education

ART OF MEDICINE

The unspoken word

"When I use a word," Humpty Dumpty said . . . "it means just what I choose it to mean—neither more nor less."

But one word—cancer—was rarely used in my local hospital. After being diagnosed with non-Hodgkin's lymphoma, cancer was not used until my third chemo session. Until then, all references had been to lymphoma or enlarged glands, not even tumour. These may be medically accurate, but they cause uncertainty. I even returned to the literature I had been given to check that lymphoma was a form of cancer.

I asked to be told as much detail as I, a non-medic but with a higher research degree, could understand. It can't be easy to get the right "pitch" for every patient, but sometimes comments were unhelpful. I was told, "You can go and get on with your life," to which I muttered, "I think I've been trying to do that anyway." Then, "If I were you, I would be very happy." These were intended to be encouraging but what do they really mean?

I later raised language issues with a consultant. The discussion was not getting far, but I spotted "CRU" on an electrocardiography form and queried its meaning. When told "complete remission unconfirmed" I asked why could this not have been used, as for me it conveys more than being told to be happy.

I'm not moaning, just asking for a straightforward approach.

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We welcome contributions to this column via our online editorial office: https://mc.manuscriptcentral.com/bmj.

CLINICAL UPDATES

Ovarian hyperstimulation syndrome (OHSS)

A new RCOG guideline does not support the use of gonadotrophin releasing hormone antagonists or dopamine agonists in women with established OHSS undergoing outpatient management owing to insufficient evidence. Non-steroidal anti-inflammatory drugs should be avoided owing to the risk of compromising renal function. Women with severe OHSS should receive thromboprophylaxis with low molecular weight heparin, with treatment taking into account individual risk factors and likelihood of conception.

http://bit.ly/1QRzCAd

Spectra Optia in sickle cell disease

New NICE guidance recommends that Spectra Optia should be considered for automated red blood cell exchange in patients with sickle cell disease who need regular transfusion. It is faster to use and needs to be done less often than manual red blood cell exchange. More long term data are needed to clarify how automated and manual exchange affect iron overload status and need for chelation therapy.

http://bit.ly/1U6KxvL

Healthcare associated infections

NICE has published a quality standard to improve outcomes related to healthcare associated infection (HAI), such as antimicrobial resistance, length of stay in acute care, and avoidable morbidity and mortality. It recommends that hospitals monitor HAIs and work with local health and social care organisations to drive quality improvement. Individual objectives on infection prevention should be linked to board level objectives and strategies. Maintenance or building of hospital facilities should involve infection control teams, and information about infections should be shared with health and social care staff in hospital and in the community.

http://bit.ly/1TSkjxx

FAST FACT—FUNGAL TOENAIL INFECTION

Fungal culture from clippings, followed by topical treatments with amorolfine 5% and tioconazole 28% for up to a year are recommended for fungal toenail infections. Success rates can be improved by self care, including:

- Avoiding exposure to warm damp conditions
- Wearing well fitting shoes, without high heels or narrow toes
- Maintaining good foot hygiene, including treating any athlete's foot (tinea pedis)
- Being meticulous with the hygiene of the affected foot or feet.

Pulsed oral itraconazole is an alternative treatment.

For more information visit *BMJ Learning* (www.ow.ly/YJI0d)

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Should we treat subclinical hypothyroidism in obese children?

Usha Niranjan, Neil P Wright

WHAT YOU NEED TO KNOW

- Hyperthyrotropinaemia comprises an isolated raised thyrotropin (>4.5 mIU/L but <10 mIU/L) without clinical symptoms, thyroid antibodies, goitre, or associated thyroidal illness
- It is common in obese children but seems to be a consequence rather than the cause of obesity and may normalise after weight loss
- Offer lifestyle measures to promote weight loss because there is no evidence to justify thyroxine treatment for subclinical hypothyroidism with obesity
- Monitor thyrotropin and free thyroxine every 6-12 months

Thyroid function tests are often requested when investigating obese or overweight children. Slightly raised thyrotropin (TSH) with normal free thyroxine—subclinical hypothyroidism (hyperthyrotropinaemia)—is a common finding. An isolated raised thyrotropin is best described as hyperthyrotropinaemia rather than subclinical hypothyroidism and by definition excludes people with clinical symptoms, positive thyroid antibodies, goitre, or associated thyroidal illness.[1 2] The adult consensus guideline defines it as a thyrotropin value between the upper limit of the local normal range and 10 mIU/L.[1] Paediatric reviews have adopted a similar definition and thresholds.[3] Reference ranges vary with the laboratory but are typically 0.45-4.5 mIU/L.[1] In paediatric practice, as in adults, thyrotropin >10 mIU/L is potentially indicative of overt hypothyroidism.[4]

An isolated increase in thyrotropin is more common in overweight children, with a reported prevalence of 7-23% in obese children compared with only 2% in normal weight children.[4 5] Thus it is unclear whether raised thyrotropin is a cause or consequence of obesity and whether thyroxine should be used to help manage these children's weight.

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@bmj.com.

HOW PATIENTS WERE INVOLVED IN THIS ARTICLE

This article was submitted before we asked authors to involve patients and report any contributions.

What is the evidence of the uncertainty?

To ascertain the association between obesity and hyperthyrotropinaemia in children, we searched the Medline, Embase, and Cochrane databases until February 2015 using the keywords "subclinical hypothyroidism", "hyperthyrotropin(a)emia", "obesity", and "treatment" in various combinations. Because of the paucity of paediatric data we also examined the literature on adults. We found several cross sectional and longitudinal studies on the association between thyroid dysfunction and obesity in adults and children and one systematic review of adult studies, but no randomised controlled trials evaluating interventions and no systematic reviews of paediatric studies.

Subclinical hypothyroidism in obese children: cause or effect?

Evidence on the association between an isolated raised thyrotropin and obesity is more limited in children than in adults, but it still supports a link between weight gain and hyperthyrotropinaemia. A recent review identified 12 mostly cross sectional studies, some of which had a longitudinal component, which found a positive association between increasing thyrotropin and increasing weight.[4] In these cohorts 7-23% of obese children had moderately raised thyrotropin with normal free thyroxine and normal or slightly raised free triiodothyronine,[4] compared with 0.3-2.0% in normal weight controls. Several large longitudinal studies have examined the effect of weight loss on thyrotropin. In one study of 246 obese children, thyrotropin was initially raised. Thyrotropin values dropped significantly in the 49 children who subsequently lost weight (P=0.035) but not in the 197 children who did not lose weight.[6] Other cohort studies also showed normalisation of thyrotropin values after weight loss.[2 5] These studies concluded that hyperthyrotropinaemia is caused by increased weight, perhaps representing an adaptive process to increase basal energy expenditure, rather than predisposing to weight gain in children.[2 5]

What's the evidence in adults?

Because of the limited paediatric data it is useful to look at the adult literature. In a recent systematic review of 29 cross sectional and longitudinal studies in adults, 18 showed a positive correlation between serum thyrotropin and measures of adiposity.[7] A study of 15 000 Norwegians found that, over a five year period, weight gain correlated with increased thyrotropin and weight loss with reduced thyrotropin.[8] It has been suggested that the increase in thyrotropin is an adaptive response of the hypothalamic-pituitary axis to weight gain in an attempt to enhance resting

GUY SOMERSET/ALAMY

WHAT PATIENTS NEED TO KNOW

- Mild thyroid hormone abnormality—where the thyroid hormone level is normal but the signalling hormone level (thyrotropin) is slightly high—is common in obese children and is called hyperthyrotropinaemia
- This is a consequence rather than the cause of obesity and may become normal after weight loss
- There is no evidence to justify thyroid hormone treatment in obese children with hyperthyrotropinaemia, which is managed with lifestyle measures that promote weight loss. However, thyroid hormone levels need to be monitored every 6-12 months because of the unlikely but possible progression to overt hypothyroidism (underactive thyroid gland)

Offer lifestyle measures to promote weight loss because there is no evidence to justify thyroxine treatment for subclinical hypothyroidism with obesity

energy expenditure,[9] rather than subclinical hypothyroidism causing the weight gain. In support of this, two small observational studies (11 and 72 patients, respectively) showed normalisation of thyrotropin after weight loss (due to dieting or bariatric surgery).[10 11] Although most studies suggest that raised thyrotropin is a consequence rather than the cause of obesity, there have been reports of bidirectional effects. However, these studies included patients with differing degrees of obesity and did not adjust for confounding factors such as age, sex, iodine intake, and distribution of body fat, making interpretation difficult.[9]

What's the role of thyroxine treatment?

The only study to evaluate the role of thyroxine treatment for hyperthyrotropinaemia in obese children was a prospective cohort study in which 15 children received 1-2 µg/kg of thyroxine as an adjunct to a lifestyle intervention programme versus 26 untreated children who received the same lifestyle intervention programme.[12] All children lost weight and their previously raised thyrotropin values fell. No statistically significant difference was seen between the thyroxine treated and untreated groups with regard to effect on body weight, body mass index, linear growth, or lipid profile.[12] Although the lack of appropriately powered, high quality studies leaves us with insufficient direct evidence regarding thyroxine treatment in obese children with hyperthyrotropinaemia, the limited evidence available suggests that it has no benefit.

RECOMMENDATIONS FOR FURTHER RESEARCH

Adequately powered randomised controlled trials with:

- Population: obese and overweight children with hyperthyrotropinaemia (raised thyrotropin with normal free thyroxine)
- Intervention and comparison: thyroxine treatment versus placebo
- Outcome: weight loss and normalisation of thyrotropin taking into consideration confounding factors such as age, sex, smoking, iodine intake, and markers of adiposity (body mass index, degree of obesity, lean body mass, distribution of body fat, waist circumference, and insulin sensitivity)[9]

In adults, a recent narrative review of six randomised controlled trials reported no significant difference in body mass index or weight with levothyroxine treatment compared with placebo in subclinical hypothyroidism.[13]

Is ongoing research likely to provide relevant evidence?

We reviewed the clinical trials.gov database and found no current studies that are looking at this specific question.

What should we do in the light of the current uncertainty?

Raised thyrotropin, which is seen in 7-23% of overweight children, is probably a consequence rather than a cause of obesity because thyrotropin tends to normalise after weight loss.[4] There is no evidence to support treatment with thyroxine in otherwise well children if thyrotropin is <10 mIU/L.[12] Most children with hyperthyrotropinaemia, with or without obesity, do not progress to develop overt hypothyroidism. In a population study of 120 000 children, 79% of those with an initially raised thyrotropin showed normal values at five year follow-up and only 0.4% of the cohort developed overt hypothyroidism requiring treatment.[14] Thus, in obese children with hyperthyrotropinaemia (thyrotropin >4.5 mIU/L but <10 mIU/L):

- Exclude the presence of goitre or clinical features of thyroid disease (tiredness, dry skin, cold skin or feeling colder, constipation, slower thinking, poor memory)
- Exclude the presence of thyroid autoantibodies
- Offer lifestyle measures, but not thyroxine treatment, to promote weight loss
- We suggest that it is prudent to monitor thyrotropin and free thyroxine every six to 12 months.

Thyrotropin levels >10 mIU/L fall outside the definition of hyperthyrotropinaemia and may indicate thyroid disease requiring referral to a paediatric endocrinologist for further assessment and investigation.[1] Children with clinical symptoms of thyroid disease, positive thyroid antibodies, or goitre also require specialist assessment.

Competing interests: None declared.

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Growing up in care

Áine Kelly describes how she began to access healthcare again after humiliating childhood experiences

My first memory of the healthcare system traumatised me for life.

I was only 7 years old when the police arrived at my house to escort my birth mother and me to hospital. They said I had to undergo a medical examination because they had reason to believe that my mother and stepfather were physically abusing me. Several adults dressed in white coats stood around the examination bed where I lay naked, humiliated, and frozen by fear. Time dramatically slowed down as they counted, measured, and photographed every single bruise, cut, burn, and abrasion on my body. The professionals kept asking me how I received my injuries, but I couldn't tell them with my birth mother in the room. Luckily, they decided that she and my stepfather had physically and emotionally abused me and I was placed into emergency foster care. This medical examination probably saved my life, but it affected my readiness to engage with healthcare.

As a child in care I was expected to attend health assessments at the hospital every six months. I would be told to strip down to my knickers and vest and perform tasks such as standing on one leg. I have no idea why—I found it humiliating and degrading—but I always did as I was told because my past had taught me that if I didn't I would be beaten. I was compulsively compliant and self reliant as a child and would often go out of my way to please my carers. I couldn't tell the difference between abusers and adults who were genuinely trying to help me.

ROSE LLOYD

I always did as I was told because my past had taught me that if I didn't I would be beaten

A better way

As an adult, I am still wary of health professionals, but I have been fortunate to find a great general practitioner. When I first started seeing her she encouraged me to go back to her every time I needed to see a doctor. This was such a great way to start because it meant she was able to get to know me and understand my past. That way I don't always have to refer to my history of abuse or repeatedly tell someone that I don't know about my birth family's medical history. There are still some routine tests that I'm too anxious to agree to, but she never judges my decisions. She simply tells me about the pros and cons and encourages me to think about it for the future. She is always smiling and looks at me when I'm talking so I always feel able to ask her even "silly" questions, such as the types of food I should be eating and how often. Growing up in care I was subjected to many different diets, none of which was particularly healthy.

As a doctor, you could help someone like me to realise that you are trustworthy by clearly explaining the reasons why you want me to do something and reassuring me that you will support me if I prefer not to. You may need to see me a few times before I feel ready to do what you are asking me to do, so don't place too much pressure on me, otherwise I will only start to avoid you.

WHAT YOU NEED TO KNOW

- When you ask for consent, don't assume that it is easy for me to say no. Explain your reasoning, and let me know that you won't criticise me if I refuse
- Always ask me whether there is anything else I want to talk about. I may be too nervous to tell you about my real problem. If necessary, reassure me and ask me to book a longer appointment with you
- Encourage me to come back to you in the future; that way you can get to know me and I may eventually learn to trust you

CPD/CME

0.5 CREDITS

For series information contact Rosamund Snow, patient editor, rsnow@bmj.com

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Medical management of renal stones

CPD/CME
1 CREDIT

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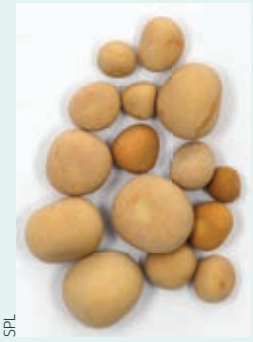
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SUMMARY

Nephrolithiasis is now recognized as both a chronic and systemic condition. Diet and environment play an important role in stone disease, presumably by modulating urine composition. Dietary modification as a preventive treatment has gained interest because of its potential to be safer and more economical than drug treatment. However, not all abnormalities are likely to be amenable to dietary therapy, and in some cases drugs are necessary to reduce the risk of stone formation. No new drugs have been developed for stone prevention since the 1980s when potassium citrate was introduced. Effective established treatment regimens are currently available for stone prevention.

About one in 11 people has a kidney stone at some point in their life.[1] More than half of those who are diagnosed with a stone will have another within 5-10 years.[2] Stone disease has been linked to several systemic disorders, including hypertension,[4] obesity,[1 5] and diabetes.[6] Although a cause and effect association has not been definitively established, the prevention of one of these disorders may affect the occurrence of the others.[7 8]

Epidemiology

Data show a linear increase in stone prevalence in the US over the past four decades, from 3.2% during 1976-80[13] to 8.8% during 2007-10 (fig 1).[1] Similarly, the age adjusted annual incidence of first time stone events in Japan more than doubled between 1965 and 2005 (from 54.2 per 100 000 to 114.3 per 100 000).[14]

Although men were two to three times more likely than women to be affected by kidney stones in the past,[15 16] recent evidence suggests that this gap is closing.[13 16 17] Recent data showed an overall prevalence of 10.6% in men and 7.1% in women (ratio 1.49).[1]

Evaluation

Screening

Prevention of recurrent stone formation involves identifying modifiable risk factors and initiating measures to correct or mitigate them. The initial evaluation is aimed at screening for those at greatest risk of recurrence (see box).

Blood tests

Certain blood tests can identify medical conditions not previously diagnosed that are associated with stone disease. Raised serum uric acid may indicate gout, with or without hyperuricosuria, and has been associated with low urine pH and uric acid or calcium oxalate stones. Low serum potassium and bicarbonate and high chloride suggest distal RTA, which increases the risk of calcium phosphate and calcium oxalate stones. Primary hyperparathyroidism is suspected when serum calcium is high or high normal and can be confirmed by measuring serum intact parathyroid hormone. Calcium phosphate stone composition and nephrocalcinosis raise suspicion of this diagnosis. High or high-normal parathyroid hormone in the setting of high or high normal serum calcium should prompt a more detailed evaluation, including parathyroid imaging or referral to an endocrine surgeon.

Urine analysis

Knowledge of previous stone composition may provide a clue to the underlying disorder, such as low urine pH in the case of uric acid stones and cystinuria for cystine stones. Stones that are composed purely of calcium phosphate raise the suspicion of underlying anatomic or metabolic disorders, such as medullary sponge kidney, primary hyperparathyroidism, or distal RTA. Calcium oxalate composition is less illuminating because of the variety and often multiplicity of the underlying disorders.

Imaging

Radiographic imaging provides a baseline assessment of stone burden and can identify anatomic or medical conditions associated with recurrent stones. Multiple stones on initial imaging, even with a first stone event, represent recurrent stone disease. The presence of a branched or staghorn calculus may reflect an infectious cause, and nephrocalcinosis implies an anatomic abnormality (medullary sponge kidney) or a metabolic condition such as primary hyperparathyroidism or distal RTA.

Metabolic testing

Metabolic testing should be pursued in patients with recurrent stones and in first time stone formers found to be at risk of recurrent stones on initial screening. Children with a kidney stone should be evaluated because of their higher incidence of genetic disorders and the long period of observation during which they may form stones.[11] Metabolic evaluation begins with analysis of one or two 24 hour urine collections obtained on a random diet. The urine is analyzed for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium, and creatinine. Indicators of animal protein intake—such as urinary sulfate and urine urea nitrogen, and estimates of urinary supersaturation—are helpful, but

WHAT YOU NEED TO KNOW

- Stone disease has been linked to several systemic disorders, including hypertension,[4] obesity,[1 5] and diabetes
- The lifetime prevalence of kidney stone disease is estimated at 1-15% and evidence shows that these numbers are rising[12]
- In the absence of high level evidence to support one drink over another, specific fluid recommendations cannot be made
- Animal protein restriction should include all forms of meat, including beef, poultry, and fish but not dairy products
- Both the AUA and EAU guidelines recommend the use of thiazides in recurrent hypercalciuric calcium oxalate and calcium phosphate stone formers[10]

optional, markers. The optimal number of 24 urine collections needed to attain maximum sensitivity in detecting urinary abnormalities is controversial, and both one and two 24 urine collections have been recommended.[21-24]

Improperly or incompletely collected urine is suspected when the urine creatinine is inconsistent with the patient's lean body weight, sex, and muscle mass. For women, 24 hour urine creatinine is generally 15-20 mg/kg and for men 18-24 mg/kg.

Treatment

Preventive strategies differ according to stone composition. Calcium based stones have the most diverse causes and the widest variety of dietary and drug treatments (fig 2).

Fluids

A universal recommendation for stone prevention is to maintain a high fluid intake. One study showed that the incremental increase in urine volume induced by a 500 mL water load significantly reduced urinary saturation of calcium oxalate in a group of stone formers and normal participants.[27] The protective effect of a high fluid intake was further validated in a randomized controlled trial (RCT) in which 199 recurrent calcium oxalate stone formers were randomized to a high fluid diet that produced a urine volume of at least 2 L a day or to a control group with no specific recommendations.[28] At the end of the five year trial, mean urine volume in the high fluid group was more than 2.5 times higher than in the control group, the recurrence rate was less than half that of the control group, and the time to recurrence was longer. Three large cohort studies found that coffee, tea, beer, wine, and orange juice were associated with a reduced risk of incident stone formation but sugar sweetened drinks and punch were associated with an increased risk of stone formation.[29] Citrus fruits and juices, which are thought to confer a protective effect against stone formation because of their high citrate content, have shown mixed results in metabolic studies that evaluated their effect on urinary stone risk factors.[30-32]

In the absence of high level evidence to support one drink over another, specific fluid recommendations cannot be made.

Calcium

Although several inherited and systemic conditions are associated with calcium nephrolithiasis,[36] the cause of most calcium based stones is unknown. Supersaturation of the urine with stone forming calcium salts provides the driving force for crystallization, and hypercalciuria is a contributing factor to calcium oxalate and calcium phosphate supersaturation. Hypercalciuria is the most common metabolic abnormality identified in stone formers, occurring in 30-60% of patients.[37]

Although increased dietary calcium intake raises urinary calcium, overall stone risk is affected by factors other than hypercalciuria.[39-41] One RCT randomized 120 male hypercalciuric calcium stone formers to a low calcium diet or a normal calcium, low sodium, low animal protein diet. It found that after five years the low calcium group had a higher rate of stone recurrence than the other group (38% *v* 20%; relative risk 0.49, 95% confidence interval 0.24 to 0.98; P=0.04). Although the decline in urinary calcium was similar in both groups, urinary oxalate increased (by 7.2 mg/day) in those on the low calcium diet but decreased (by 5.4 mg/day) in those on the normal calcium diet.

The potential for stone formation as a result of calcium supplementation is supported by the findings of the Women's Health Initiative (WHI). This study randomized 39 282 postmenopausal women without a history of stones to receive 1000 mg supplemental calcium and 400 IU vitamin D or placebo.[46] The calcium and vitamin D group was found to have a 17% higher risk of kidney stones than the control group (hazard ratio 1.17, 1.02 to 1.34).

Oxalate

Urinary oxalate levels are determined by a variety of factors, including genetic disorders (primary hyperoxaluria), dietary calcium and oxalate intake, the anatomic and functional integrity of the gastrointestinal tract, and the presence of oxalate degrading bacteria.

Urinary oxalate depends on dietary intake and endogenous metabolism, with the contribution from each source varying between individuals.[49] Depending on calcium intake, dietary oxalate can contribute up to 50% of urinary oxalate.[50-52] Although no difference in oxalate intake has been seen between stone formers and non-stone formers,[53] some investigators have found increased intestinal absorption of oxalate in hyperoxaluric stone formers.[54] Recurrent calcium oxalate stone formers with higher levels of urinary oxalate are advised to reduce their intake of oxalate-rich foods.[10]

Enteric hyperoxaluria is caused by chronic diarrhea due to intestinal resection or gastrointestinal malabsorptive conditions. Dietary measures to reduce urinary oxalate in these conditions include reducing fat intake, strictly reducing intake of oxalate-rich foods, and

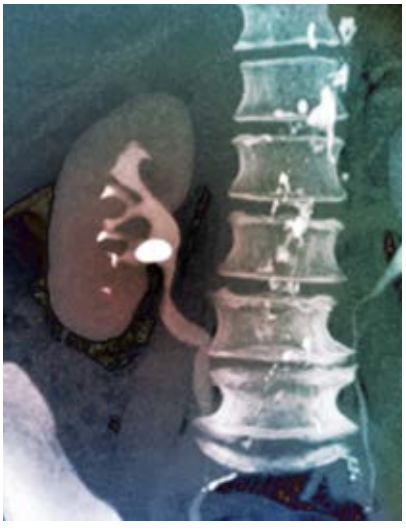
Basic screening evaluation of stone formers

History

- Stone history: number of episodes, surgical interventions, stone composition
- Medical history: risk factors, including gout, type 2 diabetes, obesity, malabsorptive conditions, distal renal tubular acidosis, sarcoidosis, hyperparathyroidism, genetic disorders (primary hyperoxaluria, cystinuria, Lesch-Nyhan syndrome, cystic fibrosis, xanthinuria, adenine phosphoribosyltransferase deficiency)
- Dietary history: high or low calcium intake, excessive animal protein intake or salt use, low fluid intake, limited intake of fruits and vegetables
- Family history of nephrolithiasis
- Drugs associated with stone formation (calcium supplements, vitamin C, carbonic anhydrase inhibitors, protease inhibitors)

Clinical studies

- Imaging: to identify anatomical abnormalities (medullary sponge kidney, ureteropelvic junction obstruction, horseshoe kidney) and to assess metabolic activity (multiplicity of stones, nephrocalcinosis)
- Blood tests
  - Creatinine
  - Sodium
  - Potassium
  - Bicarbonate
  - Chloride
  - Calcium
  - Uric acid
  - Optional: intact parathyroid hormone if indicated
- Urine:
  - Urine analysis: pH, crystals, bacteria
  - Urine culture
- Stone analysis



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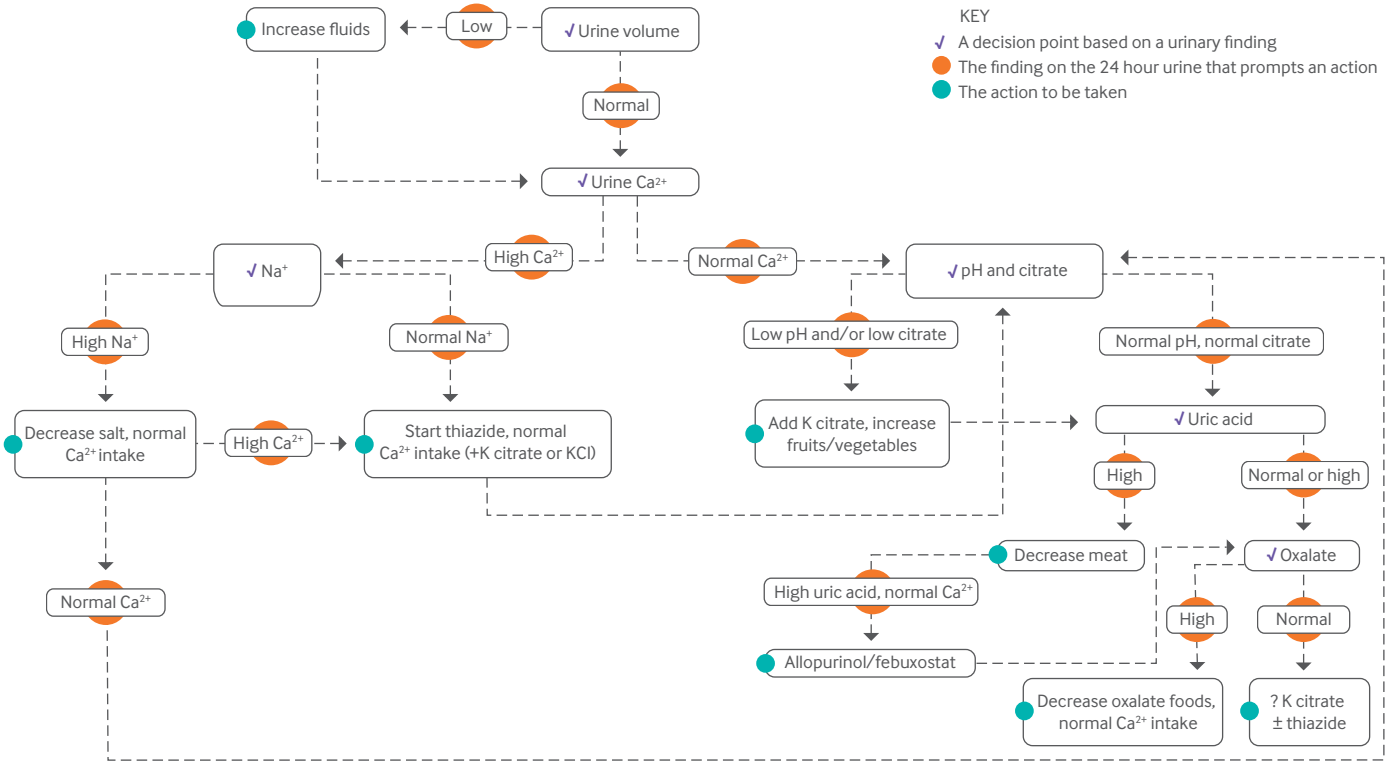


Fig 2 | **Algorithm for the management of calcium stones**

encouraging liberal consumption of low fat dairy products.

Enzymatic defects in the oxalate biosynthetic pathway can lead to markedly high oxalate concentrations, calcium oxalate stone formation, and oxalosis. Among the three forms of primary hyperoxaluria (I-III), renal failure is most commonly seen with primary hyperoxaluria type 1. Strict dietary oxalate restriction is recommended in all forms of primary hyperoxaluria.[55]

Other factors linked to higher levels of urinary oxalate are turmeric,[58] cranberry juice[59] or tablets,[60] and vitamin C. Vitamin B6 (pyridoxine), a cofactor for the conversion of glyoxylate to glycine by alanine glyoxylate aminotransferase (AGT), may reduce urinary oxalate excretion. Large cohort studies have shown an inverse association between pyridoxine intake and the risk of stone formation,[19] and a retrospective study suggested that pyridoxine, combined with dietary modification, can reduce urinary oxalate in hyperoxaluric stone formers.[62]

Citrate

Medical conditions such as distal RTA and chronic diarrheal states, and drugs such as carbonic anhydrase inhibitors that cause metabolic acidosis promote hypocitraturia.[63]

In general fruits and vegetables have a high alkali content and confer a citraturic response. A variety of citrus juices have been investigated in small metabolic studies for their effect on urinary citrate. Orange juice has shown the most consistent citraturic effect owing to its high content of potassium citrate.[30 64 65]

Epidemiologic studies have shown that people who adopt dietary habits closely resembling the "dietary approaches to stop hypertension" (DASH) diet, which is rich in fruits and vegetables, have a reduced rate of incident kidney stones.[70]

Sodium

Sodium influences stone risk by increasing urinary calcium excretion and decreasing urinary citrate. High sodium intake decreases renal proximal tubule sodium reabsorption, thus reducing renal tubular calcium reabsorption.

Sodium restriction is also an important preventive dietary measure in patients with cystinuria. Although no randomized trials have evaluated the effect of sodium restriction on cystine stone formation, small metabolic studies have consistently shown a decrease in urinary cystine excretion with reduced dietary sodium intake.[74-77]

Protein

Animal protein provides an acid load owing to the high content of sulfur containing amino acids, which leads to low urine pH and hypocitraturia.[78 79] Uric acid is the metabolic end product of purine metabolism and animal protein is a rich source of purines. Urinary uric acid has been shown to reduce the effectiveness of naturally occurring macromolecular inhibitors of calcium oxalate crystallization.[86]

The effect of restricting animal protein has been investigated in several RCTs with multicomponent dietary interventions, although the independent effect of animal protein restriction has not been evaluated.[8] Despite equivocal findings of trials, the AUA medical management of kidney stones guideline and the EAU guidelines on urolithiasis recommend restriction of non-dairy animal protein in calcium oxalate and uric acid stone formers who have relatively high levels of urinary uric acid.[10 89]

Animal protein restriction should include all forms of meat, including beef, poultry, and fish but not dairy products.

Pharmacologic management (table 1)

Calcium based stones

Thiazide diuretics

An Agency for Healthcare Research and Quality (AHRQ) review reported a meta-analysis of six RCTs with a mean follow-up of three years and found that use of thiazides, compared with placebo or no treatment, was associated with a 47% relative risk reduction in stone recurrence

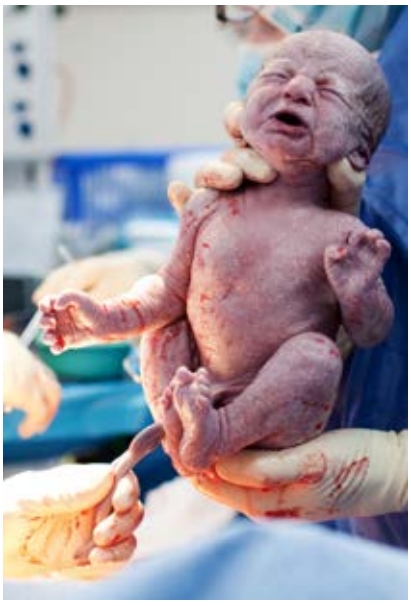
CASE REVIEW **A baby with low Apgar scores at birth**

A baby girl, weighing 3510 g (50th centile), was born at 41+1 weeks' gestation. The mother had presented in labour and initial assessment identified placental abruption and breech presentation. At emergency caesarean, the infant was found to be in the abdominal cavity after maternal uterine rupture. At initial assessment the baby was floppy and pale, with no respiratory effort and an inaudible heart rate. She was intubated at 45 seconds and a heart rate of 70 beats/min was first heard at 1 minute; this subsequently improved.

At 10 minutes of age, she remained ventilated and Apgar scores were 2 at 1 minute, 4 at 5 minutes, 4 at 10 minutes. Venous cord gas showed pH 6.6, partial pressure of carbon dioxide 20.1 kPa, base excess −25 mmol/L, bicarbonate 15.5 mmol/L. Passive cooling was started by switching off the resuscitaire's overhead warmer.

On admission to the neonatal unit, ventilator settings were on a time cycled pressure limited mode of pressure control-assist control (PC-AC), peak inspiratory pressure 16, peak expiratory pressure 5, inspiratory time 0.4 seconds, fractional index of oxygen 0.25, ventilator rate 40 breaths/min (all breaths delivered by the ventilator owing to lack of regular spontaneous breaths by the infant). Observations included: temperature 34.8°C (axilla) and 34.4°C (rectal), heart rate 179 beats/min, respiratory rate 60 breaths/min, non-invasive blood pressure 70/30 mm Hg (mean 44), oxygen saturations 97%. Clinical examination showed generalised hypotonia with some limb movements in response to handling and no obvious clinical seizure activity at the time of admission.

1 What is the most likely diagnosis?
2 What further management is needed at this stage?
3 What other relevant investigation is useful at this stage?
4 What are the prognostic indicators?
5 What are the long term outcomes of this condition?



Submitted by Sagarika Ray

Parental consent obtained.

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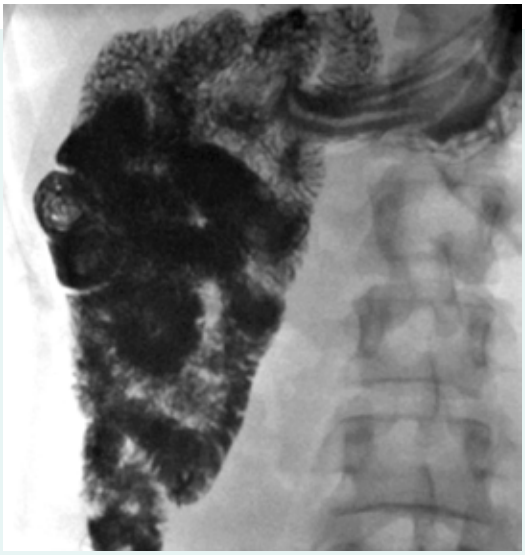

SPOT DIAGNOSIS **Abdominal pain in a 31 year old woman**

A 31 year old white woman presented with recurrent abdominal pain and distention. A barium follow through examination was performed. What is the diagnosis?

Submitted by Anuja Mitra and Nebil Behar

Patient consent obtained.

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We welcome contributions that would help doctors with postgraduate examinations. We also welcome submissions relevant to primary care. **See thebmj.com/endgames**

answers

SPOT DIAGNOSIS **Abdominal pain in a 31 year old woman**

Congenital small bowel non-rotation as indicated by loops of small bowel on the right side of the abdomen only.

CASE REVIEW **A baby with low Apgar scores at birth**

1 Hypoxic ischaemic encephalopathy (HIE).
2 Whole body therapeutic hypothermia (active cooling).
3 Cerebral function monitoring (CFM) is a valuable adjunct, but cooling therapy should not be delayed while awaiting CFM, especially if indicated on clinical grounds.
4 Indicators include results of the following: neurological and general movements assessment, CFM, electroencephalography, resistive index measured during cranial ultrasound, and magnetic resonance imaging.
5 Long term outcomes vary according to the degree of involvement of brain tissue, as noted on neuroradiological findings.

Table 1 | Pharmacologic treatments for specific urinary abnormalities

Abnormality	Drug	Dosage
Calcium stones:		
Hypercalciuria	Thiazide ± potassium citrate/ potassium chloride	Chlorthalidone (hydrochlorothiazide) 12.5-50 mg BID, indapamide 1.25-5 mg/d, chlortalidone 12.5-50 mg/d
Hypocitraturia	Potassium citrate	15-30 mEq BID
Hyperuricosuria	Allopurinol	100-300 mg/d
Hyperoxaluria:		
Primary	Pyridoxine (type I)	5-20 mg/kg/d
Enteric	Potassium citrate/citric acid (liquid formulation) Calcium supplement	10-30 mEq TID-QID titrate to reduce oxalate, take with 2 largest meals
RTA	Potassium citrate (±thiazide)	15-30 mEq BID-TID
Uric acid stones	Potassium citrate	15-30 mEq BID (titrate to pH 6-6.5)
Cystine stones	Potassium citrate, N-(2-mercaptopropionyl)glycine (tiopronin)	15-30 mEq BID (titrate to pH 7-7.5) starting dose 200 mg BID-TID and titrate to reduce cystine concentration to <250 mg/L
Struvite stones	Acetohydroxamic acid	250 mg BID-TID

BID=twice daily; RTA=renal tubular acidosis; TID=three times daily.

Table 3 | Potential adverse effects of pharmacologic management of kidney stone disease

Drug	Adverse effects	Monitoring
Thiazide	Hypokalemia, hyperlipidemia, hyperuricemia, hyperglycemia, hypocitraturia, hyperuricosuria, fatigue, erectile dysfunction	BMP, uric acid, lipid profile
Calcium supplement	Hypercalciuria (rare)	24 hour urine calcium
Potassium citrate/citric acid (liquid formulation)	Gastrointestinal upset, diarrhea	Serum potassium and creatinine
Allopurinol	Hypertransaminasemia, Stevens-Johnson syndrome	Serum liver enzymes
Cystine binding thiol drugs	Hematologic effects, proteinuria, nausea, diarrhea	CBC, BMP, urine protein
Acetohydroxamic acid	Headache, anemia, thrombophlebitis, rash, tremulousness	CBC

BMP=basic metabolic panel; CBC=complete blood count (white blood cell count, hemoglobin, hematocrit, and platelets).

rates (0.53, 0.41 to 0.68; P<0.00001).[91] As such, both the AUA and EAU guidelines recommend the use of thiazides in recurrent hypercalciuric calcium oxalate and calcium phosphate stone formers.[10]

Potassium citrate

Randomized trials have shown that potassium citrate reduces stone recurrence rates in calcium stone formers.[91 104 105] One trial that randomized 57 hypocitraturic recurrent calcium stone formers to potassium citrate or placebo found a significantly higher stone remission rate in the potassium citrate group compared with the control group (72% *v* 20%, relative risk 0.35, 0.16 to 0.75).[106] Patients with distal RTA are also treated with potassium citrate to correct the metabolic acidosis and raise urinary citrate. For patients unable to tolerate potassium citrate or in whom potassium is contraindicated, sodium bicarbonate or a combination of sodium citrate and citric acid are effective alternatives, although the calciuric effect of the sodium may offset the beneficial effect of the alkali.

Potassium citrate has been associated with gastrointestinal upset, abdominal pain, and diarrhea. Periodic monitoring with serum electrolytes and creatinine is recommended (table 3).

Allopurinol

Hyperuricosuria is detected in 15-20% of calcium stone formers.[108] Allopurinol has been shown in randomized trials to reduce stone recurrence rates in hypercalciuric and normocalciuric recurrent calcium oxalate stone formers.[109 110] Allopurinol is typically initiated when dietary measures to reduce urinary uric acid fail.

The most common adverse effect associated with allopurinol is skin rash, which in rare cases may be life threatening (Stevens-Johnson syndrome). Allopurinol can also raise liver transaminases. As such periodic monitoring of liver enzymes is recommended (table 3).

Non-calcium based stones

Uric acid stones

The most important intervention for the prevention of uric acid stones is alkali therapy to raise urine pH above solubility. Potassium citrate effectively provides an alkali load that raises urine pH and can prevent uric acid stone formation and dissolve uric acid stones.[112] The AUA medical management of kidney stones guideline recommends potassium citrate as first line treatment for the prevention of uric acid stones, with a target pH of about 6.[10] For people who continue to make stones despite adequate alkalinization or in whom the target urine pH is not attainable, allopurinol may provide additional benefit (consensus recommendation from the guideline panel).[10]

Cystine stones

Cystinuria is a rare inherited autosomal recessive condition characterized by excessive urinary excretion of cystine, orthithine, lysine, and arginine owing to a defect in intestinal and renal tubular transport of dibasic amino acids.[113 114] The primary goal of treatment in patients with cystinuria is to reduce the urinary cystine concentration to a level below the solubility limit (about 250 mg/L). Patients with cystinuria are encouraged to drink enough fluid to produce a urine volume of at least 3 L daily. Restriction of sodium and animal protein intake decreases cystine excretion.[74 115-117] All stone formers, including those with cystinuria, are advised to limit their sodium intake to less than 2300 mg (100 mEq) daily.[10]

For patients with cystinuria who continue to make stones despite dietary measures and high fluid intake, raising urine pH increases cystine solubility. Potassium citrate provides an alkali load that increases urine pH. The goal of urinary alkalinization is to achieve a urine pH of 7-7.5, although the risk of calcium phosphate stones increases at higher urine pH.

Severe cystinuria requires a cystine binding thiol drug.[118]

Struvite stones

Highly alkaline urine (pH >7.2) in the presence of urease producing organisms and a supersaturated urinary environment with respect to magnesium, ammonium, and phosphate are central to the formation of infection stones. Aggressive surgical stone removal and culture specific antibiotic therapy for prevention of recurrent infections are essential for eradication of the causative organisms, which include *Proteus* spp, *Staphylococcus aureus* and *S epidermidis*, and *Klebsiella*. Acetohydroxamic acid, a potent urease inhibitor, decreases the risk of struvite stone formation by preventing bacterial induced urease from altering the urinary milieu. Acetohydroxamic acid, along with suppressive antibiotics, is reserved for patients at high risk of recurrent struvite stone formation and those unable to undergo surgical stone removal.

Competing interests: None declared.

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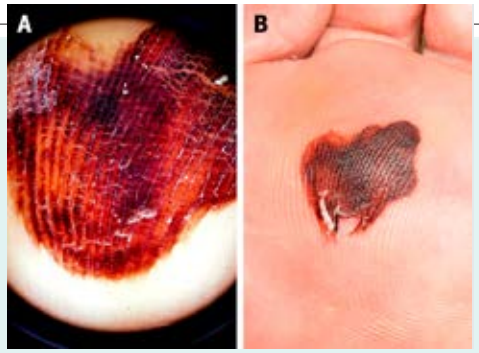
"Lightening sign" in acral dermoscopy



A woman presented with a three week history of a brown mark on the plantar surface of her left foot. Five weeks earlier she had been on a walking holiday. Examination showed asymmetrical brown discoloration with curved edges. Dermoscopy showed parallel ridged discoloration and cracks of blood, similar to bolts of lightning (A). Surface keratin was shaved off to show normal skin beneath (B). Distinguishing haemorrhage from melanocytic lesions can be difficult. The lightening sign in talon noir ("black heel"—trauma induced darkening of skin on pressure points) is a useful marker of haemorrhage on dermoscopy of acral lesions.

Helen Audrain and David DeBerker, Department of Dermatology, Bristol Royal Infirmary, Bristol, UK

Patient consent obtained.

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Find this at: http://dx.doi.org/10.1136/bmj.i365

Aspirin prevents gastrointestinal cancer, again

Call them sexist, but two cohort studies in the US continue to provide data for hundreds of useful research papers. The Nurses' Health Study was set up in 1976 as a cohort study of 121 700 US female nurses, and the Health Professionals Follow-up Study (1986) is a cohort study of 51 529 US male healthcare professionals. Those who took an aspirin tablet (325 mg or 81 mg) at least twice a week (*JAMA Oncol* doi:10.1001/jamaoncol.2015.6396), usually for headache or muscle pain, had a lower incidence of gastrointestinal tract cancers (relative risk 0.85, 95% CI 0.80 to 0.91), especially colorectal cancers (0.81, 0.75 to 0.88).

Crohn's microbiota

"Does the intestinal microbial community of Korean Crohn's disease patients differ from that of western patients?" is the intriguing title of a study in *BMC Gastroenterology* (doi:10.1186/s12876-016-0437-0). The answer is that 16S rRNA sequence data showed similar patterns of intestinal dysbiosis at the community level in Korean patients with Crohn's disease and their Western counterparts. As we continue to learn about the importance of the microbiome, comparative research like this must not be allowed to fall between two stools.

Hairy perceptions

Feeling abnormally hirsute can be a source of distress to women whose doctors don't see any abnormality at all. This emerged strongly from a study of 229 patients aged 14-52 years from a Californian polycystic ovarian syndrome clinic (*JAMA Dermatol* doi:10.1001/jamadermatol.2016.0358). Using a 36 point score, self ratings of hirsutism averaged 13.3 compared with a mean clinician rating of 8.3. Self rated hirsutism correlated with risk of depression, whereas clinician ratings did not.

Brief encounters

The NHS has long been characterised by its strong foundation in primary care. Primary care clinicians get job satisfaction from supporting people over several decades. But that is often not the perception of patients with long term conditions, according to a mixed methods study of 2001 patients undertaken five years ago (*BMC Fam Pract* doi:10.1186/s12875-016-0417-z). Participants regarded general practice as providing an essential but limited role, summed up as "minimally provided support." Since then, funding for primary care and social services has declined, and doctors leave as they can, so support for people with long term illness might now be described as sub-minimal.

App-solutely useless

A study from the American Commonwealth Fund finds that out of 1046 healthcare related, patient facing applications, 43% of iOS apps and 27% of Android apps were likely to be useful (http://www.commonwealthfund.org/). These figures are generous compared with other estimates. The fund is planning to set new standards, so perhaps there will soon be an app for checking out health apps.

Alcohol and health inequality

The ways in which alcohol can exacerbate health inequality are explored in a national telephone survey comparing areas of affluence and deprivation (*BMC Public Health* doi:10.1186/s12889-016-2766-x). Independent of total consumption, deprived drinkers were more likely to smoke, be overweight, and report poor diet and exercise. They were also more likely to binge drink, and the authors suggest that these combined factors may explain why similar levels of alcohol intake cause proportionately more harm in deprived communities.

Picturing your decision

Shared decision making should not be a Western luxury. It should underpin the working of health systems in all countries, especially the poorest. A step towards this is the first entirely pictorial option grid (*BMJ Open* doi:10.1136/bmjopen-2015-010008) developed in collaboration with patients for making decisions about the treatment of early breast cancer.

Salty non-science

Science happens when you examine a hypothesis and use experiments to contest it. Non-science is what happens when you believe a hypothesis and quote all the evidence you can to support it, while ignoring the rest. A superbly illustrated bibliometric study shows how people believing and disbelieving in the connection between salt intake and cardiovascular disease cite different sources (*Int J Epidemiol* doi:10.1093/ije/dyv184): the lines of non-science radiate from competing clusters of evidence.

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