dellinger 1985) The clinical signs of persistent or recurrent abdominal infection may be mimicked by extra-abdominal infection and by a variety of non-infectious processes, including thrombophlebitis and drug fever. (Bohnen 1992)

Evaluation of Treatment Failures and Source Control

Since Kirschner published in 1926 the treatment principles of source control it is generally accepted that surgical treatment is the decisive factor for outcome. The number of studies that have been published and the variety of therapeutic modalities used in almost every situation suggest that there is not a consensus among surgeons or infectious disease specialists as how intra-abdominal infections should be managed. (Meakins 1984) Of 79 studies only 1 had included the assessment of the adequacy of the surgical procedure in the methods section (Solomkin 2001). 12 studies have tried to give an analysis of treatment failures (Birolini 1985, Tally 1986, Fink 1989, Solomkin 1990, Berne 1993, Greenberg 1994, Dougherty 1995, Kempf 1996, Christou 1996, Solomkin 1996, Jaspers 1998, Donahue 1998). Type of infection, isolated pathogen, susceptibility, elimination of the pathogen, suspect or evident cause of clinical failure with further information on the follow-up (re-hospitalisation, survival, change of antibiotics, abdominal compartment syndrome, ICU stay) may be important factors for the analysis of treatment failures.

Solomkin et al. present an analysis of failures in their study (1990). 33/38 failures were due to persistent or recurrent infection; 21 patients underwent reoperation. Condon et al. (1995) presented information on clinical failures with regard to persistent infection. 7 patients (4 meropenem and 3 tobramycin/clindamycin) had persisting abdominal infections without clinical factors, such as specific organ involvement or extent of peritonitis that might account for treatment failure. However, there is no information on the standards they used for the evaluation of these cases in the methods section. Donahue reported that 36 patients (11.7%) required further surgery or percutaneous drainage and were considered as treatment failure (Donahue 1998). However, it is unclear whether this was due to an insufficient first operation. The authors have found no association between persistent pathogens and treatment failure (Donahue 1998). Jaspers et al. showed the characteristics of patients in whom clinical failure occurred. Unfortunately there was no further analysis done on the type of surgery and whether there was re-operation necessary. (Jaspers 1998). Solomkin investigated the microbiology of treatment failures. They found a high incidence of gram-negative organisms among patients with imipenem treatment failures who underwent reintervention. The basis for the persistence of gram-negative organisms in treatment failures remained unclear. Furthermore an association between the presence of enterococci in initial cultures and subsequent treatment failures was identified. (Solomkin 1996). Treatment failure of intra-abdominal infection may be due, in part, to the presence of resistant pathogens at the site of infection. Routine culture has been advocated. (Christou 1996)

Details of treatment failures are of considerable importance in allowing the reader to determine the potential contribution of antibiotic choice to the result. Background disease, severity of infection, type of infection treated, susceptibility of organisms and operations performed may influence the outcome. (Solomkin 1984). An adequate surgical procedure is generally agreed on and involves drainage of all fluid collections, closure or resection of any openings, and resection of inflamed tissue. The latter aspect of surgical management is the most controversial, and recommendations have ranged from complete peritoneal débridement to attention only to the source of infection. (Solomkin 2001). The criteria used to define the outcome of an antibiotic trial are not standardized. The need for a second operation to deal with the surgical infection is normally regarded as a treatment failure; however, this may be a result of an inadequate initial operation, a mechanical or anatomic situation that could not be corrected with one procedure or poor surgical judgement and not related to the antibiotic efficacy at all. (Dellinger 1991) A significantly increased risk of death in patients with shock, age greater than 65 years, alcoholism, bowel infarction or malnutrition was revealed by discriminant analysis (Pine 1983). However, shock was rarely indicated in the failure analysis.

Adverse Event Reports

Antimicrobial agents may cause a wide variety of adverse events. Pre-existing medical conditions, such as renal failure and the severity of abdominal infection as manifested by shock, may increase the incidence and severity of drug complications. Common, potentially harmful effects of antibacterial agents include hypersensitivity, nephrotoxic effects, ototoxic effects, coagulopathy, diarrhea, colitis, and perhaps fungal superinfection. (Bohnen 1992) Clinical outcome criteria and toxicity do seem to be the most appropriate evaluators of efficacy. (Solomkin 1984)

The rate of adverse events for imipenem/cilastatin has a range from 0% (Christen 1987, Geroulanos 1990, Cakmakci 1993) to 36.2% (Geroulanos 1995). In some reports the adverse events are reported with a percentage for each adverse event (Danziger 1988, Barie 1997), which does not allow a calculation of a mean of adverse events per study population. The most frequent reported side effects for imipenem/cilastatin were nausea (24%), diarrhea (20%), and vomiting (13%) (Barie 1997). Danziger reported five cases of eosinophilia, three cases of monocytosis for imipenem/cilastatin, but no case of diarrhea (Danziger 1988). Yoshioka et al. reported an adverse event rate of 0% for the use of amoxycillin/clavulanic acid in combination with metronidazole. The adverse event

rates for the combination gentamicin/clindamycin range from 3.3% to 44.4% (mean 17.2%). In case of newer antibiotics adverse event reports ranged from 0% to 48.7% (mean 18.5%) for meropenem or from 2% to 52% (mean 24.5%) for piperacillin/tazobactam. Certainly the awareness of adverse events has increased in the last 10 years. This has lead to recommendations of the Surgical Infection Society of North America not to use certain antibiotics.

Certain agents have appropriate in vitro spectra of activity but serious toxic effects and are therefore not acceptable. Chloramphenicol is myelosupressive and may lead to aplastic anaemia. Moxalactam should not be used because it's potential to cause bleeding. (Bohnen 1992). It is doubtful that all adverse events related to antibiotic treatment have been recorded in these studies. Even in the most recent study the material and methods section does not provide sufficient information on the analysis of adverse events (Solomkin 2001). The time from start of antibiotic therapy to the occurrence of severe side effects, e.g., jaundice, may be 3-4 weeks on an average (Gresser 2001). It may not be sufficient to record clinical adverse events and significant effects on laboratory parameters occurring during treatment, which is normally 5-7 days (Zanetti 1999) or if the time frame of assessment is not indicated (Barie 1997).

With all caution with regard to comparability of the study results due to missing disease severity stratification and low mortality in some studies we have summarized the adverse events and failure rates for the antibiotics which were studied best (Table 8). Adverse events may occur in up to 50% depending how accurate the reports are performed. Some antibiotics seem to be attractive due to an extraordinary low rate of adverse events, e.g., ticarcillin/clavulanic acid, which was 0.2% to 2.3% (Dougherty 1995), or not reported at all (Sirinek 1991), which is in contrast to recently reported review (Gresser 2001). The current data do not allow giving preferences for one of the studied antibiotics or antibiotic combinations. Piperacillin/tazobactam or ampicillin/sulbactam, gentamicin + clindamycin or tobramycin + clindamycin, meropenem or imipenem or aztreonam + clindamycin, cefoxitin or cefotetan or moxalactam or cefotaxime + metronidazole, they have similar adverse events and clinical failure rates.

For community-acquired infections of mild to moderate severity, single agent therapy with cefoxitin, cefotetan, or cefmetazole or ticarcillin-clavulanic acid, and for more severe infections, single agent therapy with carbapenems (imipenem) or combination therapy with either a third generation cephalosporin, a monobactam (aztreonam), or an aminoglycoside plus clindamycin or metronidazole was recommended by the SIS. (Bohnen 1992).

In case the intra-abdominal infection develops in the hospital after previous antibiotic therapy cefoxitin, cefotetan, cefotaxime, ceftriaxone should not be used because of the risk of resistant facultative gram-negative organisms. Newer agents, such as quinolones, should not be used until subjected to proper clinical trial. (Bohnen 1992). The data available for the use of quinolones in intra-abdominal infections do not yet allow general recommendations (Yoshioka 1991, Solomkin 1996, de Marie 1998). The quinolones have been subject of controversy with regard to adverse events (Donahue 1998) or there is only one study available (Solomkin 2001).

In conclusion, there have been 79 randomised antibiotic studies in intra-abdominal infections retrieved. The overall success rate of the studied antibiotics ranges from 70-100%. Unfortunately only about one fourth of the studies have used the disease severity classification, e.g., APACHE II score, despite clear recommendations. The mortality rate in antibiotic studies is still rather low (approximately 4%) and does not correspond to the average mortality in peritonitis (30-40%). Failure analysis is not uniform and only performed in about 1/5 of retrieved studies. Failure analysis should include data on diagnosis, type of operation, pathogen isolated at first operation, susceptibility and persistence of pathogen, re-operation or change of antibiotic regimen, and follow-up (ICU duration, death or survival, hospitalisation). The adequacy of the surgical procedure should be analysed according to criteria set up in the material and methods section. In case a single operation is not sufficient due to generalized inflammation of the tissue, further operation should not be determined as treatment failure when the outcome is survival. Postoperative infections should be included in antibiotic trials and may be subject to separate analysis. Adverse events should also be reported as average percentage of adverse events per study population. The time of observation of patients needs to be indicated and adverse events should be reported when occurring 30 days after treatment was started. Antibiotics for the treatment of intra-abdominal infections should be used according to the expected polymicrobial infection and known susceptibility and resistance rates within a hospital setting.

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