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Systematic Review and Meta-Analysis

Assessing Prophylactic Cephamycins Used in Colorectal Surgery: A Meta-Analysis

Yu Ding[1]*, Feng-Ying Xu[2]*, Miao Zhou[3]*, Yu-Xin Li[1], Hua He[4], Xue-Peng Zhang[1], Jian-Hua Xia[5], and Xue-Yin Shi[2]

ABSTRACT

Background: Cephamycins prophylactic used in colorectal surgery have been widely evaluated, but the uncertainty remains about the comparative effects of different antibiotics. The meta-analysis aimed to assess the efficacy of cephamycins compared with other agents used as prophylaxis in colorectal surgery.

Methods: PubMed, EMBASE, and Cochrane Library were searched for relevant studies. A meta-analysis of randomized controlled trials (RCTs) meeting the criteria was performed using Review Manager.

Results: Thirty-nine trials involving 4,755 participants were included in this meta-analysis. The cephamycins were not as effective as other antibiotics for the prevention of postoperative surgical site infection (SSI) (Risk Ratio [RR] 1.18; 95% confidence interval [CI] 1.04, 1.34; P=0.008) and had no advantages in reduction of systemic infection and distal infection. For each antibiotic belonging to cephamycins, there was no statistical difference when cefoxitin and cefotetan were compared with penicillins and cephalosporins on prevention of SSI, while cefmetazole had advantages over cephalosporins on prevention of SSI (RR 0.46; 95% CI 0.22, 0.96; P=0.04).

Conclusions: The prophylactic use of cefoxitin and cefotetan in colorectal operations has no significant advantages over other antibiotics. However, cefmetazole may be effective in the prevention of postoperative infections and its efficacy should be researched further and considered by perioperative medical staff. Therefore, it is of great importance to optimize the prophylactic use of antibiotics in colorectal operations.

From [1]Department of Anesthesiology, Changzheng Hospital, Company 12, Second Military Medical University, Shanghai, China; [2]Department of Anesthesiology, Changzheng Hospital, Second Military Medical University, Shanghai, China; [3]Jiangsu Province Key Laboratory of Anesthesiology, Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology, Xuzhou Medical College, Xuzhou, China; [4]Department of Neurosurgery, Changzheng Hospital, Second Military Medical University, Shanghai, China; [5]Department of Anesthesiology, NO. 411 Hospital of PLA, Shanghai, China.

*These authors contributed equally to this work.

Correspondence to Dr. Xue-Yin Shi at shixueyin1128@163.com or Dr. Jian-Hua Xia at jianhuaxia2000@sina.com.

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Postoperative infections occur frequently in patients having colorectal operations. The incision and anastomosis of bowel and long duration of operations result in high incidence of postoperative infection. Despite implementation of health care practices, the incidence of surgical site infection (SSI) after colorectal surgery remains as high as 26% (1, 2). This complication leads to long hospital stays, prolongs the time to starting adjuvant therapy and increases health expenditure (3). Meanwhile other types of postoperative infections such as bacteremia and unary tract infection are unbeneficial to patients' recovery and even threat to the life. Effective prevention and treatment of postoperative infection have become an imperative step for perioperative medical staff.

Numerous studies have shown that the prophylactic administration of antibiotics reduces the incidence of SSI and other postoperative septic complications after colorectal operations (4-6). Cephamycins have been widely used to prevent infection in surgeries such as gynecologic operations and appendectomy

(7-9). Cephamycins, including cefoxitin, cefmetazole, cefotetan, cefminox and so on, belong to atypical β-lactams and have similarities with cephalosporins. Cephamycins are the only agents that have a wide spectrum covering both gram-positive and gram-negative bacteria, especially their effect on gram-negative bacteria (10). Cephamycins are also used as prophylaxis in colorectal operations and the effects have been widely evaluated. However, there is controversy over cephamycins' efficacy on the prevention of infections in the colorectal operations and the role of cephamycins remains unclear. For example, one study in 2006 showed that cefotetan was less effective than ertapenem in the prevention of SSI in patients undergoing colorectal surgeries (11). Another research showed that there were no significantly differences on the incidence of SSI between cefmetazole and flomoxef (12). Aiming to provide solid conclusions for cephamycins used as prophylaxis in colorectal surgeries, we undertook this meta-analysis to evaluate the efficacy of infection control of cephamycins compared with other antibiotics in patients undergoing colorectal operations.

MATERIALS AND METHODS

Search Strategy

The following databases were reviewed by two reviewers: PubMed, EMBASE, Cochrane Library. Additional relevant cited references were identified from the retrieved papers and review articles. The range of the search was from January, 1981 to December, 2012. No language restrictions were used. Search terms included 'cephamycins', 'cefoxitin', 'cefotetan', 'cefmetazole', 'cefminox', 'randomized controlled trial (RCT) ' and 'colorectal surgery'.

Study Selection

The study selection was pre-established. Inclusion criteria: RCTs; patients undergoing colorectal operations; the administration of cephamycins for experimental group; the administration of other antibiotics for control group; the presence and absence of infection reported. Exclusion criteria: abstracts only; patients allergic to antibiotics or other contradictions of antibiotics; duplications; missing data; incorrect statistical analysis performed in the report; treatment of infection rather than prophylaxis; the administration of placebo in control group. Studies using additional agents, such as metronidazole, were also included.

Data Retrieval

Data extracted from the papers included: name of the first author, publication year, the design of the trial, the details of antibiotic administration, the type of surgery, the duration of follow-up, number of patients in each arm, number of study centers, definition of end points, and the number of end point infection.

Qualitative Assessment

The quality of all the included studies was appraised using the guidelines recommended by the Cochrane Collaboration (13). The risk of bias was evaluated in six categories: randomization and sequence generation, blinding method, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias. Every category was assessed according to three rulings: low risk, unclear risk, and high risk. The items of randomization and sequence generation, blinding method, and allocation concealment were considered as key domains and the evaluation was as follows: low risk of bias (low risk of bias for all key domains); unclear risk of bias (unclear risk of bias for one or more key domains); and high risk of bias (high risk of bias for one or more key domains). Data were independently reviewed by two people. Final inclusion of articles was determined by consensus.

Statistical Analysis

The effect of cephamycins on postoperative infections, compared with other antibiotics was estimated by calculating pooled risk ratio (RR) and its 95% confidence intervals (CI) of the incidence of infection as dichotomous data. The significance of RR overall effect was determined by Z test ($P<0.05$ was considered statistically significant). A fixed effects model was used when $I^2 \leqslant 50\%$, otherwise, a random effects model was adopted. A sensitivity analysis was performed to assess whether inclusion of the high-risk studies could significantly bias the result. It was conducted according to high and not high risk of bias (including low and unclear risk of bias). The sub-analyses were based on the kind of cephamycins and agents administered in control groups. Funnel plot was conducted to check for publication bias. Statistical analysis was performed with Review Manager (RevMan®) (Version 5.0.; The Cochrane Collaboration, Oxford, UK).

RESULTS

Study Selection

As shown in the flow diagram (Figure 1), the search of PubMed, EMBASE, Cochrane Library and reference lists yielded 324 articles. Totally 279 papers were discarded after initial screening. Two full texts (14, 15) of the remaining 45 papers couldn't be retrieved despite of efforts by electric retrieval, interlibrary loan and contacting the authors. The remaining 43 papers were carefully read and 17 articles were excluded because they did meet the criteria. Specifically, three papers (16-18) were excluded because they were not RCTs and four (11, 19-21) were excluded because they were duplications. One paper (22) was excluded because the participants were not all undergoing colorectal surgeries and the number of participants undergoing colorectal surgeries was not reported in this paper, and nine papers (23-31) were excluded because of no appropriate control arm assessing the efficient of cephamycins. Finally, the 26 papers, including 39 RCTs, met the selection criteria.

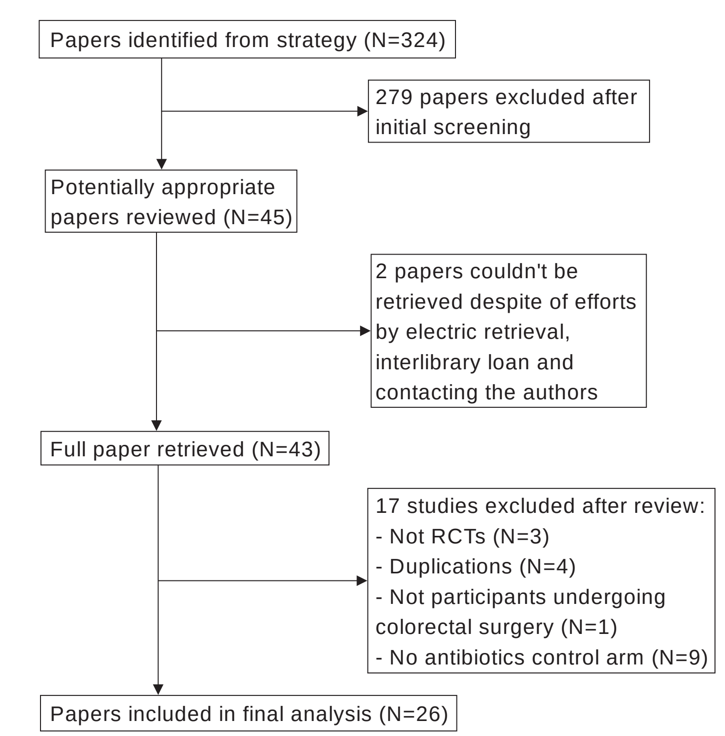


Figure 1. The Diagram Showing Studies Eligible for Inclusion in the Meta-Analysis.

Study Characteristics

Of all the included papers, two (32, 33) were published in German, one (34) was in French and one (35) was in Japanese. The remaining 22 papers were published in English. In these included 39 RCTs, 4,755 patients were involved. Totally 38 RCTs reported the present or absence of postoperative SSI such as surgical wound infection, abdominal abscess and sub phrenic abscess. Only three (34, 36, 37) reported systemic infections including sepsis, septicemia and bacteremia while six (35, 38-40) were distal infections including urinary tract infection and pneumonia. Characteristics of the included trials were shown in table.

Risk of Bias within Studies

Of the 39 RCTs included, no trial had high risk of bias in randomization and sequence generation while 16 trials had high risk of bias in blinding method and 16 had high risk of bias in allocation concealment. Totally 21 trials were evaluated as high risk, 17 were unclear risk and 1 was low risk. An overview of the risk of bias was summarized in table.

Efficacy of Cephamycins

Thirty- eight trials, involving 4,678 participants undergoing colorectal surgeries compared cephamycins with other antibiotics in preventing SSI. The cephamycins were not as effective as other antibiotics (RR 1.18; 95% CI 1.04, 1.34; P=0.008). The result was similar after sensitivity analysis with the exclusion of the high-risk studies was performed (RR 1.28; 95% CI 1.08, 1.51; P=0.005). The funnel plots (Figure 2) were drawn and did not show significant visual asymmetry.

Cefoxitin vs Penicillins

Five trials (33, 41-43), involving 1,029 participants, compared cefoxitin with penicillins including piperacillin (33, 41, 42) and ampicillin (33, 43) in preventing postoperative SSI. There

Table. Summary of Trials Included in the Meta-anaLysis.

Trials	Number	Surgery	Interventions	Outcomes	The number of study centers	Length	Risk of bias R B A C F O	Rank
Anders 1984a	132	Colorectal surgery	Cefoxitin vs cefamandole	SWI	NA	NA	U H U H U U	H
Anders 1984b	95	Colorectal surgery	Cefoxitin vs cefotaxim	SWI	NA	NA	U H U H U U	H
Anders 1984c	100	Colorectal surgery	Cefoxitin vs lamoxactam	SWI	NA	NA	U H U H U U	H
Antonelli 1985	77	Elective colorectal surgery	Cefoxitin vs cephalothin	Sepsis	1	42 days	L H H H U U	H
Armengaud 1986	60	Emergency or elective colorectal surgery	Cefoxitin vs piperacillin	SWI	1	NA	U L H U U L	H
Arnaud 1992	221	Elective colorectal surgery	Cefotetan vs amoxycillin/ clavulanic acid	Surgical wound cellulitis, surgical wound abscess, intra-abdominal abscess, peritonitis, septicaemia, bacteraemia, hyperthermia	19	30 days	L U H U L L	H
Bellantone 1988	65	Elective colorectal surgery	Cefotetan vs clindamycin plus aztreonam	SWI, urinary tract infection, respiratory tract infection	1	NA	U H H U U U	H
Corman 1993a	57	Elective colorectal surgery	Cefoxitin vs cefuroxime	SWI	1	30 days	U H U U L U	H
Corman 1993b	63	Elective colorectal surgery	Cefoxitin vs cefuroxime	SWI	1	30 days	U H U U L U	H
Fabian 1984	40*	Elective colorectal surgery	Cefoxitin vs cefonicid	SWI, intra-abdominal abscess	1	NA	L L U H L L	U
Hershman 1990	153	Elective colorectal surgery	Cefotetan vs piperacillin	SWI	NA	42 days	U L U H L L	U
Ishibashi 2009a	136	Elective surgery for colon cancer	Cefmetazole vs cefotiam	Incisional site infection, organ/space infection	1	NA	L U L H L L	U
Ishibashi 2009b	139	Elective surgery for colon cancer	Cefmetazole vs cefotiam	Incisional site infection, organ/space infection	1	NA	L U L H L L	U
Itani 2007a	257	Elective open surgery of the colon or rectum (PEG SSIs, without resection of rectum)	Cefotetan vs ertapenem	SSI	51	28 days	U L L U L L	U
Itani 2007b	259	Elective open surgery of the colon or rectum (SP SSIs, without resection of rectum)	Cefotetan vs ertapenem	SSI	51	28 days	U L L U L L	U

Table. (Continued) Summary of Trials Included in the Meta-anaLysis.

Trials	Number	Surgery	Interventions	Outcomes	The number of study centers	Length	Risk of bias						Rank
							R	B	A	C	F	O	
Itani 2007c	46	Elective open surgery of the colon or rectum (PEG SSIs, with resection of rectum)	Cefotetan vs ertapenem	SSI	51	28 days	U	L	L	U	L	L	U
Itani 2007d	108	Elective open surgery of the colon or rectum (SP SSIs, with resection of rectum)	Cefotetan vs ertapenem	SSI	51	28 days	U	L	L	U	L	L	U
Ivarsson 1982	140	Elective colorectal surgery	Cefoxitin vs doxycycline	SWI, intra-abdominal abscesses	1	30 days	U	H	H	U	U	L	H
Jagelman 1987	94	Elective colorectal surgery	Cefoxitin vs piperacillin	Peritonitis, SWI, sub-phrenic abscess, pelvic abscess	1	5 days	U	H	H	U	U	L	H
Jewesson 1997a	75	Elective colorectal surgery	Cefoxitin vs ceftizoxime	Primary site complication, distal infection	1	30 days	L	U	U	H	U	L	U
Jewesson 1997b	84	Elective colorectal surgery	Cefoxitin vs Metro-Gent	Primary site complication, distal infection	1	30 days	L	U	U	H	U	L	U
Jones 1987a	71	Elective colorectal surgery	Cefoxitin vs cefazolin	SWI	2	30 days	U	L	U	U	L	L	U
Jones 1987b	65	Elective colorectal surgery	Cefoxitin vs cefotaxime	SWI	2	30 days	U	L	U	U	L	L	U
Kaiser 1983	130	Elective colorectal surgery	Cefoxitin vs erythromycin, neomycin, cefazolin	SSI	4	30 days	U	L	H	U	U	L	H
Kikuchi 1988	126	Elective colorectal surgery	Cefmetazole vs cephalothin	Urinary tract infection, SWI, intra-abdominal abscess, unexplained fever	19	NA	L	U	U	H	U	L	U
Kow 1995a	136	Elective colorectal surgery	Cefoxitin vs cefotaxime	SWI	2	30 days	L	U	L	H	L	L	U
Kow 1995b	137	Elective colorectal surgery	Cefoxitin vs cefotaxime	SWI	2	30 days	L	U	L	H	L	L	U
Maki 1982a	62	Elective colorectal surgery	Cefoxitin vs ceftizoxime	SWI, intra-peritoneal infection, urinary tract infection, pneumonia, fever	1	30 days	U	U	H	H	U	U	H
Maki 1982b	63	Elective colorectal surgery	Cefoxitin vs cefazolin	SWI, intra-peritoneal infection, urinary tract infection, pneumonia, fever	1	30 days	U	U	H	H	U	U	H
Menzel 1993a	268	Elective colorectal surgery	Cefoxitin vs ampicillin	SWI	NA	NA	U	H	H	U	U	U	H

Table. (Continued) Summary of Trials Included in the Meta-anaLysis.

Trials	Number	Surgery	Interventions	Outcomes	The number of study centers	Length	Risk of bias R	B	A	C	F	O	Rank
Menzel 1993b	263	Elective colorectal surgery	Cefoxitin vs piperacillin	SWI	NA	NA	U	H	H	U	U	U	H
Milsom 1998	518	Elective colorectal surgery	Cefotetan vs alatrofloxacin	SWI, intra-abdominal infection, remote-site postoperative infectious complications	61	30 days	U	L	U	H	L	U	U
Panichi 1982a	46	Colorectal surgery	Cefoxitin vs metronidazole	SWI, fever	NA	5 days	U	H	H	H	U	L	H
Panichi 1982b	51	Colorectal surgery	Cefoxitin vs cephalothin	SWI, fever	NA	5 days	U	H	H	H	U	L	H
Rorbaek-Madsen 1988	397	Elective colorectal surgery	Cefoxitin vs ampicillin plus metronidazole	SWI	6	30 days	U	H	H	U	U	U	H
Shatney 1984	70*	Colorectal surgery	Cefoxitin vs cefotaxime	Peritoneal infection or SWI	5	30 days	U	H	H	U	L	L	H
Shimizu 2010	91	Colectomy	Cefmetazole vs flomoxef	SSI, pyrexia	4	30 days	L	L	L	H	L	L	L
Skipper 1992	126	Elective colorectal surgery	Cefotetan vs cefuroxime plus metronidazole	SWI, respiratory infection,urinary tract infection, intra-abdominal abscess, pelvic abscess	3	30 days	U	H	H	U	L	L	H
Stellato 1990	95	Elective colorectal surgery	Cefoxitin vs neomycin 1 g plus erythromycin	SWI	1	NA	L	U	U	H	L	L	U

*The number of patients undergoing colorectal surgery
NA: not available; SWI: surgical wound infection; SSI: surgical site infection
R: randomization sequence generation; B: blinded method; A: allocation concealment; C: complete outcome data addressed; F: free of selective reporting; O: free of other bias; L: low risk; H: high risk; U: unclear risk

was no statistical difference between cefoxitin and penicillins (RR 1.23; 95% CI 0.98, 1.54; P=0.08) (Figure 3).

Cefoxitin vs First-Generation Cephalosporins
Three trials (39, 44, 45), involving 185 participants, compared cefoxitin with first-generation cephalosporins. The controls were cephalothin in one trial (45) and cefazolin in the other two (39, 44). There was a lower incidence of postoperative SSI in the group administered cefoxitin (RR 0.27; 95% CI 0.08, 0.93; P=0.04) with almost no heterogeneity (I^2=0). However, no statistical difference were found between cefoxitin and first-generation cephalosporins when sensitivity analysis was performed (RR 0.97; 95% CI 0.06, 14.94; P=0.98) (Figure 3).

Cefoxitin vs Second-Generation Cephalosprins
Four trials (32, 46, 47), involving 282 participants, compared cefoxitin with second-generation cephalosprins including cefamandole (32), cefuroxime (46) and cefonicid (47) in preventing postoperative SSI. There was no statistical difference between cefoxitin and second-generation cephalosprins (RR 0.50; 95% CI 0.25, 1.01; P=0.05). The result was similar when sensitivity analysis was conducted (Figure 3).

Cefoxitin vs Third-Generation Cephalosprins
Seven trials (32, 38, 39, 44, 48, 49), involving 642 participants, compared cefoxitin with third-generation cephalosprins including cefotaxime (32, 44, 48, 49), ceftizoxime (38, 39). There was no statistical difference between cefoxitin and third-generation cephalosprins (RR 1.46; 95% CI 0.93, 2.30; P=0.10) (Figure 3).

Cefoxitin vs Other Atypical β-Lactams
One trial (32) involving 100 participants compared cefoxitin with lamoxactam, one kind of atypical β-lactams. There was no statistical difference in preventing SSI when the use of lamoxatam as compared with cefoxitin (RR 1.00; 95% CI 0.15, 6.82) (Figure 3).

Cefotetan vs Penicillins
Two trials (36, 50), involving 361 participants, compared cefotetan with penicillins including amoxicillin (36) and piperacillin (50). There was no statistical difference between cefotetan and penicillins (RR 1.08; 95% CI 0.63, 1.85; P=0.78) (Figure 3).

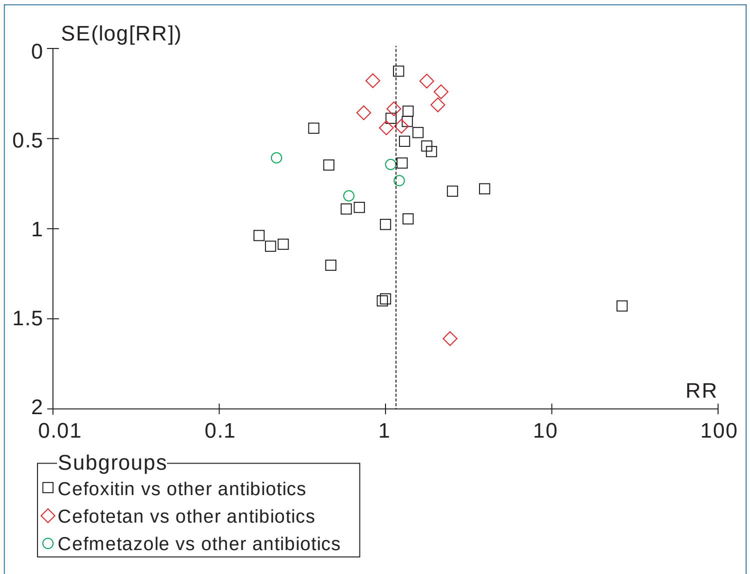


Figure 2. Funnel Plot of Surgical Site Infection in Each Group.

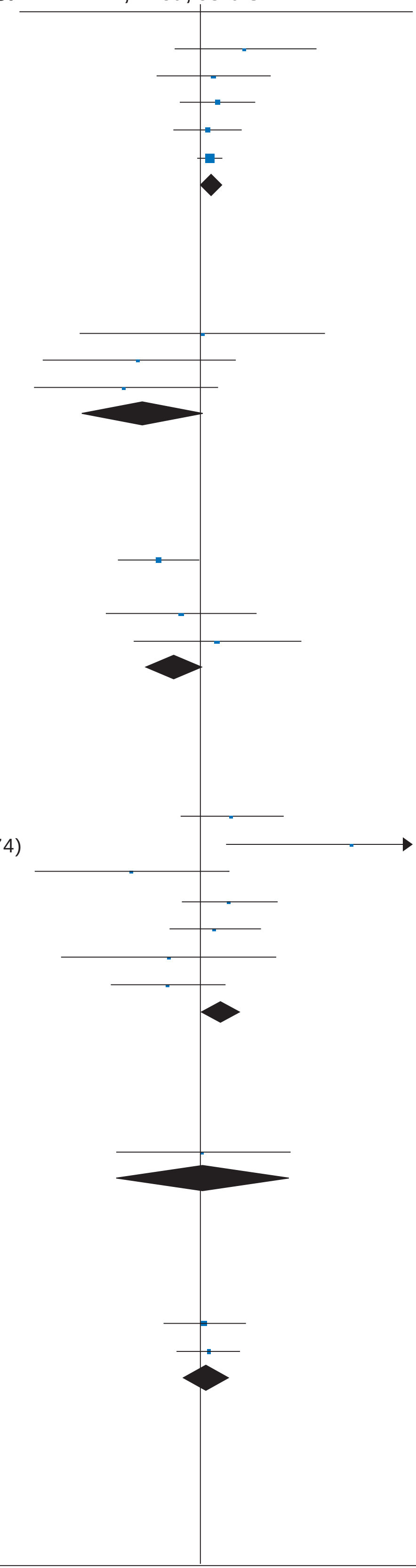
Cefotetan vs Second-Generation Cephalosprins
One trial (40) involving 104 participants compared cefoxitin with cefuroxime. There was no statistical difference in preventing SSI between two groups (RR 1.24; 95% CI 0.52, 2.94; P=0.63) (Figure 3).

Cefotetan vs Other Atypical β-Lactams
Five trials (51, 52), involving 728 participants, compared cefotetan with other atypical β-lactams including ertapenem (52) and aztreonam (51). There was a lower incidence of postoperative SSI in the group administered other atypical β-lactams (RR 1.71; 95% CI 1.33, 2.20; P<0.0001) with minimal heterogeneity (I^2=40%). We found similar results when sensitivity analysis was conducted (RR 1.71; 95% CI 1.33, 2.20; P<0.0001) (Figure 3).

Cefmetazole vs Cephalosporins
Three trials (35, 53), involving 393 participants, compared cefmetazole with cephalosporins including cefotiam (53) and cephalothin (35). Cefmetazole showed great advantages over cephalosporins in the prevention of SSI (RR 0.46; 95% CI 0.22, 0.96; P=0.04) with minimal heterogeneity (I^2=38%). The results were unchanged

Study of subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
1.3.1 Cefoxitin vs penicillins						
Aemengaud 1986	5	30	2	30	0.7%	2.50 (0.53, 11.89)
Jagelman 1987	5	43	4	43	1.4%	1.25 (0.36, 4.34)
Menzel 1993a	12	126	10	142	3.4%	1.35 (0.61, 3.02)
Menzel 1993b	12	126	12	137	4.1%	1.09 (0.51, 2.33)
Rorbaek-Madsen 1988	79	175	67	177	23.8%	1.19 (0.93, 1.53)
Subtotal (95% CI)		500		529	33.4%	1.23 (0.98, 1.54)
Total events	113		95			
Heterogeneity: Chi^2=1.00, df=4 (P=0.91); I^2=0%						
Test for overall effect: Z=1.77 (P=0.08)						
1.3.2 Cefoxitin vs first-generation cephalosporins						
Jones 1987a	1	36	1	35	0.4%	0.97 (0.06, 14.94)
Maki 1982b	1	32	4	31	1.4%	0.24 (0.03, 2.05)
Panichi 1982a	1	23	7	28	2.3%	0.17 (0.02, 1.31)
Subtotal (95% CI)		91		94	4.1%	0.27 (0.08, 0.93)
Total events	3		12			
Heterogeneity: Chi^2=1.04, df=2 (P=0.60); I^2=0%						
Test for overall effect: Z=2.07 (P=0.04)						
1.3.3 Cefoxitin vs second-generation cephalosporins						
Anders 1984a	6	63	15	59	5.5%	0.37 (0.16, 0.90)
Corman 1993a	0	27	0	30		Not estimable
Corman 1993b	2	31	3	32	1.1%	0.69 (0.12, 3.84)
Fabian 1984	2	17	2	23	0.6%	1.35 (0.21, 8.66)
Subtotal (95% CI)		138		144	7.2%	0.50 (0.25, 1.01)
Total events	10		20			
Heterogeneity: Chi^2=1.65, df=2 (P=0.44); I^2=0%						
Test for overall effect: Z=1.92 (P=0.05)						
1.3.4 Cefoxitin vs third-generation cephalosporins						
Anders 1984b	8	49	4	46	1.5%	1.88 (0.61, 5.82)
Jewesson 1997a	13	39	0	38	0.2%	26.32 (1.62, 427.74)
Jones 1987b	1	36	4	29	1.6%	0.20 (0.02, 1.70)
Kow 1995a	8	65	5	71	1.7%	1.75 (0.60, 5.07)
Kow 1995b	8	70	6	67	2.2%	1.28 (0.47, 3.48)
Maki 1982a	1	32	2	30	0.7%	0.47 (0.04, 4.91)
Shatney 1984	3	34	7	36	2.4%	0.45 (0.13, 1.61)
Subtotal (95% CI)		325		317	10.3%	1.46 (0.93, 2.30)
Total events	42		28			
Heterogeneity: Chi^2=11.98, df=6 (P=0.06); I^2=50%						
Test for overall effect: Z=1.65 (P=0.10)						
1.3.5 Cefoxitin vs other atypical β-lactams						
Anders 1984c	2	50	2		0.7%	1.00 (0.15, 6.82)
Subtotal (95% CI)		50		50	0.7%	1.00 (0.15, 6.82)
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z=0.00 (P=1.00)						
1.3.6 Cefotetan vs penicillins						
Arnaud 1992	9	103	9	105	3.2%	1.02 (0.42, 2.47)
Hershman 1990	14	75	13	78	4.5%	1.12 (0.56, 2.22)
Subtotal (95% CI)		178		183	7.7%	1.08 (0.63, 1.85)
Total events	23		22			
Heterogeneity: Chi^2=0.03, df=1 (P=0.87); I^2=0%						
Test for overall effect: Z=0.27 (P=0.78)						
1.3.7 Cefotetan vs first-generation cephalosporins						
Subtotal (95% CI)		0		0		Not estimable
Total events	0		0			

Risk ratio
M-H, fixed, 95% CI



Study of subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.8 Cefotetan vs second-generation cephalosporins						
Skipper 1992	14	68	6	36	2.8%	1.24 (0.52, 2.94)
Subtotal (95% CI)		68		36	2.8%	1.24 (0.52, 2.94)
Total events	14		6			
Heterogeneity: Not applicable						
Test for overall effect: Z=0.48 (P=0.63)						
1.3.9 Cefotetan vs third-generation cephalosporins						
Subtotal (95% CI)		0		0		Not estimable
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.10 Cefotetan vs other atypical β-lactams						
Bellantone 1988	1	32	0	26	0.2%	2.45 (0.10, 57.85)
Itani 2007a	52	126	30	131	10.5%	1.80 (1.24, 2.63)
Itani 2007b	44	138	18	121	6.8%	2.14 (1.31, 3.50)
Itani 2007c	12	18	9	28	2.5%	2.07 (1.11, 3.89)
Itani 2007d	10	51	15	57	5.1%	0.75 (0.37, 1.51)
Subtotal (95% CI)		365		363	25.1%	1.71 (1.33, 2.20)
Total events	119		72			
Heterogeneity: Chi^2=6.62, df=4 (P=0.16); I^2=40%						
Test for overall effect: Z=4.21(P<0.0001)						
1.3.11 Cefoxitin vs cephalosporins						
Ishibashi 2009a	2	54	5	82	1.4%	0.61 (0.12, 3.02)
Ishibashi 2009b	4	59	5	82	1.5%	1.08 (0.30, 3.87)
Kikuchi 1988	3	60	13	58	4.7%	0.22 (0.07, 0.74)
Subtotal (95% CI)		173		220	7.6%	0.46 (0.22, 0.96)
Total events	9		23			
Heterogeneity: Chi^2=3.25, df=2 (P=0.20); I^2=38%						
Test for overall effect: Z=2.07 (P=0.04)						
1.3.12 Cefoxitin vs penicillins						
Shimizu 2010	4	48	3	43	1.1%	1.19 (0.28, 5.04)
Subtotal (95% CI)		48		43	1.1%	1.19 (0.28, 5.04)
Total events	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z=0.24 (P=0.81)						
Total (95% CI)		1936		1979	100.0%	1.21 (1.05, 1.39)
Total events	339		283			
Heterogeneity: Chi^2=48.27, df=30 (P=0.02); I^2=38%						
Test for overall effect: Z=2.70 (P=0.007)						
Test for subgroup differences: Not applicable						

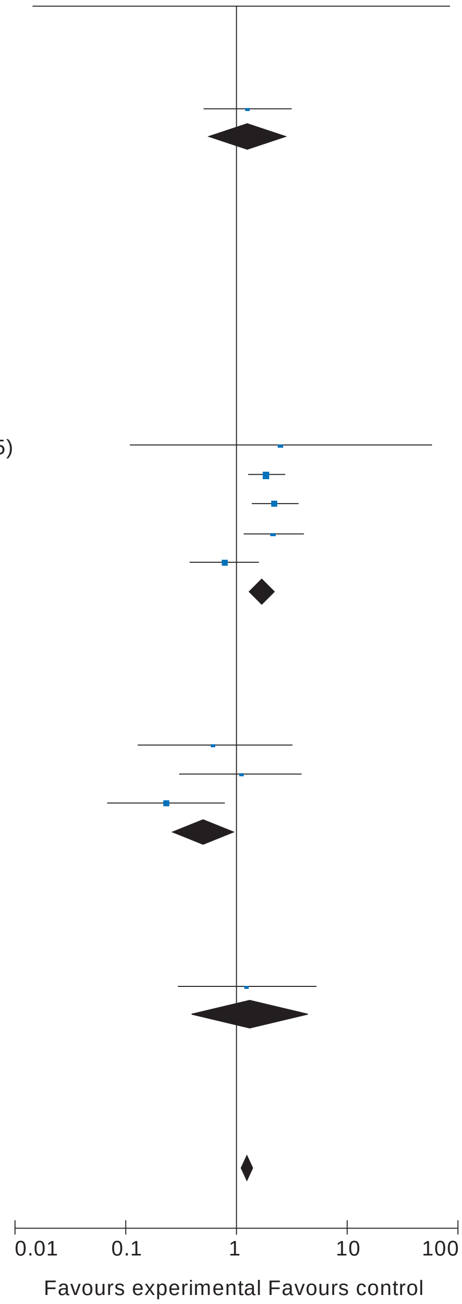


Figure 3. Comparison of the Effect of Cephamycins and Other Antibiotics on Prevention of Postoperative Surgical Site Infection.

when sensitivity analysis was conducted (RR 0.46; 95% CI 0.22, 0.96; P=0.04) (Figure 3).

Cefmetazole vs Other Atypical β-Lactams

One trial (12) involving 91 participants compared cefmetazole with flomoxef. According to the study, the incidence of SSI was similar in both groups without statistical difference. (RR 1.19; 95% CI 0.28, 5.04; P=0.81) (Figure 3).

Three trials (34, 36, 37), involving 602 participants, reported the systemic infection (Figure 4) as outcomes, comparing cephamycins with other antibiotics. There was no statistical difference in the incidence of systemic infection between two

Study of subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
Antonelli 1985	2	40	9	37	65.5%	0.21 (0.05, 0.89)
Arnaud1992	3	103	2	105	13.9%	1.53 (0.26, 8.96)
Milsom 1998	2	156	3	161	20.7%	0.69 (0.12, 4.06)
Total (95% CI)		**299**		**303**	**100.0%**	**0.49 (0.20, 1.17)**
Total events	7		14			

Heterogeneity: Chi^2=3.08, df=2 (P=0.21); I^2=35%
Test for overall effect: Z=1.60 (P=0.11)

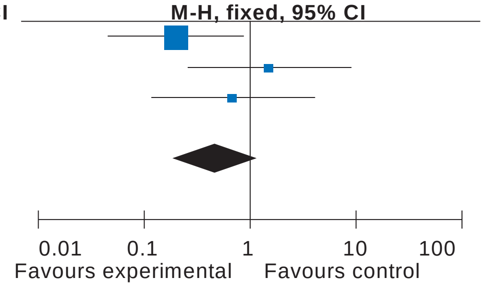


Figure 4. Comparison of the Effect of Cephamycins and Other Antibiotics on Prevention of Postoperative Systemic Infection.

Study of subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
Jewesson 1997a	5	39	5	8	25.9%	0.97 (0.31, 3.10)
Jewesson 1997b	5	39	0	45	2.4%	12.65 (0.72, 221.75)
Kikuchi 1988	1	60	0	58	2.6%	2.90 (0.12, 69.81)
Maki 1982a	2	32	2	30	10.5%	0.94 (0.14, 6.24)
Maki 1982b	2	32	1	31	5.2%	1.94 (0.18, 20.30)
Skipper 1992	10	68	8	36	53.4%	0.66 (0.29, 1.53)
Total (95% CI)		**270**		**238**	**100.0%**	**1.18 (0.68, 2.06)**
Total events	25		16			

Heterogeneity: Chi^2=5.11, df=5 (P=0.40); I^2=2%
Test for overall effect: Z=0.59 (P=0.56)

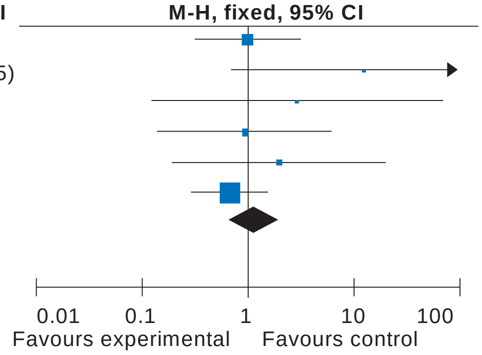


Figure 5. Comparison of the Effect of Cephamycins and Other Antibiotics on Prevention of Postoperative Distal Infection.

groups (RR 0.49; 95% CI 0.20, 1.17; P=0.11) with minimal heterogeneity (I^2=35%).

Six trials (35, 38-40), involving 508 participants, reported the presence and absence of distal infection (Figure 5), comparing cephamycins with other antibiotics. There was no statistical difference in the incidence of distal infection between two groups (RR 1.18; 95% CI 0.68, 2.06; P=0.56) with almost no heterogeneity (I^2=2%).

Risk of Bias across Studies

As was mentioned above, funnel plots were drawn. The funnel plots (Figure 2) did not show significant visual asymmetry.

DISCUSSION

Postoperative infections occur frequently in patients undergoing colorectal operations. The perioperative administration of prophylactic antibiotics is able to reduce the incidence of infection (3, 6). Cephamycins such as cefoxitin and cefotetan, have been widely use as prophylaxis in colorectal operations. However, among the studies assessing the efficacy of cephamycins, SSI rates ranged from 0% to 17% in single-agent therapy and more than half of the studies found SSI rates of > 10% (17, 23, 26-30, 36, 40, 49, 54, 55). The solid conclusion on cephamycins prophylactic used in colorectal surgery is urgently needed.

This meta-analysis focused on the efficacy of cephamycins in preventing postoperative infections for patients undergoing colorectal operations. Overall, through pooling data from eligible RCTs, we found that cephamycins had no advantages over other prophylactic antibiotic. According to the results of our meta-analysis, cefoxitin and cefotetan, recommended in colorectal surgeries by Clinical practice guidelines for antimicrobial prophylaxis in surgery (56), have no advantages over other agents such as penicillins and cephalosporins on reducing SSI. Of the 12 relevant studies cited in Clinical practice guidelines for antimicrobial prophylaxis in surgery aiming to prove the efficacy of cefoxitin and cefotetan in colorectal surgeries, one was not a randomized controlled trial and six studies had inappropriate control arms such as placebo or cephamycins themselves. Only five studies compared cephamycins with other kinds of antibiotics used as prophylaxis in colorectal operations and they were included in this meta- analysis. Therefore, the recommendation of cefoxitin and cefotetan in colorectal operations, even stated in the guideline, could not be determined yet.

The results of the meta- analysis also showed that the efficacy of cefmetazole, one kind of cephamycins, is greater than cephalosporins. Cefmetazole has an antimicrobial spectrum similar to the second- generation cephalosporins with great antibacterial activities against the aerobic bacteria and anaerobic bacteria. Its stability against β-lactamase is superior to cefoxitin. With the administration of the same dose, the serum concentration of cefmetazole is well above the cefoxitin (57). However, the sub- analysis is further limited by the absence of studies assessing the efficacy of cefmetazole and the full text of one study compared cefmetazole with moxalactam, which was probable to be included in this meta- analysis was not retrieved in study selection, mentioned in previous text. These factors lead the results not to be generalizable. The efficacy of cefmetazole should be further studied for its advantages.

In addition, the results also demonstrated that there was great difference in favor of ertapenem and aztreonam. Ertapenem is a broad-spectrum bactericidal carbapenem antibiotic. It differs from the other substances of this group by the absence of action against gram-negative nonfermenting bacilli and by a long elimination half-life, which allows once- daily administration. It is used for the treatment of community-acquired pneumonia, intra- abdominal and gynecological infections, and skin and soft tissue infections, including diabetic foot (58). Aztreonam has great antibacterial activities against gram-negative bacteria such as Pseudomonas aeruginosa. It is widely used in the therapy of hospital acquired infections. Ertapenem is recommended in colorectal procedures while aztreonam is recommended in gastroduodenale and biliary tract procedures (56). Both of them have great advantages in reduction of postoperative infection in surgeries and can be further studied on.

To our knowledge, this is the first meta-analysis assessing cephamycins administered for the prevention of postoperative infection in colorectal surgeries. We examined 26 articles, using a wide range of clinically relevant outcome variables including SSI, systemic infection and distal infection and focused on direct comparison of other agents as penicillins and cephalosporins. We used comprehensive methods to make the results solid including subgroup analysis and sensitivity analysis and the results were stable and reliable.

One limitation of this meta- analysis was that there was minimal heterogeneity in several sub-analysis. For cefoxitin vs third-generation cephalosprins, I^2 is 50%, while 40% for cefotetan vs other atypical β-lactams. The heterogeneity may come from the different dose and timing of antibiotics. The varied characters of patients results in the heterogeneity as well. A random effects model was also adopted in the two sub-analysis. We found similar results and it meant that the heterogeneity had minimal effect on the results.

In conclusion, the meta- analysis showed that the prophylactic use of cefoxitin and cefotetan in colorectal operations has no significant advantages over other antibiotics, which was contrary with the recommendation reported in 2013. However, cefmetazole may be effective in the prevention of postoperative infections. The efficacy of cefmetazole should be researched further and considered by perioperative medical staff. It is of great importance to optimize the prophylactic use of antibiotics in colorectal operations according to RCTs and provide guidelines for the administration of antibiotics.

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All authors reported no other conflicts of interest.

Yu Ding, Feng-Ying Xu, Miao Zhou, Jian-Hua Xia, and Xue-Yin Shi helped design the study; Yu Ding, Feng-Ying Xu, Miao Zhou, and Xue-Yin Shi conducted the study; Hua He helped literature collection; Yu Ding, Feng-Ying Xu, Miao Zhou, Yu-Xin Li, and Xue-Peng Zhang analyzed the data; Yu Ding, and Feng-Ying Xu wrote the manuscript.

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