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ORIGINAL ARTICLE

Acute Appendicitis in the Adult Population: Modelled Decision Analysis Supports a Conservative Approach

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Abstract
Introduction Acute appendicitis represents the commonest cause of acute intra-abdominal pathology. Appendectomy and antibiotics are the mainstay of therapy for appendicitis. Evidence is emerging that antibiotics alone may adequately treat most cases of appendicitis. Decision analysis is a quantitative method of examining alternate treatment strategies. This study describes a modelled decision analysis comparing operative and conservative management of appendicitis.
Methods The base case patient is a healthy, 23-year-old male presenting with migratory pain to the right iliac fossa (RIF) and elevated inflammatory markers. A decision tree was constructed comparing operative and conservative treatment. Rates of complications, failure of conservative therapy, recurrence and utilities were calculated via a systematic literature review. Variables were tested for sensitivity.
Results Overall, conservative management gives a significantly better outcome (51.51 vs 49.87 QALYs). Three variables proved sensitive. Once operative complication rates are lower than 11.5 %, surgical treatment becomes the optimal strategy. If rates of failure of conservative management exceed 12.9 %, surgery becomes optimal. If the utility assigned to a post-operative complication exceeds 0.44, surgery becomes optimal.
Conclusions This decision analysis supports a conservative strategy, albeit with caveats. If operative complications are low or rates of failure of conservative management remain high, surgery is the preferable strategy.

Keywords Acute appendicitis · Decision analysis · Conservative management

Introduction

Acute appendicitis is one of the commonest pathologies encountered by the general surgeon. Operative treatment of appendicitis has been the therapeutic standard for more than a century.[1] Although a proportion of surgeons still perform open appendectomy as the operation of choice,[2] laparoscopic appendectomy is safe, even in complicated appendicitis and may provide a small reduction in overall length of stay, although definitive evidence is lacking.[3,4] In spite of this, there remain significant risks associated with surgical management of appendicitis, including a long-term risk of adhesions leading to small bowel obstruction[5] as well as a risk of perioperative mortality. Furthermore, negative appendectomy carries with it an unacceptably high risk of complications, including the risk of operative re-intervention.[6] Although the idea of treating appendicitis non-operatively with antibiotics is not new, there has been a resurgence in interest in recent years, with a number of studies suggesting that non-operative management of appendicitis is feasible and may be more cost-effective than surgical intervention.[1,7–11] There remains a risk of recurrent appendicitis, however, and there is yet no consensus on whether conservative management should be in selected patients or if it is feasible to treat unselected patients with a conservative approach.[1]

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Although there is a significant body of evidence supporting conservative management of appendicitis, these studies make at most a cursory acknowledgement of how the disease impacts on patients, particularly from the perspective of quality of life. Decision analysis is a quantitative method for assessing the efficacy of different therapeutic strategies when there remains a degree of uncertainty about the optimal strategy.[12] The aim of this study was to model possible outcomes for conservative or operative management of appendicitis from the patient's perspective. As well as providing an estimate of which treatment strategy is favourable overall, decision analysis allows us to determine which variables significantly influence the optimal management strategy and determine under what conditions the optimal management strategy may shift from conservative to operative management or vice versa.

Methods

A modelled decision analysis was performed to determine the optimal management strategy. Two competing strategies were analysed: operative management and conservative management with intravenous antibiotics without a planned interval appendectomy. Decision analysis was performed as per published guidelines.[13–17]

The base case patient is a 23-year-old male presenting with a 36-h history of abdominal pain. This was chosen as representative of a typical adult patient presenting with appendicitis. He has no previous medical history. Pain began centrally before radiating to the right iliac fossa (RIF). Inflammatory markers are raised (WCC 12.5×10^3, CRP 55). On examination, his abdomen is soft, with tenderness to palpation and rebound tenderness in the RIF. A clinical diagnosis of acute appendicitis is made, and no imaging investigations are performed.

Parameters studied in decision analyses are based on published literature. A PubMed search was performed to identify articles published from 1 January 2000 to 31 March 2015 comparing operative and conservative treatment strategies for managing acute appendicitis. The search terms 'acute appendicitis', 'appendicectomy', 'appendectomy', 'antibiotics', 'conservative' and 'trial' were used in combination with the Boolean operators AND and OR. Articles identified were critically appraised by two authors independently (JCB and MEK), and papers were selected based on guidelines for including studies in decision analyses.[16] Variables included were post-operative complication rates, post-operative complications needing surgical management, rates of failure of conservative management, rates of recurrence following conservative management and rates of mortality. A weighted mean was calculated for each variable based on the number of patients included in each study. Studies included are outlined in Table 1. The highest and lowest reported figures for each variable were used for sensitivity analysis (Table 2).

A utility is the measure of the decision-maker's relative preference for a specific outcome,[16] expressed as a numerical value between 0 and 1. 0 and 1 are used as 'anchor states', where 0=death and 1=alive in full health. Utilities for other health states are then estimated based on published criteria or based on previously published decision analyses.[18] For utilities determined by expert opinion, a wide range of possible values are used for sensitivity analysis to ensure all possibilities are adequately explored. Utility estimates are represented in Table 3. Utilities are then used to calculate quality-adjusted life years (QALY) for each outcome in the decision tree as per published guidelines.[16] The time spent in each healthcare state for this study was based on values gathered from the literature review. Length of hospital stay was assumed to be 3 days for appendicitis treated either operatively or conservatively.[1,9,19] Standard recovery post-discharge was estimated at 10 days.[1,9] For those patients who developed a complication, total hospital stay was estimated at 10 days.[1,7] Patients who failed initial conservative therapy were assumed to have had a 2-day trial before progressing to operative management.[1] QALYs were estimated based on time spent in these healthcare states.

A decision tree was constructed using TreeAge Pro (TreeAge Software, Inc.). This tree examines possible outcomes following either conservative or operative management

Table 1 Characteristics and conclusions from papers included in calculating input variables for decision analysis

Paper	Number of patients	Methodology	Conclusions
Hansson et al.[1]	369	Prospective RCT: antibiotics vs appendectomy	Non-operative management favourable
Oliak et al.[7]	77	Retrospective review: non-operative management perforated appendicitis	Non-operative feasible
Park et al.[8]	278	Prospective non-randomised: antibiotics vs appendectomy, diameter <10 mm	Non-operative feasible
Styrud et al.[9]	252	Prospective RCT: antibiotics vs appendectomy	Non-operative feasible, risk of recurrence/complications needs to be explored
Tingstedt et al.[10]	93	Retrospective review: antibiotics vs appendectomy	Non-operative feasible
Vons et al.[11]	243	Prospective RCT: antibiotics vs appendectomy uncomplicated appendicitis	Non-operative management non-inferior

Table 2 Variables included in the study

Variable	Weighted mean	Range	References	Sensitive	Threshold
Operative complications	15.63 %	2.5–48 %	1, 7–11	Y	11.5 %
Re-operation	1.86 %	1.6–2 %	1, 7	N	N/A
Failed conservative management	9.35 %	5–13 %	1, 7–9, 11	Y	12.9 %
Recurrence post conservative management	15.05 %	6.5–25 %	1, 7–9, 11	N	N/A
Mortality	0.1 %	0.09–0.15 %	19	N	N/A

Weighted means were calculated for each variable, and the plausible range based on published literature is represented. Threshold values for sensitive variables are given

of the base case patient (Fig. 1). Complications considered were those that have a significant impact on quality of life, including wound infection, dehiscence, intra-abdominal abscess, small bowel obstruction and cardiac/respiratory compromise.

Sensitivity analysis is the process of repeatedly analysing the decision tree, using different values to determine how they affect the outcome of interest. One-way sensitivity analysis was performed for all variables included in the model. This investigates the robustness of our base case estimates and determines how they impact on the optimal management technique. If the management strategy did not change with manipulation of a variable, it was considered not sensitive. If the manipulation of a variable changed the optimal strategy, this was considered a sensitive variable and was included in subsequent two-way and three-way sensitivity analysis.

Results

Six papers were identified in the literature review that adequately reported on outcomes following operative or conservative management of appendicitis in the adult population. These included three randomised controlled trials,[1,9,11] one prospective non-randomised trial[8] and two retrospective studies.[7,10] These collectively describe 1377 patients; 40.6 % (n=560) were treated conservatively. Mortality estimates were based on a retrospective analysis of national data from the USA.[20]

Table 3 Estimates of utilities and thresholds from one-way sensitivity analysis

Utility	Value	Range	References	Sensitive	Threshold
Well	1.0	–	–	N/A	N/A
Operation	0.15	0–0.65	12, 18	N	N/A
Post-op state	0.25	0–0.77	12, 18	N	N/A
Post-op complication	0.2	0–0.65	12	Y	0.44
Re-operation	0.15	0–0.65	12, 18	N	N/A
Mortality	0		–	N/A	N/A

Utility estimates are based on published literature. Where utilities are sensitive, threshold values are given

The base case analysis showed that overall, the conservative approach gave a QALY pay-off of 51.51 QALYs as compared with 49.87 for the operative approach. There was no difference in QALY pay-off when the patient recovers fully with no complications following either operative or conservative management (56.99 QALYs for either strategy). The differences in pay-offs are due to the likelihood of enduring a complication and the subsequent effect that will have on quality of life.

The results of the one-way sensitivity analysis are presented in Tables 2 and 3, along with the corresponding threshold values. Three variables proved sensitive in the model: rates of operative complication, rates of failure of conservative management and the utility assigned to a surgical complication (how that complication impacts on quality of life).

Once the rate of post-operative complications is less than 11.5 % of patients, operative management becomes the optimal strategy (Fig. 2a). If the likelihood of conservative management failing on the index admission exceeds 12.9 %, operative management becomes the optimal strategy (Fig. 2b). If the quality of life (utility) assigned to a surgical complication exceeds 0.44, operative strategy becomes the optimal treatment (Fig. 2c).

Three-way sensitivity analysis is represented in Fig. 3. When complications are at the lowest plausible range (2.5 %) and failure of conservative management and the utility of complications are kept at their baseline value, operative strategy is the optimal management (Fig. 3a). The maximum plausible value for post-operative complications where operative management is the optimal strategy is 30 %. This depends on failure of conservative management and the utility of the post-operative state being at the maximum of their plausible ranges. When the chance of failure of conservative management is at its baseline, operative management becomes the optimal management strategy once the complication rate is less than 19 %, with a maximum utility value for the utility of complications. When the chance of failure of conservative management is at its lowest plausible range (5 %), operative strategy is the optimal strategy once complication rates are

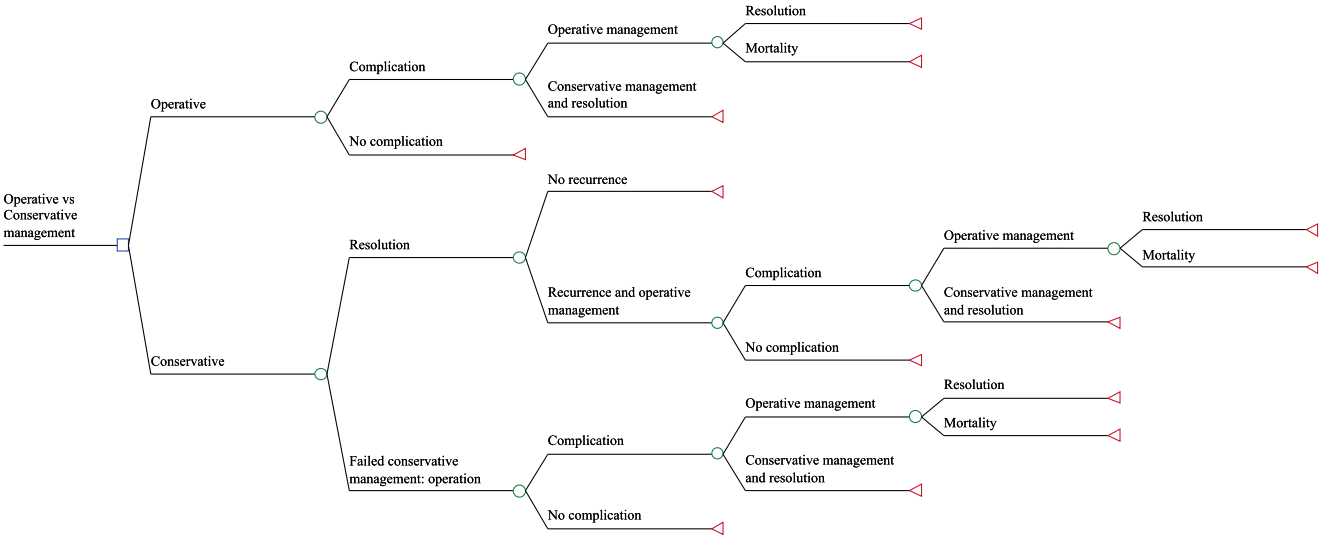

Fig. 1 Decision tree used in analysis

less than 8 % and the utility of complications is greater than 0.44. When the utility of complications is at the lowest plausible value, operative management is the optimal strategy once the complication rate is less than 5 % and the chance of failure of conservative management is 5 %.

Discussion

There remains considerable debate around the issue of conservative management of appendicitis. This modelled decision analysis examines different therapeutic strategies from the patient's perspective. In this case, we have used a base-case of a fit and healthy 23-year-old male, with a life expectancy of 80 years presenting with clinical evidence of acute appendicitis. This base-case patient was chosen to reflect a typical case presenting to our institution. The reasons behind this are twofold. Firstly, the median age of presentation of acute appendicitis is in the third decade.[21] Secondly, in young healthy patients, a diagnosis of acute appendicitis can be made with confidence based on clinical history and examination, reserving imaging for cases of diagnostic uncertainty.[22] This is the type of unselected patient with acute appendicitis who may benefit from conservative therapy, even in the context of a perforated appendicitis.[1] When all values in the decision analysis are at their baseline, the decision analysis supports the use of conservative management in this case. This takes into account the risk of failed conservative management and recurrence of appendicitis requiring eventual operative management. In this case, we have deliberately chosen a patient who has presented with a clinical picture highly suggestive of acute appendicitis who has not undergone imaging. Although some recommend routine use of CT scanning for all cases of suspected appendicitis,[11] others maintain that compared to clinical examination and clinical scoring algorithms, radiological investigations are a less good predictor of appendicitis.[23] We felt that the addition of a radiological element to this analysis would add a potential confounding factor. Furthermore, concerns remain about radiation exposure linked to CT use, although these are reducing with evidence that low radiation dose CTs may adequately visualise the appendix.[24]

Although our initial analysis supports conservative management of acute appendicitis, as with any modelled decision analysis, the interpretation of results is of vital importance in understanding how the interplay of different variables influences outcomes. This analysis has shown that three variables influence the treatment strategy.

The first sensitive variable is complication rates in patients undergoing appendectomy. There is a wide variation in reported complication rates, from a low of 2.5 up to 48 %.[5,10,11] There is no definitive evidence that there is a difference in complications between open and laparoscopic appendectomy.[25] One-way sensitivity analysis suggests that from the patient's perspective, once the likelihood of complications drops below 11.5 %, operative management is the optimal strategy. The threshold for complication rates in this context is very important in shaping policy decisions. Although the weighted mean seems high, with just over 15 % of patients suffering a post-operative complication, this is based on a number of recent studies. The authors feel that if institutions can demonstrate with robust audit data that their complication rate is well below the threshold value, then adopting an operative management strategy may be justified. It is however important to consider this finding in the context of the other sensitive variables highlighted in this model.

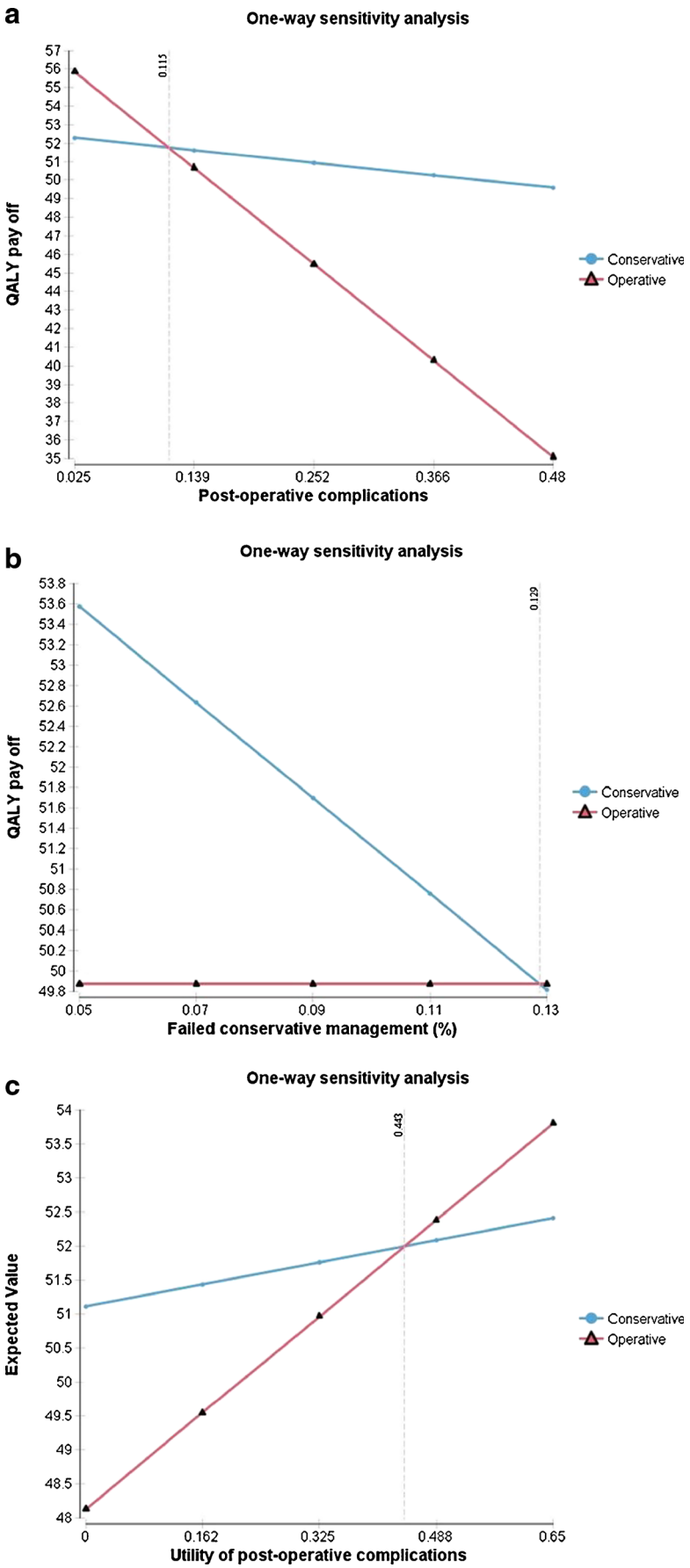

Fig. 2 **a** One-way sensitivity analysis of complication rates shows threshold value of 11.5 %. **b** One-way sensitivity analysis of chance of failed conservative management shows threshold of 12.9 %. **c** One-way sensitivity analysis shows utility of post-op complications with a threshold of 0.44

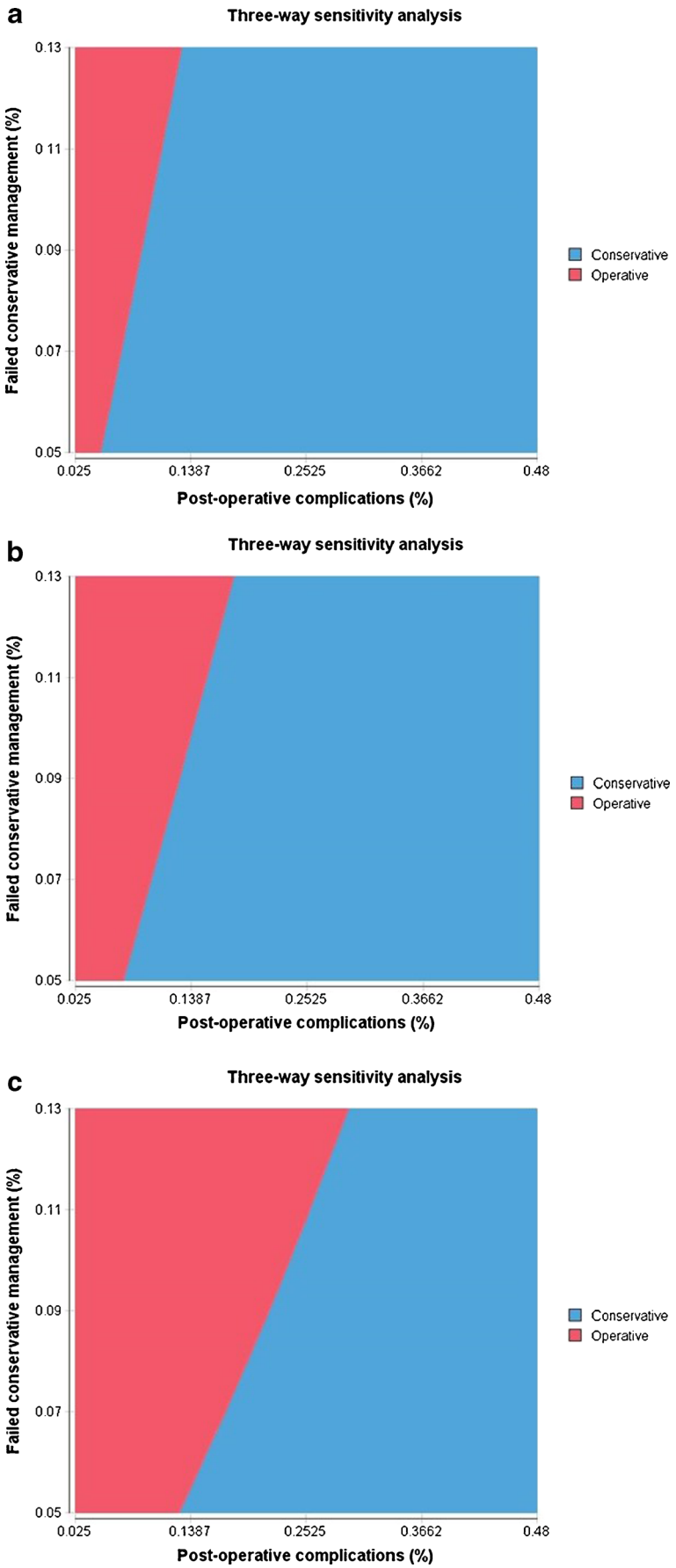

Fig. 3 **a** Three-way sensitivity analysis with utility of complications at 0.1. **b** Three-way sensitivity analysis with utility of complications at 0.375. **c** Three-way sensitivity analysis with utility of complications at 0.65

The second sensitive variable is the risk of failure of conservative management. There is again a wide variation in reported rates of failure in the published literature.[1,7–9,11] All of the quoted studies are supportive of conservative management of appendicitis, so it is not unreasonable to suggest that there may be a publication bias and that the real incidence of failed conservative management may in fact be higher than that estimated in this study. Our one-way sensitivity analysis suggests that if the rate of failure of conservative management exceeds 12.9 %, operative management becomes the optimal strategy. For the purpose of this model, we have defined a failure as progression to surgical treatment within 3 days of commencing conservative treatment due to a failure to respond. One RCT suggested that conservative management can be considered to have failed if there is no improvement in symptoms within 24 h,[9] while others suggest failure as a recurrence of symptoms or operative intervention within 30 days of the index admission.[1,11] Of those who present with recurrence, there appears to be a trend towards a recurrence being a relatively early event. Hansson et al. reported that one third of recurrences occurred within 10 days of initial discharge, with the remainder occurring between 3 and 16 months following treatment.[1] These early recurrences may represent failed initial management rather than true recurrences. Oliak reports that the majority of recurrences occur between 3 and 6 months.[7] Although there is no study giving a life-long risk of recurrence of appendicitis, it appears that recurrent appendicitis appears to be a relatively early event. Of note, the risk of recurrence following a successful trial of conservative management was not a sensitive variable. The weighted mean was estimated at 15 %, with a plausible range from 6.5 to 25 %. On further probing our model, the threshold value for this variable to influence outcomes is a recurrence rate of 40.3 %. If rates of recurrence were indeed this high in clinical practice, the authors feel that this would render a conservative management strategy untenable in most patients.

The third sensitive variable was the utility assigned to a surgical complication. This is a measure of the quality of life experienced following a surgical complication. There is no published utility value specifically looking at this condition for acute appendicitis. The estimate in this study was based on that used in a previous surgical decision analysis examining management strategies for diverticular peritonitis.[12] A broad range of plausible values were tested to adequately determine how this utility may affect the outcome of this decision analysis. It must be remembered that even when validated models are used to predict utilities, they remain estimates. In this decision analysis, when the quality of life (utility) assigned to a surgical complication exceeds 0.44, operative management becomes the optimal strategy. In essence, if the impact of a complication on quality of life is substantially less than that considered the baseline value, operative management may in fact be the optimal strategy. The utility estimates used in this study were based on previously published studies.[12,18] However, there will always be an element of subjectivity in terms of how patients assess their quality of life following a complication. Our model is based on the best available estimates, but if patients find that their quality of life is not impacted as severely as we believe by complications, this may favour an operative strategy.

Three-way sensitivity analysis allows us to examine how alterations in these variables can lead to changes in the optimal strategy. Although one-way sensitivity analysis suggests that complication rates need to be less than 11.5 % for operative management to be the optimal treatment, the model in fact accepts a complication rate of up to 30 % so long as the rate of failed conservative management and the utility of post-operative complications are at the upper range of plausible values. Similarly, even with low rates of failed conservative management, operative management can remain the optimal strategy as long as complication rates are low and the utility of complications is high. Furthermore, even if the utility of complications is at the lowest estimated value, operative management can remain the optimal strategy once complication rates are less that approximately 5 %.

The interplay of these variables has implications for the management of acute appendicitis. If complication rates in an institution are high and there is a low rate of failed conservative management of appendicitis, it is clear that non-operative management is an acceptable management strategy. If however complication rates are very low, operative management gives the patient the lowest impact in terms of quality of life. Furthermore, if complications impact less on patients' quality of life than we fear, operative management may in fact offer the best outcome for individual patients. The challenge that the authors notes is how to tailor this to individualised patient care. Hansson et al. found no significant difference between patients failing conservative therapy and those responding to antibiotic treatment.[1] Di Saverio et al. however reported that the Alvarado score and Andersson score may predict the failure of conservative management.[23] Others have found that haematological parameters such as neutrophil-lymphocyte ratio (NLR) may be accurate predictors of severity of appendicitis.[26]

A potential limitation of decision analysis lies in the data used to derive the values included in the analysis. This is consistent with systematic reviews and meta-analyses in this area, which suggest a high likelihood of selection bias.[27] One of the strengths of a decision analysis however is the ability to test the sensitivity of variables within the reported ranges. This allows a better

understanding of which variables influence outcome and at what thresholds. The other potential limitation is in the use of utilities as estimates of healthcare states. Although the utilities used here are based on previously published studies, patient perceptions of their specific healthcare states can widely vary. This is particularly true when it comes to the area of complications. What one patient may find to be a major inconvenience may not affect another patient to nearly the same degree. Again, this can be compensated for by using a wide variety of values in the sensitivity analysis.

To our knowledge, this is the first study to use a decision analysis to compare outcomes for operative and conservative management of acute appendicitis. Using published data, we have constructed a robust model featuring a number of sensitive variables. We have shown that the three key issues when deciding between operative or conservative management are the risk of post-operative complications, the rates of failed conservative management and patient perception around having a post-operative complication. This analysis supports the use of conservative management in the adult population based on the values published in the surgical literature. However, we have also shown that in certain circumstances, operative management may still be the optimal intervention. We believe that this may assist policy formation within institutions as to the optimal approach to acute appendicitis.

Conclusion

The optimal management of acute appendicitis remains challenging. Conservative management is feasible and desirable in circumstances where there is a low likelihood of failure or a high chance of post-operative complications. However, if there is a high risk of failure of conservative management, operative intervention should be the treatment of choice. This paper will help guide decision making in individual institutions based on local audit data.

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