Acute appendicitis is the most common abdominal condition requiring emergency surgery. It results from inflammation of the vermiform appendix, which is a tubular structure attached to the base of the caecum.

Why is appendicitis missed?
The classical presentation of appendicitis appears in only about 50% of patients. Appendicitis can affect all age groups, and presentation may be influenced by the patient’s age and the anatomical position of the appendix. An accurate history may not be possible from the very young or from older people presenting with confusion.

Pregnancy seems to protect against appendicitis, but it is the most common non-obstetric emergency requiring surgery in pregnancy. Presentations in pregnant women may be atypical (due to anatomical displacement of the appendix by the gravid uterus) or mistaken for the onset of labour; tenderness may be located anywhere on the right side of the abdomen or may be minimal if the inflamed appendix is displaced posterolaterally.

The diagnostic accuracy of general practitioners in relation to appendicitis is high (92% of paediatric cases correctly diagnosed) and the non-specificity of symptoms and signs is the predominant reason for a delay in diagnosis.

Why does this matter?
Appendicitis is a progressive inflammatory process, and the incidence of perforated cases rises with the duration of symptoms. Therefore, prompt diagnosis and treatment are essential for reducing the increased risk associated with advanced inflammation. After the first 36 hours following the onset of symptoms the average rate of perforation is between 16% and 36%, and the risk of perforation is 5% for every subsequent 12 hour period. Perforation rates are higher in elderly people and young children, possibly because of a delay in diagnosis. However, actual perforation rates are difficult to calculate accurately due to the frequency of undiagnosed cases of resolving appendicitis.

How is appendicitis diagnosed?
Clinical features
Diagnosis of acute appendicitis relies on a thorough history and examination, and the presence or absence of any particular individual symptom or sign cannot be relied upon to diagnose or exclude appendicitis.

In the assessment of a patient with suspected appendicitis, studies have demonstrated that pain migration (positive likelihood ratio 2.06) and evidence of peritoneal irritation (localised direct or indirect tenderness (1.29-2.47), rigidity (2.96), guarding (2.48), rebound (1.99), and percussion tenderness (2.86) are the most useful clinical findings associated with a positive diagnosis.

Abdominal pain is the primary presenting complaint of patients with acute appendicitis. However, the sequence of vague abdominal pain followed by vomiting with migration of the pain to the right iliac fossa first described by Murphy may be present only in around 50% of patients. Typically, the patient describes a periumbilical or epigastric pain that intensifies during the first 24 hours, becoming constant and sharp, and migrates to the right iliac fossa. Loss of appetite is often a predominant feature, and constipation and nausea are frequently present. Profuse vomiting is rarely a major feature in simple appendicitis. The patient can be flushed, with a dry tongue and associated fetor oris. The presence of pyrexia (up to 38°C) with tachycardia is common. Abdominal examination reveals localised tenderness and muscular rigidity after localisation of the pain to the right iliac fossa. The site of maximal tenderness is often said to be over McBurney’s point, which lies two thirds of the way...
KEY POINTS
Appendicitis is a predominantly clinical diagnosis, and no single individual symptom or sign can be relied upon to diagnose or exclude it.
A history of fever or pain migration and evidence of peritoneal irritation have been found to be the most useful clinical features in making the diagnosis.
A raised CRP and white cell count can support the diagnosis.
The classical presentation can be influenced by the age of the patient and anatomical position of the appendix.

Scoring systems
Scoring systems have been developed to aid the diagnosis of appendicitis. They aim to estimate the probability of the condition in an individual patient compared with a large number of similar patients from which the system was developed. The best known of the several systems developed is the Alvarado score, although more recently the appendicitis inflammatory response (AIR) score correctly classified a higher proportion of patients into low probability and high probability groups. The scores use history and examination findings along with inflammatory markers to achieve a summed numerical score. In a study of 545 patients with suspected appendicitis, the receiver operating characteristic area for the AIR score was 0.93 compared to 0.88 for the Alvarado score (P=0.0007).

Anatomical considerations in the presentation of acute appendicitis
- Retrocaecal/retrocolic (20%)—Right loin pain is often present, with tenderness on examination. Muscular rigidity and tenderness to deep palpation are often absent because of protection from the overlying caecum. The psoas muscle may be irritated in this position, leading to hip flexion and exacerbation of the pain on hip extension (psosas stretch sign).
- Subcaecal and pelvic (51%)—Suprapubic pain and perineal fullness are often prominent, and tenderness to examination. There may be muscle spasm of the external iliac and gluteal muscle groups, with guarding and rebound tenderness. A palpable mass may be present, and the mass effect on the overlying caecum may result in right iliac fossa tenderness. Wasting of the right iliac fossa. Demonstration of Rovsing’s sign (palpation of the left iliac fossa causes pain in the right iliac fossa due to peritoneal irritation) may also aid in the diagnosis of appendicitis. In atypical cases, clinical assessment of the right groin and hip is important, particularly in paediatric patients, to rule out pathology in this region.

Investigations
There is no specific laboratory test for appendicitis although simple blood tests may support the diagnosis as the majority of patients with appendicitis will have a neutrophil predominant leucocytosis. Combining C-reactive protein and white cell count can provide a likelihood ratio for appendicitis of up to 23.32 depending on values taken. In contrast, when all inflammatory markers are normal, appendicitis is unlikely.

To assess for obstetric related conditions, pregnancy testing is mandatory in women of child bearing age.
Urinalysis may be abnormal in almost half of patients with acute appendicitis because of inflammation adjacent to the right sided urinary tract and bladder.

Appendicitis is predominantly a clinical diagnosis that can be supported by simple blood tests—specialist tests aren’t usually required. However, the most frequently used radiological investigations are ultrasonography (sensitivity and specificity of 86% and 81%) and computed tomography (94% and 95%), although the latter should be used with caution to minimise radiation exposure.

How is appendicitis managed?
Appropriate resuscitation followed by expedient appendicectomy either by the open or laparoscopic approach is the treatment of choice. All patients should receive broad spectrum perioperative antibiotics as this decreases the incidence of postoperative wound infections and abscess formation.

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References
A PATIENT’S JOURNEY

Living with alkaptonuria

Simon Laxon, Lakshminarayan Ranganath, Oliver Timmis

Simon Laxon, who was diagnosed with a rare genetic disorder, alkaptonuria, soon after birth, describes his journey in understanding the condition and finding hope for a cure.

I was born in 1966, and within a few days of my birth my parents knew that something was wrong. There were dark purple stains in my nappies, so my mother took me to a consultant at my local hospital for investigation.

After a meeting of specialist doctors, one of my nappies was sent for tests. The doctors suspected porphyria, but the test came back negative. A urine test led to the discovery of a rare genetic disorder. The doctors explained it would cause a type of arthritis: not crippling like rheumatoid arthritis, but one that would cause aches and pains as well as turning the cartilage in my ears blue. My parents felt there was no need to worry, so I grew up fairly normally. I was quite athletic at school and trained several times a week.

In 1987 I developed a duodenal ulcer and had to go into hospital, where doctors rediscovered the genetic disorder (my original records had been lost). This time a name was put to it: alkaptonuria. The doctors knew little about it, but told me I would develop mild arthritis and that my urine would turn black if left to stand. We explained about the meeting of the specialists when I was only a couple of weeks old and the stained nappies. The doctors said that this was a symptom of alkaptonuria and was nothing to worry about, as the genetic defect was harmless.

It took me a year to overcome the ulcer. By this time I was starting to suffer with aches and pains in my lower back. I found that I could not get back into a physically active lifestyle because my body hurt so much after every attempt. At the time I did not realise how much damage this disorder would do to me.

I found that the pain and stiffness were starting to affect my work. I was a brake prototype engineer, working underneath vehicles. I would spend a lot of time bending or crouching and noticed that my back became very stiff and ached to the point where I would have to stop work. If I sat down for a long period of time, I would not be able to stand up straight for at least 10 minutes because of the stiffness.

In 1997 I started to get severe pain in my lower back. My doctor told me to rest, but after the pain worsened he referred me to a specialist rheumatologist. I was sent for a radiograph of my back, which led to a diagnosis of degenerative disc disease. The rheumatologist told me nothing could be done and discharged me.

The pain still interfered with my job, so my works manager sent me to a private physiotherapist. After an examination the physiotherapist referred me to an orthopaedic surgeon, as he suspected ankylosing spondylitis. A few weeks later, I collapsed with intense pain in my lower back. I was taken to hospital and admitted for 10 days. A magnetic resonance imaging scan showed degeneration of the cartilage in my lower back. I was told again that the problem was mechanical back strain and degenerative disc disease and that nothing could be done. I was discharged from hospital but was unable to work—as a result I lost my job.

In 1998 I was invited to meet a geneticist, Victor McKusick, from Johns Hopkins University. He told me that alkaptonuria does cause early onset arthritis as well as a vast number of other problems. He took photographs of my ochronotic ear cartilage and explained that my black earwax was also due to alkaptonuria. He confirmed that it was to blame for the pain in my joints. Armed with this information I went back to my doctor who referred me to another rheumatologist.

My new rheumatologist had experience of treating patients with alkaptonuria, so he knew that my problems were connected. He wanted to see me every three months and take blood and urine samples for testing. A year later he retired and the rheumatologist who took over from him still treats me to this day. He is aware of the destructive nature of alkaptonuria and regularly sends me for blood, urine, and bone density tests.

In December 1998 my pain management doctor per-

USEFUL RESOURCES

AKU Society (www.alkaptonuria.info) — UK based support group for alkaptonuria patients, family, and carers. Founded in 2003 by Dr Ranganath and Robert Gregory. Communications project manager, Oliver Timmis oliver@akusociety.org

ALCAP (www.alcap.fr) — France based support group for alkaptonuria patients, family, and carers

AKU Society North America (www.alkusociety.org) — USA based support group for alkaptonuria patients, family, and carers

AKU communities (www.rarediseasecommunities.org/en/community/alkaptonuria-aku) — an online community and support forum for alkaptonuria patients, part of rare disease communities, a joint project between EURORDIS and NORD
Alkaptonuria causes considerable morbidity in adulthood due to severe premature destructive spondyloarthropathy. It is a rare genetic disorder arising from a lack of homogentisate dioxygenase, the enzyme responsible for metabolising dietary phenylalanine and tyrosine through homogentisic acid (HGA). Because it is very rare—a prevalence of around 1 in 500,000 in most populations, including the UK—it is often missed or not considered at first presentation, as in this case. It is present at birth as dark urine and staining of nappies and can be confirmed by a simple laboratory measurement of HGA in urine. It is often considered a curiosity in children, and patients are sent away with false reassurance. Misleading and potentially detrimental advice can be given regarding diet, occupation, and lifestyle. Patients who are not followed up after diagnosis are often lost to the system—as were Simon’s original records—which is problematic in a disease that causes severe disability in early adulthood. The initial diagnosis is an opportunity to screen siblings.

Most HGA is excreted by the kidneys. The remaining HGA is oxidised via benzoquinone acetic acid to a melanin-like polymer and deposited in connective tissues, a process termed ochronosis. By their late twenties most patients experience severe back pain, often accompanied by blue-black pigmentation of the pinna, with scleral pigmentation developing soon after due to progressive ochronosis. Progressive arthritic pain affecting large synovial joints (especially knees, hips, and shoulders) is also seen. The combination of back and joint pain, and pigmentation of the ear and eye with a background of black urine should alert a medical practitioner to a diagnosis of alkaptonuria.

Other than joint cartilage damage, manifestations of alkaptonuria include those due to high HGA (stones in kidney, prostate, gall bladder, and salivary gland), ochronosis (visible external pigmentation in eye, ear, skin, and teeth), and ochronotic tissue damage (pigment alters material properties of tissues, leading to ruptures of tendons, ligaments, muscle; bone fractures, as well as cardiac valve damage, also occur). Current management of alkaptonuria is palliative, dependent on appropriate lifestyle choices and pain relief. Low protein diets and ascorbic acid are of unproven value as treatments. Effective analgesic management, physiotherapy to keep joints supple, and ultimately arthroplasty for total joint failure are required. There is a potentially effective HGA lowering treatment that does not involve gene or enzyme replacement. This agent, nitisinone, inhibits p-hydroxy phenyl pyruvate dioxygenase, the enzyme leading to formation of HGA. Despite its unequivocal lowering of HGA, and anecdotal descriptions of clinical benefit including pain relief—as experienced by Simon—there is no clinical trial evidence of its effectiveness. This is largely because the natural history of alkaptonuria is not well understood. Researching a rare disease to increase understanding and to develop effective treatments can be challenging. A well designed clinical trial exploring the potential of nitisinone in alkaptonuria is urgently required to alleviate this currently untreatable disease.

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In 2000 I was searching the internet for alkaptonuria research when I came across an article by Charles Scriver of McGill University in Canada. I made contact and he sent me a copy of the paper he had written on alkaptonuria. I kept in touch and found that another patient in the UK wanted to set up a website dedicated to helping those with alkaptonuria. He put me in touch with Robert Gregory, who is now the manager of the AKU Society in the UK. I signed up and have been a member ever since. Their aim, and that of Lakshminarayan Ranganath and his team at the Royal Liverpool University Hospital, is to find a cure for alkaptonuria.

I also came across the National Institute of Health (NIH) in the United States. They were looking for people to take part in a new study on nitisinone, an unlicensed drug that prevents the accumulation of the homogentisic acid that causes the damage in alkaptonuria. I contacted them and in February 2001 I flew out to the NIH. I spent the next week having a vast array of tests before flying home.

In 2004 I had arthroscopy on my knees. My orthopaedic surgeon told me that my left knee showed signs of ochronosis, but my right one looked normal. To date, I have had a further three arthroscopies and a meniscus repair.

In June 2005 I was asked to return to the NIH. This time I was to participate in the study of nitisinone and return every four months for follow-up appointments. While on nitisinone I felt normal again. All the pain seemed to disappear and the stiffness seemed to ease completely. I could play games with my children—something that I could not do before—and we were a normal family. This seemed to happen after being on the drug for only a week, and continued for the four years I was on it. I was deeply saddened when I received an email from the NIH saying that they were to stop the trial. It felt that this was the only hope that we had, as an AKU Society, and now that was gone.

Last year I travelled to the Royal Liverpool University Hospital to take part in their alkaptonuria clinical evaluation programme under Dr Ranganath, a consultant in metabolic medicine. I stayed at the hospital for three days while scans, radiography, and other tests were performed. Work like this is helping to advance medical knowledge about alkaptonuria. Without this glimmer of hope, future alkaptonuria sufferers face years of severe pain and joint replacements. We are hoping a cure will be found so that future generations will not have to go through what we have.

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