CLINICAL PRACTICE

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Treatment of Acute Uncomplicated Appendicitis

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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A previously healthy 28-year-old woman presents to the emergency department with a 2-day history of abdominal pain that began in the umbilical area and migrated to the right lower abdomen. She is a single mother who works remotely and is raising a 5-year-old child. Her temperature is 37.8°C; other vital signs are normal. She rates her pain at 7 on a scale of 1 to 10, with 10 representing the worst possible pain. Examination reveals tenderness in the right lower quadrant, with moderate localized rebound. The result of a pregnancy test is negative, as is the result of a polymerase-chain-reaction assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Her white-cell count is 12,500 per cubic millimeter. Computed tomography (CT) performed after the intravenous administration of contrast material shows a dilated, inflamed appendix without appendicolith, abscess, perforation, or tumor. How would you manage this case?

THE CLINICAL PROBLEM

Acute appendicitis is the most common reason for emergency abdominal surgery. The peak incidence occurs among persons 10 to 19 years of age, and the lifetime risk is 7 to 8%.[1] Untreated appendicitis, when associated with rupture, can lead to abscess, peritonitis, sepsis, and death. Uncomplicated appendicitis (i.e., localized appendicitis), which has traditionally been treated with urgent appendectomy, accounts for approximately 80% of cases. In the past three decades, numerous trials of nonoperative treatment in patients with acute uncomplicated appendicitis have been conducted,[2-6] and the use of antibiotic agents as a first strategy has become acknowledged as a safe option. In this article, we review the expected outcomes associated with initial operative and nonoperative treatment of acute uncomplicated appendicitis and offer guidance on counseling patients to help them chose between the two approaches.

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STRATEGIES AND EVIDENCE

APPENDECTOMY

Appendectomy requires general anesthesia and, typically, hospitalization, although outpatient surgery is possible.[7] Patients with rupture and a large abscess or phlegmon (complicated appendicitis) are usually treated with antibiotics and, if possible, undergo percutaneous drainage to avoid more extensive operations, such as ileocecectomy.[8]

Appendectomy is a relatively low-risk surgery. In the United States and Europe, most surgeries are performed laparoscopically, an approach that is associated with

KEY CLINICAL POINTS

TREATMENT OF ACUTE UNCOMPLICATED APPENDICITIS

- Patients with acute, localized, uncomplicated appendicitis (approximately 80% of all appendicitis cases) are candidates for appendectomy or nonoperative treatment.
- Nonoperative treatment includes analgesia, antibiotics for 7 to 10 days, and careful follow-up.
- With surgery, appendicitis cannot recur, and the incidence of subsequent hospitalization is lower than with nonoperative treatment. Surgery requires general anesthesia and in most instances an overnight hospital stay.
- Nonoperative treatment is associated with a shorter duration of disability than appendectomy, does not routinely require hospitalization, and is not associated with an increased risk of rupture. Over 5 years, approximately 30 to 40% of patients who had been treated with antibiotics will undergo appendectomy, although rates vary with patient characteristics and practice patterns.
- Patients with appendicolith who receive nonoperative treatment are more likely than those without an appendicolith to undergo appendectomy.
- Patients should be informed of the advantages and disadvantages of both strategies and should participate in decision making.

fewer wound infections and faster recovery than open appendectomy but may be more costly.[9] Approximately 8% of adults with suspected appendicitis that is confirmed on CT have a normal appendix at operation.[10] The 30-day case fatality rate associated with appendectomy among patients with uncomplicated appendicitis is approximately 0.5 per 1000; among elderly persons, the fatality rate is about twice as high as it is among adolescents.[11] Although most patients are candidates for appendectomy, nonoperative treatment is more often considered in patients for whom surgery poses an increased risk of complications.

OPERATIVE VERSUS NONOPERATIVE TREATMENT

Nonoperative treatment is a strategy in which patients first receive antibiotics with the aim of avoiding surgery. Appendectomy is reserved for patients who do not have a response to antibiotics or have recurrence of appendicitis. Outcomes in more than 4000 patients with uncomplicated appendicitis who received nonoperative treatment have been reported in at least 10 randomized, controlled trials and 5 prospective comparative studies as well as in more than 20 other investigations,[2-6] most of which were conducted in Asia, Europe, and the United States.

Investigations of operative and nonoperative treatment have involved children and adults with localized appendicitis. In most studies, the diagnosis was confirmed on imaging (excluding patients with findings suggesting tumor or abscess), though some investigations relied on clinical evaluation with selective imaging (Table 1). Most studies excluded patients in whom appendicolith was identified on imaging. Appendicolith is found in approximately 25% of patients in whom appendicitis is confirmed on imaging and is associated with an increased likelihood of appendiceal rupture; it is unclear whether the appendicolith is involved in causing rupture or impairing its healing.[12] Patients with severe sepsis, immunodeficiency, or inflammatory bowel disease and those who were pregnant were also excluded. A minority of trials excluded patients who reported having symptoms for more than 48 hours, who had a white-cell count of 18,000 per cubic millimeter or more, or who had an appendiceal diameter of more than 11 mm.

To summarize the effectiveness of operative versus nonoperative treatment, we reviewed three large, multicenter investigations in which imaging was used to confirm diagnosis (typically ultrasonography in children and CT in adults) and that accounted for approximately two thirds of all such patients in comparative investigations. These included two randomized, controlled trials involving adults: the Finnish trial Appendicitis Acuta (APPAC), which included 530 participants and reported outcomes over a period of 5 years,[13,14] and the U.S. trial Comparison of the Outcomes of Antibiotic Drugs and Appendectomy (CODA), which included 1552 participants and reported outcomes at 90 days.[3] What we believe to be the largest pediatric trial, which involved 1068 children between the ages of 7 and 17 years, was that conducted by the Midwest Pediatric Surgery Consortium (MWPSC) at 10 children's hospitals.[4] Treatment was assigned in accordance with parent or patient preference, and 1-year outcomes were reported. Nonoperative treatment was chosen

Table 1. Considerations in Identifying Appropriate Candidates for Nonoperative Treatment of Appendicitis.

Appropriate candidates
Patients have a clinical diagnosis of localized appendicitis without examination findings of diffuse peritonitis or imaging evidence of large abscess, phlegmon, perforation, or tumor.
Patients are hemodynamically stable, without evidence of severe sepsis or septic shock.
Patients are not pregnant or immunocompromised and have no history of inflammatory bowel disease.
Cautions
Patients with imaging-identified appendicolith (which is present in approximately 25% of patients and is associated with appendiceal rupture) are at increased risk for complications such as abscess and undergo appendectomy more frequently than patients without appendicolith.
Antibiotic response may be delayed in patients who are 45 years of age or older and in those who have appendicolith, extraluminal fluid or air, fever, or elevated inflammatory markers and in those who have had symptoms for more than 48 hours, all of which are associated with appendiceal abscess.

in 35% of cases, and the characteristics of the children in the families that selected this treatment were similar to those in families that selected surgery. The CODA trial, unlike the MWPSC study and the APPAC trial, included patients with appendicolith.[3,4,13] In the APPAC trial, almost all appendectomies were open, whereas nearly all surgeries in the CODA trial and the MWPSC study were laparoscopic.

Likelihood of Surgery

The percentage of patients who undergo appendectomy after initially receiving treatment with antibiotics varies depending on the patient population and the duration of follow-up. In the APPAC trial, 94% of the patients with appendicitis who received antibiotics improved during initial hospitalization, and 27% underwent appendectomy within 1 year.[13] In the MWPSC study, the initial frequency of response was 86%, and 33% of the children underwent appendectomy at 1 year.[4] In the CODA trial, among participants who received antibiotics, those without appendicolith had an initial response rate of 92% and those with appendicolith had an initial response rate of 78%. Appendectomy rates at 90 days were 25% and 41%, respectively.[3] In the subgroup with an appendicolith, as compared with those who had surgery, those who received antibiotics had more percutaneous drainage procedures (6 more per every 100 patients), but surgeries more extensive than appendectomy (e.g., ileocecectomy) were rare and occurred with similar frequency in those undergoing appendectomy. In two trials reporting follow-up for 5 years, 30 to 40% of the patients who received treatment with antibiotics ultimately underwent appendectomy, usually within 1 to 2 years (Fig. 1).[14,15]

Complications

In the APPAC and CODA trials and the MWPSC study, the risks of complications and adverse events among those receiving antibiotics who did not have appendicolith were lower than or similar to the risks among those who underwent appendectomy.[3,4,13] At 5 years, the incidence of complications in the APPAC trial was similar among those who had initial appendectomy and those who had initially been treated with antibiotics but subsequently had appendectomy.[14] There is no evidence that delaying surgery while taking antibiotics increases the risk of perforation. In the CODA trial, for example, investigators observed that the incidence of perforation among patients who did not have appendicolith was lower among those receiving antibiotics than among those who underwent surgery, and among those who had appendicolith, the rates of perforation were similar among those who received antibiotics and those who underwent surgery.[3] Among participants in the CODA trial who had appendicolith, the proportion with at least one complication that met the definition of the National Surgical Quality Improvement Program (e.g., an abscess of any size) was higher in the group treated only with antibiotics than in the group that underwent appendectomy (14% vs. 3%); the incidence of serious adverse events was similar in the two groups (6% vs. 4%).[3] No participant deaths were noted in the initial reports of the APPAC or CODA trials or the MWPSC study.

Disability

In both the APPAC trial and the MWPSC study, the median number of days during which participants were unable to participate in normal activities or to work at 1 year was lower among those who received antibiotics than it was among those who had surgery (7 days vs. 19 days and 4 vs. 7 days, respectively).[4,13] Similarly, the group receiving antibiotics in the CODA trial had fewer mean days of disability at 90-day follow-up (5 vs. 8, respectively).[3]

Quality of Life

Clinical trials have shown similar quality of life after nonoperative treatment and appendectomy. In the CODA trial, findings from the 30-day assessment of the European Quality of Life–5-Dimensions (EQ-5D) test, in which mobility, self-care, usual activities, pain, anxiety, and depression are assessed, showed that quality of life in the antibiotics-first group was noninferior to that in the appendectomy group.[3] Among children in the MWPSC study who were treated nonoperatively, scores assessing physical, emotional, social, and academic functioning were superior at 30 days and similar at 1 year to the scores of children who underwent appendectomy.[4] Findings on quality life in the APPAC trial were also similar in the groups at 7 years on the EQ-5D-5L (known as the European Quality of Life 5-Dimension 5-Level questionnaire).[16]

Health Care Utilization

Whereas hospitalization was required for patients who were in the nonoperative group in the APPAC trial and the MWPSC study, in the CODA trial, patients whose condition was stable were allowed to be discharged from the emergency department, and discharge occurred in slightly less than half of the patients.[3,4,13] In the CODA trial, patients assigned to receive antibiotics had the same length of stay in the emergency department and hospital for their index visit as those assigned to the appendectomy group (mean, 1.3 days) but had a greater number of later hospitalizations and emergency department or urgent care visits that were not associated with hospitalization (24% vs. 5% and 9% vs. 5%, respectively) over a period of 90 days.[3] In the MWPSC study, over a period of 1 year, there were more later hospitalizations but fewer other emergency department visits (including urgent care visits; personal communication: P. Minneci) among patients who received antibiotics as compared with those who underwent surgery (23.0% vs. 3.0%, and 3.5% vs. 7.0%, respectively).[4]

Cancer Detection

In rare instances, cancer may cause appendicitis or symptoms mimicking appendicitis, or it may be found incidentally on appendectomy. In a study of 21,069 appendectomy specimens, researchers detected cancer in 0.9%, with a lower incidence of detection among persons younger than 50 years of age and among those with uncomplicated appendicitis.[17] Thus, nonoperative treatment carries a small risk of delayed diagnosis and disease progression; data are lacking to inform the effect of diagnostic delay on patient outcomes. At the 5-year follow-up in the APPAC trial, cancer was diagnosed in 4 of 272 patients who had been assigned to surgery (all at initial appendectomy), as compared with none of the 260 patients who had been assigned to receive antibiotics.[14]

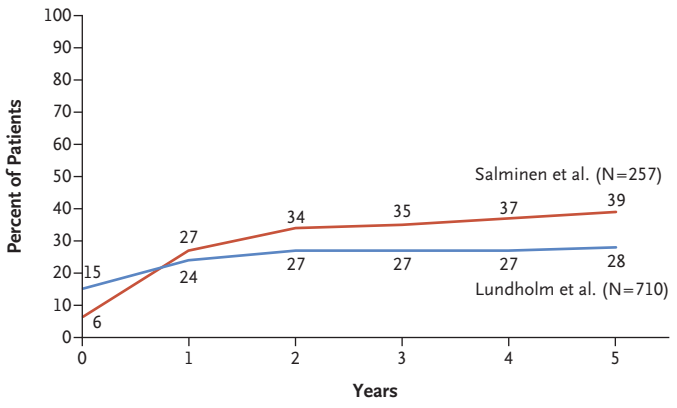

Figure 1. Five-Year Incidence of Appendectomy among Adult Patients with Acute Appendicitis Initially Treated Nonoperatively.

The incidence of appendectomy following initial care is shown for two reports of clinical investigations.[1] Salminen et al.[14] reported outcomes from a randomized trial involving adults with uncomplicated appendicitis confirmed on computed tomography (CT). Patients with appendicolith were excluded. Lundholm et al.[15] reported outcomes from a randomized trial and from observational studies in adults; some patients with complicated appendicitis and appendicolith were included. Not shown is the incidence of appendectomy reported at early follow-up from the largest known comparative investigations involving adults and children.[3,4] The Comparison of the Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial included 776 adults who received antibiotic treatment, 212 of whom had appendicolith identified on CT. At 90 days, of those treated with antibiotics, 25% of those without appendicolith and 41% of those with appendicolith had undergone appendectomy.[3] In a pediatric trial conducted by Minneci et al.,[4] ultrasonography was the primary form of imaging used in diagnosis, and patients with appendicolith were excluded. Among the children included in the trial, 370 were treated with antibiotics. At 1 year, 33% of the children had undergone appendectomy.

SHARED DECISION MAKING

A common concern among adult patients and the parents of nonadult patients is that an inflamed appendix will burst without emergency surgery and cause death.[18-20] This notion has largely been abandoned, and patients should be assured that they have time to consider treatment options. Shared decision making is recom-

mended,[21] wherein clinicians avoid a specific recommendation and instead provide objective information and assess patient priorities and preferences. For example, clinicians might state, "There are two safe options with different advantages and disadvantages. The best choice depends on which outcomes are most important to you. Let's discuss." Physicians should be aware of subtle biases that can accompany explanations of treatment pros and cons, such as stating that an antibiotics-first strategy "fails" in about one third of patients and "succeeds" in about two thirds rather than reporting the percentages of patients who subsequently do or do not undergo appendectomy. Patients' previous surgical experience, work and family responsibilities, schedule flexibility, travel plans, and expected out-of-pocket expenses may be important considerations.[22]

TREATMENT

Control of Pain and Nausea

Pain should be controlled before treatment is discussed. Concerns that pain control may lead to diagnostic inaccuracy in the detection of appendiceal rupture are unwarranted.[23] The administration of nonsteroidal antiinflammatory drugs before appendectomy has been shown to be safe (i.e., without an increased risk of bleeding) and spares the use of opiates. Multimodal analgesics are most effective, especially when prescribed to be taken on a scheduled basis as compared with an as-needed basis.[24] Antiemetics can also provide symptomatic relief.

Use of Antibiotics

A parenteral antibiotic regimen that is active against aerobic Gram-negative and anaerobic bacteria and consistent with community-acquired intraabdominal infection guidelines should be initiated as soon as the diagnosis of appendicitis has been reasonably established, regardless of whether treatment will be operative or nonoperative.[25,26] If nonoperative treatment is anticipated, then the administration of a long-acting parenteral antibiotic, such as ertapenem or ceftriaxone, along with high-dose, once-daily metronidazole, can facilitate early discharge (including, in some cases, after one dose in the emergency department), especially if there is concern regarding recurrent nausea or initial adverse reactions to oral medications.[27,28] Parenteral antibiotics are followed by oral regimens, such as metronidazole, administered with an advanced-generation cephalosporin or fluoroquinolone, for a total of 7 to 10 days. Although ampicillin–sulbactam and amoxicillin–clavulanate have been used effectively in some trials, current guidelines recommend against their use because of high rates of *Escherichia coli* resistance to these antibiotics.[26] In some cases, patients may be treated only with oral antibiotics. In a trial in which 7 days of oral moxifloxacin was compared with 2 days of intravenous ertapenem followed by 5 days of oral levofloxacin and metronidazole, 70.2% of those in the former group and 73.8% of those in the latter group did not undergo appendectomy at 1 year, although fully oral treatment was not shown to be noninferior.[5] For patients who undergo appendectomy, antibiotics should be discontinued postoperatively.[26]

Disposition

In the United States, most patients go home from the hospital the day after undergoing laparoscopic appendectomy.[3,4] Individual recovery times vary, but patients usually return to normal activities within 1 to 2 weeks. Those who have laparoscopic surgery return to normal activities approximately 5 days sooner than those who have open surgery.[9] Patients are typically advised that they can return to work or school when they feel well enough but should avoid strenuous activity for 3 to 5 days after laparoscopic surgery and for 10 to 14 days after open surgery.[29]

After the initiation of antibiotics only, pain, fever, leukocytosis, and anorexia typically resolve within approximately 2 days in patients with uncomplicated appendicitis (as compared with approximately 3 days in those with complicated appendicitis).[8,30-33] After 24 hours, approximately half the patients will have substantial symptom resolution. Pain also resolves more quickly than with surgery.[33] In the absence of the development of peritonitis or severe sepsis, a 48-hour antibiotic trial with continued assessment appears to be safe in patients whose condition is stable and who have only localized tenderness. It is not routinely necessary to track levels of inflammatory markers or to obtain additional imaging studies, but these steps may be useful in patients whose response to antibiotics is slow.

As many as approximately 20% of patients with uncomplicated appendicitis confirmed on CT are found during surgery to have appendiceal rupture and abscess.[3] Patients with appendicolith identified on CT, those with extraluminal fluid or air, those who are older than 45 years of age, and those who have fever, symptoms for more than 48 hours, and elevated levels of inflammatory markers (findings associated with appendiceal abscess) may be anticipated to have a delayed response to antibiotics.[8,34]

Emergency department discharge can be considered in adults who receive nonoperative treatment once their condition is deemed to be stable on clinical assessment, their pain is controlled, and they are able to take oral fluids. They should also be able to adhere to treatment guidelines and be amenable to follow-up. A standard diet can be resumed as long as food is tolerated. Other patients are initially hospitalized for further observation and supportive care. Data are lacking on outpatient treatment in children.

Follow-up

After discharge, all patients should be advised to contact their doctor if they have persistent or increasing pain, fever, or vomiting. Those who have had surgery should contact their doctor if they have redness at the site of the wound, swelling, or drainage. Those who receive nonoperative treatment should be contacted within 1 to 2 days after discharge to evaluate their progress; if there are concerns, reexamination should be conducted. It is important to advise patients to seek medical attention if they have symptoms suggesting recurrence or symptoms suggesting another pathologic condition, such as weight loss.

If appendicitis recurs, surgery is commonly performed and may be preferred in adults who are 40 years of age or older given the possibility that they have appendiceal cancer, although this finding is rare. Several studies have reported success with antibiotic retreatment that is similar to that used in the management of diverticulitis; with reduced recurrence risk after 1 year, this strategy may be a reasonable strategy in younger patients.[2] In adults 40 years of age or older who have had successful nonoperative treatment of complicated appendicitis, some experts recommend follow-up colonoscopy or screening with full-dose, contrast-enhanced CT within 3 months after symptom resolution, but data are lacking regarding the effectiveness of this strategy in patients with uncomplicated appendicitis.[35]

Table 2. Guidelines from Professional Societies on the Treatment of Acute Uncomplicated Appendicitis.

Professional Society and Year	Recommendation
American Association for the Surgery of Trauma,[37] 2018	Surgery or a nonoperative approach is reasonable.
National Institute for Health and Care Excellence,[38] 2019	For now, surgical treatment is the accepted standard, but medical treatment, including antibiotics, may be an alternative. There is an increasing body of evidence in support of nonoperative treatment.
World Society of Emergency Surgery,[35] 2020	High-quality evidence supports nonoperative treatment with antibiotics. This safe alternative to surgery should be discussed in selected patients without appendicolith.
American College of Surgeons,[39] 2020	High-quality evidence indicates that most patients can be treated with antibiotics rather than appendectomy. However, patients with appendicolith who are treated with antibiotics have a higher risk of complications than those without appendicolith.

GUIDELINES

Guidelines from professional societies changed from appendectomy being primarily recommended in 2015 to nonoperative treatment now being endorsed as a safe first-line alternative (Table 2).[35-39]

AREAS OF UNCERTAINTY

Trials in which outcomes among patients who underwent appendectomy were compared with outcomes among those who received antibiotics were not blinded, and criteria for the absence of a response to antibiotics and the need for surgery have been subjective and neither monitored nor enforced (e.g., a 48-hour antibiotic trial).[4,40] In some cases, appendectomies have been performed at the request of the patient when there were no clinical indications for surgery, and treatment decisions may have been influenced by patient and provider bias (e.g., knowledge of the association of appendicolith with rupture). Comfort with shared decision making and commitment to an antibiotic trial may increase as

the traditional narrative regarding the treatment of appendicitis is revised and as experience with this newer form of care increases. Data are limited regarding the benefits and risks of nonoperative treatment in certain populations (e.g., pregnant women and elderly patients).[41,42] Uncertainty remains regarding the care of patients with appendicolith, and it is not known whether the incidence of recurrent appendicitis among these patients differs from that among those without appendicolith. Special considerations may apply in remote settings and in cases in which surgery entails additional risk. Long-term data are needed from the CODA trial and others to better inform the cumulative risk of appendectomy after initial nonoperative treatment. Resistance of Enterobacterales to fluoroquinolones and β-lactams (the latter mediated by β-lactamase production) is emerging.[43] Further study is needed to guide the selection of patients for whom nonoperative treatment is appropriate and to inform best practices for the use of oral antibiotic regimens and outpatient treatment — an approach that may be possible in most cases.[33]

A randomized trial in which supportive care and antibiotics was compared with supportive care alone in selected low-risk patients hospitalized with uncomplicated appendicitis showed no significant between-group differences in treatment failure rates, suggesting that some cases of appendicitis may resolve spontaneously[44]; more study is needed to determine when such a strategy may be safe.[45] The clinical effects of delayed diagnosis of appendiceal cancer when appendicitis is managed nonoperatively are uncertain; the rarity of cancers makes this issue challenging to study. In addition, it remains unclear whether the appendix serves a useful function. Some studies have reported an association between appendectomy and an increased risk of intestinal cancer, but findings are inconclusive.[46]

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has clinical findings consistent with acute appendicitis. She is a candidate for either nonoperative treatment or appendectomy. Through shared decision making, we would objectively review outcomes associated with operative and nonoperative treatments and explore the patient's priorities. She should be assured that she is not at increased risk for appendiceal rupture or death if she does not undergo emergency surgery.

If the patient chooses nonoperative treatment, a long-acting parenteral antibiotic, such as ertapenem, should be administered. As long as her pain and nausea can be effectively controlled and her condition is clinically stable, she is a candidate for outpatient care while receiving oral antibiotics such as cefdinir and metronidazole in order to cover both Gram-negative and anaerobic bacteria. A regimen of 7 to 10 days would be appropriate.

Initiation of pain control with a scheduled regimen of nonsteroidal antiinflammatory drugs and acetaminophen, as well as opiates (as needed), is recommended. An antiemetic agent should also be prescribed and taken as needed for the next few days. Improvement should be expected during a 48-hour period. Follow-up — including in the form of a telemedicine visit — is advisable. Worsening symptoms would prompt referral back to the emergency department. Diffuse peritonitis, sepsis, or the absence of improvement after 48 hours would be indications for appendectomy.

Disclosure forms as provided by the authors are available with the full text of this article at NEJM.org.

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