The NOTA study: non-operative treatment for acute appendicitis: prospective study on the efficacy and safety of antibiotic treatment (amoxicillin and clavulanic acid) in patients with right sided lower abdominal pain

Gregorio Tugnoli, Eleonora Giorgini, Andrea Biscardi, Silvia Villani, Nicola Clemente, Gianluca Senatore, Filippo Filicori, Nicola Antonacci, Franco Baldoni, Carlo De Werra, Salomone Di Saverio

ABSTRACT

Background: Case control studies that randomly assign patients with diagnosis of acute appendicitis to either surgical or non-surgical treatment yield a relapse rate of approximately 14% at one year. It would be useful to know the relapse rate of patients who have, instead, been selected for a given treatment based on a thorough clinical evaluation, including physical examination and laboratory results (Alvarado Score) as well as radiological exams if needed or deemed helpful. If this clinical evaluation is useful, the investigators would expect patient selection to be better than chance, and relapse rate to be lower than 14%. Once the investigators have established the utility of this evaluation, the investigators can begin to identify those components that have predictive value (such as blood analysis, or US/CT findings). This is the first step toward developing an accurate diagnostic-therapeutic algorithm which will avoid risks and costs of needless surgery.

Methods/design: This will be a single-cohort prospective observational study. It will not interfere with the usual pathway, consisting of clinical examination in the Emergency Department (ED) and execution of the following exams at the physician’s discretion: full blood count with differential, C reactive protein, abdominal ultrasound, abdominal CT. Patients admitted to an ED with lower abdominal pain and suspicion of acute appendicitis and not needing immediate surgery, are requested by informed consent to undergo observation and non operative treatment with antibiotic therapy (Amoxicillin and Clavulanic Acid). The patients by protocol should not have received any previous antibiotic treatment during the same clinical episode. Patients not undergoing surgery will be physically examined 5 days later. Further follow-up will be conducted at 7, 15 days, 6 months and 12 months. The study will conform to clinical practice guidelines and will follow the recommendations of the Declaration of Helsinki. The protocol was approved on November 2009 by Maggiore Hospital Ethical Review Board (ID CE09079).

Trial Registration: ClinicalTrials.gov identifier: NCT01096927.

BACKGROUND

Acute appendicitis is one of the most common urgent conditions seen in general surgery practice. Complications can be severe and include perforation and generalised peritonitis. Traditionally, surgical appendectomy has been the primary treatment, even in cases of unconfirmed diagnosis, given the low incidence of major complications. However, in 15–30% of cases the appendix is found to be free of disease upon resection. As appendectomy is associated with surgical wound infection, intestinal obstruction due to adhesions, pneumonia, and tubal infertility in females, the possibility of using conservative treatment merits investigation.

Non-operative treatment of a suspected appendicitis has safety implications. Delaying surgery may increase the risk of perforated appendicitis, intra-abdominal abscesses, and localised or diffuse peritonitis before surgery and wound infection, increased risk of adhesions and subsequent adhesive small bowel obstruction (ASBO) and infertility after surgery. Anaesthesia carries its own risks, and there can also be intraoperative (vascular...
lesions, enterotomies, urinary tract lesions, etc), early surgical postoperative (haematoma/bleeding, colonic fistula, surgical site infection (SSI), intra-abdominal abscess, adhesions and ileus/obstruction) with subsequent re-operation, late surgical postoperative (adhesions and subsequent ASBO and tubal infertility, incisional hernias) and general postoperative complications.

Surgery may be associated with a longer hospital stay and higher costs compared with NOM with antibiotics, but delayed treatment and a perforated appendix may worsen morbidity, duration of sick leave and costs. However, NOM with antibiotics may be a cost-effective alternative to surgery in a large percentage of patients without increasing the risk, and may reduce hospital stay and costs in both developed and third world countries.

There is considerable debate regarding the utility of conservative treatment compared with surgical treatment in some cases of acute appendicitis, as few studies have addressed this issue to date. If conservative treatment is to be considered, it will be very important to make an accurate diagnosis and assessment in every patient in order to select the most appropriate treatment.

The idea that appendicitis may resolve spontaneously is not new. In 1908 Alfred Stengel wrote: “Treated in a purely medical or tentative manner, the great majority of patients with appendicitis recover”. Restrained indications with few negative appendectomies are associated with a low incidence of diagnosed non-perforated appendicitis and a secondary high proportion of perforated appendicitis, but no increase in the incidence of perforations. This suggests that appendicitis in a significant number of patients may resolve undiagnosed. Resolving appendicitis may also be indicated by a history of recurrent appendicitis, which can be found in up to 6.5% of patients operated on for appendicitis.

When perforation results from delayed treatment, the associated increase in morbidity and mortality must be weighed against the risks of a negative appendectomy. The excess mortality associated with non-perforated appendicitis and with negative appendectomy with a discharge diagnosis of non-specific abdominal pain, suggests that appendectomy itself carries risks. The decrease in mortality that may be achieved by one prevented perforation is therefore negated by each negative appendectomy.

Other reports indicate that immediate appendectomy can be avoided for at least 24 h without increasing morbidity if antibiotics are administered. Other authors suggest that appendectomy may not be necessary for the majority of patients with acute uncomplicated appendicitis, as the condition resolves spontaneously in many patients and in others may be treatable with antibiotics alone. This approach has many advantages, including high success and low recurrence rates, reduced morbidity and mortality, less pain, shorter hospitalisation and sick leave, and reduced costs.

In light of this, routine interval appendectomy after initial successful conservative treatment does not seem justified and should be abandoned. In fact, traditional interval appendectomy may prevent recurrent appendicitis in only 6.7% of patients after conservative treatment of acute appendicitis with an appendiceal mass. Thus 93.3% would have an unnecessary appendectomy.

A recent meta-analysis comparing conservative treatment with acute appendectomy for complicated appendix may resolve spontaneously.
appendicitis (abscess or phlegmon) and including 1572 patients (847 patients received conservative treatment and 725 had acute appendectomy) showed that conservative treatment was associated with significantly fewer overall complications, wound infections, abdominal/pelvic abscesses, ileus/bowel obstructions and re-operations. Furthermore, there were significantly fewer overall complications in conservative treatment groups during sensitivity analysis of studies including only paediatric patients, high-quality studies, more recent studies, and studies with larger groups of patients.\(^{15}\)

In particular, a randomised clinical trial (RCT) of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients showed that treatment efficacy was 90.8% for antibiotic therapy and 89.2% for surgery. In this trial minor complications were similar between the groups, while major complications were threefold higher in patients who had an appendicectomy (p<0.050). In total, 2.9% of the operated patients underwent a second operation, 3% of them developed abscesses, 2.4% postoperative small bowel obstruction (SBO), 1.8% wound rupture or wound hernia, 0.6% pulmonary embolism and 0.6% postoperative cardiac complications, and 1.2% underwent subsequent ileocaecal resection. Wound infection occurred in 7.6% and 1.2% of the patients had anaesthesia-related problems.\(^{16}\)

In another RCT comparing appendicectomy with antibiotic treatment in acute appendicitis, the complication rate in the surgery group was 14% (17/124) and was mainly due to wound infections. In the surgery group, time in hospital, sick leave taken and time lost from work were respectively 2.6, 6.0 and 10.1 days.\(^{2}\)

The cumulated risk of surgically treated SBO after appendicectomy was 0.41% after 4 weeks, 0.63% after 1 year and 1.30% after 30 years of follow-up, compared with 0.003% at 1 year and 0.21% after 30 years of follow-up among non-operated controls, with perforated appendicitis, negative appendicectomy and high age risk factors for developing subsequent SBO.\(^{17}\)

A further paper reviewing 1777 patients who underwent appendicectomy for acute appendicitis, showed the overall SBO rate to be 2.8% over an average 4.1-year follow-up period or 0.0069 cases per person-year.\(^{18}\)

The laparoscopic approach also carries risks, including intraoperative complications ranging from 3.1% to 7.7%, surgical postoperative complications ranging from 6.1% to 1.9%, general postoperative complications ranging from 4.9% to 1.5% and rates of re-operations ranging from 3.4% to 0.7%.\(^{19}\)

A comparison of 3025 open versus 14174 laparoscopic appendectomies showed SSI occurred in 4% and 1.2%, deep incisional wound infection in 1.2% and 0.2%, wound disruption in 0.3% and 0.1%, organ space infection in 1.3% and 1.7%, pneumonia in 0.6% and 0.3%, renal failure in 0.2% and 0.3%, urinary tract infection (UTI) in 0.5% and 0.4%, deep vein thrombosis in 0.4% and 0.1%, sepsis in 1.4% and 1.0% and septic shock 0.3% and 0.1%, respectively. Appendectomy may also be associated with mortality (0.3% for open and 0.1% for laparoscopic).\(^{20}\)

Another large population based appraisal including 32683 patients reported morbidity and mortality for both open and laparoscopic appendectomy.\(^{21}\) Overall morbidity was 8.84% and 4.46%, respectively, serious morbidity 4.23% and 2.58%, SSI 6.65% and 3.26%, serious morbidity/mortality 4.26% and 2.60%, and mortality 0.13% and 0.07%. Superficial SSI incidence was, respectively, 3.89% and 1.26%, deep incisional SSI 0.99% and 0.24%, organ space SSI 1.72% and 1.79%, wound disruption 0.45% and 0.06%, pneumonia 0.43% and 0.24%, pulmonary embolism 0.08% in both open and lap groups, sepsis or septic shock 2.16% and 1.15%, bleeding 0.01 and 0.04% and UTIs 0.36% and 0.37%.

The long term follow-up of a RCT of open versus laparoscopic appendicectomy showed a 42.3% incidence of overall complications in the open surgery group versus 12.8% in the laparoscopic group, with wound-related complications as high as 30.77% versus 4.2%.\(^{22}\) After a mean follow-up of more than 9 years, 5.7% and 6.4% of patients, respectively, had adhesions or adhesion-related symptoms and 0.2% underwent another operation for adhesions. The risk of SBO after open appendectomy is between 0.33 and 1.51%.

Finally, it has been demonstrated that a history of perforated appendix in childhood does not seem to have long term negative consequences on female fertility. This may have important implications for the management of young women with suspected appendicitis as the liberal attitude to surgical exploration with a subsequently high rate of removal of a normal appendix is no longer justified by a perceived increased risk of infertility after perforation.\(^{23}\)

In addition, a liberal attitude to exploration among patients with suspected appendicitis does not prevent perforations.\(^{24}\)

Hansson et al.\(^{16}\) conducted a RCT investigating the efficacy of conservative treatment compared to surgery for acute appendicitis. They reported that conservative treatment with antibiotics was efficacious in 91% of cases, with a 14% relapse rate at 12-month follow-up. One third of relapses occurred within the first 10 days of hospital discharge, while most of the remaining two thirds occurred between 3 and 16 months following discharge. The rates of minor complications such as diarrhoea, vomiting and nosocomial infections were similar among patients treated conservatively and those treated surgically. The incidence of major complications such as appendiceal abscess, paralytic ileus and pulmonary embolism, however, was significantly higher in those treated surgically (p<0.05).

A recent prospective randomised study conducted by Malik A and colleagues\(^{1}\) compared antibiotic therapy to appendicectomy in acute appendicitis. The authors reported that conservative treatment was not only safe
and efficacious, but also caused the patients less pain than surgery, reducing the need for analgesia (p<0.001). Ten per cent of conservatively treated patients relapsed within 12 months of discharge.

A multicentre randomised trial conducted in Sweden yielded similar results: the rate of relapse in antibiotic treated patients was 14% at 1 year after discharge. Interestingly, this was equal to the rate of postoperative complications in patients treated surgically.

Based on these reports, with the diagnostic accuracy of acute appendicitis being as high as 71%—87% with a combination of modern preoperative investigations, conservative treatment with antibiotics seems to valid for cases of suspected or probable/proven acute appendicitis. Relapse rate is low and complications are no higher than the rate of surgical complications.

RATIONALE
Case control studies that randomly assign patients with suspected acute appendicitis to either surgical or non-surgical treatment show a relapse rate of approximately 14% at 1 year. It would, therefore, be useful to determine the relapse rate of patients treated according to the results of a thorough clinical evaluation, including physical examination and laboratory results (all characteristics used to determine the Alvarado score as well as radiological evaluation. Imaging such as ultrasound may be helpful but is not usually necessary in diagnosing acute appendicitis and deciding its further treatment (operative or non-operative). As the Alvarado and AIR scores are based only on clinical and laboratory characteristics, only clinical signs and symptoms and laboratory values are routinely evaluated in patient with suspected acute appendicitis. If this clinical evaluation is effective, we would expect patient selection to be better than chance, and the relapse rate to be below 14%. Once we have established the utility of this evaluation, we can begin to identify those components that have predictive value (such as blood chemistry analysis or CT findings). This would be a first step towards developing an accurate diagnostic—therapeutic algorithm which could be used to avoid the risks and costs of needless surgery.

Much research into the cause of diseases relies on cohort, case—control or cross-sectional studies. Observational studies also have a role in research into the benefits and harms of medical interventions. Randomised trials cannot answer all important questions about a given intervention. For example, observational studies are more suitable for detecting rare or late adverse effects of treatments, and are more likely to provide an indication of what is achieved in daily medical practice.

STATISTICAL ANALYSIS
Data will be entered into a spreadsheet using Epi-Info (v 6.04d, Centers for Disease Control and Prevention) and analysed using SPSS software (v 15.0, SPSS). Descriptive statistics will be reported as mean and SD for normally distributed variables and median and IQR for variables not normally distributed. The 2 analysis of variance will be used to compare differences for categorical variables. ORs with 95% CIs will be calculated. Student’s paired sample t test will be used to compare mean differences between continuous variables. The Mann—Whitney U test will be used to compare non-
parametric continuous variables (eg, age, white cell count). Statistical significance will be defined as \( p < 0.05 \). Variables with clinically relevant cut-off points will be dichotomised.

In order to determine independent predictors of the short and long term efficacy of antibiotic treatment (in terms of failure rate of conservative treatment, recurrence rate of clinical episodes of acute appendicitis and definite improvement without need for surgery within 1 year of follow-up) in the general study population, numerous variables will be assessed including demographic characteristics (sex, age), clinical features (past medical history, gynaecological status, IBD history), clinical status (body temperature), laboratory studies (white cell count, neutrophils count, C reactive protein), whether or not empiric antibiotics were previously administered, and time to administration and duration of treatment with amoxicillin and clavulanic acid.

Univariate analyses will be used to identify which variables with a \( p \) value less than 0.20 should be included in the multivariate models. Stepwise backward logistic regression will be used to determine whether these covariates are independent predictors of treatment efficacy; covariates will be eliminated when \( p \) values are greater than or equal to 0.05.

The same methods will be used to assess predictors of abdominal pain after discharge, length of hospital stay, number of outpatient clinic follow-up appointments and sick leave.

Finally, cost analysis will be carried out on antibiotic course, length of hospital stay, outpatient clinic follow-up appointments and sick leave days.

**STUDY OBJECTIVES**

**Main objective**

The main objective is to evaluate the outcome of patients treated conservatively and assess the reliability of the initial clinical evaluation in predicting which conservatively-treated patients should have been treated surgically.

The primary outcomes are:

1. Short term efficacy of antibiotic treatment: failure of conservative treatment with 7 days of amoxicillin and clavulanic acid therapy, defined as readmission due to lack of clinical improvement and/or worsening abdominal pain and/or localised/diffuse peritonitis.

2. Long term efficacy of antibiotic treatment: efficacy of antibiotic therapy for acute appendicitis defined as incidence of recurrences of clinical episodes of appendicitis up to follow-up at 1 year (at 7 days, 15 days, 6 months, 1 year).

3. Long term efficacy of antibiotic treatment (no need for surgery): efficacy of antibiotic therapy for acute appendicitis defined as definite improvement without the need for surgery up to follow-up at 1 year (at 7 days, 15 days, 6 months, 1 year).

4. Safety of antibiotic treatment: major side effects/drug- or treatment-related complications (ie, allergy or other treatment-related complications such as abscess formation).

The secondary outcomes are:

1. Minor complications: minor side effects/drug- or treatment-related complications (ie, bloating, diarrhoea, flatulence, headache, heartburn, nausea and vomiting) (at 7 days, 15 days).

2. Abdominal pain after discharge: assessment of abdominal pain/discomfort evaluated by means of a numerical rating scale (at 7 days, 15 days).

3. Length of hospital stay: length of clinical observation as an inpatient for non-operated patients.

4. Outpatient clinic follow-up: number of follow-up appointments scheduled in the outpatient clinic.

5. Sick leave: number of days of sick leave needed by the patient.

6. Cost analysis: analysis of the costs of antibiotics, length of hospital stay, outpatient clinic follow-up appointments and sick leave days.

**Secondary objective**

An additional objective is to identify clinical, laboratory and imaging findings that are predictive of failure of conservative treatment and/or relapse of appendicitis and need for appendectomy within 1 year.

**STUDY DESIGN**

This is a single cohort prospective non-randomised observational study. No experimental interventions or treatments will be employed beyond routine clinical care.

A flowchart of the study is given in figure 2 and a tempogram showing the study steps is given in figure 1.
ESTIMATED ENROLMENT AND STUDY DATES
The estimated sample size of the study population is 160 patients in 1 year, which is the average number of patients assessed annually by the emergency surgical team in our hospital for suspected acute appendicitis, conservatively treated with antibiotics and observed. The crude incidence of acute appendicitis is 86 per 100 000 inhabitants per year, varying between 74 and 96 per 100 000 during a 5-year period in Norway in an urban and rural catchment area with 265 000 inhabitants. A peak incidence of acute appendicitis was found in patients 13–40 years of age, with more males than females in this age group (ratio 1.34:1.00). Among young children and the elderly, significantly (p=0.002) more females had acute appendicitis.29 A further paper reported the incidence of appendicitis to be about 100 per 100 000 person-years in Europe/America.30

The appendectomy rate continues to decrease, although the incidence of appendicitis is now nearly stable and the incidence of perforated appendicitis has not changed (approximately 20 per 100 000 person-years) over the last 30 years. These data suggest the rate of surgery for acute appendicitis is decreasing in an attempt to avoid unnecessary appendectomies.

The catchment population of Bologna is half a million people. Maggiore Hospital is the largest hospital in the city and covers the northern area. The numbers of patients aged over 14 years admitted to the emergency department with right iliac fossa pain and/or suspected appendicitis have been monitored for the last 3 years and range from 328 to 443 cases/year.

The study start date is January 2010, the estimated study completion date is December 2010 and the estimated primary date of completion of follow-up is December 2011 (the final data collection date for all primary outcome measures and 1 year follow-up).

INCLUSION AND EXCLUSION CRITERIA
Any patient, male or female, above the age of 14 years (non-paediatric), who returns for a follow-up visit 5 days after an emergency department visit and consents to participation between 1 January 2010 and 31 December 2010 will be eligible for inclusion in the study.

Specifically, the inclusion criteria are:
1. Age >14 years
2. Lower/right iliac fossa abdominal pain
3. Clinical suspicion of acute appendicitis, that is:
   - Alvarado score 5–6 (equivocal for acute appendicitis)
   - Alvarado score 7–8 (probable appendicitis)
   - Alvarado score 9–10 (highly probable appendicitis)
4. Informed consent (patient or legal representative).

Figure 2 CONSORT 2010 flow diagram.
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| **Title and abstract** | 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract  
(b) Provide in the abstract an informative and balanced summary of what was done what was found | 2–3 |
| **Introduction** | 2 | Explain the scientific background and rationale for the investigation being reported | 5–10 |
| **Objectives** | 3 | State specific objectives, including any prespecified hypotheses | 12–14 |
| **Methods** | 4 | Present key elements of study design early in the paper | 14 |
| **Setting** | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 10–11/14–16 |
| **Participants** | 6 | (a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
(b) For matched studies, give matching criteria and the number of controls per case | 15 |
| **Variables** | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 10–11/12–14 |
| **Data sources/measurement** | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 11–12 |
| **Bias** | 9 | Describe any efforts to address potential sources of bias | 4 |
| **Study size** | 10 | Explain how the study size was arrived at | 14 |
| **Quantitative variables** | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 11–12 |
| **Statistical methods** | 12 | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) If applicable, explain how matching of cases and controls was addressed  
(e) Describe any sensitivity analyses | 11–12 |
| **Results** | 13* | (a) Report numbers of individuals at each stage of study—for example, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
(b) Give reasons for non-participation at each stage | Not yet applicable |
| **Descriptive data** | 14* | (a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders  
(b) Indicate number of participants with missing data for each variable of interest | Not yet applicable |

Continued
Exclusion criteria are:
1. Diffuse peritonitis
2. Antibiotic (penicillin) documented allergy
3. Ongoing previously commenced antibiotic therapy
4. Previous appendectomy
5. Positive pregnancy test
6. IBD history or suspicion of IBD reoccurrence.

Follow-up assessment will be by telephone interview (or email). No interviewer training will be necessary as the surgeons conducting the study will also conduct the phone interviews. Informed consent will be obtained from the patient (or guardian) before enrolling him/her in the study. Confidentiality of personal and health information will be guaranteed and will only be accessible to the surgeons responsible for the study. Members of the project management team are as follows: study chair: Gregorio Tugnoli, MD; principal investigators: Salomone Di Saverio MD, Eleonora Giorgini MD, Nicola Antonacci, Andrea Biscardi, MD, Nicola Clemente MD and Silvia Villani MD. The over-seeing authority is the Bologna Local Health District Ethics Committee (approval number CE 09079). The study follows the recommendations of the Declaration of Helsinki and conforms with the accepted best practice guidelines of the STROBE statement for observational studies (cohort, case-control or cross-sectional designs) (table 1).

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**Acknowledgements** The authors would like to acknowledge the head of the Department of Emergency of the Bologna Local Health District, Dr Giovanni

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### Table 1 Continued

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<td>Outcome data</td>
<td>Report numbers in each exposure category, or summary measures of exposure</td>
<td>Not yet applicable</td>
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<tr>
<td>Main results</td>
<td><em>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% CI). Make clear which confounders were adjusted for and why they were included</em>&lt;br&gt;<em>(b) Report category boundaries when continuous variables were categorized</em>&lt;br&gt;<em>(c) If relevant, consider translating estimates of RR into absolute risk for a meaningful time period</em></td>
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<tr>
<td>Other analyses</td>
<td>Report other analyses done—for example, analyses of subgroups and interactions, and sensitivity analyses</td>
<td>Not yet applicable</td>
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<tr>
<td>Discussion</td>
<td>Summarise key results with reference to study objectives</td>
<td>Not yet applicable</td>
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<tr>
<td>Limitations</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
<td>Not yet applicable</td>
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<tr>
<td>Interpretation</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
<td>Not yet applicable</td>
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<td>Generalisability</td>
<td>Discuss the generalisability (external validity) of the study results</td>
<td>Not yet applicable</td>
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<td>Other information</td>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based</td>
<td>Not yet applicable</td>
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org/*
Gordini MD, MPH for his support for the study and advice on public health policy. The authors would also like to acknowledge SIPAD (Società Italiana Patologia Apparato Digerente - Italian Society for Digestive Diseases) for acting as patron of the study.

Competing interests None.

Ethics approval Ethical Review Board of Maggiore Hospital - Bologna Local health district.

Contributors GT, EG, SDS contributed to the conception and design of the study, acquisition of data, and analysis and interpretation of data. SDS drafted the manuscript and revised it critically for important intellectual content. GT, NA, EG and SDS conceived the study, participated in its design and coordination and helped draft the manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

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*BMJ Open* 2011 1: originally published online February 23, 2011
doi: 10.1136/bmjopen-2010-000006
Notes

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