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Characterisation and Safety of Intraperitoneal Perioperative Administration of Antibacterial Agents: A Systematic Review

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ABSTRACT

Background Intraperitoneal drug administration applies treatment at the site of diseases with gynaecological, urological, or gastrointestinal origin. The objective of this systematic review was to investigate perioperative intraperitoneal administration of antibacterial agents to characterise the drugs used and their safety profile.

Methods A protocol was registered at PROSPERO (CRD42016038956). A systematic review was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A search was performed in PubMed and EMBASE on the 22nd of April 2016. The inclusion criteria were original articles involving at least 5 patients where antibacterial agents were administered intraperitoneally during or after abdominal surgery as prophylaxis or treatment of infection. Languages were limited to English, German, Danish, Norwegian, or Swedish articles.

Results 79 studies were included which used a total of 12 different antibacterial classes. Aminoglycosides, 1st and 2nd generation cephalosporins, tetracyclines, and penicillins were most commonly administered intraperitoneally during or after surgery. The antibacterial agent was usually administered intraperitoneally as monotherapy. However, some studies administered combination regimens with heparin or with another antibacterial agent. The most frequent combination was aminoglycosides and lincosamides. In total, 43 % of studies lacked information regarding adverse events. The most frequently reported adverse event was discomfort or pain during administration, especially with use of oxytetracycline.

Conclusion At least 12 different classes of antibacterial agents have been administered intraperitoneally during or after surgery as prophylaxis or treatment of intraabdominal infections. Intraperitoneal administration seems safe although use of oxytetracycline may cause discomfort or pain.

Introduction

Intraperitoneal administration of drugs is mostly known in the context of peritoneal dialysis-associated peritonitis. Here, it seems superior to intravenous treatment [1]. Yet, intraperitoneal drug administration has various other indications. It has been practiced in surgery as prophylaxis or treatment of infection [2, 3] and for pain relief [4, 5]. In oncology, intraperitoneal administration is promising especially for treatment of disseminated ovarian cancer [6]. Finally, it has been used to administer insulin in diabetes mellitus, where it seems to improve glycaemic control for some subgroups of patients [7, 8]. However, complications to intraperitoneal administration do occur. Most complications were related to the catheter needed for administration such as pain or obstruction, in other words complications due to technical issues [6]. Therefore, intraperitoneal administration in relation to surgery grants an advantage since an access is already provided. In addition, when a

disease requires abdominal, gynaecological, or urological surgery the intraperitoneal administration allows the first dose to be administered at the site of the disease. Higher intraperitoneal concentrations are gained through intraperitoneal than intravenous administration, which could make it more efficient [9, 10]. Lastly, when the drug is administered during surgery, patients will be anaesthetised and, thus, there will be no discomfort during administration.

However, before intraperitoneal administration of antibacterial agents as prophylaxis or treatment of infection in surgery can be implemented it is important to evaluate whether this can be done safely. Therefore, our aim was to investigate intraperitoneal administration of antibacterial agents during or after surgery to characterise the drugs used and the safety of intraperitoneal administration.

Materials and Methods

Protocol and registration

The review was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. A protocol was registered at PROSPERO prior to data extraction with registration number: CRD42016038956 [12].

Eligibility criteria

The criteria (PICOS) for studies included in the systematic review were: Participants: Patients undergoing surgery; Interventions: Intraperitoneal administration of antibacterial agents (instillation, irrigation, or lavage) during or after abdominal surgery as prophylaxis or treatment of infection; Comparisons: No control group required; Outcome: antibacterial agents used; and Study design: Original data reported on at least 5 participants. As we wished to characterise the literature on intraperitoneal administration of antibacterial agents all types of studies were included.

Information sources

The search was conducted using PubMed and Excerpta Medica database (EMBASE). Overall, PubMed covered articles from 1946 to present. The coverage of EMBASE was from 1947 to present. As the systematic review covered articles from a wide timespan, authors of the included studies were not contacted. The search strategy of the systematic review was developed together with a professional research librarian. The search was conducted on 22nd of April 2016.

Search

The same search terms were used in PubMed and EMBASE, however, the MeSH terms of PubMed was modified to fit to the search criteria of EMBASE. The exact search terms for PubMed were:

((((((intraperitoneal OR intraperitoneally OR intra-peritoneal OR intra-peritoneally OR (abdominal AND cavity) OR (peritoneal AND cavity)) AND (irrigation OR irrigations OR lavage OR lavages OR douching OR douchings OR administrated OR administration)) OR ("injections, intraperitoneal" [Mesh])) AND (infections))) NOT (("animals" [Mesh]) NOT ("humans" [Mesh])))

Similarly, the search terms for EMBASE were:

((((intraperitoneal OR intraperitoneally OR intra-peritoneal OR intra-peritoneally OR (abdominal AND cavity) OR (peritoneal AND cavity)) AND (irrigation OR irrigations OR lavage OR lavages OR douching OR douchings OR administrated OR administration)) OR (intraperitoneal drug administration.mp.)) AND (infections))

In EMBASE, the search was limited to journal articles only and Medline journals were excluded to reduce the number of duplicates. There were no restrictions for the time of publication. Articles written in English, German, Danish, Norwegian, or Swedish were included in this systematic review.

Study selection

The records of the searches were imported into an Excel sheet (Office 2016, Microsoft), where duplicates were removed. Hereafter, all records, which did not fulfil the language requirements, were removed. The title and abstract of the remaining records were screened by 2 independent reviewers according to the abovementioned PICOS. Thereafter, the full-text articles of remaining records were screened. The systematic search was supplemented with relevant articles identified from the reference lists of the included studies (snowballing). Any differences concerning inclusion in the review were settled by discussion within the author group.

Data collection process

Data were extracted from the included articles and typed into predefined tables in an Excel sheet. All entries were double-checked for typing errors. When there was any doubt of how data should be extracted, this was discussed and consensus was reached within the author group.

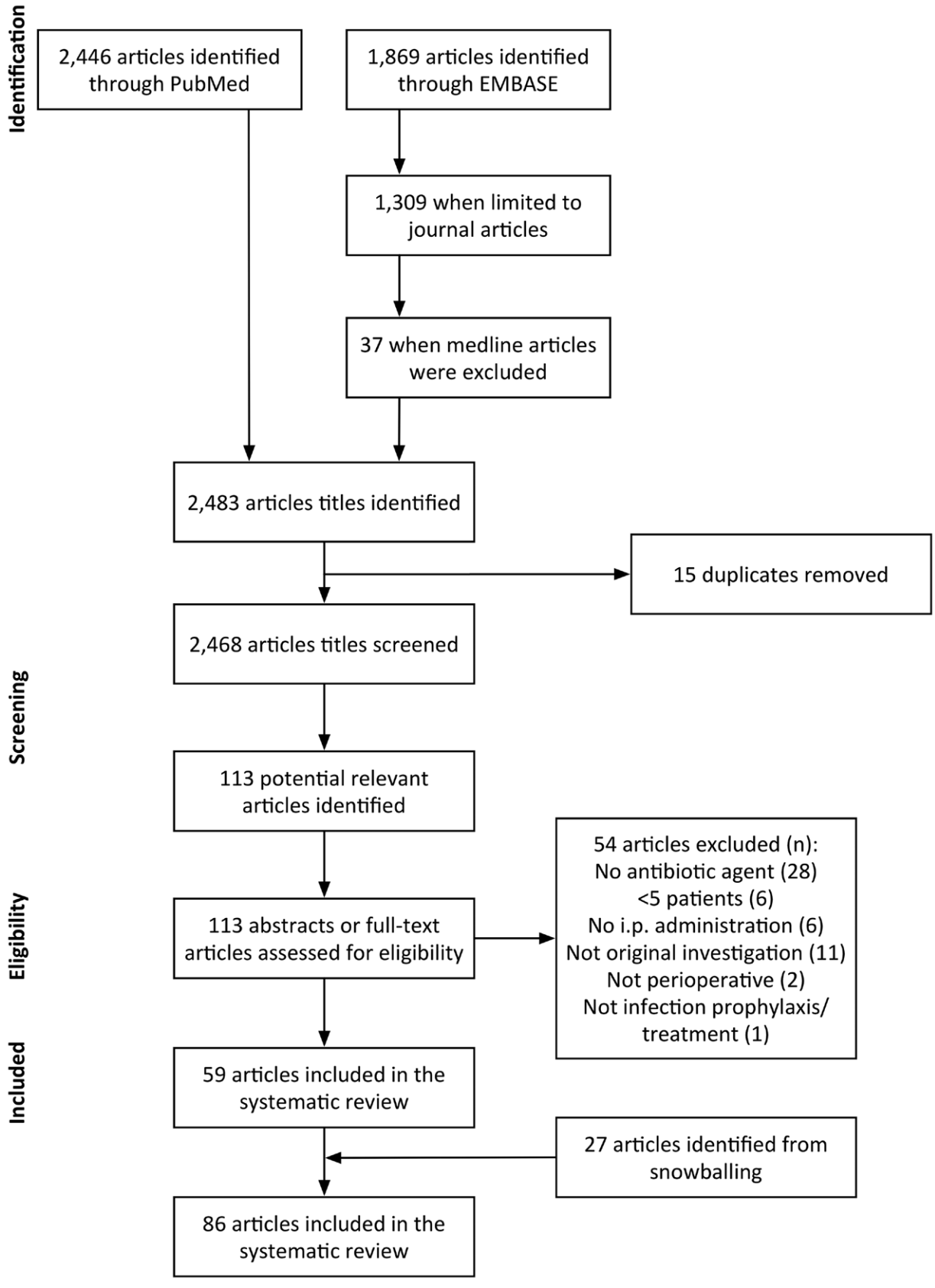
Data items

The extracted variables were: study design, number of participants, type of surgery, diagnosis, drug name, brand name, drug class (ATC class [13]), type of intraperitoneal administration (instillation/irrigation/lavage), dwell time of intraperitoneal administration, dose and/or concentration, administration interval and duration, timing of administration (during/after surgery), administered alone or in combination with other drugs or antibacterial agents, administration of other antibacterial agents (per os/intramuscular/intravenous/ subcutaneous/suppositories), adverse events or effects of intraperitoneal administration (yes/no), time of follow-up, and how adverse events/effects were reported.

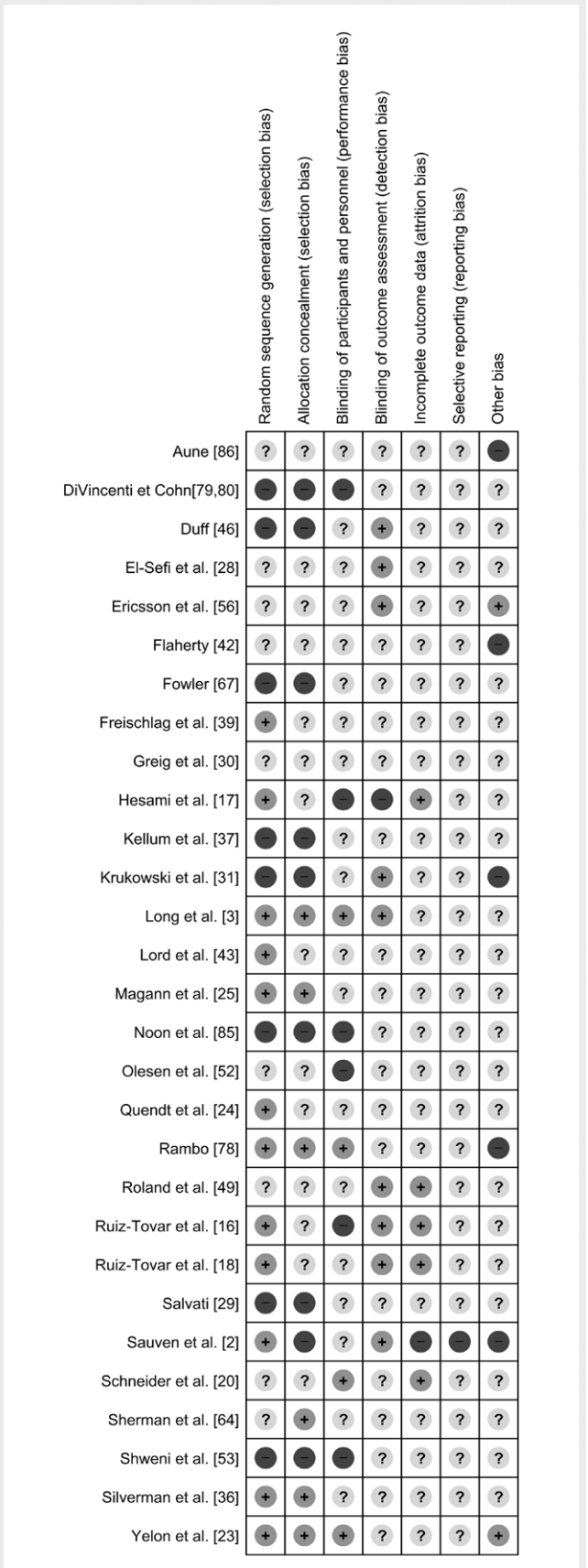
Simplifications of the extracted variables were made in order to uniform the reported categories. The simplifications included: type of surgery, diagnosis, and drug class. The following definitions for type of intraperitoneal administration were used: instillation, when the administered agent was left in the intraperitoneal cavity; irrigation, when the agent was applied and then removed by suction shortly after application; and lavage, when the drug was applied to and removed from the peritoneal cavity repeatedly over time.

Risk of bias in individual studies

The risk of bias was assessed using 2 different tools. Randomised controlled trials (RCTs) were assessed with the Cochrane Handbook for Systematic Review for Intervention's "Risk of bias" assessment tool [14]. Non-randomised observational studies with a control group were assessed with the Newcastle-Ottawa scale (NOS) [15].



▶ **Fig. 1** A flowchart that shows the process of the review including screening of the articles' title and abstract, screening of full-text articles, reasons for exclusion of articles, articles found through snowballing, and the total number of included articles in the review.



▶ **Fig. 2** Risk of bias summary of the review author's judgement for the randomised controlled trials.

Summary measures

The primary outcome was characterisation of antibacterial agents administered intraperitoneally in the perioperative period. The secondary outcomes included doses and concentrations of antibacterial agents, combinations of antibacterial agents, and adverse effects of intraperitoneal administration. The preliminary searches revealed that a meta-analysis could not be conducted.

Results

79 studies were included in this review [2, 3, 16–99]. However, to adequately extract study data more than one article was referenced in 6 of the included studies [33–35, 70, 71, 75, 76, 88, 89, 95, 96] yielding a total of 86 included articles.

The number of articles screened, eligibility assessment, reasons for exclusion, and the number of articles found through snowballing are given in ▶ **Fig. 1**. The baseline characteristics of the included studies are presented in **Table S1**. The antibacterial agents were administered intraperitoneally by instillation in 42 %, irrigation in 33 %, and lavage in 33 % of the studies (some studies had more than one type of intraperitoneal administration).

Bias

There were 29 RCTs included in this systematic review, where 8 of these were quasi-randomised. The bias assessment is presented in ▶ **Fig. 2**.

There were 28 prospective and 22 retrospective cohort studies. 22 of these studies included a comparison group and could be assessed for bias using the Newcastle-Ottawa scale. The assessed studies had a median of 3 stars and ranged from 0–6 stars (a score of 0–9 stars may be achieved: a low number of stars correspond to high risk of bias).

Primary outcome: characterisation of antibacterial agents

The characterisation of the classes of antibacterial agents administered intraperitoneally and the specific drugs are presented in **Table S1**. In total, the use of 12 different classes of antibacterial agents were reported (▶ **Fig. S1**). The antibacterial agents most commonly administered were aminoglycosides in 31 %, 1st generation cephalosporins in 16 %, tetracyclines in 12 %, penicillins in 12 %, and 2nd generation cephalosporins in 7 % of the studies. Of the included studies, 67 % were conducted in the 1970s and 1980s. The differences in reports over time of the most commonly administered antibacterial agents are presented in ▶ **Fig. S2**.

Secondary outcomes

Doses and concentrations of antibacterial agents used intraperitoneally were not reported consistently and differed substantially. The ranges for the most common drug classes are presented in ▶ **Table 1**. In 9 % of the studies, no dose was reported and in 10 % of the studies no concentration was reported.

Most of the antibacterial agents were administered as monotherapy intraperitoneally dissolved in saline, Ringer's lactate, or

▶ **Table 1** Doses and concentrations of the antibacterial agents most commonly administered intraperitoneally.

Drug class Drug name	Single dose range, mg	Concentration range, mg/ml	Intraperitoneal daily dose range, mg †	Defined daily dose [13] parenteral, mg
Aminoglycosides				
Gentamicin	I: 80-240 L: 10-15	I: 0.08-4.8 L: 0.01-0.015	I: 80-240 L: 240	240
Kanamycin	I: 250-1,000 L: 20-1,000	I: 0.1-50 L: 0.025-1	I: 250-3,000 L: 200-10,000	1,000
Neomycin	I: 125-20,000 L: 500 *	I: 1-500 L: 2 *	I: 150-20,000 L: 500 *	1,000‡
Streptomycin	I: 500-2,000	I: 4	I: 500-2,000	1,000
Tobramycin	I: – *	I: – *	I: – *	240
Cephalosporins 1st generation				
Cefazolin	I: 1,000-2,000 L: – *	I: 2-100 L: 2.5 *	I: 1,000-2,000 L: – *	3,000
Cefalotin	I: 150-60,000 L: 50-5,000	I: 1-40 L: 0.05-0.1	I: 1,000-16,000 L: 600-1,200	4,000
Cefradine	I: 500 *	I: 50 *	I: 500 *	2,000
Cefaloridine	I: 1,000 * L: – *	I: 1 * L: – *	I: – * L: – *	3,000
Cephalosporins 2nd generation				
Cefamandole	I: 2,000 L: 50-2,000	I: 2-2.5 L: 0.05-4	I: 2,000 L: 800-4,000	6,000
Cefotetan	I: 1,000 *	I: 1 *	I: 1,000 *	4,000
Cefoxitin	I: 2,000 *	I: 2 *	I: – *	6,000
Penicillins				
Ampicillin	I: 1,000-6,000 L: 25-1,000	I: 1-60 L: 0.025-1	I: 2,000-6,000 L: 1,000-56,000	2,000
Penicillins	I: 1,200-2,400 L: 600-6,000	I: – L: 0.6-3	I: 1,200-2,400 L: 4,800-36,000	3,600
Tetracyclines				
Oxytetracycline	I: 125-500 L: 500	I: 1-2 L: 1-2	I: 1,000-2,000 L: 500 *	1,000
Tetracycline	I: 500-2,000 L: –	I: 1-50 L: 1	I: 500-7,000 L: –	1,000
Doxycyclin	L: 50 *	L: 0.05 *	L: 500 *	100

I: instillation or irrigation, L: lavage, 1st: first generation, 2nd: second generation, †: the day of surgery, * : only one study/all studies administered the same dose/concentration, ‡: per os, –: no dose/concentration stated or reported per kg bodyweight

water for injection. In 16 studies, combinations of antibacterial agents were administered into the peritoneal cavity (**Table S1**). The most common combinations reported were aminoglycosides combined with either lincosamides [16, 18, 32, 62], penicillins [40, 51, 70, 71], or 1st generation cephalosporins [43, 59]. Another often used combination was 1st generation cephalosporins and nitroimidazoles [28, 38]. In one study, 3 antibacterial agents were administered in combination [55]. Also, heparin was administered together with antibacterial agents in 31 % of studies performing lavage presumably to prevent the lavage fluid from clotting [45, 51, 52, 61, 66, 67, 70, 71, 81].

Reports on adverse events were missing in 43 % of the studies, and another 41 % of the studies specified that there were no adverse events related to the intraperitoneal administration of drugs. Adverse events of different degrees were reported in 16 % of the studies due to intraperitoneal administration of antibacterial agents [47, 51, 52, 63, 65, 75–77, 90, 91, 93–96]. The details of these studies' adverse events are presented in ▶ **Table 2**. The most commonly reported adverse event was various degrees of discomfort or pain during drug administration. One study reported that pain was relieved when the instillation was diluted [96]. All studies administering oxytetracycline reported discomfort or pain during the administration [90, 91, 94–96]. In 2 studies administering either kanamycin or cefamandole, serious adverse events were reported: one was an allergic reaction causing hypotension [47], the other had an uncertain relation to the intraperitoneal treatment but resulted in death [93].

Other results

The remaining variables were sparsely reported and are therefore only presented in brief. Co-administration of antibacterial agents by other administration routes was reported in 67 % of the included studies. However, one third of these studies did not report which concomitant antibacterial agents were used. In 11 % of the studies, it was specified that the intraperitoneal antibacterial agent was the only drug administered [40, 42, 47, 61, 63, 77, 81, 90, 95, 96], and 20 % of the studies lacked a description on whether other antibacterial agents had been administered [3, 25, 26, 37, 43, 46, 54, 66, 72, 73, 82, 83, 88, 89, 93, 98, 99].

Dwell time was reported in 25 % of the studies [16, 18, 22, 26, 32, 36, 38, 44, 47, 48, 54–56, 61, 63, 67, 70–72, 81]. In lavage studies, the dwell time ranged from 10 min to 4 h, median 45 min. In irrigation studies, it ranged from one min to one h, median 3 min.

In total, only 16 % of studies reported on follow-up [16–18, 23, 28, 33–36, 39, 41, 45, 49, 68, 75, 76]. In these studies, the time of follow-up ranged from 2 weeks to 42 months after discharge with a median of one month.

Discussion

▶ **Table 2** Reported adverse events in the included studies for each drug class.

Drug class Study	Year	Drug name	Dose, mg	Concentration, mg/ml *	Type of i. p. administration	Adverse event/Serious adverse event, n (%)
Aminoglycosides						
Moukhtar et Romney [51]	1980	Kanamycin	1,000	0.5	Lavage	AE: Sinus infection, n = 1 (8%)
Raine et al. [63]	1976	Tobramycin	2–3 mg/kg bw	0.4-0.6 mg/ml/ kg bw	Instillation	AE: Rise in urea and in creatinine, n = 1 (8%)
Pissiotis et al. [77]	1972	Kanamycin	250/500	12.5/25	Instillation	AE, 250 mg: local irritation, n = 1 (6%) and severe burning, n = 2 (13%) AE, 500 mg: local irritation at instillation, n = 1 (4%)
Prigot et al. [93]	1958	Kanamycin	500	25	Instillation	SAE: Comorbid patient did not wake up postoperatively and died, n = 1 (3%)
Schatten [95, 96]	1956/ 1953	Neomycin	500»125	2	Lavage	AE: discomfort at instillation, n = 5 (28%)
Cephalosporins 1st generation						
Smith [65]	1976	Cefalotin	1,000	10	Instillation	AE: Mild to moderate abdominal discomfort for several days, n = 6 (3%)
Smith [75, 76]	1973/ 1972	Cefalotin	1,000	10	Instillation	AE: Mild abdominal discomfort, n = 3 (4%)
Cephalosporins 2nd generation						
Rudd et al. [47]	1982	Cefamandole	2,000	2-2.5	Irrigation	SAE: Allergic reaction causing hypotension shortly after irrigation, n = 1 (< 1%)
Penicillins						
Moukhtar et Romney [51]	1980	Penicillins	6,000	3	Lavage	AE: Sinus infection, n = 1 (8%)
Olesen et al. [52]	1980	Ampicillin	1,000	1	Lavage	AE: Oedema of the flank, n = 6 (60%)
Tetracyclines						
Köves et al. [90]	1960	Oxytetracyclin	500	2	Lavage	AE: Painful cramps on administration, n = 20 (100%)
Adwan et al. [91]	1958	Oxytetracyclin	500	1	Instillation	AE: Discomfort on rapid flow n = – (–%)
Diamond et Impink [94]	1957	Oxytetracyclin	500	1	Instillation	AE: Pain at instillation, n = 1 (5%)
Schatten [95, 96]	1956/ 1953	Oxytetracyclin	250–500	2	Lavage	AE: Discomfort (from bloating to burning pain) during administration, n = 11 (55%)

AE: adverse event, bw: bodyweight, i.p.: intraperitoneal, n: number, SAE: serious adverse event, 1st: first generation, 2nd: second generation, /: or. »: followed by, –: not described, * : if not otherwise stated

We found that the most common antibacterial agents administered intraperitoneally during and after surgery were aminoglycosides, 1st and 2nd generation cephalosporins, tetracyclines, and penicillins. Most studies administered a single antibacterial agent; however, some studies co-administered the antibacterial agent with another antibacterial agent and/or heparin. The most frequent combination was aminoglycosides and lincosamides. Of the reported adverse events, the most frequently ones were discomfort or pain during administration, especially when using oxytetracycline.

It was not within the scope of this review to recommend specific agents. Antibacterial therapy given as prophylaxis or treatment of infection in relation to surgery depends on the underlying disease. The disease can have various origins, e. g., gynaecological, urological, or gastrointestinal. Most studies in this review administered antibacterial agents intraoperatively and intraperitoneally as prophylaxis or treatment of peritonitis originating from the gastrointestinal tract. This type of abdominal infection is usually polymicrobial [100] involving both aerobic and anaerobic bacteria [101, 102]. Therefore, empirical treatment is based on broad-spectrum and/or combination therapy, and recommendations have varied geographically and over time depending on drug availability and epidemiology of resistance prevalence.

More than 40% of the included articles did not report whether adverse events were present or not. Some of the missing descriptions may be explained by historical differences regarding reporting. Nowadays, it is mandatory to report possible harms, side-effects, and adverse events when conducting research on drug administration. Both the checklist of the CONSORT statement and ClinPK clearly describe this necessity [103, 104]. The most com-

monly reported adverse events were discomfort or pain during intraperitoneal administration of the antibacterial agents. Notably, oxytetracycline provoked discomfort or pain in all studies where it was given intraperitoneally. Unfortunately, details on the composition of oxytetracycline used in the studies were sparse. The composition of the drug used for instillation, irrigation, or lavage seemed to be the most reasonable explanation for the discomfort. Discomfort during intraperitoneal administration has been reported in peritoneal dialysis [105]. Over the past couple of years, biocompatible fluids have been developed [106]. Previously, the dialysis fluids had an approximate pH of 5 to decrease glucose degradation products in the dialysis fluid [107, 108]. Pain during administration of dialysis fluid decreased when pH was neutralised [108–111]. It would therefore seem reasonable to aim for close to neutral pH when preparing antibacterial solutions for intraperitoneal administration in the awake patient. Another possible explanation could be the osmolarity of the fluids administered intraperitoneally. The fluids used in peritoneal dialysis are hyperosmolar (> 500 mosm/l) to ensure ultrafiltration across the peritoneal membrane. It is not known whether osmolarity directly influences discomfort during administration [112]. Nonetheless, the compositions of fluids administered intraperitoneally affect the peritoneal lining over time. Thus, chronic changes of the mesothelial cells occur in patients undergoing peritoneal dialysis with fluids of high pH and high osmolarity [113], whereas patients, who underwent peritoneal dialysis with biocompatible fluids, avoided these impairments [106, 114, 115].

The strength of this systematic review is the large number of studies included through both the systematic search and snowballing. The review includes articles published over a large timespan and it therefore provides an excellent coverage of intraperitoneal administration of antibacterial agents. However, it has some limitations. As in all reviews, outcomes are limited by the data possible to extract. Initially, we had hoped to investigate the clinical outcome of intraperitoneal administration of antibacterial agents during or after surgery. However, our preliminary search revealed that this would not be possible. The large timespan also entailed that approaches and methods for reporting differed. This resulted in large heterogeneity of the studies. We observed this in both the study design (RCTs, small pharmacokinetic trials, prospective cohorts, and larger retrospective cohort studies) and in the type of intraperitoneal administration used (instillation, irrigation, and lavage). This made it difficult to make comparisons overall. Thus, we chose a more narrative aim. Further, the bias assessment indicated either a high or unclear risk of bias in most studies, which was due to a combination of insufficient reporting and outdated methodology. However, the primary outcome, characterisation of the agents used, was not prone to be biased.

In conclusion, 12 different antibacterial drug classes have been administered intraperitoneally in the perioperative setting. The most common were aminoglycosides, 1st and 2nd generation cephalosporins, tetracyclines, and penicillins. Intraperitoneal administration of antibacterial agents consisted mostly of monotherapy, however, combination therapies did occur. Overall, intraperitoneal administration of antibacterial agents seemed safe with few and mild adverse events, although pain or discomfort with administration in the awake patient may occur, especially when using oxytetracyclines. Thus, antibacterial agents can safely be administered intraperitoneally. In order to reduce discomfort and pain at administration and according to experiences from peritoneal dialysis, it seems advisable to aim for neutral pH and iso-osmolarity and to avoid oxytetracyclines in the awake patient.

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None.

Conflicts of interest

None.

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