Journal of Surgery
Van Genderen PJJ, et al. J Surg 10: 11480
www.doi.org/10.29011/2575-9760.11480
www.gavinpublishers.com
Research Article

# Is Loperamide Use an Independent Risk Factor for A Fatal outcome of Toxic Megacolon? - A Narrative Clinical Review

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**Citation:** van Genderen BM, van Genderen PJJ (2025) Is Loperamide Use an Independent Risk Factor for A Fatal outcome of Toxic Megacolon? - A Narrative Clinical Review - J Surg 10: 11480 DOI: 10.29011/2575-9760.011480

**Received Date:** 27 October 2025; **Accepted Date:** 03 November 2025; **Published Date:** 05 November 2025

**Abstract**

**Background:** Loperamide, a phenylpiperidine opioid derivative, is widely used as an empirical and generally safe over-the-counter antidiarrheal agent. Although rare, several reports have linked loperamide use to Toxic Megacolon (TM), a life-threatening condition characterized by severe dilatation of an inflamed colon and systemic toxicity. However, this association remains unclear due to confounding comorbidities and concomitant medications.

**Objective:** This review aimed to determine whether loperamide use should be considered an independent risk factor for a fatal outcome of TM.

**Methods:** A systematic literature search was performed in accordance with PRISMA guidelines. A total of 222 articles describing 496 TM cases were identified and analyzed for risk factors associated with fatal outcomes.

**Results:** Among 496 TM patients, 80 (16.1%) experienced a fatal outcome, and 30 (6.0%) had used loperamide within three months prior to TM onset. Backward logistic regression identified Charlson Comorbidity Index (CCI) score (OR 1.21, 95% CI 1.02–1.43), antidiarrheal regimen without loperamide (OR 2.41, 95% CI 1.17–4.96), and a complicated course of TM (OR 7.53, 95% CI 4.34–13.09) as significant independent predictors of fatality. Loperamide use was not retained as an independent variable in the final model. Quality assessment rated 85.1% (189/222) of included studies as methodologically low.

**Conclusion:** Current evidence does not support loperamide as an independent risk factor for fatal toxic megacolon. The findings are limited by incomplete data and low methodological quality across much of the available literature.

**Keywords:** Complication; Fatal; Imodium; Loperamide; Megacolon; Review; Severe; Toxic

## Introduction

Loperamide, commonly known by its brand name Imodium®, is a phenylpiperidine opioid derivative widely used as a safe, over-the-counter antidiarrheal agent for both acute and chronic diarrhea [1]. Its antidiarrheal effect arises from potent μ-opioid receptor agonism within the myenteric plexus of the colon, which reduces propulsive activity, increases non-propulsive contractions, and enhances water and electrolyte absorption [1,2]. Loperamide exhibits limited oral bioavailability due to extensive first-pass hepatic metabolism via CYP3A4 and CYP2C8 and strong plasma protein binding [2]. Moreover, as a P-glycoprotein substrate, loperamide is effectively excluded from the central nervous system, confining its action to the periphery and minimizing morphine-like central effects [1]. At therapeutic doses, common adverse effects include constipation, nausea, and headache, whereas overdose or concurrent inhibition

of P-glycoprotein (e.g., by verapamil or ketoconazole) can result in central opioid toxicity and respiratory depression [3]. In recent years, misuse of loperamide at supratherapeutic doses to alleviate opioid withdrawal or induce euphoria has been increasingly reported, sometimes resulting in life-threatening cardiac arrhythmias [3,4]. Toxic megacolon is a severe complication characterized by colonic dilation with systemic toxicity, associated with significant morbidity and mortality [5-12]. Predisposing factors include electrolyte disturbances such as hypokalemia and the use of agents that impair gastrointestinal motility, including opioids, anticholinergics, loperamide, and certain antidepressants [6-11]. Pathophysiologically, deep inflammatory extension into the colonic muscle layers disrupts neuromuscular tone, compounded by the release of relaxant mediators such as nitric oxide, leading to colonic dilatation [5,6]. Although most cases occur secondary to underlying colitis (e.g., ulcerative, infectious, or antibiotic-associated) [5-11], a few reports have implicated loperamide use, often in the presence of confounding comorbidities or co-medications [13-18]. Given that loperamide is sometimes prescribed in patients already predisposed to toxic megacolon, its role as an independent or contributory risk factor warrants careful evaluation. This review aims to assess whether available evidence supports loperamide use as an independent risk factor for fatal outcomes in toxic megacolon.

## Methods

The review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines where applicable [19]. As a result of the design of the underlying studies, mainly consisting of case report and series, a formal PRISMA systematic review and meta-analysis was not deemed possible.

### Data Sources and Search Strategies

The search for bibliographic information was conducted in several electronic databases, namely Medline, EMBASE, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar. This search encompassed articles on toxic megacolon from inception through February 9, 2024. A comprehensive search strategy was employed, utilizing both descriptors and free terms that were relevant to the review question. These search strategies were tailored to each specific bibliographic database with the assistance of a biomedical information specialist from the Erasmus Medical Centre Rotterdam library (Appendix 1). All retrieved results were stored in an Endnote file and subsequently uploaded in Covidence (https://www.covidence.org) for further analysis and supplemented with articles that were identified during manual screening of reference lists. The screening of eligible publications was conducted independently by two evaluators. Initially, the titles and abstracts of all citations were reviewed. Subsequently, the full text of potentially relevant citations was assessed. In the event of discrepancies, consensus was sought between the two reviewers. If consensus could not be reached, a third independent party would be consulted for the final decision.

### Inclusion and Exclusion Criteria

English served as a language restriction, signifying that all articles written in languages other than English were omitted from the analysis. In order to be included, articles had to focus on patients diagnosed with toxic megacolon and provide sufficient individual patient data allowing proper risk factor analysis. Selection criteria include case reports or case series studies of toxic megacolon. Reviews, cohort studies, case-control studies and other clinical studies were also considered for inclusion as long as they provided sufficient data on individual cases. Congress abstracts, poster presentations and poster abstracts were excluded. Only studies conducted on human subjects were included; animal and experimental in vitro studies were excluded. Patients diagnosed with acute colonic pseudo-obstruction (Ogilvie syndrome), patients with congenital megacolon (such as Hirschsprung disease), acquired megacolon due to obstruction (such as fecal impaction or volvulus) or chronic megacolon due to American trypanosomiasis (Chagas disease) were excluded from the analysis as well.

### Data Extraction and Assessment

Data extraction was conducted by a single reviewer, utilizing a purpose-built data extraction form. Subsequently, a second reviewer crosschecked the extracted data. The collected data encompassed various aspects, including the demographic details of the cases, their clinical presentation (including information on current and previous illnesses), medication usage (including loperamide), potential trigger events in the three months preceding the toxic megacolon event (including endoscopy, barium enema, and loperamide use), results from physical examinations and diagnostic tests (such as imaging), treatment administered, patient outcomes and follow-up information. Follow-up was censored 90 days after the diagnosis of toxic megacolon. Special attention was given to any past or current antidiarrheal treatment or combination of antidiarrheal treatments that the patient had received in the three months before the diagnosis TM was made.

### Data Synthesis and Analysis

Extracted data were collected in an EXCEL file after reaching data consensus and subsequently imported into MedCalc for further statistical analysis. For conveniency of analysis, data was summarized as categorical data and grouped according to the principal outcome of toxic megacolon, *i.e.* a fatal outcome or not. Missing categorical data were grouped with data in which the characteristic was absent.

### Definitions

**Jalan diagnostic criteria for toxic megacolon:** Many authors consider the (adapted) diagnostic criteria of Jalan (see Appendix 2) as the most widely accepted clinical criteria for toxic megacolon [6, 8, 12]. They constitute of the following criteria:

- Radiographic evidence of colonic distension
- At least three of the following:
- Fever >38.6 ºC (101.5 º
- F)
- Heart rate ≥ 120/min
- Neutrophilic leucocytosis>10.5x$10^9$/L
- Anemia
- In addition to the above, at least one of the following:
- Dehydration
- Altered consciousness
- Electrolyte disturbances
- Hypotension

Cases with toxic megacolon were labeled as *typical* cases if the patient fulfilled the adapted diagnostic criteria of Jalan for toxic megacolon [6,8]; patients not fulfilling the diagnostic criteria were labeled *atypical* TM cases.

### Complicated Course Of Toxic Megacolon

A complicated course of toxic megacolon was defined as a course associated with complications like proven sepsis or bacteremia, significant bleeding requiring blood transfusions, hemodynamic shock or a demonstrated perforation of the colon.

### Charlson Comorbidity Index (CCI) Score

The Charlson Comorbidity Index is a weighted index consisting of 19 conditions to predict risk of death within 1 year of hospitalization for patients with specific comorbid conditions [20]. A free online calculator (available at www.mdcalc.com) was used to determine a CCI score for each patient.

### Antidiarrheal Regimen

An anti-diarrheal regimen was defined as the past or current use of anticholinergic antidiarrheals (like atropine, hyoscamine, dicyclomine, scopolamine, propantheine or clindinium-chlordiazepoxide), narcotic antidiarrheals (like loperamide, diphenoxylate or codein), absorbent antidiarrheals (like kaolin, cholestyramine or colestipol), antisecretory antidiarrheals (like octeotride or racecadotril), non-adsorbable broad spectrum antibiotics like rifaximin and adstringent agents like bismuth salicylate in the three months preceding the TM event. Loperamide (whether or not combined with other antidiarrheals) was reported as a separate (dichotomous) antidiarrheal regimen given the specific interest in loperamide in the context of risk factors for a fatal outcome of toxic megacolon.

### Methodological Quality

To assess the methodological quality of case reports and case series, a revised tool for quality appraisal and synthesis was employed [21]. This tool will evaluate four domains: selection, representativeness of cases and ascertainment of outcome and exposure. This resulted in 5 criteria in the form of questions with a binary response (yes/no), whether the item was of high quality or not. These question are listed in Appendix 3. When all 5 criteria were fulfilled the quality of the report was considered good (high methodological quality), moderate when 4 were fulfilled and poor (low methodological quality) when ≤3 were fulfilled. The assessment was carried out by one investigator, with a random sample being crosschecked by another investigator.

### Statistical Analysis

Univariate analysis using Mann Whitney test for continuous (not normally distributed) variables and Fisher's exact test for categorical variables identified risk factors for fatal toxic megacolon. A two-tailed $P<0.05$ was considered statistically significant. Variables that were significant to $P=0.10$ and variables that had *a priori* clinical significance were then analyzed using multivariable logistic regression modeling with fatal toxic megacolon as the dependent (outcome) variable using a backward elimination regression approach. ROC curve analysis was reported as the area under the curve with their respective 95% confidence intervals of the final model. All statistical analyses were performed using MedCalc Statistical Software package version 22.030 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024).

## Results

### Studies Characteristics

A total of 2216 studies were identified through database searching after duplicates had been removed (Figure 1). After screening of titles and abstracts, 447 articles were selected for full-text assessment; 222 articles of them were included in the review (Appendix 4), providing sufficiently detailed case histories of 496 patients with toxic megacolon [13-18, 22-236]. The putative etiologies of TM of these 496 cases are shown in Table 1. Three major etiological clusters could be discerned: one cluster of patients with an inflammatory colitis ($n$=308 cases), another cluster of patients ($n$=162) with an infective colitis and a cluster of

miscellaneous causes of colitis constituting the remaining 26 patients, respectively. Eighty of 496 (16.1%) cases with toxic megacolon had a fatal outcome. Thirty of 496 (6.0%) had used loperamide in the three months preceding the TM event. The general characteristics of the 496 included cases are shown in Tables 2,3, grouped according loperamide use or not.

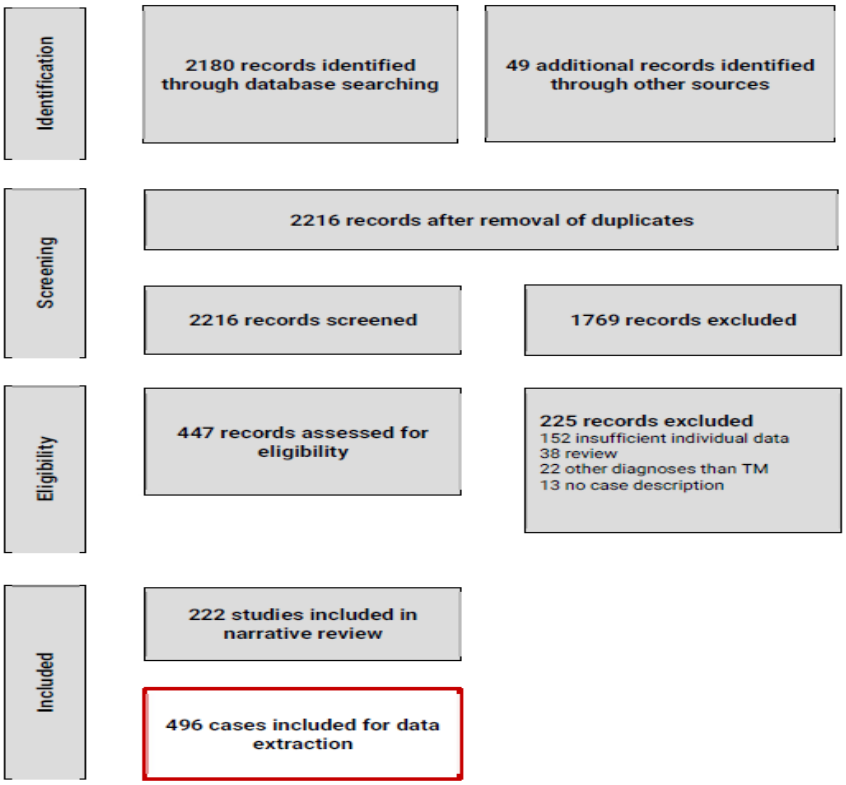


**Figure 1:** Flowchart for literature search on cases with toxic megacolon.

| **Inflammatory colitis** | | | | **Infective colitis** | | |
|---|---|---|---|---|---|---|
| (n=308) | n | % | | (n=162) | n | % |
| Ulcerative colitis | 243 | 78.9 | | Clostridioides difficile | 80 | 49.4 |
| Crohn's colitis | 49 | 15.9 | | Salmonella species | 22 | 13.6 |
| IBD (unspecified) | 9 | 2.9 | | Campylobacter species | 16 | 9.9 |
| Indeterminate colitis | 3 | 1.0 | | Entamoeba histolytica | 12 | 7.4 |
| Behçet's disease | 2 | 0.6 | | CMV virus | 10 | 6.2 |
| Collagenous colitis | 1 | 0.3 | | Shigella species | 7 | 4.3 |
| Adult onset Still's disease | 1 | 0.3 | | Cryptosporidium species | 2 | 1.2 |
| | | | | Escherichia coli | 2 | 1.2 |
| **Miscellaneous colitis** | | | | HIV/AIDS | 2 | 1.2 |
| (n=26) | n | % | | | | |
| Drug-induced | 8 | 30.8 | | Rota virus | 2 | 1.2 |
| Invasive malignancies | 6 | 23.1 | | Yersinia species | 2 | 1.2 |
| Benign disorders | 5 | 19.2 | | Unspecified infective colitis | 2 | 1.2 |
| Intoxication | 3 | 11.5 | | Pseudomonas species | 1 | 0.6 |
| Ischemic | 3 | 11.5 | | Bacillus licheniformis | 1 | 0.6 |
| Idiopathic | 1 | 3.8 | | Aspergillosis | 1 | 0.6 |

**Table 1:** Putative etiologies of toxic megacolon, divided by etiological subgroup.

| | **Patients with toxic megacolon** | | |
|---|---|---|---|
| | Loperamide use (n=30) | No Loperamide (n=466 ) | P-value |
| **Putative etiology of TM**, n (%) | | | **P=0.0015** |
| Inflammatory colitis (IBD) | 10 (33.3%) | 298 (63.9%) | |
| Non-IBD colitis | 20 (66.7%) | 168 (36.1%) | |
| **Age**, median (IQR) | 41.5 | 39.0 | P=0.2213[2] |
| | (33.0-53.0) | (23.0-56.0) | |
| **Sex**, n (%) | | | P=0.8512 |
| Male | 17 (56.7%) | 252 (54.1%) | |
| Female | 13 (43.3%) | 214 (45.9%) | |
| **Charlson Comorbidity Index**, median (IQR) | 0 | 0 | P=0.6684[2] |
| | (0-2) | (0-2) | |

| | | | |
|---|---|---|---|
| **Other antidiarrheal treatment**, n (%) | | | |
| Yes | 0 (0%) | 217 (46.6%) | **P<0.0001**[1] |
| No/unknown | 30 (100%) | 199 (53.4%) | |
| **One or more trigger factors for TM**, n (%) | | | |
| Yes | 30 (100%) | 464 (99.6%) | P=1.0000[1] |
| No/unknown | 0 (0%) | 2 (0.4%) | |
| **Fulfilling Jalan criteria**, n (%) | | | |
| Typical | 5 (16.7%) | 63 (13.5%) | P=0.5864[1] |
| Atypical/unknown | 25 (83.3%) | 403 (86.5%) | |
| **Dilatation colon > 6 cm**, n (%) | | | |
| Yes | 28 (93.3%) | 439 (94.2%) | P=0.6921[1] |
| No/unknown | 2 (6.7%) | 27 (5.8%) | |
| **Management**, n (%) | | | |
| Medical | 16 (53.3%) | 154 (33.0%) | **P=0.0289** |
| Medical and surgical | 14 (46.7%) | 312 (67.0%) | |
| **Complicated course**, n (%) | | | |
| Yes | 10 (33.3%) | 139 (29.8%) | P=0.6843 |
| No/unknown | 20 (66.7%) | 327 (70.2%) | |
| **Fatal course**, n (%) | | | |
| Yes | 4 (%) | 76 (16.3%) | P=0.8023 [1] |
| No/unknown | 26 (%) | 390 (83.7%) | |
| [1] Fisher's exact test; [2] Mann-Whitney test | | | |

**Table 2:** General characteristics and outcomes of the patients with Toxic Megacolon (TM), subdivided by loperamide use or not.

| **FATAL OUTCOME** (80 out of 496 patients) | | | | | | |
|---|---|---|---|---|---|---|
| **Independent variables** | **Coefficient** | **Std.error** | **Wald** | **P-value** | **Odds ratio** | **95% CI** |
| Age | 0.01505 | 0.0089942 | 2.8014 | 0.0942 | | |
| Charlson Comorbidity Index | 0.18899 | 0.086439 | 4.7806 | **0.0288** | 1.21 | 1.02-1.43 |
| Antidiarrheal regimen other than loperamide | 0.88093 | 0.36728 | 5.7529 | **0.0165** | 2.41 | 1.17-4.96 |
| Complicated course | 2.01954 | 0.28177 | 51.369 | **<0.0001** | 7.53 | 4.34-13.09 |
| Antibiotic use | -0.69729 | 0.37558 | 3.4468 | 0.0634 | | |
| Constant | -3.66858 | 0.42778 | 73.5442 | **<0.0001** | | |
| | | | | | | |
| **COMPLICATED COURSE** (149 out of 496 patients) | | | | | | |
| **Independent variables** | **Coefficient** | **Standard Error** | **Wald** | **P-value** | **Odds ratio** | **95% CI** |
| Medical and surgical management | 1.95745 | 0.28789 | 46.2311 | **<0.0001** | 7.08 | 4.03-12.45 |
| Inflammatory colitis | -0.69346 | 0.26999 | 6.597 | **0.0102** | 0.5 | 0.29-0.85 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Antibiotic use | 0.41963 | 0.23237 | 3.2611 | 0.0709 | | |
| Corticosteroid use | -0.42272 | 0.25605 | 2.7255 | 0.0988 | | |
| Constant | -1.87612 | 0.30665 | 37.4309 | **<0.0001** | | |

**Table 3:** Outcomes of multivariable logistic regression analysis for independent variables for either a fatal outcome or a complicated course of toxic megacolon.

### Demographics And Co-Morbidities

As shown in Table 2, patients using loperamide did not significantly differ from those who did not use loperamide with regard to age, sex, CCI score, presence of one or more trigger factors for TM, fulfilling Jalan criteria, dilated colon > 6 cm, complicated course of TM nor did outcome differ. TM patients using loperamide had significantly less frequent a surgical management of TM and significantly more frequently a non-IBD etiology of TM, respectively. More than half of the non-loperamide users had used an antidiarrheal regimen other than loperamide in the three months preceding the TM event.

### Potential Trigger Factors In The 3 Months Preceding Toxic Megacolon Event

As shown in Appendix 5, patients with loperamide had undergone endoscopy significantly more frequent and used antibiotics and corticosteroids significantly more frequent than TM patients who did not use loperamide. However, all but 2 patients (who did not use loperamide) had at least one trigger factor for TM.

### Management And Prognosis After Diagnosis Of Toxic Megacolon

As shown in Table 2, patients who did not use loperamide had significantly higher rates of a surgical intervention than TM patients who used loperamide. TM patients who used loperamide did not significantly differ from patients who did not use loperamide regarding a complicated course of TM nor the outcome of TM. In Appendix 6 the complication rates of bacteremia/sepsis, shock, perforation and severe bleeding are shown. There were no significant differences in complication rates between TM patients that had used loperamide or not.

### Risk Factor Analysis

Backward logistic regression analysis of 496 TM patients identified Charlson Comorbidity Index (CCI) score (OR 1.21 [95% CI 1.02-1.43]), any antidiarrheal regimen not containing loperamide (OR 2.41 [95% CI 1.17-4.96]) and a complicated course of TM (OR 7.53 [95% CI 4.34-13.09]) as significant independent variables for a fatal outcome of TM. Loperamide was eliminated as an independent variable from the regression model best explaining the data.

### Quality Assessment

Quality assessment of the 222 articles included in the review was rated as of poor methodological quality in the majority (189/222, 85,1%) of the included papers. Methodological quality was rated as high in 6 papers (2.7%) and as moderate in 27 (12.2%) papers (Appendix 3).

## Discussion

### Diagnostic Criteria For Toxic Megacolon

The current analysis showed that toxic megacolon may be associated with a broad array of underlying medical conditions, including inflammatory bowel disorders and many causes of infective colitis. Even though the adapted Jalan criteria for toxic megacolon have been reported as the most widely accepted ones, in practice they are not consistently used. In this study only in 68 of 496 (13.7%) TM cases the adapted Jalan criteria were fulfilled. This low acceptance rate may relate to the observation that the original Jalan criteria [12] were based on a retrospective analysis of 55 cases of whom the full clinical course was recorded and a known outcome, whereas clinical practice would benefit more from an accurate decision-making tool derived from well-designed prospective studies. In addition, the current analysis further suggests that the adapted Jalan criteria lack sufficient predictive power for a fatal outcome of toxic megacolon. Future prediction models should pay specific attention which parameters best reflect the two major pathophysiological hallmarks of toxic megacolon: severe dilatation of an inflamed colon and clinical signs of systemic toxicity.

### Independent Risk Factors For A Fatal Outcome Of Toxic Megacolon

In this narrative clinical review independent variables for a fatal outcome of toxic megacolon were identified by analyzing detailed case histories from a group of 496 published TM cases. In the analysis of all 496 TM cases CCI score, any antidiarrheal regimen other than loperamide and a complicated course of TM were identified as independent risk factors for a fatal outcome.

### Use Of Loperamide And Any Antidiarrheal Regimens In Relation To Outcome

Loperamide was eliminated as an independent variable from the

regression model best explaining the data. There was not sufficient evidence found to support the hypothesis that loperamide should be considered as an independent risk factor for a fatal outcome of TM. Although speculative, this may suggest that loperamide in itself is not capable of inflicting the typically required deep tissue or even transmural colonic inflammation that is pivotal for the development of toxic megacolon. This assumption, however, is further strengthened by the observation that misuse and intentional overdose of loperamide in patients without any other underlying disorder is primarily associated with potentially fatal cardiac conduction disorders and arrhythmias whereas gastrointestinal manifestations like toxic megacolon have not been reported despite the widespread use of loperamide since its market introduction in the early 1970s [1-3].

### Use of Loperamide As Effect Modifier

Based on their of action, loperamide and other antidiarrheal regimens could also be considered as effect modifying drugs in patients with toxic megacolon, worsening outcome by additional inhibition of GI motility in an already compromised colonic motile system. In this respect it is certainly remarkable that loperamide users had similar complication rates in comparison to TM patients not using loperamide, suggesting that from a clinical point of view no clear effect modification became apparent, even though a facilitating role of loperamide in the pathophysiology of toxic megacolon could not be excluded.

### Limitations of The Study

The quality of any review is rather dependent on the quality of the articles underlying the review, including their inherent biases like publication and selection biases. A structured quality assessment of all included articles rated the methodological quality of the majority of the included articles as low, which mainly related to insufficient data regarding some parameters. This may probably hamper the generalizability of the current findings to some extent, even though missing data were included in the statistical analyses. On the other hand, the rather high number of case reports - originating from all continents – that were included in the analysis will certainly contribute to the generalizability of the findings but also underlines the global occurrence of toxic megacolon and that there is a continuing need for identification of clinically sound predictive parameters derived from properly designed studies.

## Conclusions

Based on the analysis of all patient data Charlson Comorbidity Index score, an antidiarrheal regimen not containing loperamide and a complicated course of TM were identified as independent variables for a fatal outcome of toxic megacolon. There was not sufficient evidence to support the hypothesis that loperamide should be considered as an independent risk factor for a fatal outcome of TM. The study was limited by incomplete data and low methodological quality of many case reports included in this review.

## Acknowledgements

The authors wish to express their gratitude to Mr. Lennert Slobbe for inspiring discussions. Mr. Menno Dreischör is thanked for his valuable statistical advices. Mr. Wichor Bramer is thanked for his help in defining the various search strategies to retrieve the literature.

## Declarations

### Author contributions

Both authors contributed to the study conception and design. Material preparation and data collection were done by both authors. Principal data analysis was done by Perry JJ van Genderen. The first draft of the manuscript was written by Perry JJ van Genderen and both authors had input in the various revisions of the manuscript. Both authors read and approved the final manuscript.

### Conflict of interest

No disclosure or conflicts of interest relevant to this submission. The work presented here was evaluated by the University of South Wales as part of the Master of Science (Expedition and Wilderness Medicine) thesis of Perry JJ van Genderen. It has not published elsewhere nor under consideration for publication at another journal.

### Ethical approval

This submitting narrative clinical review is a retrospective systematic review of findings of only published case reports and case series. Ethical clearance was granted by the University of South Wales.

### Funding

Not applicable

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