Oral antibiotics for perforated appendicitis is not recommended

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REVIEW ARTICLE

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In Denmark more than 6,000 patients undergo appendicitis surgery annually, and one third of these patients have perforated appendicitis [1]. The treatment for perforated appendicitis is usually intravenous (IV) antibiotic therapy for a minimum of three days after surgery, i.e. the patient will remain hospitalized for a minimum of three days after surgery. Early conversion to oral (PO) treatment has been attempted for various intra-abdominal infections [2-7]. These studies have consistently shown that early conversion from intravenous to PO antibiotic therapy was at least as good as an IV antibiotic therapy alone [2-7]. A common characteristic in these studies has been an overall good effect of IV/PO antibiotic therapy in all intra-abdominal infections, including acute appendicitis. However, none of these studies provided details for each intra-abdominal infection, but only common, pooled data for all intra-abdominal infections. An assessment of the effect of early conversion to PO antibiotics for perforated appendicitis is therefore not possible on the basis of these studies.

The purpose of this article was to provide an overview of studies on perforated appendicitis that specifically examined the differences between PO antibiotic therapies and IV antibiotic therapy after surgery.

MATERIAL AND METHODS

A search was made on Medline, Embase and The Cochrane Library. The following keywords were used individually and in combination: *acute/perforated appendicitis, antibiotic, oral.* The following MeSH-terms were used: *appendicitis, perforated,* and *antibiotic* – both individually and in combination. All human studies published in English on the treatment of perforated appendicitis with PO antibiotics after surgery were included. In addition, the reference lists of the individual articles were reviewed manually to identify additional studies. The publication date of the included studies ranged from 1966 to 15 September 2009.

RESULTS

The database search yielded five studies specifically addressing the treatment of acute perforated appendicitis with PO antibiotics [8-12]. In one study (PO-study), patients received only PO antibiotics [8]. In the remaining four studies (IV/PO studies), patients with perforated appendicitis received IV antibiotics followed by PO antibiotics, see **Table 1** [9-12]. Four additional studies were found on the treatment of intra-abdominal infections generally with PO antibiotics. In these studies, however, all types of intra-abdominal infections were included without specific details about the underlying disease. These four studies were therefore not included in this review. Study details for the included studies are given in Table 1. Two of the studies were randomized [8, 10], two were prospective [11, 12] and one was retrospective [9]. The study periods were two to three years for four of the studies [8-11], and the study period was not specified in the fourth study [12].

ORAL ANTIBIOTIC STUDIES

Banani et al [8] included 114 patients (PO group) receiving exclusively PO metronidazole 500 mg every eight hours both pre- and postoperatively. The control group (IV group) included 120 patients who preoperatively received IV ceftizoxime four times per day (750-1,000 mg/dose for adults and 20-25 mg/kg/dose for children under the age of 15 years) if there was no pus in the abdomen, or postoperative triple-drug therapy consisting of IV penicillin (100,000 units/kg/day), chloramphenicol (50-80 mg/kg/day) and gentamicin (5-6 mg/kg/day) if there was visible pus during surgery. In both groups, the duration of antibiotic therapy was 3-6 days, depending on the classification of the acute perforated appendicitis.

The exclusion criteria comprised: patients with generalized peritonitis, immunosuppressive patients, allergy to antibiotics, children < 4 years and adults > 50 years, pregnancy and patients who received antibiotics before they were admitted to the hospital.

The complication rates were 19% in the PO group

! ABBREVIATIONS

IV = Patients who continued with intravenous antibiotics after the initial intravenous antibiotic therapy
IV/PO = Patients whose treatment was converted to oral antibiotics after the initial intravenous antibiotic therapy
NO = Patients who only received initial intravenous antibiotic therapy
PB = Patients who received placebo after the initial intravenous antibiotic therapy
PO = Patients who received only oral antibiotics.

Patient receiving intravenous antibiotics after an appendectomy.

and 18% in the IV group. Intra-abdominal abscesses occurred in four (4%) patients in the PO group and five (4%) in the IV group. The treatment was re-laparotomy in three patients from the PO group and four from the IV group. The remaining patients recovered with PO metronidazole for two weeks or IV gentamicin for 6-7 days.

INTRAVENOUS/ORAL ANTIBIOTIC STUDIES

The four IV/PO studies were heterogeneous, but patients with acute perforated appendicitis underwent appendectomy in all of the studies, and initially they received intravenous antibiotics, typically for 4-5 days. Subsequently, patients were divided into one of two groups receiving PO antibiotics/continued IV antibiotics, placebo or no antibiotics (see Table 1). On average, the initial IV administration lasted 4-5 days, while the average period of subsequent PO treatment was 5-7 days.

In the study by *Adibe et al,* patients received IV ampicillin-sulbactam alone or in combination with gentamicin, and PO antibiotics consisted of trimethoprim-sulphamethoxazole and metronidazole [9]. *Rice et al* gave PO amoxicillin-clavulanate potassium (40 mg/kg/day) and IV treatment consisted of ampicillin (400 mg/kg/day), gentamicin (7.5 mg/kg/day) and clindamycin (40 mg/kg/day) [10]. In the study by *Taylor et al,* patients received IV amoxicillin/sulbactam and the PO antibiotics consisted of amoxicillin/clavulanate for patients over 18 years and levofloxacin for patients under 18 years [11]. *Gollin et al* gave IV ampicillin (200 mg/kg/day), gentamicin (7.5 mg/kg/day) and metronidazole (30 mg/kg/day), while the PO antibiotic regimen consisted of trimethoprim/sulphamethoxazole (10 mg/kg/day) and metronidazole (30 mg/kg/day) [12].

The criteria for conversion to PO therapy varied between the four studies, although a common criterion was that enteral feeding should be tolerated for PO therapy to be initiated. In two of the studies, conversion from IV to PO antibiotics was made regardless of fever or leucocytosis [10, 12]. In two other studies, PO antibiotics were initiated when there was a resolution in abdominal pain, tenderness, distension, fever [9, 11] and a decrease in the white blood cell count [11].

Exclusion criteria also varied between studies and were, e.g. presence of gangrenous appendicitis, intraoperative bowel perforation, laparoscopic surgery, other infections, allergy to antibiotics, immunosuppression, renal failure, neutropenia, pregnancy, development of intra-abdominal abscess or wound infection before conversion to PO antibiotics. The total number of patients who had received antibiotic therapy with initial IV administration and subsequent conversion to PO administration was 152, and the typical age group in the studies was been between one and 22 years [9-12].

Complications during PO treatment were found in all four studies, and the complication rate was 0-30% in the control groups and 4-26% in the intervention groups. None of these studies saw a significant difference in complication rate between the groups. Eight patients developed wound infections: four were treated with incision, drainage and oral antibiotics during hospitalization [11], three were given with antibiotics as outpatients [12], and the treatment afforded the last patient was not stated [10]. Postoperative intra-abdominal abscesses were observed in four patients, one patient was treated with percutaneous drainage and IV antibiotics [11], while three other patients received only IV antibiotics [9].

Complications in the control groups were found in 22 (14%) patients: six with abscesses, three with wound infections, two with *Clostridium difficile* colitis, one had a phlegmonous infection, two had problems with peripherally inserted central catheters, one was dehydrated, two had small bowel obstructions, one patient experienced a toxic reaction due to the antibiotics, and three had persistent fever for more than three days.

Conversion of the scheduled PO antibiotic therapy to IV treatment occurred in two of the four studies [10, 11]. In total, three patients (2%) had their treatments converted. The reason was that one patient

TABLE 1

Patient data and endpoints in the published studies.

	Group	n	Age	IV-days	PO-days	Additional AB	Laparoscopy %	Complications (%)	Mortality
Banani et al [8]	IV	120	4-50	3-6	–	1	0	5 (4)	0
	PO	114	4-50	–	3-6	1	0	4 (4)	0
Adibe et al [9]	IV	102	8,8	9.1+7	–	0	80	13 (13)	0
	IV/PO	47	9,7	4.7	7	0	91	2 (4)	0
Rice et al [10]	IV	10	13	10	–	3	0	3 (30)	0
	IV/PO	16	12	4.6	5.4	1	0	1 (6)	0
Taylor et al [11]	PB	22	22	4.3	–	4	25	6 (27)	0
	IV/PO	23	20	4.3	7	2	17	6 (26)	0
Gollin et al [12]	NO	8	1-15	4.5	–	0	52	0 (0)	0
	IV/PO	66	1-15	4.5	7	0	52	3 (5)	0

Additional AB: patients who received additional intravenous or oral antibiotics

developed a wound infection [10], and two patients developed intra-abdominal abscesses [11].

EXPENSES

The differences in cost associated with the use of PO antibiotics compared with IV antibiotics were also studied. In two of the IV/PO studies, a difference in cost associated with the two antibiotic therapies was found [9, 10]. *Rice et al* found that conversion to PO treatment resulted in savings of $1,500 per patient, while the corresponding savings were $4,000 per patient in the study by *Adibe et al.* The PO study found a 30% reduction in cost when only PO antibiotics were used [8]. Calculations were based on the price of antibiotics, the construction of intravenous access, nursing care expenses and hospital stay.

DISCUSSION

The available literature is sparse and the applied regimens cannot be readily transferred to a Danish context. Thus, in some studies patients received IV therapy for 4-5 days before they received PO treatment, whereas our usual routine for perforated appendicitis is IV antibiotics for three days after surgery. The objective of the current literature review was, on the basis of the current evidence to assess whether a switch to PO therapy alone after surgery may be made, and as a result whether the patient could be discharged sooner after the operation than is currently the case. However, the current evidence does not support a conclusion of this nature.

The usual treatment for patients with acute perforated appendicitis is appendectomy combined with antibiotic therapy. Such treatment is supported by numerous controlled trials and a Cochrane review [13]. Patients with acute appendicitis undergoing surgery and antibiotic therapy have fewer wound infections and intra-abdominal abscesses than patients receiving placebo [13]. In recent years, it has been debated whether the optimal method of administration of antibiotics in these patients is by the IV route. The usual method in Denmark is IV administration of antibiotics (a single, two or three drugs, depending on local policy) given as a single dose during surgery, and if there has been visible pus or faeces in the abdomen, the antibiotic therapy continues for three days, also IV therapy.

In the randomized study by *Banani et al,* in which the use of PO antibiotics was compared with IV antibiotics, no significant differences were found in the two groups' outcomes in terms of infectious complications [8]. This study is encouraging, but unfortunately did not use a regimen comparable to our usual routine. A change of the IV antibiotic therapy for PO therapy alone would be a big step towards minimizing the use of medication and the need for hospitalization after surgery. Rescheduling IV to PO therapy is therefore an important step in development of optimized patient treatment in this patient group. However, to our knowledge no studies specifically address this issue, and we therefore need to examine the current Danish regimen with three days of IV treatment against a group that receives an intraoperative IV single-dose intravenous therapy followed by PO treatment alone.

Other studies have examined different antibiotic treatment regimens, consisting of an initial IV antibiotic administered over a period of several days with subsequent conversion to PO administration [9-12]. The results from these trials were that patients with a combined regimen had fewer complications and shorter hospitalization periods than patients in the group receiving only IV therapy, while the economic costs were lower in the combined regimen groups. The investigated regimens are, however, far from usual clinical practice, where the maximum treatment duration is typically three days for complicated cases. Furthermore, the designs of the four trials were not similar and the inclusion and exclusion criteria used were not standardized.

The prolonged treatment with IV antibiotics used in the IV/PO studies was probably based on recommendations from past publications, that patients with acute perforated appendicitis should receive a minimum of ten days of IV antibiotics [14-16]. Other studies have recommended at least 5-7 days of IV antibiotics until there is no fever or leucocytosis for 24 hours [17]. In a recent study of 272 patients with perforated appendicitis, it was shown that halving the period during which patients received intravenously administered antibiotics was not associated with an increase in the complication rate [18]. Considering that the vast majority of hospitals in Denmark treat these patients with three days of IV antibiotics, the basis for comparison with the available scientific literature is not optimal. Denmark has a good tradition of general caution with the use of antibiotics with a view to reducing the risk of resistance and unnecessary side effects.

CONCLUSION

There is presently not sufficient evidence to support shifting the currently preferred three days of IV antibiotic treatment for perforated appendicitis in Denmark to a PO regimen immediately after surgery. Controlled randomized studies should be performed comparing the current regimen for perforated appendicitis (IV antibiotics starting during operation and continuing for three days) with a regimen consisting of IV antibiotics during surgery and a PO regimen in the convalescence period.

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CONFLICTS OF INTEREST: None

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