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Perioperative Infection Prophylaxis and Risk Factor Impact in Colon Surgery

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Key Words

Colon resection · Antibiotic prophylaxis · Ceftriaxone · Cost-benefit analysis · Risk factors · Postoperative infection · Cephalosporins · Penicillins

Abstract

Background: A prospective observational study was undertaken in 2,481 patients undergoing elective colon resection in 114 German centers to identify optimal drug and dosing modalities and risk factors for postoperative infection. ***Methods:*** Patients were pair matched using six risk factors and divided into 672 pairs (ceftriaxone vs. other cephalosporins, group A) and 400 pairs (ceftriaxone vs. penicillins, group B). End points were local and systemic postoperative infection and cost effectiveness. ***Results:*** Local infection rates were 6.0 versus 6.5% (group A) and 4.0 versus 10.5% (group B); systemic infection rates in groups A and B were 4.9 versus 6.3% and 3.3 versus 10.5%, respectively. Ceftriaxone was more effective than penicillins overall (6.8 vs. 17.8%, $p < 0.001$). Length of postoperative hospital stay was 16.2 versus 16.9 days (group A) and 15.8 versus 17.6 days (group B). Of the six risk factors, age and concomitant disease were significant for systemic infection, and blood loss, rectum resection and immunosuppressive therapy were significant for local infection. Penicillin was a risk factor compared to ceftriaxone ($p < 0.0001$). Ceftriaxone saved € 160.7 versus other cephalosporins and € 416.2 versus penicillins. ***Conclusion:*** Clinical and microbiological efficacy are responsible for the cost effectiveness of ceftriaxone for perioperative prophylaxis in colorectal surgery.

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Introduction

The use of antibiotics for perioperative prophylaxis in colorectal surgery is now generally undisputed, although debate continues on the optimal choice of drug(s) and administration modalities. Efficacy can only be assessed by reviewing the overall incidence of perioperative bacterial complications (including related mortality) and not simply the wound infection rate. For this reason, prophylaxis is best evaluated in terms of postoperative risk prevention. The more effective the prophylaxis, particularly against secondary infectious complications (e.g. pneumonia), the greater the decrease not only in surgical risk but also in cost, in terms of staff time, drugs, laboratory investigations, use of equipment, (re)operation and length of hospital stay.

Third-generation cephalosporins are highly effective against gram-negative intestinal bacteria. Ceftriaxone, which is particularly suited to postoperative prophylaxis due to its sustained duration of activity, was compared in this observational study to other beta-lactams (cephalosporins and penicillins) with respect to postoperative risk prevention and cost effectiveness in a large patient population under routine practice conditions.

Patients and Methods

This prospective observational study on perioperative infection prophylaxis was conducted between September 1, 1996 and September 30, 1997 in Germany in 2,513 patients undergoing elective colon resection in 114 centers.

Patients

Exclusion criteria were suppurative peritonitis, other preexisting infections requiring antibiotic therapy, emergency surgery, mechanical ventilation for more than 12 h, granulocytopenia (<1,000/mm^3) and autoimmune deficiency syndrome.

Table 1. Patient distribution

Patient status	Patients
Documented	2,513
Protocol violators	32
Evaluable	2,481
Post-matching	
Ceftriaxone/other cephalosporins[1] (group A)	672/672
Ceftriaxone/broad-spectrum penicillin[2] (group B)	400/400
Unmatched	337

[1] Cefotiam (n = 270); cefazolin (n = 130); cefoxitin (n = 66); cefotaxime (n = 31).

[2] Mezlocillin (n = 168); amoxicillin/clavulanic acid (n = 106); ampicillin/sulbactam (n = 104); miscellaneous (n = 22).

End Points

The end points of the study were clinical efficacy (no local or systemic infection in the first 10 postoperative days) and cost effectiveness measures (pre- and postoperative antibiotic therapy and length of postoperative hospital stay). Local infectious complications consisted of the following: suppurating wound; abscess (localized or diffuse); peritonitis, and suture failure. Systemic complications comprised: pneumonia and other respiratory tract infection; urinary tract infection; venous catheter infection, and sepsis. Subanalyses examined the impact of risk factors on local and systemic postoperative infection rates.

Antibiotic Prophylaxis

As befits an observational study, the choice of antibiotics and administration modalities was left to the practitioners, who followed their departmental practice. The recommended schedule for ceftriaxone was a single preoperative dose supplemented by metronidazole for anaerobe cover.

Statistical Analysis

Statistical analysis (Factum GmbH, Offenbach/Main, Germany) was performed using SPSS for Windows, release 6.1.3 (October 1995). Descriptive p values were calculated using McNemar's test or a t test for paired samples. To exclude bias, patients were risk matched into pairs using the following six criteria: operation duration (< or >2 h); blood loss (< or >3 red

Table 2. Group distribution (%) of main risk factor matching criteria

Criterion	Group A (672 pairs)	Group B (400 pairs)
Age >65 years	58.3	56.3
Operation duration >2 h	65.3	58.3
Blood loss >3 red cell concentrates	1.8	3.8
Colon + rectum resection	20.1	19.3
Preexisting diabetes mellitus, hepatic, renal or airways disease	33.4	37.3
Immunosuppressive therapy or radiation	3.6	1.8

Table 3. Group demographics, preoperative diagnosis and concomitant disease

Parameter	Group A (672 pairs)		Group B (400 pairs)	
	ceftriaxone	other cephalosporins	ceftriaxone	penicillins
Age, years	65.9	66.1	65.4	66.0
Height, cm	168.5	167.7	168.7	169.0
Weight, kg	72.6	72.1	73.0	73.9
Sex (male), %	49.1	45.2	46.8	48.0
Colon carcinoma, %	65.8	69.9	66.0	73.0
Diverticulitis, %	18.6	14.7	18.3	15.5
Crohn's disease, %	1.8	0.9	1.5	1.3
Ulcerative colitis, %	1.9	0.9	2.5	0.5
Preexisting ileus/severe intestinal stenosis, %	15.0	12.5	14.8	11.8
Preexisting colostomy, %	7.1	5.4	6.5	2.8
Prior abdominal surgery, %	4.8	4.3	3.8	3.0
Concomitant disease, %	63.1	64.1	68.3	64.0
Cardiovascular, %	46.4	43.5	50.0	46.0
Diabetes mellitus, %	12.4	13.9	13.0	16.0
Chronic airways, %	11.9	9.8	15.8	10.0
Obesity, %	10.9	11.3	14.0	13.0

cell concentrates); colon resection plus rectum resection (yes/no); age (< or >65 years); preexisting diabetes mellitus, hepatic, renal or airway disease (yes/no); immunosuppressive therapy (e.g. steroids) or radiation (yes/no). Patients paired for all six criteria were assigned to group A (ceftriaxone vs. other cephalosporins) or group B (ceftriaxone vs. penicillin).

Risk analysis to validate the matching criteria was performed in the total evaluable population (n = 2,481) after excluding protocol violators (n = 32). Antibiotic regimes were tested in this population for their impact on postoperative infection rates and the results were expressed as odds ratios (OR). A significance level of $p < 0.05$ was used in all tests.

Patient Groups

Group A comprised 1,344 patients and group B 800 patients (table 1). The distribution of the six matching risk factors is shown in table 2. Groups A and B did not differ in respect to demographics, preoperative diagnosis, risk factors or type of colon resection (tables 3–5).

Table 4. Type of colon resection (%) in groups A and B

Colon resection	Group A (672 pairs)		Group B (400 pairs)	
	ceftriaxone	other cephalosporins	ceftriaxone	penicillins
Cecum and ascending colon	23.5	25.6	24.0	25.0
Transverse colon	6.6	4.9	5.5	8.0
Descending colon	14.9	13.2	11.5	11.5
Sigmoid colon	32.9	39.0	37.3	37.8
With protective colostomy/ileostomy	8.1	9.9	8.1	8.6
Rectum (deep anastomosis)[1]	20.1	20.1	19.3	19.3
With protective colostomy/ileostomy	17.8	23.0	19.5	15.6
Other colon surgery	16.5	16.1	17.0	12.3
Creation of colostomy	8.9	7.7	7.8	7.8
Colostomy reversal	5.8	3.4	4.8	2.3

[1] Matching criterion.

Table 5. Nonmatching operative risk factors in groups A and B

Risk factor	Group A (672 pairs)		Group B (400 pairs)	
	ceftriaxone	other cephalosporins	ceftriaxone	penicillins
Operation duration, min	153	156	147	148
Blood loss, ml	423	467	436	460
Clean bowel, %	94.5	91.2	91.8	92.3
Intraoperative bowel irrigation, %	4.6	4.6	4.3	5.8
Stapler anastomosis, %	34.1	39.1	36.8	27.5
Abdominal drainage, %	86.9	89.6	87.3	91.8

Dosage and Concomitant Prophylaxis

Antibiotics and administration modalities are shown in tables 6 and 7. Ceftriaxone was administered in 90% of cases as a single preoperative 2-gram dose. The average duration of prophylaxis with the other beta-lactams was 2–3 days. Only amoxicillin/clavulanic acid was administered for a shorter period, i.e. 1.36 days. In group A, concomitant metronidazole was given to 62.2 and 80.5% of ceftriaxone and other cephalosporin patients, respectively, and in group B, to 66.3 and 51.0% of ceftriaxone and penicillin patients, respectively. Concomitant gentamicin was given to 4.9% of other cephalosporin patients and 1% of penicillin patients. Other concomitant antibiotic therapy was given to 1.7% of ceftriaxone patients and 0.6% of other cephalosporin patients in group A and 0.8% of both subgroups in group B.

Standard Microbiology

This was performed intraoperatively for suspected infection and in postoperative infections.

Table 6. Antibiotic dosage and administration modalities in group A

Antibiotic	Schedule	Frequency of use, %	Mean dose, g	Duration days
Ceftriaxone			1.99	1.49
	1 × 2 g	90.3		
Cefotiam			2.90	2.33
	1 × 2 g	67.4		
	2 × 2 g	11.1		
	3 × 2 g	13.3		
Cefuroxime			2.49	2.41
	1 × 1.5 g	53.1		
	2 × 1.5 g	12.6		
	3 × 1.5 g	20.0		
Cefazolin			3.25	1.99
	1 × 2 g	58.5		
	2 × 2 g	20.8		
	3 × 2 g	20.8		

Table 7. Antibiotic dosage and administration modalities in group B

Antibiotic	Schedule	Frequency of use, %	Mean dose, g	Duration days
Ceftriaxone			2.00	1.48
	1 × 2 g	89.3		
Mezlocillin			4.77	2.17
	1 × 2 g	25.6		
	1 × 4 g	25.6		
	3 × 2 g	31.0		
Amoxicillin/clavulanic acid			2.49	1.36
	1 × 2.2 g	74.5		
	2 × 2.2 g	9.4		
Ampicillin/sulbactam			5.61	2.64
	1 × 3 g	51.0		
	3 × 3 g	26.0		

Results

Clinical Results

The rates of infectious complications in the first 10 postoperative days were 10.0% with ceftriaxone versus 10.9% with other cephalosporins in group A, and 6.8 versus 17.8% with ceftriaxone versus penicillin in group B (table 8). Physicians' impressions rated prophylaxis effective in 92.4 and 83.8% of ceftriaxone and other cephalosporin patients in group A, and in 91.8 and 83.3% of ceftriaxone and

Table 8. Infectious complications (n) in the first 10 postoperative days

Complication	Group A (672 pairs)		Group B (400 pairs)	
	ceftriaxone	other cephalosporins	ceftriaxone	penicillins
Local complications				
Suppurating wound	22	20	11	18
Abscess	7	11	2	9
Peritonitis	2	3	0	4
Suture failure	9	10	3	11
Total local complications	40 (6.0)	44 (6.5)	16 (4.0)	42 (10.5)
Systemic infections				
Pneumonia	7	16	6	14
Other respiratory tract infections	3	3	1	1
Urinary tract infection	17	18	4	18
Venous catheter infection	5	3	2	6
Sepsis	1	1	0	3
Other systemic infection	0	1	0	0
Total systemic infections	33 (4.9)	42 (6.3)	13 (3.3)	42 (10.5)
Total infection rate	67 (10.0)	73 (10.9)	27 (6.8)	71 (17.8)*

Figures in parentheses represent percentages. * $p < 0.001$ for ceftriaxone versus penicillin.

penicillin patients in group B. Adverse events (whether related to antibiotics or not) occurred in fewer than 5% of cases: 4.5 and 3.9% in the ceftriaxone and other cephalosporin subgroups, respectively, in group A, and 4.3 and 3.0% in the ceftriaxone and penicillin subgroups, respectively, in group B. There were 0 and 4 postoperative inpatient deaths in the ceftriaxone and other cephalosporin subgroups, and 1 and 2 in the ceftriaxone and penicillin subgroups.

Microbiology

Postoperative pathogens were markedly fewer with ceftriaxone compared to other antibiotics: 23 versus 45 gram-positive isolates, and 28 versus 58 gram-negative isolates, respectively (table 9). Gram-negative infection rates were lower with ceftriaxone than with other cephalosporins. The rates of both gram-negative and gram-positive infections were lower with ceftriaxone than with penicillin. Pathogen distribution in postoperative wound and airway infections (table 10) showed a majority of *Escherichia coli* and other Enterobacteriaceae, followed by staphylococci, enterococci and *Pseudomonas* spp. No airway or wound infections due to *Pseudomonas* spp. occurred with ceftriaxone. There were also fewer enterococcal and staphylococcal wound infections with ceftriaxone than with penicillin (1 vs. 4, and 4 vs. 9, respectively).

Risk Analysis

Rectum resection (OR = 1.55, p = 0.022) and concomitant disease (OR = 1.65, p = 0.0001) were prognostically significant risk

Table 9. Postoperative gram-positive/gram-negative infections (n)

Sample site	Group A (672 pairs)		Group B (400 pairs)	
	ceftri-axone	other cephalosporins	ceftri-axone	peni-cillins
Airways	1/2	1/6	0/0	3/2
Blood	0/2	0/0	0/1	2/1
Wound	12/11	13/21	6/8	13/14
Urine	3/2	4/6	1/2	9/8
n_{total}	16/17	18/33	7/11	27/25
Total pathogens (n = 154)	33	51	18	52

Table 10. Pathogen distribution (n) in postoperative wound and respiratory tract infections

Isolate	Group A (672 pairs)		Group B (400 pairs)	
	ceftri-axone	other cephalosporins	ceftri-axone	peni-cillins
Respiratory tract				
Enterobacteriaceae	2	1	0	2
Pseudomonas spp.	0	4	0	0
Other	1	2	0	3
Wound				
Staphylococci	3	3	4	9
Enterococci	7	9	1	4
Escherichia coli	5	10	3	9
Other Enterobacteriaceae	3	4	3	2
Pseudomonas spp.	0	4	0	1
Bacteroides spp.	3	2	2	2
Other bacteria	2	2	1	0

factors for postoperative infection (table 11). Further analysis showed age and concomitant disease to be significant risk factors for systemic complications, while blood loss, rectum resection and immunosuppressive therapy were significant risk factors for local complications. Operation duration of more than 2 h was associated with a nonsignificant increase in postoperative complications (table 12). Five of the six matching criteria significantly impacted on the postoperative infection rate, thereby confirming their suitability for unbiased patient pairing.

Testing antibiotic regimes for an impact on postoperative infection in the total population showed penicillin to be a significant risk factor compared to ceftriaxone (OR = 2.18, $p < 0.0001$), and prophylaxis without metronidazole for anaerobe cover (OR = 1.79, $p < 0.0001$). Analysis of the individual antibiotic

Table 11. Risk factors for postoperative infection

Risk factor	Infection, %	OR	p
Age ≤/>65 years	10.7/12.1	1.15	0.265
Operation duration ≤/>2 h	10.0/12.4	1.28	0.063
Blood loss ≤/>3 red cell concentrates	11.3/17.6	1.70	0.064
Colon + rectum resection (no/yes)	10.5/15.4	1.55	0.022
Concomitant disease (no/yes)	15.6/10.0	1.65	0.0001
Immunosuppressive therapy (no/yes)	11.2/17.1	1.63	0.063
Ceftriaxone/other cephalosporins	9.3/11.0	1.21	0.214
Ceftriaxone/penicillin	11.0/18.3	1.80	0.0005
Ceftriaxone +/– metronidazole	7.7/11.8	1.61	0.012
Other cephalosporins +/– metronidazole	9.6/17.0	1.93	0.014
Penicillin +/– metronidazole	13.8/22.7	1.84	0.013

Table 12. Risk factors for local and systemic postoperative infection

Risk factor	Local infection, %	p	Systemic infection, %	p
Age ≤/>65 years	6.8/5.7	0.239	4.5/6.8	0.014
Operation duration ≤/>2 h	5.2/6.9	0.082	5.1/6.2	0.222
Blood loss ≤/>3 red cell concentrates	5.9/14.3	0.001	5.8/5.5	0.908
Colon + rectum resection (no/yes)	5.6/8.8	0.007	5.5/7.0	0.185
Concomitant disease (no/yes)	5.8/7.3	0.199	4.5/9.3	<0.001
Immunosuppressive therapy (no/yes)	5.9/13.3	0.002	5.8/5.7	0.982

Table 13. Main postoperative cost factors

Factor	Group A (672 pairs)		Group B (400 pairs)	
	ceftriaxone	other cephalosporins	ceftriaxone	penicillin
Postoperative antibiotic therapy	83 (12.4)	110 (16.4)	46 (11.5)	100 (25.0)
Mechanical ventilation (from 1st postoperative day)	2 (0.3)	4 (0.6)	0	2 (0.5)
Reoperation	34 (3.6)	26 (3.9)	9 (2.3)	14 (3.5)
Hospital stay (days)	16.2	16.9	15.8	17.6*

Figures in parentheses represent percentages. * $p < 0.001$ for ceftriaxone versus penicillin.

regimes confirmed the necessity of concomitant metronidazole with both cephalosporins and penicillin in elective colon surgery (table 11).

Cost Effectiveness

Differences in prophylactic efficacy are reflected in the incidence and severity of local and systemic postoperative infection, postoperative antibiotic requirements, admission to intensive care (with or without mechanical ventilation) and reoperation. The main differences found in the present study in the relationship between prophylactic regime and postoperative complications were in postoperative antibiotic requirements and duration of hospital stay (table 13). Ceftriaxone shortened hospital stay (by 0.7 days in group A, and by 1.8 days in group B). Using a daily rate of € 229.6 for inpatients (general rate plus a 20% departmental rate in the surgical department of the Munich-Grosshadern Hospital, 1997), ceftriaxone saved € 160.7 over other cephalosporins and € 413.2 over penicillin. Although the cost of reoperation, an undoubtedly substantial factor, was not calculated due to the complexities involved, it was partly covered in costing the length of postoperative stay.

Discussion and Conclusions

The First (German) National Prevalence Study (NIDEP) showed that wound infection is only the third most common type of nosocomial infection (15.1%) [1], preceded by infection of the urinary tract (40.2%) and lower airways (19.7%). Wound infection only becomes significant when it requires reoperation, as with deep-seated infection or abscess formation. Secondary systemic infection, on the other hand, almost always prolongs hospital stay. Postoperative pneumonia and septicemia always involve serious illness and increased mortality. Preoperative prophylaxis should thus aim at effective postoperative risk prevention by decreasing postoperative systemic complications as well as wound infection.

The risk of postoperative secondary infection does not end with the tying of the last suture. The risk of postoperative pneumonia increases with the duration of intubation anesthesia and postoperative ventilation. Many factors affect individual risk, e.g. pain, ileus and chronic lower airways disease. Urinary tract infection increases with postoperative retention or catheter drainage. Effective antibiotic levels thus need to be sustained over the early postoperative risk period to decrease complications, primarily systemic infection. The advantage of a long-acting cephalosporin such as ceftriaxone is that a single preoperative dose provides 24 h of cover. Prophylaxis with short-acting antibiotics, on the other hand, requires 2–3 doses over the same period. In addition to duration of activity, the microbiological spectrum is also an important consideration in selecting an antibiotic for visceral and abdominal surgery, which requires maximal cover against gram-negative bacteria, primarily *E. coli,* but also other Enterobacteriaceae. Third-generation cephalosporins have significant advantages in this regard over conventional cephalosporins and particularly over penicillin [2].

Our data do not indicate whether the greater efficacy of ceftriaxone (nonsignificant vs. other cephalosporins, significant vs. penicillin) was due to longer duration of activity and/or a broader spectrum. The study was observational and comprised only a recommendation for 24 h of prophylaxis. The design left the choice of dosage to the physician. The efficacy of a single dose of ceftriaxone is probably due to the drug's specific pharmacokinetic profile, which ensures bactericidal concentra-

Table 14. Wound infection rates and preoperative prophylaxis with different generations of cephalosporin [6]

Cephalosporin generation	Wound infection rate, %
First and second (n = 1,079)	14.8
Third (n = 340)	7.9

tions against susceptible organisms for 24 h. In a report on the Dutch Trauma Trial, the authors noted that the mean serum concentration of 2 g of ceftriaxone 1 h after administration was 177 mg/l – well above the minimum inhibitory concentration for microorganisms causing infections in accident surgery [3]. Ceftriaxone also attains good tissue concentrations and can even demonstrate high bactericidal concentrations in bile in the case of cholestasis [4]. A matter for discussion is whether the tissue concentration in addition to the local concentration in the bowel might be effective in the prophylaxis of anastomosis insufficiency. An analogous mechanism has been demonstrated for preventing leakage of esophago-intestinal anastomosis [5].

A further result of our study is an overall view of the prophylactic regimes currently used for colon surgery in Germany. The treatment duration of ceftriaxone was only 1.5 days (median), compared to 2–3 days for the comparators (except amoxicillin/clavulanic acid). Its superiority is thus more likely to be due to a more potent spectrum than to a longer duration of activity.

A 1991 literature review [6] concluded that, at least in colon surgery, third-generation cephalosporins appeared to be clinically more effective than first- and second-generation cephalosporins, and thus display a better cost/benefit ratio (table 14).

In a prospective randomized double-blind study of perioperative prophylaxis with ceftriaxone 2 g ± metronidazole versus cefazolin 1 g + metronidazole in colorectal surgery [7], postoperative airway and urinary tract infections were more frequent with cefazolin ($p < 0.01$). All the deaths were in the cefazolin group, and all resulted from postoperative sepsis. Other studies have also reported greater efficacy with ceftriaxone in colon surgery [8–10]. In particular, a meta-analysis of 43 randomized comparative studies of perioperative prophylaxis with single-dose ceftriaxone versus other cephalosporins in a total of 13,482 patients found lower overall rates of infection with ceftriaxone – by 30% in wound infections, 47% in urinary tract infections and 19% in respiratory tract infections [11].

Our study did not address the impact of concomitant metronidazole. Although in one study, the authors concluded that it is not always necessary to give metronidazole in addition to ceftriaxone for perioperative prophylaxis [7], many authors have recommended this combination as advantageous [8, 9]. In the present study, metronidazole was combined with ceftriaxone in approximately 65% of cases, compared to 80% with other cephalosporins and only approximately 50% with penicillin. The results of our risk analysis also confirm that metronidazole needs to be administered with all beta-lactams, since postoperative infectious complications were significantly reduced in each case.

Detailed studies have already shown that effective antibiotic prophylaxis not only enhances postoperative outcome but also substantially lowers costs [12, 13]. It is thus not surprising that in our study, the greater overall efficacy of prophylaxis with ceftriaxone versus other beta-lactams in colon resection decreased costs by decreasing the postoperative infection rate.

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