Parenteral Fosfomycin in Gastrointestinal Surgery: A Systematic Review

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ABSTRACT

Background To investigate if perioperative parenteral administration of fosfomycin given before or during gastrointestinal surgery could protect against postoperative infectious complications and characterise the administration of fosfomycin and its harms.

Methods This systematic review included original studies on gastrointestinal surgery where parental administration of fosfomycin was given before or during surgery to ≥ 5 patients. We searched three databases on March 24 2023 and registered the protocol before data extraction (CRD42020201268). Risk of bias was assessed with Cochrane Handbook risk of bias assessment tool or the Newcastle-Ottawa Scale. A narrative description was undertaken. For infectious complications, results from emergency and elective surgery were presented separately.

Results We included 15 unique studies, reporting on 1,029 patients that received fosfomycin before or during gastrointestinal surgery. Almost half of the studies were conducted in the 1980s to early 1990s, and typically a dose of 4 g fosfomycin was given before surgery co-administered with metronidazole and often repeated postoperatively. The risk of bias across studies was moderate to high. The rates of infectious complications were low after fosfomycin; the surgical site infection rate was 0–1 % in emergency surgery and 0–10 % in elective surgery. If reported, harms were few and mild and typically related to the gastrointestinal system.

Conclusion There were few postoperative infectious complications after perioperative parenteral administration of one or more doses of 4 g fosfomycin supplemented with metronidazole in various gastrointestinal procedures. Fosfomycin was associated with few and mild harms.

Introduction

A great challenge of modern medicine is the rise in antimicrobial resistance. The World Health Organisation ranked antimicrobial resistance as one of the top 10 global public health threats [1]. A possible solution to this threat could be the re-entry of the use of older antibiotics [2] such as fosfomycin. Fosfomycin, a phosphoenolpyruvate analogue [3], is a bactericidal antibiotic agent that interferes with the first step of the bacterial cell wall synthesis, where it irreversibly inhibits the enzyme enolpyruvyl transferase [4]. It has a half-life of 1.9–3.9 hours in plasma [5] and is eliminated by unchanged excretion into the urine [6]. Fosfomycin has shown good

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tissue penetration, thus, reaching sufficient concentrations to kill bacteria [5]. Fosfomycin is generally well-tolerated. Common harms reported after intravenous administration of fosfomycin were gastrointestinal symptoms such as nausea, vomiting, and diarrhoea, and less than 0.01 % of the reported adverse reactions would be classified as serious adverse events [7]. Fosfomycin has been used for prophylactic treatment of urinary and abdominal infections and for treatment of multi-drug resistant Gram-positive and Gram-negative aerobic bacteria and could thus be a promising antimicrobial agent in gastrointestinal surgery [8]. It is, therefore, relevant to characterize the clinical experience and evidence for the use of fosfomycin as prophylaxis or empirical treatment in association with abdominal surgery.

We aimed to investigate if perioperative parenteral administration of fosfomycin given before or during emergency or elective gastrointestinal surgery could protect against postoperative infectious complications. Secondly, we aimed to characterize the use of fosfomycin regarding dose, timing, surgical indication, and harms in gastrointestinal surgery.

Materials and methods

This systematic review was reported according to Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 guideline [9]. Before data extraction, we registered a protocol at PROSPERO (registration number: CRD42020201268) [10].

The eligibility criteria were participants undergoing emergency or elective gastrointestinal surgery having received parenteral administration of fosfomycin either before or during surgery and prescribed as either empirical antimicrobial mono- or polytherapy. No comparison group was required, but the study design had to be an original study covering any type of trial and studies where the number of participants was ≥ 5, thus, the exclusion criterion was case reports reporting on < 5 patients.

The information sources included three databases: PubMed (1966–now), Embase (1974–now), and Cochrane CENTRAL, and there were no limitations on dates or languages. The search strategy that was used in these three databases was developed together with a professional research librarian and the last day of the search was March 24, 2023. The search strategy included search terms for fosfomycin combined with terms on surgery or surgical procedures. The specific search string for PubMed was: (((fosfomycin) OR phosphomycin)) AND ((((surgery) OR surgical) OR procedure) OR procedures). The adapted search string in Embase was: (fosfomycin.mp. or exp fosfomycin/ or phosphomycin.mp.) and (exp abdominal surgery/ or exp biliary tract surgery/ or exp colon surgery/ or exp colorectal surgery/ or exp elective surgery/ or exp gastrointestinal surgery/ or exp general surgery/ or exp surgery/ or surgery.mp. or (operations or operated or operate or operation or operating).mp.). Lastly, the adapted search string in Cochrane CENTRAL was: (fosfomycin OR phosphomycin) AND ((operation OR operations OR operating) OR (procedure OR procedure) OR (surgery OR surgically)). The systematic search was supplemented with a screening of the reference lists of the included studies for relevant studies (backward citation search).

The selection process was done using the screening tool Rayyan [11] and was divided into three parts. Firstly, duplicates were removed. Secondly, two independent reviewers screened the titles and abstracts of the reports against the eligibility criteria. Thirdly, two independent reviewers screened full-text articles against the eligibility criteria. Furthermore, we excluded studies when specific data on patients receiving fosfomycin were not retrievable, and when fosfomycin was solely administered after gastrointestinal surgery for sepsis or postoperative infectious complications.

Data extraction was done by one reviewer, and extracted data were checked for accuracy by another reviewer. Data reported in other languages than English were translated and discussed thoroughly during extraction. The extracted variables included: characteristics of the studies, specification of fosfomycin administration, postoperative complications and mortality, and reports on harms. If possible, we also extracted data for any of the control groups. An exhausting list of all variables can be seen in the PROSPERO protocol [10]. Due to sparse reporting of several variables, these were left out of the final review.

Bias assessment was done independently by two authors or a contributor, so bias assessment was only done by those not involved in the included study. The tools used depended on the study design, thus, the risk of bias in randomised controlled trials (RCTs) was assessed with the Cochrane Handbook risk of bias assessment tool 1 [12], and the risk of bias in observational cohort studies was assessed with the Newcastle-Ottawa Scale (NOS) [13].

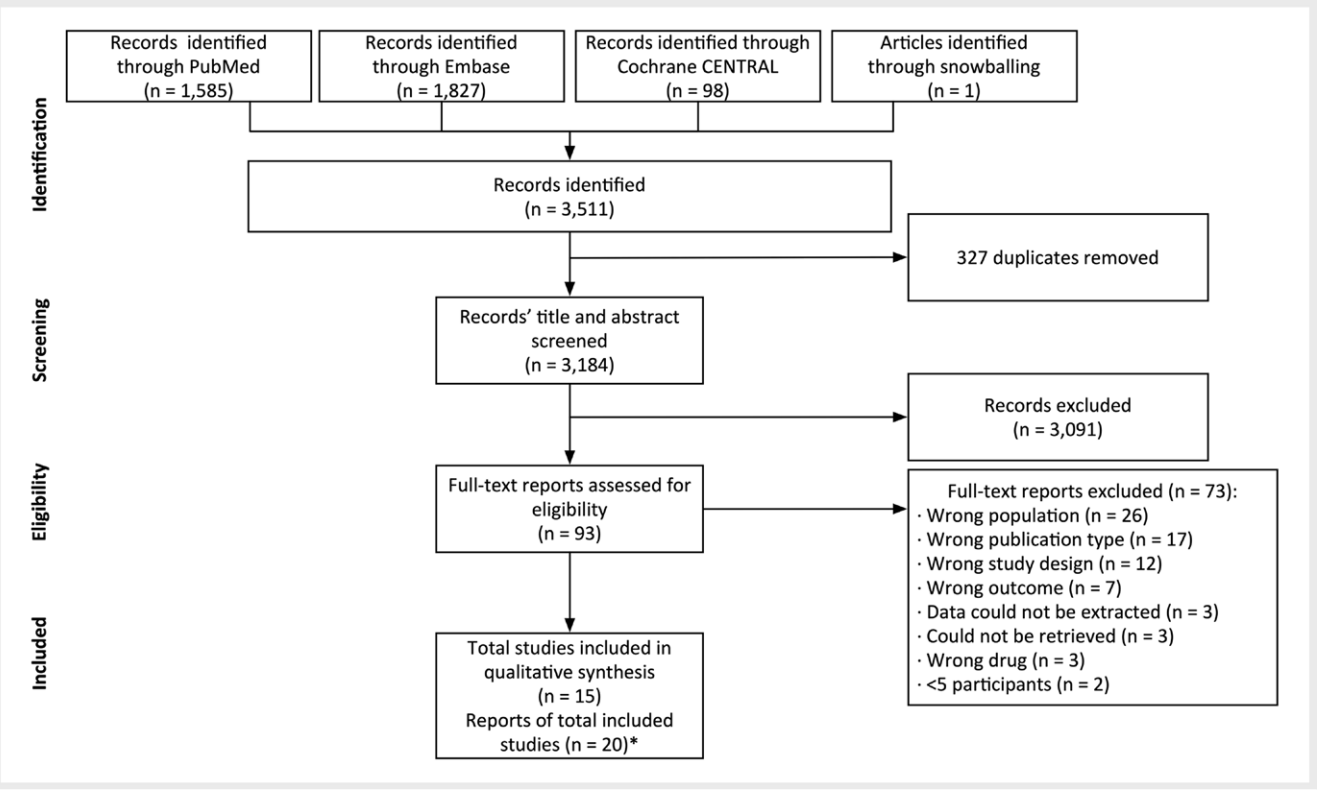
We primarily set out to characterise the use of fosfomycin administered parenterally before or during gastrointestinal surgery, focusing on postoperative complications such as surgical site infection (SSI), intraabdominal abscess, sepsis, and mortality due to infectious complications. Furthermore, we wanted to characterise the use of fosfomycin in emergency or elective surgery, dose and timing, all-cause mortality, and harms. Synthesis of results across studies can only be applied if methodological and clinical heterogeneity is low [14]. We deemed it impossible in this review, as there were tremendous differences in diseases, indication for and the type of surgery as well as the dose of fosfomycin and the comparison groups. Therefore, we used ranges to summarise the data across included studies and supplemented this with the specific extracted data from each study presented in tables or figures together with proportions and 95 % confidence intervals (CI), using OpenMeta[Analyst] software [15]. For infectious complications, we presented data within the two subgroups emergency and elective surgery.

As we did not assess a difference, e. g. neither effect nor risk, we did not investigate the risk of reporting bias through funnel plots. As no formal meta-analysis was conducted, the certainty of evidence could not be assessed with the GRADE approach.

Results

After searching databases and removing duplicates, 3,511 articles were screened in title and abstract and the selection process is depicted in ▶ **Fig. 1**. Finally, 15 unique studies [16–30] were included in this systematic review as five reports had overlapping populations with the included studies [31–35].

The characteristic of the included studies is depicted in ▶ **Table 1**. The majority of the included studies were RCTs [16, 20–24, 26–28], three studies were retrospective cohort studies [19, 29, 30],



▶ **Fig. 1** A flowchart that shows the process of the systematic review including screening of the articles' title and abstract, screening of full-text articles, reasons for exclusion of articles, and the total number of included studies in this systematic review. * Five reports were not included as they had overlapping populations with included studies [31–35].

▶ **Table 1** Characteristics of the included studies and fosfomycin administration where n refers to the number of participants undergoing abdominal surgery. IV: intravenous, IP: intraperitoneal, IM: intramuscular, n: number of participants, Pro: prospective cohort study, Q-RCT: Quasi-randomized controlled trial, RCT: randomized controlled trial, Retro: retrospective cohort study.

Authors	Year	Study design	Type of surgery	Total n	Fosfomycin administration			
					n	Dose (g)	Total dose (g)	Route
Fonnes et al. [16]	2020	Q-RCT	Emergency	12	6	4	4	IP
Dorn et al. [17]	2019	Pro	Elective	27	27	8	8	IV
Fonnes et al. [18]	2019	Pro	Emergency	14	14	4	4	IP
Shinagawa et al. [19]	2006	Retro	Elective	162	68	4	6–10	IV
Unemura et al. [20]	2000	RCT	Elective	242	7	2	2–16	IV
Andåker et al. [21]	1992	RCT	Elective	517	259	8	16	IV
Nøhr et al. [22]	1990	RCT	Elective	149	72	8	8	IV
Andåker et al. [23]	1987	RCT	Emergency	381	190	4	4/16/64[a]	IV
Lindhagen et al. [24]	1984	RCT	Elective	49	26	2	8	IV
Müller et al. [25]	1982	Pro	Elective	40	40	4	4/8[b]	IV
Lindhagen et al. [26]	1981	RCT	Elective	58	30	2	32	IV
Cardia et al. [27]	1980	RCT	Mixed	25	12	1	4	IM
Bianca et al.[28]	1979	RCT	Mixed	263	129	1	3	IM
Germiniani et al. [29]	1979	Retro	Mixed	365	120	1	3	IM
Gallardo et al. [30]	1977	Retro	Emergency	29	29	4–6	20–30	IM

[a] Patients were divided into three groups (increasing severity of disease): group A (only one preoperative dose)/ group B (one preoperative dose and three postoperative doses)/ group C (one preoperative dose and three postoperative doses for 5 days). [b] Patients were divided into two groups: one dose before surgery (n = 23)/two doses 8–10 days after surgery (n = 17).

and three studies were prospective cohort studies [17, 18, 25]. Nearly half of the studies were carried out in the 1980s to early 1990s [21–27]. Almost half of the studies were carried out in Scandinavia with four from Sweden [21, 23, 24, 26] and three from Denmark [16, 18, 22], respectively. The remaining studies were from Italy [27–29], Japan [19, 20], Germany [17, 25], and Spain [30]. The included studies reported on a median (range) of 58 (12–517) patients each, totalling 1,029 patients receiving fosfomycin in connection with gastrointestinal surgery (▶ **Table 1**). The studies included patients of both sexes, however, one study only included males [18] (**Supplementary File Table 1**). The age of patients was sparsely reported. Most of the patients treated with fosfomycin (51 %) had undergone an elective procedure [17, 19–22, 24–26], the most common being colorectal procedures or cholecystectomy (**Supplementary File Table 1**). Almost one-fourth of patients treated with fosfomycin (23 %) underwent an emergency procedure [16, 18, 23, 30] including laparoscopic cholecystectomy or appendectomy. The remaining three studies reported on a mixed population of patients undergoing either an elective or emergency procedure [27–29].

Fosfomycin and other antimicrobial agents

Regarding the administration of fosfomycin, the median (range) dose of fosfomycin was 4 g (1–8 g) (▶ **Table 1**). Fosfomycin was administered before surgery in 73 % of studies [17, 19–22, 24–29, 36], the median was 1 hour preoperatively but it ranged from 30 minutes to 6 hours preoperatively. Two studies administered fosfomycin during the procedure [16, 18]. In two-thirds of the studies, the postoperative course was also supplemented with fosfomycin. The postoperative regimens listed from fewest to most administrations were as follows: one administration of fosfomycin was given in two studies 8 hours postoperatively [21], two administrations were given either at 5- and 12 hours [28, 37], or 6- and 12 hours [27] postoperatively, and in two studies the patients received fosfomycin three times every 8 hours for 24 hours [24] or with various intervals [36], see ▶ **Table 1**. In one study, the patients received fosfomycin four times daily postoperatively for either 3–7 days [38]. Lastly, three studies gave fosfomycin regularly (time interval not reported) for some days [19] up to 2 days [20], or 5 days [30] after surgery.

Co-administration with another antimicrobial agent was given in some studies and was most often metronidazole [21–24, 26], however, in 46 % of studies fosfomycin was administered as monotherapy [19, 20, 25, 27–30] (**Supplementary File Table 1**).

Risk of bias across included studies

The bias assessment according to Cochrane Handbook Risk of bias assessment tool 1 [12] can be seen in **Supplementary File Fig. 1**. The nine RCTs [16, 20–24, 26–28] included were assessed, however, one was a quasi-randomized clinical trial [16], thus resulting in a high risk of bias for the domains' random sequence generation and allocation concealment. For most domains, there was unclear risk of bias in 67 % to 89 % of included RCTs. The exception was for the domains regarding 1) blinding of participants and 2) personal and incomplete outcome data where 44 % and 0 %, respectively, had unclear risk of bias. It was also in these two domains where many RCTs had low risk of bias (33–67 % of RCTs). Other sources of bias that were noted concerned conflicts of interest and funding. In total, 88 % of studies had no conflicts of interest statement [20–24, 26–28]. In most RCTs, a funding statement was either not reported [20, 23, 24] or had insufficient details on the role of funders and/or drug providers [21, 22, 26–28]. In two RCTs [22, 27], the risk of bias for this domain was ultimately assessed to be high, see **Supplementary File Fig. 1**.

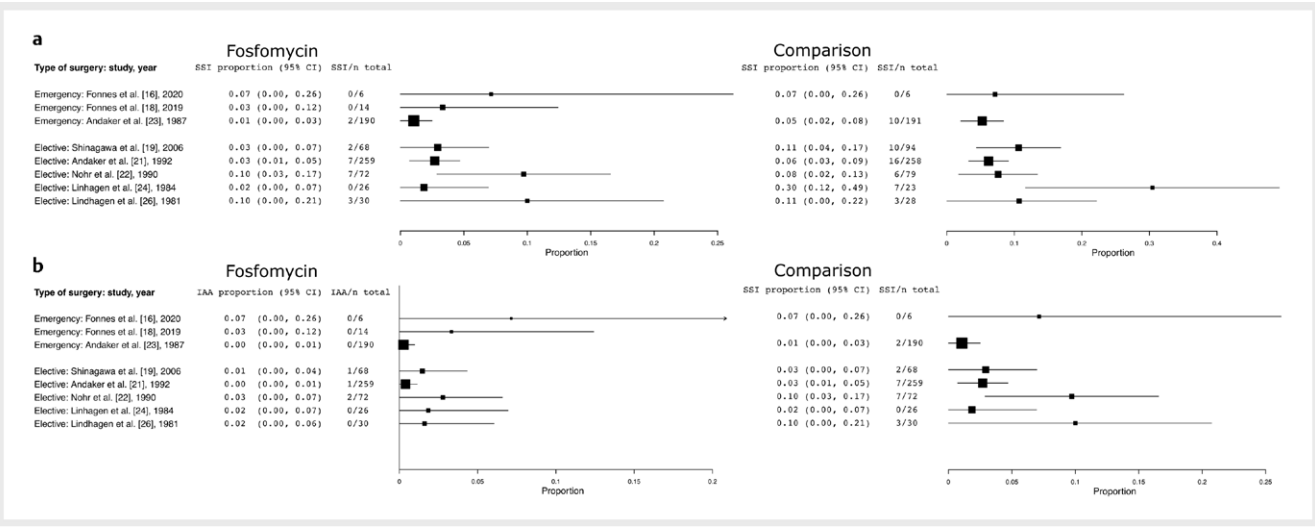
For the retrospective [19, 29, 30] and prospective [17, 18, 25] cohort studies, bias was assessed using NOS [13]. According to this scale, the studies are graded with a score of zero to nine stars across three categories: 1) selection, 2) comparability, and 3) outcome. A low number of stars equal a high risk of bias and vice versa. The assessed studies were given a median of 3 stars and ranged from 1–5 stars, the bias assessment of the individual studies can be seen in **Supplementary File Table 1**. For the category selection, all studies demonstrated that the outcome SSI was not present at start of study, thus given a star, but only four studies provided documentation for the ascertainment of preoperative parenteral administration of fosfomycin and could be given a star for this [17, 18, 25, 29]. Only one study was awarded one out of two possible stars for the category comparability [19]. For the last category outcome, none of the studies could be given a star for the item assessment of outcome as it was not blinded, not record linked, or not described. Also, follow-up was only long enough for the outcome SSI to occur in two studies that were each given one star for this item [18, 19].

Postoperative infectious complications

The postoperative complications were categorised into four types of complications: SSI, intraabdominal abscess, sepsis, and death due to infectious complications. Five studies did not contribute with data as they did not report on this outcome [17, 20, 25, 30] or they also included patients with other indications for the antimicrobial treatment than gastrointestinal surgery, so relevant data could not be extracted [27–29]. There was a very sparse use of the classification system for postoperative complications according to the Clavien Dindo classification [39] for studies published after 1992.

The rate of SSI was reported by eight studies [16, 18, 19, 21–24, 26] (▶ **Fig. 2a**). SSI was mostly defined as wound infection with the presence of pus/purulent material [21–24, 26]. One study measured the temperature, pulse, and blood pressure together with clinical findings [19]. The rates of SSI for patients receiving fosfomycin vs. comparison group ranged from 0–1 % vs. 0–5 % for emergency procedures and 0–10 % vs. 6–30 % for elective procedures, depicted in ▶ **Fig. 2a**. The study with the highest SSI rates (in the comparison group only receiving metronidazole) was terminated prematurely [24].

The rate of intraabdominal abscess was reported by eight studies [16, 18, 19, 21–24, 26] (▶ **Fig. 2b**). An intraabdominal abscess was mostly diagnosed either by imaging (ultrasonography or computer tomography) or laparotomy [21–23] or by "clinical and bacteriological signs of intraabdominal process causing illness" [24, 26]. The rate of intraabdominal abscesses for patients receiving fosfomycin vs. comparison group was 0 % vs. 0–1 % for emergency procedures and 0–3 % vs. 0–10 % for elective procedures (▶ **Fig. 2a**).



▶ **Fig. 2** Forest plot of the proportions and 95 % confidence intervals (CI) for **a**. surgical site infection (SSI) and **b**. intraabdominal abscess (IAA) in each study for patients receiving fosfomycin (left panel) or a comparison regimen (right panel). The studies have been sub-grouped according to type of surgery e. g. emergency or elective and with reference in brackets. The study with the highest SSI rates was terminated prematurely because of more postoperative infectious complications in patients in the comparison group that only received metronidazole [24].

The rate of sepsis was reported by four studies [16, 18, 21, 22] (data not shown). Sepsis was defined as e. g. "clinical, with malaise and fever" [21] or "temperature > 38.5 °C, together with rigors and poor general condition" [22]. No patients were reported to suffer from sepsis in the two emergency studies with small populations [16, 18]. For elective procedures, the rate of sepsis for patients receiving fosfomycin vs. comparison ranged from 1–2 % vs. 1–3 %.

The mortality rate due to infectious complications was reported by seven studies [16, 18, 19, 21–24] (data not shown). The cause of the reported mortality due to infectious complications was intraabdominal infection [21] or peritonitis [22]. The rate of mortality due to infectious complications was 0 % regardless of antibiotic regimen for emergency procedures and ranging from 0–1 % for elective procedures both for patients receiving fosfomycin and patients receiving any comparison regimen.

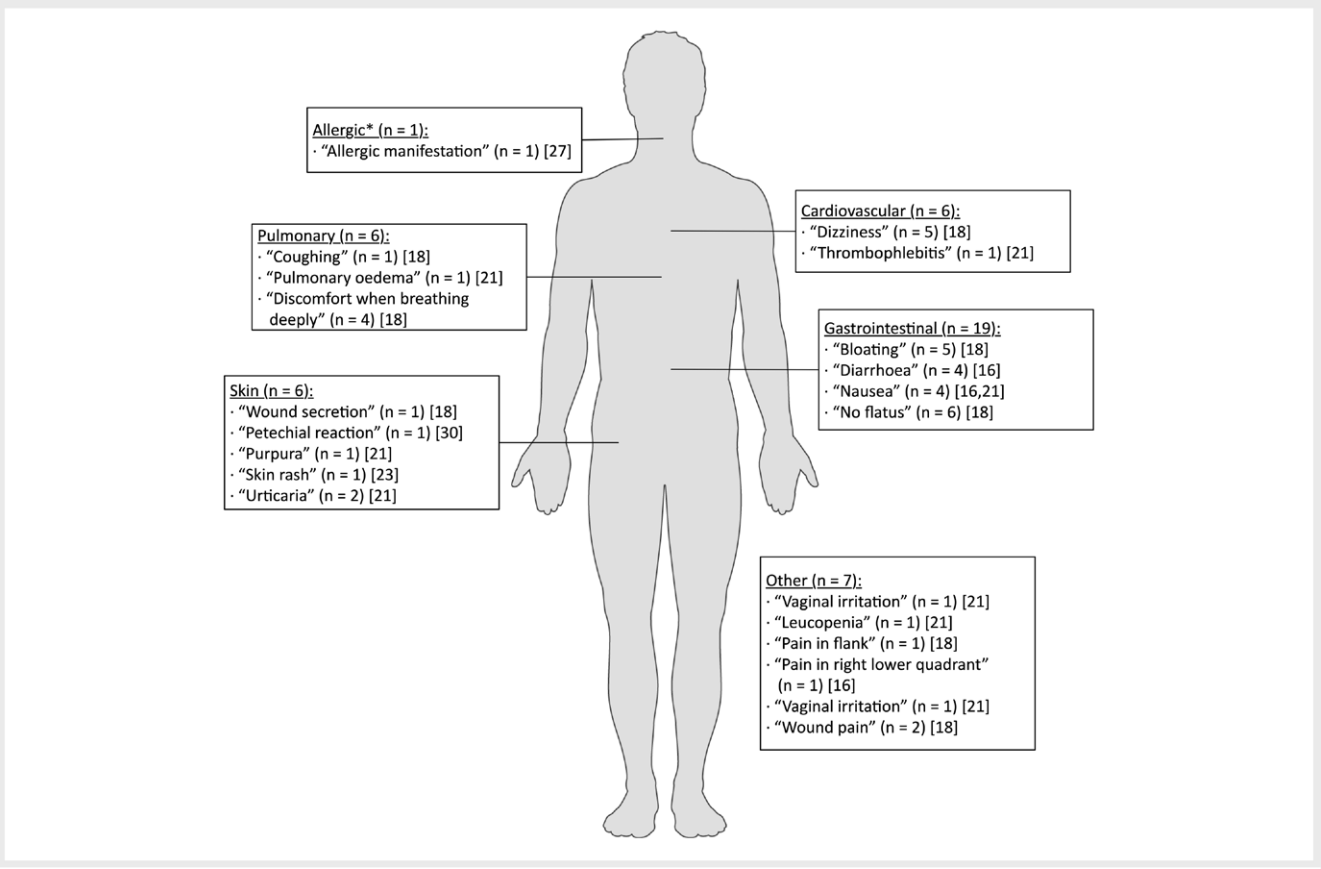
Harms

Reports on harms were missing in three of the included studies, reporting on a total of 256 patients receiving fosfomycin [20, 28, 29]. Of the studies that reported on harms, six of these described that there were no harms due to treatment with fosfomycin, covering a total of 263 patients [17, 19, 22, 24–26]. Harms of different degrees were reported in six studies that reported on 510 patients in total [16, 18, 21, 23, 27, 30]. An overview of the reported harms is illustrated in ▶ **Fig. 3**, however, the harms occurring after discharge was not included [18]. All in all, there were few harms, and most were related to the gastrointestinal system (n = 19). One harm was probably a serious adverse reaction, although details were sparse in the study, and it was unclear if the patients had received fosfomycin or the comparison regimen [27]. Most reported harms were deemed to be adverse events or reactions.

Discussion

This systematic review found that perioperative parenteral administration of fosfomycin was primarily used in the 1980–1990s for a variety of both elective and emergency gastrointestinal procedures. Often, a dose of 4 g fosfomycin was administered an hour before surgery together with metronidazole, and this was followed by one or more postoperative doses. There were few postoperative infectious complications such as SSIs in patients receiving fosfomycin as well as patients receiving the comparison antimicrobial agents. Harms were inconsistently reported, were few, and most were deemed to be adverse events or reactions that were related to the gastrointestinal system.

This systematic review has several strengths. We performed a systematic search for articles after a medical research librarian had been consulted to help ensure a broad and specific literature search. We had no language bias, as all relevant articles no matter the language were included. A protocol was registered at PROSPERO [10] to keep stringency, thoroughness, and transparency through the conduct of the systematic review. Furthermore, registering a protocol at PROSPERO reduced the risk of selective reporting. The screening of articles was conducted independently by blinded reviewers, hence, not influencing each other in the screening process. Finally, we reported according to PRISMA 2020 guideline [9]. However, this review also has some limitations. Despite our best efforts, one report [40] found by searching the reference list of included report with overlapping data [33] could not be retrieved despite expert assistance from the Royal Danish Library. It was an abstract from 1988 on 371 participants in a controlled clinical trial that possibly could have contributed with data [40]. We had no language bias, but some information or nuances could have been lost during translation due to the inclusion of all languages. Some of this systematic review's limitations were due to a lack of transparency in the reporting of the included studies. Most of the studies were conducted in the 1980–1990s, thus before the implementa-



▶ **Fig. 3** Distributions and types of the harms in the studies that reported harms (total n = 510 patients) with reference in brackets. * not clearly reported whether this was after fosfomycin or comparison treatment, "Allergic manifestation" was further elaborated as "modest hypotension, skin rashes, pruritus and laryngospasm" [27].

tion of reporting guidelines such as STROBE [41] for cohort studies, CONSORT [42] for RCTs, and ClinPK statement [43] for pharmacokinetic studies. This was especially evident for the risk of bias assessment for RCTs where most domains had unclear risk of bias due to insufficient information in 67 % to 89 % of the included RCTs. For bias assessment of the cohort studies, the total number of awarded stars was low due to the lack of a comparison group (comparability can be awarded up to two stars). Furthermore, there was often no description of how the outcomes were assessed, and follow-up was not long enough for SSIs to occur [13]. Also, harms and postoperative complications were sparsely reported and not always well-defined by the authors for instance by using definitions by ICH-GCP [44] or the Clavien-Dindo classification of complications [39].

This systematic review provides an important overview of the use of fosfomycin in gastrointestinal surgery that could become relevant, e. g. due to the emerging resistance to currently used antimicrobial agents. In urology, fosfomycin has been used as antimicrobial prophylaxis during prostate biopsies [45] as fluoroquinolones were associated with harms and emerging resistance [46]. A meta-analysis of 1,239 patients undergoing prostate biopsy found that fosfomycin compared with fluoroquinolones halved the risk of infectious complications [45]. The combination of fosfomycin and metronidazole could be a potential option to consider in gastrointestinal surgery as prophylaxis or empiric treatment in conjunction with surgical source control. For now, however, the use of systemic fosfomycin is restricted by the European Medical Agency as a reserve agent for the treatment of serious infections [47]. However, systemic fosfomycin has been used for several indications, resulting in few harms, and these were mainly gastrointestinal such as diarrhoea and nausea (5 %) [7] as also seen in this systematic review. One single oral dose of fosfomycin to treat uncomplicated urinary tract infections in adults has been widely used for several years, and this indication was left untouched by the European Medicines Agency [47]. Oral fosfomycin is generally well tolerated and side effects are mainly gastrointestinal [48]. Recently, fosfomycin was confirmed to be safe also in pregnant women regarding the risk of congenital anomalies in a larger register-based French study where more than 2,700 women received fosfomycin during their first trimester [49]. All in all, the European Medicines Agency currently allows oral fosfomycin in uncomplicated urinary tract infections and prostate biopsies [47].

Conclusion

There were few postoperative infectious complications after perioperative parenteral administration of fosfomycin in various gastrointestinal procedures, though the studies were primarily published in the 1980–1990s. One dose of 4 g fosfomycin sometimes supplemented with a few postoperative doses was often used together with metronidazole. Harms were few and mild but inconsistently reported.

Other information

Protocol and registration

A protocol was registered at PROSPERO, registration number: CRD42020201268, before data extraction [10].

Authorship contribution statement

Siv Fonnes: Conceptualization, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization. Masja Klindt Fonnes: Validation, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. Barbara Juliane Holzknecht: Conceptualization, Writing – Review & Editing. Jacob Rosenberg: Conceptualization, Writing – Review & Editing, Supervision.

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Conflicts of Interest

Siv Fonnes, Barbara Juliane Holzknecht, and Jacob Rosenberg were authors of two of the included studies [16, 18], but report no conflicts in relation to that.

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