REPRINT

Journal of Chemotherapy Vol. 13 - Special Issue n. 1 (182-?) - 2001

Antimicrobial Prophylaxis for Abdominal Surgery: Is There a Need for Metronidazole?

U. MITTELKÖTTER

Department of Surgery, University of Würzburg, Germany.

Correspondence: Dr. Ulrich Mittelkötter, Chirurgische Universitätsklinik Würzburg, Josef-Schneider-Str. 2, D-97080 Würzburg, Germany. Tel.: +49931-2011-bleep; Fax: +49931-201-3330. E-mail: wiwag@chirurgie.uni-wuerzburg.de

Summary

The objective of the present multicenter observational study was to assess postoperative infections as a function of risk factors and antibiotic prophylaxis under everyday clinical conditions. 2513 patients from 114 centers in Germany who received infection prophylaxis prior to elective colonic resection were included in the study between 1st September 1996 and 30th September 1997. In the descriptive analysis of the study it was noted that 36.1% of the patients had received no prophylaxis with metronidazole despite the fact that the study protocol recommended the use of this drug in preoperative antibiotic combinations. The present analysis therefore considers the influence of metronidazole on the postoperative infection rate. To exclude any bias due to intergroup differences in risk profile, the groups with and without metronidazole were subjected to a matched-pair analysis. Matching parameters were: duration of operation, blood loss, age, diabetes mellitus, hepatic, renal, or chronic airways disease, immunosuppressive therapy, and rectal resection. This led to the formation of 800 pairs that were matched with respect to these parameters. The 800 pairs were then stratified into the following treatment groups: Group 1: long-acting cephalosporin (ceftriaxone) with or without metronidazole (n = 2 x 491); Group 2: short-acting cephalosporins with or without metronidazole (n = 2 x 133); Group 3: broad-spectrum penicillins with or without metronidazole (n = 2 x 176).

In all three treatment groups combination therapy with metronidazole was found to be significantly superior. Postoperative infection rates with and without metronidazole were 9.4% and 18.7% respectively in Group 1, 12.0% and 25.6% respectively in Group 2, and 19.9% and 29.0% respectively in Group 3. The lowest infection rate was thus achieved by means of preoperative infection prophylaxis with ceftriaxone plus metronidazole. Thus, preoperative administration of metronidazole in addition to a long-acting beta-lactam antibiotic is strongly advised in elective colon surgery, as absence of antibiotic cover against anaerobic colonic flora leads to a significantly higher postoperative infection rate.

Key words: **antibiotics, colon surgery, prophylaxis, metronidazole.**

 ISSN 1120-009X

INTRODUCTION

Infection rates of up to 50% in elective colon surgery performed without antibiotic prophylaxis have led to widespread use of perioperative antibiotic prophylaxis. The use of various antibiotic combinations has now reduced mean infection rates to about 15% [1]. In addition to preoperative colonic lavage, systemic antibiotic therapy is given perioperatively in elective operations with the aim of reducing the number of normal bacteria in the large intestine [1]. Reduction of aerobic and anaerobic colonic flora is important in this respect. Although there is no standard form of antibiotic prophylaxis, use of penicillins and cephalosporins has become established for perioperative infection prophylaxis [1]. It is generally recommended that these substances, which are effective against aerobes, be given in combination with metronidazole, which is effective against anaerobes. Alternatively, combinations of penicillins with a beta-lactamase inhibitor are also recommended [2].

A surprising finding of a year-long observational study in which 2513 consecutive patients from 114 German surgical departments was that 908 patients (36.1%) received perioperative infection prophylaxis without metronidazole. The present analysis therefore considers the influence of metronidazole on the rate of postoperative infections. To exclude any bias due to intergroup differences in risk profile, the groups with and without metronidazole were subjected to a matched-pair analysis.

PATIENTS AND METHODS

Between 1st September 1996 and 30th September 1997 a total of 2513 patients from 114 German surgical departments were enrolled in a prospective observational study on perioperative infection prophylaxis. During this period the participating hospitals enrolled consecutive patients who satisfied certain selection criteria. Patients with intra-abdominal or other clinically demonstrable infection at the time of the operation were excluded. Other exclusion criteria were emergency operations, need for mechanical ventilation at the outset, acquired immunodeficiency, and granulocytopenia of <1000/µl. In order to achieve comparable treatment groups with and without metronidazole, all patients underwent a matched-pair analysis. Matching parameters were: duration of operation, blood loss, age, diabetes mellitus, hepatic, renal, or chronic airways disease, immunosuppressive therapy, and rectal resection. This led to the formation of 800 pairs that were matched in terms of these parameters. For the remaining 913 patients no matched partner could be found. The 800 pairs were stratified into the following prophylaxis groups:

- Group 1: long-acting cephalosporin (ceftriaxone) with or without metronidazole (n = 2 x 491)
- Group 2: short-acting cephalosporins with or without metronidazole (n = 2 x 133)
- Group 3: broad-spectrum penicillins with or without metronidazole (n = 2 x 176)

In most cases only one antibiotic dose was given preoperatively. The daily doses indicated below are median values. In Group 1 only ceftriaxone, a typical long-acting third-generation cephalosporin, was used (dose: 2 g). The following cephalosporins were used for perioperative infection prophylaxis in Group 2: cefotiam 2 g (n = 85), cefuroxime 1.5 g (n = 67), cefoxitin 2 g (n = 63), cefazolin 2 g (n = 40), cefotaxime 2 g (n = 11). The following penicillins were used for perioperative infection prophylaxis in Group 3: mezlocillin 4 g (n = 154), ampicillin/sulbactam 3 g (n = 89), amoxicillin/clavulanic acid 2.2 g (n = 96), ampicillin 2 g (n = 7), and piperacillin/tazobactam 4.5 g (n = 6).

The primary endpoint of the study was the occurrence of infections within the first 10 postoperative days. Infections were classified as either local complications of wound healing or else systemic secondary infections such as pneumonia, urinary tract infections, venous catheter infections, and sepsis. Secondary endpoints of the study were need for re-operation, total duration of treatment, time spent in intensive care, and time-course of body temperature and leukocyte count.

The statistical analysis including the matched pairs assignment was performed by Factum GmbH, D-63065 Offenbach/Main. The statistical calculations were performed using the statistics program SPSS for Windows,

release 6.1.3, October 1995. The level of significance of the descriptive *p*-values was set at <0.05. Values were calculated by means of the McNemar test, the paired *t*-test, or the Mann-Whitney U-test.

RESULTS

The groups were comparable in terms of duration of operation, blood loss, presence of other diseases such as diabetes mellitus, hepatic, renal, and chronic airways disease, immunosuppressive therapy, and previous bowel anastomosis. This was true also of the age, height, weight, and sex of the patients. The preoperative diagnoses that formed the indication for elective colonic resection are listed in *Table 1*. Preoperative bowel preparation was performed in almost all patients (95.49–98.5%). No significant group differences were found either in this respect or with respect to the subsequent operation. The left side of the colon was operated on in about 50%, and the right side of the colon in about 25%, of cases (*Table 2*). A stoma was created only in 11.4–18.8% of cases. Here again there were no statistically significant intergroup differences. In patients undergoing tumor operations there were no intergroup differences with respect to tumor stage, lymph node involvement, or presence of metastases.

TABLE 1 - *Demographic data and preoperative diagnosis**.

	Ceftriaxone with vs. without metronidazole		**Other cephalosporins with vs. without metronidazole**		**Penicillins with vs. without metronidazole**	
	+	**–**	**+**	**–**	**+**	**–**
Male/female (%)	48.5 / 51.5	47.7 / 52.3	46.6 / 53.4	48.9 / 51.1	50.0 / 50.0	47.2 / 52.8
Age (years)	65.3	65.5	67.1	69.0	66.7	66.4
Weight (kg)	72.6	73.0	72.5	72.6	74.8	73.3
Colon carcinoma (%)	64.8	64.8	70.7	69.9	71.6	74.4
Diverticulitis (%)	19.1	18.7	12.0	16.5	20.5	13.6
Other diagnoses	19.6	22.0	26.4	18.7	13.1	14.8

* Categories not mutually exclusive

TABLE 2 - *Type of colon operation (%)**.

	Ceftriaxone with vs. without metronidazole		**Other cephalosporins with vs. without metronidazole**		**Penicillins with vs. without metronidazole**	
	+	**–**	**+**	**–**	**+**	**–**
Resection of cecum plus ascending colon (right hemicolectomy)	22.4	24.9	23.3	26.3	23.9	26.1
Transverse colon	6.5	6.7	4.5	6.0	6.8	6.8
Descending colon (left hemicolectomy)	11.4	15.5	18.8	6.0	14.2	10.8
Sigmoid colon	36.3	33.8	33.8	36.8	36.9	39.8
Rectum (deep anastomosis)	18.7	18.7	27.1	27.1	19.3	19.3
Other colon operations	14.5	17.5	18.1	9.0	12.5	10.8
Creation of a stoma (incl. ileostomy)	13.9	11.4	18.8	10.5	10.8	17.1

* Categories not mutually exclusive

Clinical results – primary endpoint

In all three treatment groups combination therapy with metronidazole was found to be significantly superior. Postoperative infection rates with and without metronidazole were 9.4% and 18.7% respectively in Group 1, 12.0% and 25.6% respectively in Group 2, and 19.9% and 29.0% respectively in Group 3 (*Table 3*).

Table 4 shows the rates of occurrence of the various types of local and systemic infections. Use of metronidazole reduced local infections, in particular. Metronidazole brought about a significant reduction in infections in Group 1 and Group 2, whereas with penicillins (Group 3) there was only a tendency to a reduction in local and systemic infections. The rate of both local and systemic postoperative infections was lowest in Group 1 (ceftriaxone) and was further reduced by addition of metronidazole (*Table 4*).

The range of pathogens isolated after the operation is shown in *Table 5*. Use of metronidazole resulted in a tendency to a reduction in infections due to *Escherichia coli* and *Bacteroides*. In parallel with its low rate of infections, Group 1 had the lowest proportion of positive cultures (*Table 5*).

TABLE 3 - *Occurrence of infection within first 10 postoperative days (%)**.

	Ceftriaxone with vs. without metronidazole		**Other cephalosporins with vs. without metronidazole**		**Penicillins with vs. without metronidazole**	
	+	**–**	**+**	**–**	**+**	**–**
N	491	491	133	133	176	176
Postoperative infection	9.37	18.74	12.03	25.56	19.9	28.98
	p = 0.000		p = 0.008		p = 0.009	
Local infection	6.53	13.64	8.27	18.8	13.65	15.91
Systemic infection	2.84	5.1	3.76	6.76	6.25	13.07

* Categories not mutually exclusive

TABLE 4 - *Local and systemic postoperative infections (%).*

	Ceftriaxone with vs. without metronidazole		**Other cephalosporins with vs. without metronidazole**		**Penicillins with vs. without metronidazole**	
	+	**–**	**+**	**–**	**+**	**–**
N	491	491	133	133	176	176
Local infections	*6.53*	*13.64*	*8.27*	*18.8*	*13.65*	*15.91*
	p = 0.000		p = 0.039		p = 0.319	
Wound abscess, epifascial	4.08	9.98	6.02	13.54	11.94	9.09
Wound abscess, subfascial	1.02	0.61	1.5	1.5	1.14	2.84
Other	1.43	3.05	0.75	3.76	0.57	3.98
Systemic infections	*2.84*	*5.1*	*3.76*	*6.76*	*6.25*	*13.07*
	p = 0.004		p = 0.109		p = 0.074	
Pneumonia	1.42	1.43	0.75	4.51	1.7	5.12
Urinary tract infection	1.02	2.65	2.26	0.75	3.98	5.68
Venous catheter infection	0.2	1.02	0	0.75	0.57	2.27
Sepsis	0.2	0	0	0.75	0	0
Other	0	0	0.75	0	0	0

Secondary endpoints

As leukocyte count and body temperature remained normal postoperatively in all three groups, no group differences could be shown with respect to these parameters. In all three groups, however, use of metronidazole reduced the frequency of postoperative antibiotic therapy and of reoperation, while in the ceftriaxone group use of metronidazole also reduced the length of hospital stay (*Table 6*).

DISCUSSION

Diseases of the large intestine account for a significant proportion of visceral operations and are especially associated with advanced age of patients and an increased incidence of perioperative complications. Perioperative antibiotic prophylaxis has become an essential tool for optimizing the quality of surgical care in hospitals and success rates in the individual patient [1]. The wound classification proposed by Cruse [3] established a basis for perioperative antibiotic prophylaxis of wound infections. According to the literature, as many as 10–50% of laparotomy wounds become infected. Lippert and Gastinger found infection rates of 16.9% and 20.7% for emergency and elective interventions, respectively [4]. Taylor *et al*. [5] reported the occurrence of 1994 disturbances of wound healing in 11–18% of cases, while Löhde *et al*. [6] found a rate of 14%. In contrast, the rate of wound infections is only about 9% in general surgery and 3% in aseptic procedures [7]. These figures can be regarded as benchmarks of surgi-

TABLE 5 - *Pathogens isolated postoperatively (%).*

	Ceftriaxone with vs. without metronidazole		Other cephalosporins with vs. without metronidazole		Penicillins with vs. without metronidazole	
	+	–	+	–	+	–
N	491	491	133	133	176	176
Staph. aureus	0.41	1.02	0	0	2.84	2.27
Staph., coag.-neg.	1.22	1.22	1.5	0	1.14	3.98
Enterococcus faecalis	1.43	1.43	3.01	1.5	2.27	1.7
Enterobacteriaceae	0.61	0.61	1.5	0.75	0.57	0.57
E. coli	0.41	1.22	2.26	3.76	3.98	5.68
Bacteroides	0.41	0.81	0	1.5	0.57	0.57
Pseudomonas spp.	0	0	2.26	0.75	0	0.57
Klebsiella spp.	0.2	0.2	0	0	0.57	0
Overall frequency of pathogens	5.70	7.33	11.28	9.02	12.50	16.48

TABLE 6 - *Postoperative antibiotic therapy (%), re-operation (%), and length of hospital stay (days).*

	Ceftriaxone with vs. without metronidazole		Other cephalosporins with vs. without metronidazole		Penicillins with vs. without metronidazole	
	+	–	+	–	+	–
N	491	491	133	133	176	176
Antibiotic therapy	8.55	17.21	8.27	27.07	21.02	26.70
Re-operation	2.65	4.07	3.76	5.26	2.84	3.41
Length of hospital stay	16.4	18.2	18.6	18.7	17.9	18.3

cal quality. The effectiveness of a given form of perioperative antibiotic prophylaxis in septic colonic surgery can thus be estimated on the basis of the wound infection rates achieved in various hospital surgery departments.

However, the quality of colonic surgery is determined not just by wound infection rates, but also to a large extent by the rate of systemic secondary infections such as pneumonia and urinary tract infections, which contribute to increased mortality [8]. These infections are important from both a medical and an economic perspective, since they delay the initiation of other therapeutic modalities such as adjuvant chemotherapy in colonic carcinoma, prolong the length of hospital stay, and substantially increase costs. At a time of spending limits and introduction of the DRG (diagnosis related group) system, the need to avoid serious secondary infections is assuming increasing economic importance, and the present analysis of the value of perioperative antibiotic prophylaxis was undertaken with this in mind.

Surprisingly, perioperative infection prophylaxis using a combination of penicillins or cephalosporins plus metronidazole is not standard practice in elective colonic surgery in German hospitals. Inadequate use of antibiotic prophylaxis has also been reported in other countries [9-11]. The results reported here underline the importance of the widely accepted recommendation that metronidazole, or else clindamycin, should be used in perioperative antibiotic prophylaxis in order to reduce anaerobic intestinal flora [2]. The discrepancy that exists between this recommendation and everyday hospital practice may be attributable to earlier reports according to which addition of metronidazole brought no [12], or only a minor and statistically insignificant, benefit [8,13-18].

The study upon which the present analysis is based was published previously by Rau *et al*. [19]. The primary endpoints of that study were the rate of postoperative infections with the long-acting cephalosporin ceftriaxone versus the short-acting cephalosporins cefuroxime, cefotiam, cefoxitin, and cefotaxime (Group A) and with ceftriaxone versus broad-spectrum penicillins (Group B). The patients were accordingly divided into matched pairs (ceftriaxone vs. other cephalosporins [group A] and ceftriaxone vs. penicillins [group B]). The lowest overall rate of postoperative infections was achieved with ceftriaxone, there being a statistically significant difference with respect to penicillins (6.8% vs. 17.8%). This difference can be explained on the basis of the high rate of penicillin resistance shown by *E. coli*, which is commonly present in infections arising after colon surgery [20]. The division undertaken by Rau *et al.* into groups receiving ceftriaxone, short-acting cephalosporins, or broad-spectrum penicillins was also adopted in the present analysis, in which, however, patients in the groups with and without metronidazole were matched to form pairs of equal risk. In all three treatment groups the use of metronidazole conferred a definite benefit. At the same time, the superiority of ceftriaxone demonstrated by Rau *et al*. was confirmed by the present analysis in that infection prophylaxis with ceftriaxone plus metronidazole resulted in the lowest postoperative infection rate (9.4%) [19].

Earlier studies comparing first and second-generation cephalosporins with third-generation cephalosporins and penicillins in terms of wound infection rates have yielded conflicting results [8,21-23]. Studies by the present authors found ceftriaxone to be superior [24,25]. Other authors found no difference between single-shot and multiple-dose antibiotic administration in terms of postoperative infection rates [26-31]. Depending on the duration of the operation and the time of their administration, however, short-acting antibiotics may need to be given a second time if optimal antibiotic protection is to be achieved.

The choice of antibiotic for perioperative prophylaxis in colon surgery must take account of the expected range of aerobic and anaerobic organisms in the colonic flora, the pharmacokinetics and pharmacodynamics of the drugs under consideration, the effective time window available, and the risk of infection in the individual patient. The risk of development of resistance in the individual patient is negligible. In the hospital setting, however, perioperative antibiotic prophylaxis must be subjected to quality control and chosen on the basis of the resistance situation in the hospital concerned.

Thanks to their good efficacy against Gram-negative pathogens, in particular the commonly present *E. coli*, cephalosporins enjoy at least a microbiological advantage for prophylactic use in colon surgery. A precondition for this, however, is that anaerobic pathogens must also be

covered. The present analysis of a large-scale matched-pairs controlled study provides convincing evidence of the clinical benefits of such a combined prophylactic regimen. The microbiological tests performed as part of the study revealed no evidence that prophylaxis with cephalosporins leads to any selection of enterococci. The good results achieved with ceftriaxone plus metronidazole may be due to the almost 100% coverage of *E. coli* and *Bacteroides* spp. provided by this combination and to the long duration of action of ceftriaxone that results from an elimination half-life of 8 hours.

In summary, the use of perioperative antibiotic prophylaxis with cephalosporins, and in particular with ceftriaxone, in colon surgery can be recommended on the basis of the present analysis [32]. The beta-lactam antibiotics investigated in the study should always be given in combination with metronidazole or another antibiotic that is effective against anaerobic organisms.

REFERENCES

[1] Song F, Glenny A-M. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. Br J Surg 1998; 85: 1232–41.

[2] Konsensus: Standortbestimmung zur Antibiotikaprophylaxe bei chirurgischen Eingriffen. Zentralbl Chir 1998; 123: 1188–90.

[4] Lippert H, Gastinger I. Die chirurgische Qualitätssicherung am Beispiel der operativen Therapie des colorectalen Carcinoms. Chirurg 1995; 66: 344–49.

[5] Taylor EW, Lindsay G, West of Scotland Surgical Infection Study Group. Selective decontamination of the colon before elective colorectal surgery. World J Surg 1994; 18: 926–32.

[3] Cruse PEJ (AUTHOR, PROVIDE NAMES OF FIRST 3 AUTHORS IF MORE THAN 6, OR ALL 6 NAMES IF LESS) *et al.* A 5-year prospective study of 23649 surgical wounds. Arch Surg 1973; 107: 206–10.

[6] Löhde E, Scholz L, Gemperle A *et al*. Vergleichsanalyse von Mezlocillin/Metronidazol und Amoxicillin/Clavulansäure als "one-shot"-Antibiotikaprophylaxe bei kolorektalen Eingriffen. Zent bl Chir 1992; 117: 325–30.

[7] Grundmann R, Hofferek B. Wundinfektions- und Komplikationsrate nach allgemeinchirurgischen Eingriffen. Chirurg 1981; 52: 570–76.

[8] Lumley JW, Siu SK, Pillay SP, *et al*. Single dose ceftriaxone as prophylaxis for sepsis in colorectal surgery. Aust NZ J Surg 1992; 62: 292–6.

[9] Delgadillo L, Ramirez R, Cebrecos J, Arnau JM, Laporte JR. The use of antibiotics in surgical prophylaxis. The characteristics and consequences. Med Clin (Barc) 1993; 100: 404–6.

[10] Kappstein I, Daschner FD. Use of perioperative antibiotic prophylaxis in selected surgical procedures — results of a survey in 889 surgical departments in German hospitals. Infection 1991; 19: 391–4.

[11] Lim VK, Cheong YM, Suleiman AB. The use of surgical antibiotic prophylaxis in seven Malaysian hospitals. Southeast Asian J Trop Med Public Health 1994; 25: 698–701.

[12] Favre JP, Bouchet Y, Clotteau JE, *et al*. Prophylactic use of cefotaxime in colonic and rectal surgery. J Antimicrob Chemother 1984; 14 (Suppl B): 247–53.

[13] Claesson BE, Filipsson S, Holmlund DE, Matzsch TW, Wahlby L. Selective cefuroxime prophylaxis following colorectal surgery based on intra-operative dipslide culture. Br J Surg 1986; 73: 953–7.

[14] Corman M, Robertson W, Lewis T, Odenheimer DB, Zegarra P, Prager ED. A controlled clinical trial. Cefuroxime, metronidazole, and cefoxitin as prophylactic therapy for colorectal surgery. Complications Surg 1993; 12: 37–40.

[15] Cunliffe WJ, Carr N, Schofield PF. Prophylactic metronidazole with and without cefuroxime in elective colorectal surgery. A prospective randomised double-blind study. J R Coll Surg Edinb 1985; 30: 123–5.

[16] Hakansson T, Raahave D, Hansen OH, Pedersen T. Effectiveness of single dose prophylaxis with cefotaxime and metronidazole compared with three doses of cefotaxime alone in elective colorectal surgery. Eur J Surg 1993; 159: 177–80.

[17] Haverkorn MJ. Peroperative systematic prophylaxis in colorectal surgery. Drugs Exp Clin Res 1985; 11: 111–14.

[18] Mittermayer H, Gross C, Brucke P. Single dose cefuroxime/ metronidazole versus metronidazole alone in elective colorectal surgery. Am Surg 1984; 50: 418–23.

[19] Rau HG, Mittelkötter U, Zimmermann A, Lachmann A, Koehler, L, Kullmann KH. Perioperative infection prophylaxis and risk factor impact in colon surgery. Chemotherapy 2000; 46: 353–63.

[20] Focht J, Nösner K. Erregerhäufigkeit und Resistenzsituation von Beta-Lactam-Antibiotika 1997. Arzneimitteltherapie 1998; 9: 276–78.

[21] Jones RN, Wojeski W, Bakke J, Porter C, Searles M. Antibiotic prophylaxis of 1036 patients undergoing elective surgical procedures. A prospective randomized comparative trial of cefazolin, cefoxitin and cefotaxime in a prepaid medical practice. Am J Surg 1987; 153: 341–6.

[22] Reynolds JR, Jones JA, Evans DF, Hardcastle JD. Do preoperative oral antibiotics influence sepsis rates following elective colorectal surgery in patients receiving perioperative intravenous prophylaxis? Surg Res Comm 1989; 7: 71–7.

[23] Rowe-Jones DC, Peel AL, Kingston RD, Shaw JF, Teasdale C, Cole DS. Single dose cefotaxime plus metronidazole versus three dose cefuroxime plus metronidazole as prophylaxis against wound infection in colorectal surgery: multicentre prospective randomised study. Br Med J 1990; 300: 18–22.

[24] Mittelkötter U, Reith HB, Haarmann W, Kozuschek W. Effectiveness of different antibiotic prophylaxis on wound healing and hospital stay in colonic surgery. 6th BICON, Leipzig, 1996. Antiinfect Drugs Chemother 1996; 14: 81.

[25] Mittelkötter U, Reith HB, Lee U, Haarmann W, Kozuschek W. Effectiveness of different prophylactic antibiotic regimens regarding colorectal surgery. XXX. World Congress of the International College of Surgeons, 25–29 November 1996, Kyoto, Japan. In: Osahiko Abe, Kiyoshi Inokuchi, Ken Takasaki (ed.), Monduzzi Editore International Proceedings Division, 1996: 515–18.

[26] Bittner R, Butters M, Rampf W, Kapfer X. Duration of the preventive use of antibiotics in colorectal surgery—single administration versus short-term prevention. Langenbecks Arch Chir 1989; 374: 272–9.

[27] Grundmann R, Burkardt F, Scholl H, Koelschbach D. One versus three doses of metronidazole/mezlocillin for antibiotic prophylaxis in colon surgery. Chemioterapia 1987; 6 (Suppl 2): 604–5.

[28] Kow L, Toouli J, Brookman J, McDonald PJ. Comparison of cefotaxime plus metronidazole versus cefoxitin for prevention of wound infection after abdominal surgery. World J Surg 1995; 19: 680–6.

[29] Lohr J, Wagner PK, Rothmund M. Perioperative Antibiotica Prophylaxe bei elektiven colorectalen Eingriffen. Chirurg 1984; 55: 512–14.

[30] Mendel V, Jung D, Heymann H. Single-shot antibiotic prophylaxis in colon surgery. Chemioterapia 1987; 6 (Suppl 2): 597–600.

[31] Tuchmann V, Breyer S, Ganzinger U. Preventive use of antibiotics in colorectal interventions. Short-term versus one-shot prevention—a multicenter study. Fortschr Med 1988; 106: 537–40.

[32] Mittelkötter U, Kullmann KH, Reith HB, Thiede A. Freiburg: Karger-Verlag, Antiinfektivatabelle 1999.