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# The Human Appendix and Antibiotics: Choice and Beneficence

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## 1 | Introduction

The surgical removal of the appendix has been practiced for more than a hundred years. During this time, improvements in surgical technique, anaesthesia and hospital systems, allied with an increasingly knowledgeable public, have produced remarkable benefits.

Recently, Non-Operative Management (NOMA) of some forms of appendicitis with antibiotics has attracted interest and the guarded support of Surgical Societies and Guidelines [1–3].

The biology of the human appendix is incompletely understood, and there is growing awareness that it may not be a mere evolutionary vestige [4, 5]. The consequences of appendectomy, despite the surgical experience of a hundred years, are unclear, as is the impact of antibiotics on the inflamed appendix and the gut.

## 2 | Not All Appendicitis Is Equal

The work of Andersson has brought the difference between perforating appendicitis (complicated appendicitis [CA]) and non-perforating appendicitis (uncomplicated appendicitis [UA]) to recent surgical attention [6]. This understanding was reinforced during the COVID-19 pandemic when mild disease did not present to hospital [7, 8].

The historical record showed that this was widely known and understood (Figure 1) [9]. Over a hundred years ago, senior

clinicians including McBurney [10], Treves [11], Fitz [12], Osler [13, 14] and Short [15], amongst others, all commented on this and incorporated ‘NOMA’ into treatment strategies. By the first decades of the 20th century, this was rapidly subsumed by the belief that early operation on all patients with appendicitis prevented perforation and thus mortality.

The trend of the population mortality of appendicitis in North America to 1950 is summarised in Figure 2 [16]. What role did antibiotics play?

To quote the author Wangenstein, ‘It is obvious from a glance at the figure, and at the fall of the mortality of appendicitis that penicillin was not an important factor in the decline. The precipitous fall in the mortality occurred between 1940 and 1942. Penicillin was not available to civilian hospitals in this country until the Spring of 1944, by which time the slope of the fall had flattened considerably [16]’. This is a surgical achievement.

## 3 | The Inflammatory Biology of Appendicitis

In CA a virulent inflammatory reaction causing gangrene and necrosis [17–19] allows gut bacteria to escape from the lumen into the peritoneal cavity and is a clear indication for antibiotics. Histological examination of appendectomy specimens from acute cases contrasted with interval appendectomy suggests that the acute inflammatory process changes to chronic and granulomatous inflammation in delayed appendectomy, supporting an effect of antibiotics in modulating the anti-bacterial process [20], though morphological restoration may not occur.

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TABLE 21  
The London Hospital (1920–29)

Classes.	Cases.		Deaths.		Case fatality per cent.	
	M.	F.	M.	F.	M.	F.
Appendicitis, acute ..	3,156	2,387	93	59	2.9	2.5
Appendicitis with diffuse peritonitis.	451	311	130	68	28.8	21.9
Appendicitis with abscess	557	439	38	29	6.8	6.6
Total, acute ..	4,164	3,137	261	156	6.2	5.0
Appendicitis, sub-acute, recurrent and chronic.	830	1,151	4	9	0.5	0.8
Total .. ..	4,994	4,288	265	165	5.3	3.8

St. Thomas's Hospital (1920–29)

Classes.	Cases.		Deaths.		Case fatality per cent.	
	M.	F.	M.	F.	M.	F.
Appendicitis, acute ..	1,214	822	39	24	3.2	2.9
Appendicitis with spreading peritonitis (1921–23 missing).	105	85	32	34	30.5	40.0
Appendicitis with abscess	151	98	11	5	7.3	5.1
Total, acute ..	1,470	1,005	82	63	5.6	6.3
Appendicitis, quiescent ..	507	669	3	3	0.6	0.4
Total .. ..	1,977	1,674	85	66	4.3	3.9

FIGURE 1 | Source: Young and Russell [9].

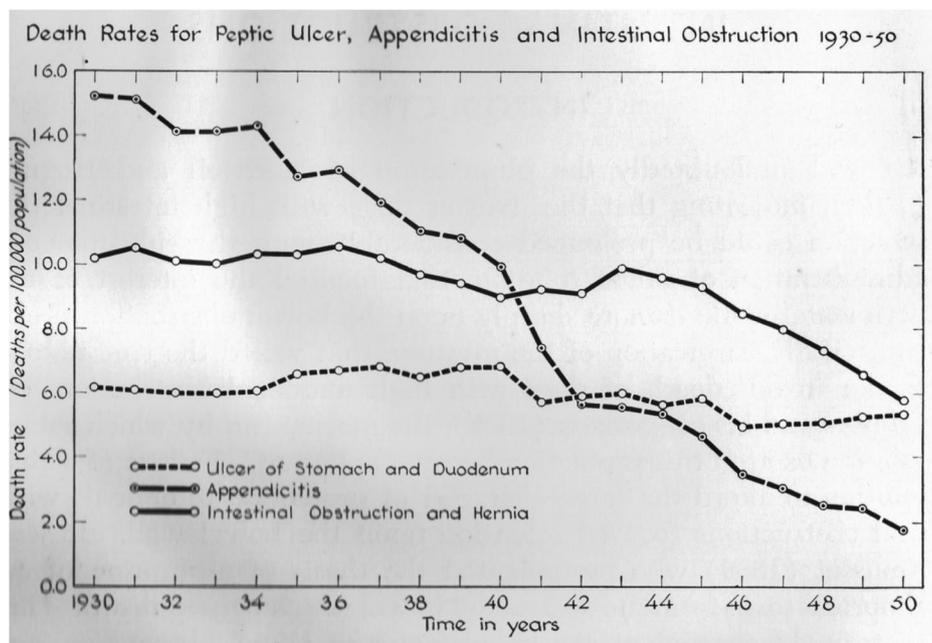


FIGURE 2 | Source: Wangenstein [16].

In UA a different allergic or antiviral reaction causes inflammation and resolution, without necrosis or bacterial escape [8, 21–25], and therefore no clear indication for antibiotics.

#### 4 | Is an Antibiotic Only Strategy Adequate for Treating Unselected Patients (Both CA and UA) With Appendicitis in Adults?

A summary of the available evidence of the treatment of ‘unselected’ adult patients with antibiotics for appendicitis is provided in Table 1.

While these studies make robust attempts to ensure that both classes of patients are included, inevitably participating surgeons would exclude CA patients with severe disease, shock and sepsis [26].

The Styurd study [27] shows a success rate of 72% at 1 year, and Hansson [28] builds on this 81%, with 70% having no long-term recurrences.

The experience of Coldrey (Table 1) [29] needs careful consideration. This paper published in 1959 was received with considerable reservation by the surgical profession in that era of ‘early appendectomy prevents perforation’.

The two groups for 1956, 1957, all treated with antibiotics alone without exception, totalled 334 patients 44 of whom came to early appendectomy, 14.4%. Abscesses were reported in a further 24, 7.2%. Overall failure and complication together amounted to 22% of unselected patients with appendicitis, though without mortality, treated by antibiotics and later surgical rescue. Long term follow up was not reported.

The early 1950s was a time when bacterial infections would have been highly susceptible to antibiotics. The repertoire of penicillin, streptomycin, chloramphenicol and terramycin that was available to Coldrey would have been potent. Seventy years later, that antibacterial potency is likely to have waned [1, 30].

The remarkable CODA [26] study invokes the spirit of Coldrey, but its exclusion criteria make it similar to the other non-inferiority studies of antibiotics in UA. Despite the recurrence rate of 29% at 90 days, this study was shown to be ‘non-inferior’ as the primary end point was a quality-of-life assessment at 1 month, rather than recurrence.

These studies, *while being mindful of their limitations and their exclusion of severe disease (apart from Coldrey)*, suggest that a policy of antibiotics alone in unselected adult patients (i.e., including both CA and UA) may succeed in up to four in five patients without surgery, with a *minority* requiring surgical rescue but the possibility of delayed recurrence. When antibiotic strategies are enforced, as on submarines [31, 32], similar response rates are reported. In austere environments and difficult situations, especially where small children are involved [33, 34], this may yet be an option.

#### 5 | Studies of Antibiotic Treatments of Children and Adults With UA

Selection of cases for study is based on clinical scoring systems, inflammatory markers on blood tests and imaging, though it may still lack precision. This process is well described [3, 26, 35].

The many excellent meta-analyses [36–39] available describe consistently the benefits of non-operative management in UA. These relate to cost, analgesic requirements, days off work, patient acceptability and quality of life assessments. Complications of surgery are well known.

Many of the clinical trials are designed as non-inferiority studies [35, 40–43] and where CA is excluded. Patients are recruited on the basis of ‘Shared Decision Making’ [1]. The largest of these shows [43] that antibiotics are about 75% as good as appendectomy [26, 44] in providing successful management and discharge of admissions for UA, while about 40% have their appendix removed within 5 years [45]. Failure of antibiotic treatment in these studies is a result of continuing or recurrent pain, perforation being rare.

These large and sophisticated trials tell us a great deal about appendicitis. A singular characteristic is the number of exclusions in patients judged eligible. In The Lancet Paediatric Trial, 10% of eligible patients were accepted for randomisation [35]. In CODA, this figure was 19% [26]. Despite this, early failure occurred in 16% of the antibiotic group, 34% in 1 year in *The Lancet* study and in 11% and 29% in 90 days in the CODA study. These numbers suggest that the adoption of NOMA outside these meticulous and well-supported studies may be hazardous, particularly in regional areas and developing nations.

Antibiotic treatments are based on the unlikely proposition that UA has a similar pathology and perforation risk as CA [46]. This suggests a ‘Category Mistake’ in the design of these trials. Antibiotics are being used empirically to treat a condition, UA, which does not produce gangrene, perforation, or bacterial peritonitis. There are now two methodologically satisfactory randomised controlled trials clearly demonstrating that antibiotics are not better than a placebo in managing UA [47, 48].

Gene expression studies enhanced by AI may soon become available, which will allow further diagnostic precision and differentiation between syndromes of appendicitis [21, 49] and should enhance further studies of NOMA.

#### 6 | What Are the Consequences of Non-Surgical Treatment of UA With Antibiotics?

Antibiotic use, while often lifesaving, is neither harmless nor inconsequential.

1. The continuing exposure to the risk of appendicitis.

In the 5-year follow-up of UA reported by Salminen et al., 40% recurred within 5 years. This is five times the population

**TABLE 1** | Major trials comparing surgery with antibiotics in *unselected* cases of appendicitis.

Study	Inclusion/exclusion	C	R	Failure rate	Complications
Coldrey 1953–1955	Observational study Excluded all patients presenting with history less than 24 h (609). All these had surgery. History longer than 24 h (137) had antibiotics only.	N	N	Unknown delayed operation (included in 609 overall)	1 death-frail elderly in antibiotic group/5 abscess total in both groups
1956–1957	All patients presenting with appendicitis (334). No exclusions			48 required operation (14.4%). Total failure 48 + 24 = 72 (22%). No long-term follow up	24 abscesses formed. Only 4 required drainage. Rest treated with antibiotics. No deaths
Styrud	Men Only. 124 surgery/128 antibiotic	Y	Y	14% antibiotic group operated within 24 h. 14% recurred within 1 year. Total failure 28%	14% complications in surgery group
Hansson 2009	369 patients randomised. 202 abs/167 surgery. In ab group 96 crossed over to surgery. 19 patients because of 'surgical judgement'	Y	Y	In ab group (106) 5 required early operation. 15 recurrences within 1 year. Total failure rate 19% Further approx. 15% recurrences at 5 years [74]	Major complications three times higher in surgical group. No deaths
Coda 2020	8168 patients with appendicitis assessed. 4181 were enrolled, 1552 randomised; 776 each arm. Primary endpoint EQ-5D at 30 days. Secondary endpoint operation within 90 days	Y	Y	30 day EQ-5D showed non-inferiority of ab treatment. Operation in ab group, 11% in 48 h, 20% in 30 days, 29% at 90 days	NSQP defined complications 8.1% in antibiotic group, 3.0% in surgery group. Abscess drainage 2.5% in abs group, 0.5% in surgery group. No deaths

Abbreviations: C, control group; EQ-5D European Quality of Life-5 Dimensions; R, randomization.

prevalence of appendicitis of 8%. Most recurrences occurred in the first year, and the curve flattened out considerably afterward [50]. This suggests that an ongoing low-grade inflammatory focus may be present, which may have long-term implications.

2. Complications of antibiotic use are well known, reported in up to 20% of hospitalised patients [51], but have been recorded in only a small minority of patients in the treatment of UA [26, 52].
  3. Where antibiotic treatments for UA have been used over the years, the range of antibiotics used is increasing. Current recommendations include ampicillin, amoxicillin-clavulanate, fluoroquinolones, ceftriaxone and ertapenem, amongst the last lines of defense in bacterial infections [1, 30]. Repeat courses of antibiotics are recommended for symptom recurrence [26, 30].
  4. Antibiotic use in childhood is associated with the risk of sepsis [53], allergy and asthma [54], inflammatory bowel disease [55], celiac disease [56] and irritable bowel syndrome [57] in later life. This may be associated with long-term changes to the developing microbiota [53].
  5. Recurrent *C difficile* infections are difficult to treat and are highly associated with antibiotics, particularly fluoroquinolones [58].
  6. Antibiotic use is independently associated with a subsequent development of bowel cancer [59], in addition to the association of bowel cancer alone with appendicitis in some populations [60–62].
  7. A diagnosis of appendicitis without a code for appendectomy in Swedish mortality statistics has been associated with an increased incidence of appendix cancer (standard incidence ratio 35, 95% CI 26–46), right-sided colon cancer (SIR 7.5, 95% CI 6.6–8.6) and small bowel cancer (SIR 3.2, 95% CI 1.6–5.6) [63]. A near contemporaneous linkage [64] study using the same databases showed no increased risk of bowel or appendix cancer in those treated with appendectomy.
  8. The incidence of appendix cancer, usually given as 1% of appendectomy specimens, is increasing in North America and Canada [65, 66], where the incidence of appendicitis itself is decreasing [67], and the frequency of antibiotic treatments is increasing [68].
- In the Australian population of 25 million, 170/100 000 cases of appendicitis occur per 100 000 per annum [69]. If 25% of cases were treated non-surgically (UA), appendix cancer would be missed, or diagnosis delayed in 1%. This works out to approx. One hundred six cases every year.
9. Appendix abscess when subject to interval appendectomy shows a high incidence of appendix cancer [63, 70, 71].
  10. In the face of surging anti-microbial resistance worldwide, the need for Antibiotic Stewardship should be supported by surgeons [72].

## 7 | Conclusion

Antibiotic use in perforated appendicitis, phlegmon and abscess (CA) is uncontroversial in both children and adults, together with surgical intervention as required [3].

The research involving UA and antibiotics as sole therapy is a reprise of the historical record of conflict between surgeons and physicians in the management of appendicitis of more than a century ago.

NOMA remains a worthy objective which will be enhanced by improved diagnostic precision. Alternatives to antibiotic use should be explored, simple analgesics and anti-inflammatories amongst them.

Appendicitis is a global disease, with a considerable unmet surgical need, ongoing mortality and societal cost [73]. Antibiotics are an adjunct to surgical management.

In the context of obtaining surgical consent, ‘Shared Decision Making’ sets a high standard. Surgeons should continue to manage appendicitis, including with antibiotics where clearly indicated.

### ■ Primum non Nocere

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#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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