Original Article

Cefazolin as surgical antimicrobial prophylaxis in hysterectomy: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective: Current practice guidelines recommend cefazolin, cefoxitin, cefotetan, or ampicillin-sulbactam as first-line antibiotic prophylaxis in hysterectomy. We undertook this systematic review and meta-analysis of randomized controlled trials (RCTs) to determine whether cefazolin, with limited antianaerobic spectrum, is as effective in preventing surgical site-infection (SSI) as the other first-choice antimicrobials that have more extensive antianaerobic activity.

Methods: We searched PubMed, Scopus, Web of Science, Cochrane Central, and EMBASE for relevant randomized controlled trials (RCT) in any language up to January 23, 2018. We only included trials that measured SSI (our primary outcome) defined as superficial, deep, or organ space. We excluded trials of β-lactams no longer in clinical use.

Results: In terms of SSI incidence, cefazolin use was not inferior to its comparator in 12 of 13 individual RCTs included in the analysis. The meta-analysis summary estimate showed a significantly higher SSI risk with cefazolin versus cefoxitin or cefotetan (risk ratio, 1.7; 95% CI, 1.04–2.77; $P = .03$). However, most studies included nonstandardized dosing and duration of antimicrobial prophylaxis, had indeterminate or high risk of bias, did not include patients with gynecological malignancies, and/or were older RCTs not reflective of current clinical practices.

Conclusion: Due to inherent limitations associated with old RCTs with limited relevance to contemporary surgery, an RCT of cefazolin versus regimens with significant antianaerobic spectrum is needed to establish the optimal choice for SSI prevention in hysterectomy.

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Surgical site infections (SSIs) are the most common and costly healthcare-associated infections (HAIs). In the United States, ~160,000–300,000 SSIs occur each year, with annual healthcare costs of $3.5–$10 billion.[1] The prevention of SSI is increasingly important as the number of surgical procedures performed in the United States continues to rise. The Centers for Disease Control and Prevention (CDC) estimates that approximately half of SSIs are preventable using evidence-based strategies.[2] In addition, SSI prevention is recognized by healthcare organizations, payers, and governmental agencies, including the Centers for Medicaid and Medicare Services, as a national patient safety priority, with hospital performance tied to reimbursement.[3]

For more than 20 years, the medical literature has documented that the appropriate perioperative prophylactic use of anti-microbial agents can reduce the incidence of postoperative SSI.[4–6] Hysterectomies are among the most prevalent surgical procedures

in United States, performed in >600,000 women each year. Among them, up to 2% are complicated by SSI,[1] and these are associated with longer hospital stays, higher risk of readmission,[7] and an additional $5,000 in healthcare costs for each hysterectomy-related infection.[7] According to the American College of Obstetricians and Gynecologists (ACOG) practice guidelines, women undergoing abdominal or vaginal hysterectomy should receive a preoperative, single-dose antimicrobial.[8] This recommendation is evidence-based and has been established by randomized placebo-controlled trials (RCTs) in which timely administration of preoperative antibiotics has shown significant SSI reductions in patients undergoing hysterectomy.[9,10]

Cephalosporins are the most thoroughly studied antimicrobial prophylaxis agents. These drugs are effective against many gram-positive and gram-negative microorganisms. They also share the features of demonstrated safety, acceptable pharmacokinetics, and a reasonable cost per dose.[6] In particular, cefazolin is widely used and is generally viewed as the prophylactic guideline-recommended antimicrobial agent of first choice for abdominal or vaginal hysterectomy.[8,11] Antibiotics with broader spectrum, including more extensive antianaerobic activity, such as cefotetan, cefoxitin, or ampicillin-sulbactam, are also first-line recommended options. Head-to-head comparative data between these

antibiotics and cefazolin in terms of efficacy in SSI prevention for women undergoing hysterectomy are scarce, and it remains unclear whether the added antianaerobic spectrum provides a prophylactic advantage. This issue is important from the standpoint of antibiotic stewardship and the desire to use the narrowest-spectrum antibiotic indicated. Therefore, we undertook a meta-analysis to examine the efficacy of cefazolin compared with other antimicrobials for prevention of SSI in women undergoing hysterectomy, focusing specifically on agents with broad antianaerobic activity.

Methods

Search strategy

We conducted our study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[12] We searched PubMed (including MEDLINE), Scopus, Web of Science, Cochrane Central databases, EMBASE, and abstracts from relevant proceedings and conferences through January 23, 2018, without restrictions to language or date range. We manually reviewed the references of systematic reviews and meta-analyses previously published on this topic to identify additional eligible studies. A librarian (S.J.) assisted with the literature search. To identify eligible studies, we used the following medical subject headings with the "AND" function: cephalosporins, surgical wound infection, hysterectomy, clinical trials. We used the following keywords (text words) with the "OR" function: antibiotic prophylaxis, cefazolin, postoperative, postsurgical, infection, complications, and random allocation.

Inclusion criteria

We included RCTs comparing cefazolin (any dose) with other systemic antimicrobials administered as surgical prophylaxis agents in women undergoing abdominal and/or vaginal hysterectomy. To be included, studies had to provide information on the primary outcome and calculation of a risk ratio. We excluded studies of antimicrobial agents that are no longer manufactured or clinically used in the United States for surgical antimicrobial prophylaxis.

Outcome definitions

Our primary outcome of interest was SSI, as defined by CDC criteria.[6] As such, we included studies where the reported primary or secondary outcome was described in terms consistent with this definition, despite slight changes in terminology over time. Therefore, we considered the following reported outcomes as consistent with SSI: wound infection, vaginal cuff infection, pelvic infection, infected hematoma, deep pelvic abscess, abdominal wound infection, surgical wound infection, and postoperative skin and soft-tissue infection. Although "febrile morbidity" is a clinical outcome frequently reported in older trials of antimicrobial prophylaxis, we did not include it into our study because the relationship with SSI versus other postoperative etiologies cannot be precisely determined.

Data extraction and assessment of study quality and risk of bias

We abstracted data on study setting, sample size, indications for surgery (benign and/or malignant), type of surgery (abdominal and/or vaginal hysterectomy), prophylactic antibiotic used (dose and duration), duration of follow up, loss to follow up, and incidence of SSI.

We assessed risk of bias using the GRADE guidelines for randomized controlled trials.[13] We assigned a rating of *high* risk of bias if fewer 4 of the GRADE criteria were fulfilled, an *indeterminate* risk of bias if information on at least 3 of the GRADE criteria were not specified, and a *low* risk of bias if 4 or more of the 7 GRADE criteria were fulfilled. One author (A.P.V.) abstracted the data; each report was identified by the search strategy described above and independently reviewed by a second author (N.S.). Disagreements regarding data extraction, risk of bias assessment, and study inclusion were resolved by discussion among the authors.

Statistical analysis

We performed meta-analyses to obtain pooled estimates of the risk ratio (RR) and 95% confidence interval (CI) for SSI associated with cefazolin versus other antimicrobials. We conducted subgroup analyses for abdominal versus vaginal hysterectomies and for different groups of comparison antimicrobials. We used the I^2 test to assess the SSI estimates that could be attributed to study heterogeneity,[14] and we conducted fixed-effects meta-analysis for $I^2 < 25\%$, and random effects model for $I^2 > 25\%$. We assessed publication bias using a funnel plot and the Eggers statistical test.[15,16] We analyzed statistical data with Comprehensive Meta-Analysis (CMA) version 2.0 software (Biostat, Englewood, NJ).

Results

Study selection

Figure 1 shows our review process for study selection. After de-duplication, we screened the titles and/or abstracts of 418 unique references for eligibility; of these, we reviewed 40 full-text articles, and ultimately included 13 studies in the review and meta-analyses. The main reasons for study exclusion were comparator antimicrobials no longer manufactured or clinically used in the United States (n = 12); primary outcome of interest (ie, SSI) not reported (n = 3); gynecological surgeries other than hysterectomies (n = 2); and other reasons (n = 10) (Fig. 1).

Study and patient population characteristics

The characteristics of the 13 RCTs are presented in Table 1. Most studies were conducted during 1979–2003, with only 2 studies performed within the last 10 years. Publication languages included English in 12 studies and Italian in 1 study.[17] Most of the studies enrolled women undergoing hysterectomies in university-affiliated hospitals within United States (5 trials), Europe (4 trials), Asia (3 trials), and Canada (1 trial). None of the trials included laparoscopic surgeries. Nine studies reported the indications for hysterectomy, which included primarily benign gynecological conditions. One study included 2 patients with endometrial carcinoma,[17] and 2 other studies mentioned the inclusion of 17%–20% patients with neoplastic disease, not otherwise specified.[18,19]

Abdominal hysterectomy, vaginal hysterectomy, or both were performed in 3, 3, and 7 studies, respectively (3,528 total patients). The overall SSI rates for abdominal and vaginal hysterectomy were 5.5% and 3%, respectively. One study[20] included gynecological
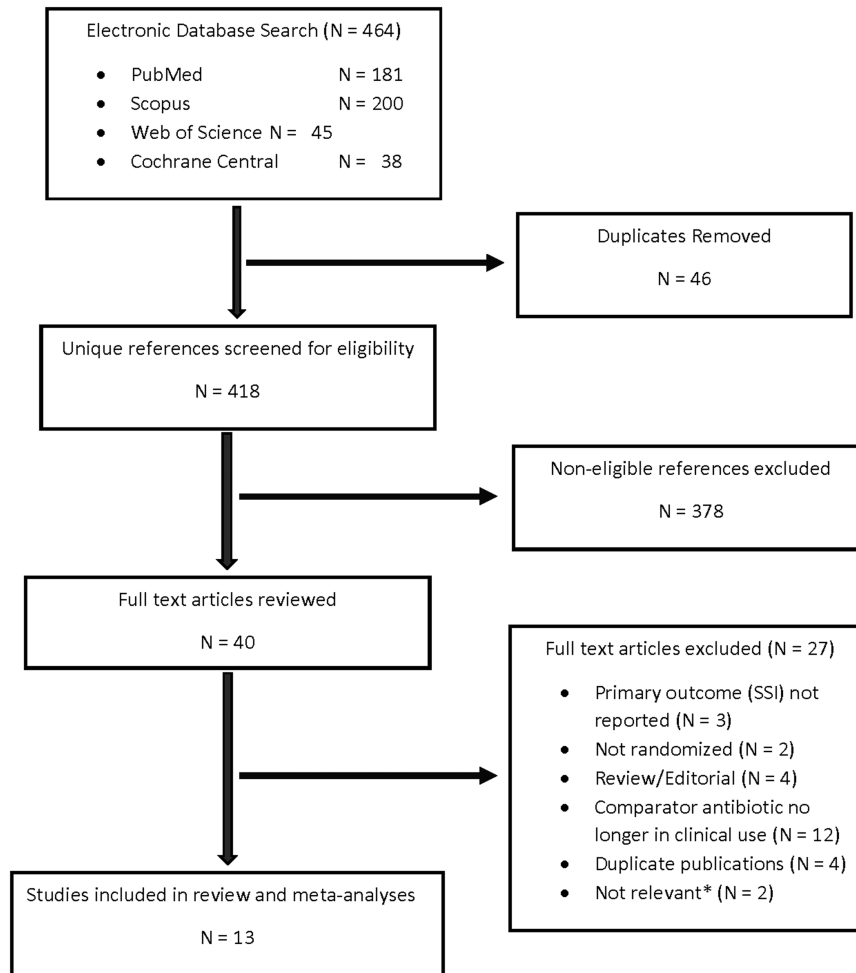
Fig. 1. Flowchart of study selection from the literature review. *Studies included obstetric-gynecological surgeries other than hysterectomy. Abbreviation: SSI, surgical site infection.

surgeries other than hysterectomy in 95 of 798 patients enrolled (12%). Clinical outcomes for this study were reported based on randomized antimicrobial drug arm, but they were not stratified by type of surgery performed. Meta-analyses with and outside this study showed no significant differences in results. We, therefore, chose to retain this study into our final analysis because of its relatively large sample size and because the majority (88%) of the patients underwent abdominal hysterectomy.

Antimicrobial prophylaxis characteristics

There was significant clinical heterogeneity among studies regarding antimicrobial prophylaxis choice and dosing, with antimicrobials administered in varying doses, either as a single preoperative dose in some studies, or as additional postoperative doses within first 48 hours of surgery in others (Table 1). None of the studies specified whether antimicrobial dosing was adjusted based on patient's weight/body mass index and/or renal clearance, although 2 studies did specify antimicrobial redosing intraoperatively for extensive blood loss or surgery duration > 3 hours.[20,24]

Clinical outcome definitions and reporting

Definitions and reporting for the clinical outcome of our interest, SSI, were generally consistent between studies. They included the

following terms: surgical wound infection, vaginal cuff infection, postoperative vaginal wound infection, infected pelvic abscess or hematoma, pelvic infection requiring parenteral antimicrobial therapy, abdominal wound infection, pelvic cellulitis. We also included the following phrases: "any surgical wound which drained purulent or serous material, together with or without positive cultures" and "pelvic infection, defined as fever plus ≥1 of the following: purulent drainage from the vaginal cuff, abdominal pain with rebound tenderness and/or guarding, localized tenderness with a tender adnexal mass on bimanual palpation, or bacteremia with or without hypotension" (Table 1).

Study quality and risk of bias

Details related to randomization, such as the randomization sequence for treatment allocation, and details related to treatment concealment and blinding were not reported in 5 studies,[17,19,21–23] and were not present in 3 studies,[18,20,24] rendering 8 studies at indeterminate and high risk of bias, respectively. An intention-to-treat analysis was performed in only 1 study.[25] Table 3 shows details related to risk of bias for the studies included in the systematic review and meta-analysis.

As shown by the funnel plot in Figure 2, publication bias was not present, and the Egger test of the intercept lacked statistical significance ($P = .11$).

Table 1. Characteristics of Randomized Controlled Studies Included in the Meta-analysis

Study (First Author, Year)	Study Period	Study Setting	Hysterectomy Type	Study Population	Prophylactic antimicrobials		Clinical Outcome[a]
					Cefazolin	Comparator	
Baldoni, 1989[17]	? Prior to 1989	Italy, university setting, multicenter	Abdominal and vaginal	Surgery for benign indications (n = 78); endometrial carcinoma (n = 2); median surgery duration: 50–60 min	Cefazolin 1 g IV × 3 doses	Cefotetan 2 g IV once	Surgical wound infection; vaginal cuff infection
Chongsomchai, 2002[36]	1997–1999	Thailand, university setting	Abdominal	Surgery for benign indications mostly; 10% patients with CIN (n = 22)	Cefazolin 1 g IV once	Ampicillin 1 g IV once	Surgical wound infection; vaginal cuff infection
Cormio, 2003[20]	1999–2002	Italy, university setting	Abdominal and vaginal	Surgery for benign indications only	Cefazolin[b] 2 g IV once	Amoxacillin-clavulanate[b] 2.2 g IV once	Surgical wound infection
Grossman, 1979[21]	1975–1977	US, university setting	Abdominal and vaginal	Indications for surgery not specified	Cefazolin 500 mg IV on call to OR and every 6 h × 48 h	Penicillin G 1 million units IV on call to OR and every 6 h × 48 h	Surgical wound infection; postoperative vaginal wound infection; vaginal cuff infection
Hemsell, 1984[37]	1982–1983	US, university setting, multicenter	Vaginal	Indications for surgery not specified	Cefazolin 1 g IM once, then 1 g IV × 2 doses postop	Ceftriaxone 1 g IM once, placebo IV × 2 doses postop	Infected pelvic abscess or hematoma; vaginal surgical margin infection
Hemsell, 1985[38]	1982–1983	US, university setting	Abdominal and vaginal	Indications for surgery not specified	Cefazolin 1 g IM once, then 1 g IV × 2 doses postop	Ceftriaxone 1 g IM once, placebo IV × 2 doses postop	Wound infection; infected pelvic abscess or hematoma
Hemsell, 1987[39]	1983–1985	US, university setting	Vaginal	Surgery for benign indications mostly; included women with CIN	Cefazolin 1 g IM once 2 g IM once	Cefoxitin 2 g IM once Cefotaxime 1 g IM once	Pelvic infection requiring parenteral antimicrobial therapy
Hemsell, 1995[22]	1989–1992	US, university setting	Abdominal	Surgery for benign indications only	Cefazolin 1 g IV once	Cefotetan 1 g IV once	Infected pelvic hematoma; pelvic abscess; abdominal wound infection
Jyothi, 2010[24]	2004–2005	India, governmental hospital in rural setting	Abdominal and vaginal	Surgery for benign indications only	Cefazolin[c] 2 g IV once	Amoxicillin-clavulanate[c] 2.4 g IV once	Abdominal wound infection; vaginal cuff infection
Periti, 1988[18]	1988	Italy, university setting, multicenter	Abdominal and vaginal	Included 17% of patients with neoplastic disease	Cefazolin 2 g IV × 2 doses	Cefotetan 2 g IV once	Any surgical wound that drained purulent or serous material, together with or without positive cultures
Periti, 1988[19]	? Prior to 1988	Italy, university setting, multicenter	Abdominal and vaginal	Included 15%–18% patients with neoplastic disease	Cefazolin 2 g IV × 2 doses	Cefotaxime 2 g IV once	Any surgical wound that drained purulent or serous material, with or without positive cultures
Phoolcharoen, 2012[25]	2008–2009	Thailand, university setting	Abdominal	Excluded patients with suspected gynecological malignancies; excluded patients with immune compromise	Cefazolin 1 g IV once	Ceftriaxone 1 g IV once	Wound infection; vaginal cuff infection
Stiver, 1990[23]	? Prior to 1990	Canada, university setting	Vaginal	Included 7 patients with neoplasia	Cefazolin 1 g IV × 4 doses	Ceftriaxone 1 g IV once	Pelvic infection, defined as fever plus 1 or more: purulent drainage from the vaginal cuff, abdominal pain with rebound tenderness or guarding, localized tenderness with tender adnexal mass on bimanual palpation, or bacteremia with or without hypotension

Note. IV, intravenous, IM, intramuscular; CIN, cervical intraepithelial neoplasia; OR, operating room; postop, postoperatively.
[a]Defined as surgical site infection (SSI) in our study.
[b]Antimicrobial redosed for extensive blood loss (>1,500 mL) or surgery duration >3 h.
[c]Antimicrobial redosed for extensive blood loss (>1,000 mL) or surgery duration >3 h.

Table 2. Incidence of Surgical Site Infection (SSI) by Antimicrobial Prophylaxis Regimen and Randomized Controlled Trial of Women Undergoing Abdominal or Vaginal Hysterectomy

Study	Cefazolin SSI / N	Comparator SSI / N	Risk Ratio (95% CI)	P Value
Baldoni et al, 1989[17]	**Cefazolin**	**Cefotetan**	1.91 (0.49–7.40)	.35
Abdominal	5/25	3/26		
Vaginal	0/10	0/14		
Total	5/35	3/40		
Chongsomchai et al, 2002[36]	**Cefazolin**	**Ampicillin**	0.64 (0.26–1.58)	.33
Abdominal	7/110	11/110		
Cormio et al, 2003[20]	**Cefazolin**	**Amoxicillin-clavulanate**	0.98 (0.14–6.94)	.99
Abdominal	2/352	2/346		
Grossman et al, 1979[21]	**Cefazolin**	**Penicillin G**	1.56 (0.59–4.21)	.35
Abdominal	9/79	4/76		
Vaginal	1/28	2/26		
Total	10/107	6/102		
Hemsell et al, 1984[37]	**Cefazolin**	**Ceftriaxone**	2.03 (0.19–21.85)	.56
Vaginal	2/63	1/64		
Hemsell et al, 1985[38]	**Cefazolin**	**Ceftriaxone**	0.97 (0.29–3.27)	.97
Abdominal	4/54	4/54		
Vaginal	1/60	1/57		
Total	5/114	5/111		
Hemsell et al, 1987[39]	**Cefazolin 1 g**	**Cefoxitin**	1.44 (0.25–8.28)	.68
Vaginal	3/53	2/51	0.69 (0.12–3.97)	.68
	Cefazolin 2 g	**Cefotaxime**		
	2/53	3/55		
Hemsell et al, 1995[22]	**Cefazolin**	**Cefotetan**	1.96 (1.08–3.56)	.03
Abdominal	30/258	15/253		
Jyothi et al, 2010[24]	**Cefazolin**	**Amoxicillin-clavulanate**	0.75 (0.07–7.82)	.81
Abdominal and vaginal	1/24	2/36		
Periti et al, 1988[18]	**Cefazolin**	**Cefotetan**	0.67 (0.15–3.01)	.16
Abdominal	2/124	4/116		
Vaginal	1/43	0/35		
Total	3/167	4/151		
Periti et al, 1988[19]	**Cefazolin**	**Cefotaxime**	1.77 (0.79–3.94)	.16
Abdominal	13/139	9/138		
Vaginal	5/74	1/64		
Total	18/213	10/202		
Phoolcharoen et al, 2012[25]	**Cefazolin**	**Ceftriaxone**	0.48 (0.18–1.31)	.61
Abdominal	6/160	12/160		
Stiver et al, 1990[23]	**Cefazolin**	**Ceftriaxone**	.17 (0.01–3.67)	.15
Vaginal	0/73	2/65		

Note. CI, confidence interval.

Table 3. Risk of Bias Summary for the Studies Included in the Systematic Review and Meta-analysis

| Study First Author, Year	Random Allocation Sequence	Allocation Concealed	Blinding	Loss to Follow-Up Accounted For	Complete Outcome Reporting	Early Termination	Other	Bias Grade[a]
Baldoni, 1989[17]	No	?	?	Yes	Yes	No	No	Indeterminate
Chongsomchai, 2002[36]	Yes	Yes	Yes	Yes	Yes	No	No	Low
Cormio, 2003[20]	No	No	No	Yes	Yes	No	Yes	High
Grossman, 1979[21]	?	?	Yes	?	No	No	?	Indeterminate
Hemsell, 1984[37]	Yes	?	Yes	Yes	Yes	No	No	Low
Hemsell, 1985[38]	?	Yes	Yes	Yes	Yes	No	No	Low
Hemsell, 1987[39]	Yes	Yes	?	Yes	Yes	No	No	Low
Hemsell, 1995[22]	Yes	?	?	Yes	Yes	No	Yes	Indeterminate
Jyothi, 2010[24]	?	?	No	?	No	No	Yes	High
Periti, 1988[18]	?	No	No	Yes	Yes	No	Yes	High
Periti, 1988[19]	?	?	?	Yes	Yes	No	Yes	Indeterminate
Phoolcharoen, 2012[25]	Yes	Yes	Yes	No	Yes	No	No	Low
Stiver, 1990[23]	?	?	Yes	?	Yes	No	?	Indeterminate

[a]According to review author.
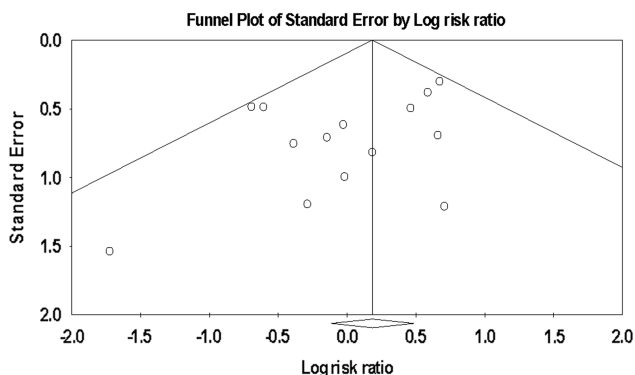
Fig. 2. Funnel plot to evaluate publication bias for randomized controlled trials of cefazolin as antimicrobial surgical prophylaxis in women undergoing abdominal or vaginal hysterectomies. Publication bias was not detected; the Egger test of the intercept was not statistically significant (2-tailed P value = .11273).

Meta-analysis of the efficacy of cefazolin compared with other antimicrobials in preventing surgical-site infection among women undergoing hysterectomy

Among the 13 RCTs included in the study, 1,782 patients received cefazolin and 1,746 patients received a comparator antimicrobial for surgical prophylaxis. The SSI incidence and relative risk for cefazolin versus other antimicrobials reported in individual RCT is presented in Table 2. Only 1 study found the comparator antimicrobial (cefotetan) to be associated with significantly less SSI than cefazolin (P = .03).[22] For all other studies, the difference in SSI incidence for patients receiving prophylaxis with cefazolin versus a comparator antimicrobial was not statistically significant.

Comparison with agents that have broad antianaerobic spectrum. The results of the meta-analysis for the SSI risk ratio of cefazolin versus another cephalosporin agent with broad anti-anaerobic spectrum (cefoxitin or cefotetan) are shown in Figure 3. Among the 513 patients in the cefazolin arm, 41 SSIs (8%) were recorded, and among the 495 patients in the comparator (cefoxitin or cefotetan) arm, 24 SSIs (4.8%) were recorded. Compared with cefoxitin or cefotetan antimicrobial prophylaxis, cefazolin had a significantly higher risk of posthysterectomy SSI (relative risk [RR], 1.7; 95% confidence interval [CI], 1.04–2.77; P = .03).

The addition of amoxicillin-clavulanate (a penicillin-based antibiotic with antianaerobic agent) to cefoxitin or cefotetan showed a trend for higher post-hysterectomy SSI with cefazolin (RR, 1.6; 95% CI, 0.98–2.64; P = .06) (Fig. 4).

Comparison with penicillin-based antibiotics. When compared with penicillin G, ampicillin, or amoxicillin-clavulanate, cefazolin showed no statistically significant difference in the relative risk of SSI among women undergoing hysterectomy (RR, 0.96; 95% CI, 0.52–1.76; P = .89) (Supplemental Figure 1).

Comparison with other cephalosporin agents without broad antianaerobic activity. Compared with second- or third-generation cephalosporins that have limited antianaerobic spectrum, cefazolin's SSI relative risk was not statistically significant among women undergoing hysterectomy (RR, 0.66; 95% CI, 0.36–1.22; P = 0.18) (Supplemental Fig. 2).

Discussion

In this meta-analysis, the efficacy of cefazolin for SSI prevention in hysterectomy was significantly lower than that of other

Cefazolin vs Cefoxitin or Cefotetan

Study name	Statistics for each study				Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	p-Value	
Baldoni et al, 1989	1.90	0.49	7.40	0.35	
Hemsell et al, 1987 1st	1.44	0.25	8.28	0.68	
Hemsell et al, 1995	1.96	1.08	3.56	0.03	
Peritti et al, 1988	0.68	0.15	2.98	0.61	
	1.70	1.04	2.77	0.03	

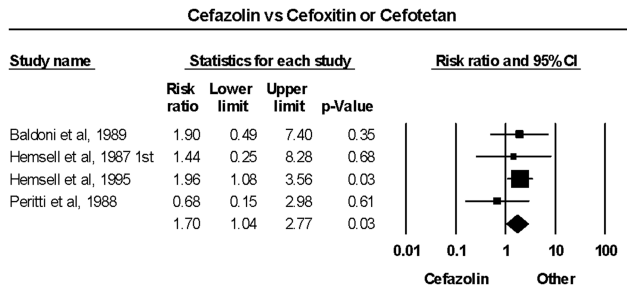0.01   0.1   1   10   100

Cefazolin   Other

Fig. 3. Forest plot, meta-analysis of relative risk for SSI with cefazolin versus other cephalosporin antimicrobials with antianaerobic activity (cefotetan, cefoxitin) among women undergoing abdominal or vaginal hysterectomy. Fixed effects model. Heterogeneity $I^2 = 0$, *P* value = .623.

Cefazolin vs Cefoxitin, Cefotetan, or Amoxicillin-clavulanate

Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Hemsell et al, 1987	1.470	0.235	9.183	0.412	0.680	
Peritti et al, 1988	0.672	0.148	3.054	-0.514	0.607	
Baldoni et al, 1989	2.056	0.454	9.307	0.935	0.350	
Hemsell et al, 1995	2.088	1.094	3.983	2.234	0.026	
Jyothi et al, 2010	0.739	0.063	8.635	-0.241	0.810	
Cormio et al, 2003	0.983	0.138	7.017	-0.017	0.986	
	1.636	0.992	2.699	1.929	0.054	

0.01   0.1   1   10   100
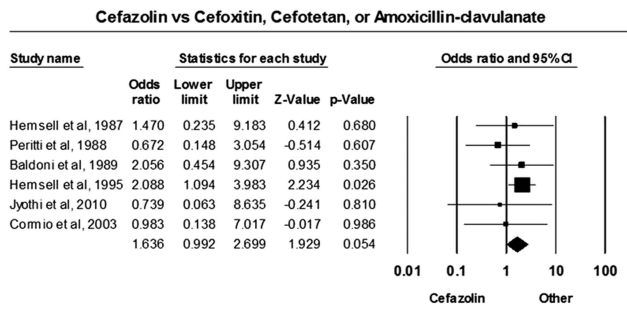
Cefazolin   Other

Fig. 4. Forest plot, meta-analysis of relative risk for surgical site infection (SSI) with cefazolin versus β-lactam with antianaerobic activity (cefoxitin, cefotetan, or amoxicillin-clavulanate) among women undergoing abdominal or vaginal hysterectomy. Fixed effects model. Heterogeneity $I^2 = 0$; *P* value = .756.

cephalosporins with broader antianaerobic activity, namely cefoxitin or cefotetan. Although not statistically significant, the trend toward lower efficacy was still present when we added amoxicillin-clavulanate, another β-lactam antibiotic with significant antianaerobic spectrum, into the meta-analysis. Our findings are plausible considering the pathophysiology and microbiology underlying SSI in gynecological surgery. Postoperative infections after gynecological surgery are primarily polymicrobial, with enterococci, aerobic-gram-negative bacilli, and anaerobic bacteria, including *Bacteroides* spp frequently isolated. In addition to the skin as the usual site of contamination for gram-positive pathogens, endogenous bacteria migrating from the vagina and endocervix can gain access to the operative sites. The endogenous flora of the lower reproductive tract in women includes facultative and obligate anaerobic species. Anaerobes are particularly predominant in bacterial vaginosis, long recognized as an SSI risk factor in women undergoing hysterectomy.[26–30] The recent clinical study by Till et al,[31] not included in our meta-analysis as it is an observational trial, provides further support for the consideration of agents with good antianaerobic spectrum to antimicrobial prophylaxis in hysterectomy. In a large retrospective cohort study including 18,255 hysterectomies in 73 hospitals during 2012–2015, combination prophylaxis with cefazolin plus metronidazole resulted in significantly lower SSI rates than cefazolin alone.[31] Additionally, a recent retrospective cohort study by Uppal et al[32] of 21,358 patients from the Michigan Surgical Quality Collaborative undergoing hysterectomy between 2012 and 2015 reported that the rate of SSI was significantly higher in patients receiving non-β-lactam antimicrobials than in those receiving β-lactam antimicrobials.

We found no significant difference in the SSI relative risk when cefazolin was compared with penicillin-based β-lactam antibiotics (penicillin G, ampicillin, amoxicillin-clavulanate) or with second- or third-generation cephalosporins that lacked antianaerobic spectrum.

Any conclusions regarding optimal surgical antibiotic prophylaxis in hysterectomy are tempered by the significant limitations of the literature in this field. First, most cefazolin trials are old, with no representation of laparoscopic procedures and with only 1 RCT published within the last decade.[25] Variations in antibiotic dosing and perioperative duration, lack of standardized weight-based dosing, and lack of information regarding antimicrobial redosing in relation to duration of surgery introduce significant clinical heterogeneity and make comparisons with contemporary standard of practice difficult. Second, most hysterectomies performed in these studies were due to benign surgical indications. The exclusion of patients with underlying gynecological malignancies, especially ovarian cancers that are usually clinically advanced at presentation and require complex debulking procedures, renders the choice of optimal surgical antibiotic prophylaxis uncertain in these cases. Third, the methodological rigor is low or indeterminate in many of the older studies; we identified a high potential for bias in more than half of the studies. Lastly, most studies reported "postoperative fever" as a major clinical outcome for antibiotic prophylaxis. Although some cases of postoperative fever may be due to SSI, this is a nonspecific outcome, potentially attributable to a variety of other infectious or noninfectious processes. Its exclusion from our analysis may have underestimated the true incidence of SSI.

To our knowledge, this is the first meta-analysis that frames the question of surgical antibiotic prophylaxis in terms of comparative efficacy for cefazolin versus antimicrobials with broader antianaerobic spectrum—a clinically relevant question for contemporary surgery. Previous meta-analyses in the field have focused on the preventive benefits of antibiotic prophylaxis in general and have included antimicrobials that are no longer used for this clinical purpose.[9,33–35] Due to the antiquated nature of the published RCT on this topic, and their inherent limitations stated above, the question cannot be answered conclusively from the evidence-based literature available at this time.

In conclusion, the question of optimal antimicrobial prophylaxis for SSI prevention in contemporary hysterectomy deserves further study, and RCTs are needed to assess the efficacy of cefazolin versus other antimicrobials with broader antianaerobic spectrum. The enrollment of patients undergoing complex surgical procedures due to underlying gynecological malignancies, and the inclusion of laparoscopic as well as open surgical approaches should be prioritized for future trials. In addition, given the known deleterious effects of broad-spectrum antimicrobials on the gut microbiome, future studies of comparative efficacy should also explore the adverse effects of broader antianaerobic spectrum on gut microbiota, in addition to the effects on SSI prevention. (Table 3)

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