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Vaginal Transmission of Cancer from Mothers with Cervical Cancer to Infants - Page 5

Diagnosis and Treatment of Anal Fissures in 2021 - Page 10

Health Digest

1 Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

The efficacy and safety of sodium–glucose cotransporter 2 inhibitors such as sotagliflozin in preventing cardiovascular events in patients with diabetes with chronic kidney disease with or without albuminuria have not been well studied. In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events.

Dear Doctor,

We are proud to publish the next issue of the "Health Digest" written exclusively for medical professionals for their education and well-being.

Enjoy reading…

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Research News

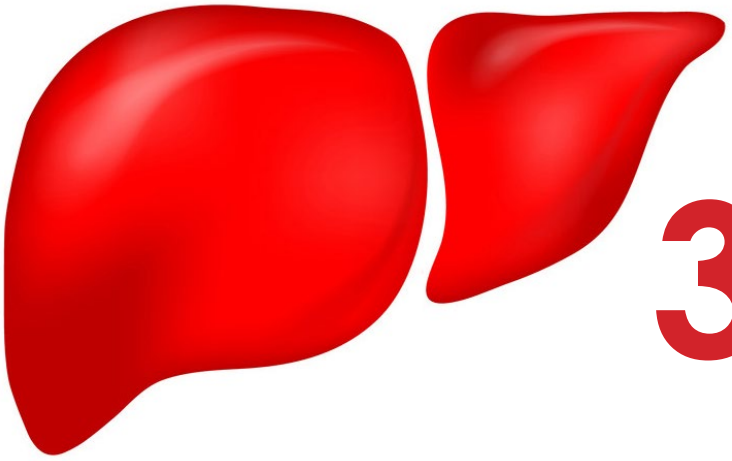
2 Antibiotics are as good as surgery for appendicitis, study reports

Antibiotics could be used instead of appendectomy to treat appendicitis in some patients, according to a study that compared the treatments in 1552 patients.

Researchers carried out a non-blinded, non-inferiority, randomised trial comparing a 10 day course of antibiotics with appendectomy in appendicitis patients across 25 centres in the US. They reported that antibiotics were non-inferior to appendectomy at 30 days, based on a quality of life questionnaire (mean difference, 0.01 points; 95% confidence interval, -0.001 to 0.03).

The researchers said their findings "may be particularly relevant during the covid-19 pandemic, as patients and clinicians weigh the benefits and risks of each approach, considering individual characteristics, preferences, and circumstances."

Antibiotics could be considered for uncomplicated appendicitis, "based on the surgeon's judgment and the patient's condition."



3 Sofosbuvir for Hepatitis C Genotype 2 or 3 in Patients

Importance Hepatitis C virus (HCV) infects more than 185 million individuals worldwide. Twenty percent of patients chronically infected with HCV progress to cirrhosis. New, simpler therapeutics using direct-acting antivirals that target various stages of the HCV life cycle are in development to eradicate HCV without concomitant interferon.

What you need to know

- After acute exposure to hepatitis C virus (HCV), about 55% to 85% of patients develop chronic hepatitis C
- Most acute and chronic infections are asymptomatic; however, hepatic inflammation is often present and can lead to progressive hepatic fibrosis
- The goal of treatment is to eradicate the virus, achieve a sustained virological response, and prevent disease progression
- Interferon based treatment regimens are no longer recommended for HCV infection as oral, direct acting antiviral agents are now considered first line therapy
- Long term complications of chronic HCV infection include cirrhosis and hepatocellular carcinoma

What causes it?

Hepatitis C virus (HCV) is an infectious, hepatotropic virus belonging to the Flavivirus family, and is transmitted by percutaneous blood exposure. The most common worldwide cause is unsafe injection practices during medical treatment. Infection is also common in people who inject drugs. Less commonly, it is spread through sexual activity, perinatally, intranasal drug use, or after accidental blood contact (such as haemodialysis). Blood and blood products not screened for HCV have also been sources of infection. About 10% of people with HCV infection have no recognised risk factor.

How does it present?

Acute infection

After initial exposure to the virus, most patients are asymptomatic. About 30% of patients have features such as fatigue, arthralgia, or jaundice, associated with a transient rise in serum aminotransferases, particularly alanine aminotransferase, but fulminant hepatic failure is extremely rare.

Chronic infection

Chronic hepatitis C infection is generally defined as persistence of HCV RNA in the blood for at least six months.

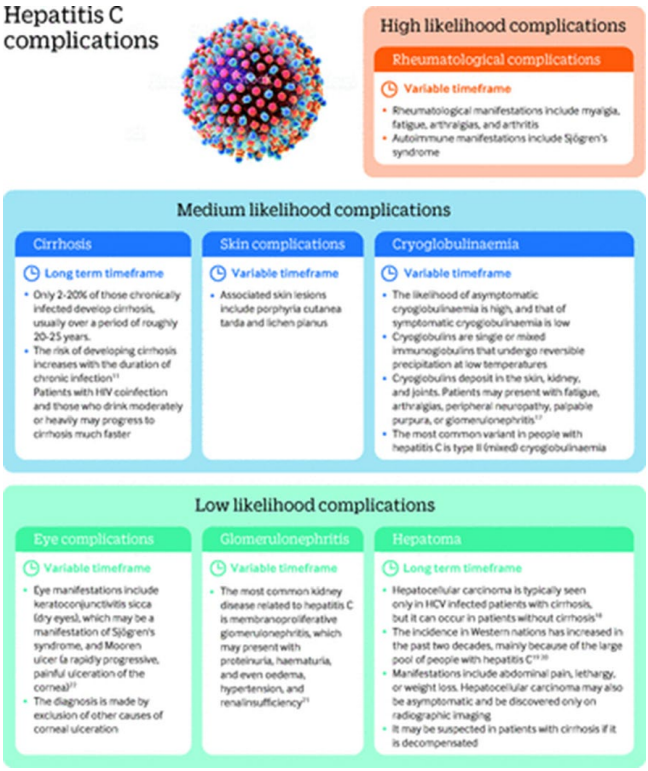
Patients are usually asymptomatic but may present with features of decompensated cirrhosis (such as jaundice, ascites, and hepatic encephalopathy) or hepatocellular carcinoma.

Occasionally, patients may present with extrahepatic manifestations (such as vasculitis, renal complications, and porphyria cutanea tarda.

Factors that influence the development of chronic liver disease

-Include older age at time of infection

-Male sex.



Concurrent chronic hepatitis B,

-HIV infection,

-high alcohol intake

Treatments:

NICE recommends sofosbuvir as an option for treating chronic hepatitis C in adults

Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase with in vitro activity against all HCV genotypes.7 In a phase 2 study of treatment for 12 weeks with sofosbuvir and ribavirin in patients with HCV genotype 2 or 3 infection, 10 of 10 previously untreated patients (100%) and 17 of 25 previously treated patients (68%) had a sustained virologic response. This oral regimen had an acceptable safety profile, with no premature discontinuations of sofosbuvir therapy owing to adverse events.

CONCLUSIONS

In a single-group study of sofosbuvir combined with peginterferon–ribavirin, patients with predominantly genotype 1 or 4 HCV infection had a rate of sustained virologic response of 90% at 12 weeks.

In a noninferiority trial, patients with genotype 2 or 3 infection who received either sofosbuvir or peginterferon with ribavirin had nearly identical rates of response (67%). **Adverse events were less frequent with sofosbuvir than with peginterferon.**

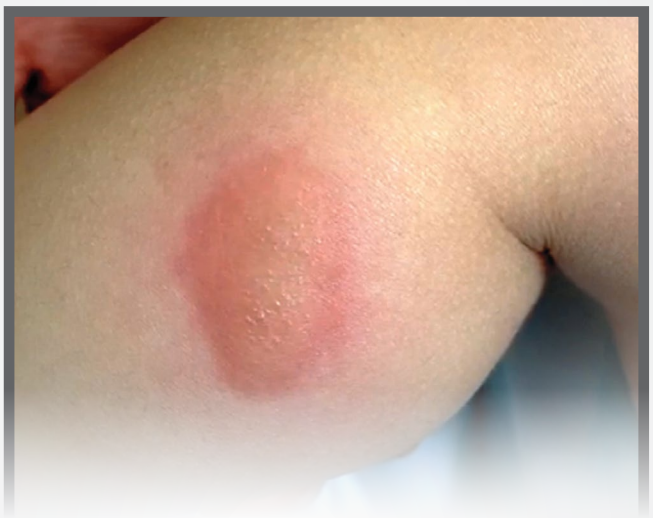
: Current treatments for hepatitis C infection

Drug regimen components (which may be given with or without ribavirin) include:

- Daclatasvir plus sofosbuvir
- Elbasvir/grazoprevir combination
- Ledipasvir/sofosbuvir combination
- Ombitasvir/paritaprevir/ritonavir combination with or without dasabuvir
- Sofosbuvir plus simeprevir
- Sofosbuvir/velpatasvir combination
- **Emerging treatments for hepatitis C infection**
- Sofosbuvir/velpatasvir/voxilaprevir combination
- Glecaprevir/pibrentasvir combination
- Second generation NS5a inhibitors
- Second generation NS5a inhibitors (other than velpatasvir) with pangenotypic activity as well as activity against resistant variants from first generation inhibitors are in development
- Non-specific cytoprotective agents may be helpful by blocking the cell injury caused by the virus infection. Ongoing research is evaluating molecular approaches to treating hepatitis C infection, such as small interfering RNA particles (gene silencing).

IMAGES IN CLINICAL MEDICINE

A Pulsating Leg



A 21-month-old boy presented to a pediatric emergency department with a 1-day history of a pruritic rash on his left leg.He had a temperature of 39.2°C and a normal heart rate and blood pressure.

-Physical examination,

He appeared well and had no heart murmur.On the left lower leg, an edematous erythematous plaque was pulsating with alternating erythema and blanching in synchrony with his pulse Quincke's sign is an alternating blanching and flushing of a specific site, in rhythm with arterial pulsation. This sign typically refers to capillary pulsations visualized in the fingernail bed that are associated with aortic insufficiency. However, the term can also be used to describe alternating blanching and flushing seen in other focal areas, such as observed in our patient who had Quincke's sign at the site of a suspected insect bite.

It was thought that the localized vasodilatation and edema present at the site of the insect bite caused arterioles to be unable to maintain adequate pressure during diastole, resulting in this pulsating blanching and flushing phenomenon.

***Treatment** for this patient included oral dimethindene maleate (an antihistamine). Within 3 hours, the pulsations stopped, and the edema and redness diminished.*

4 Zinc Deficiency–Associated Dermatitis

A 4-month-old boy who had been exclusively breast-fed was brought to the clinic with a 6-week history of a progressively worsening rash.

Physical examination revealed widespread, well-defined, erythematous, erosive plaques on the abdomen (Panel A), arms (Panel B), legs, diaper area, face, and scalp. No other abnormal physical or developmental findings were observed.

A **skin biopsy** was performed and revealed irregular orthokeratosis and parakeratosis, a reduced granular cell layer, and pallor of keratinocytes in the upper epidermal layers, findings that were suggestive of zinc deficiency.

Laboratory studies showed a serum zinc level of 226 µg per liter (3.5 µmol per liter) (reference range, 600 to 1200 µg per liter [9.2 to 18.4 µmol per liter]),

A **diagnosis** of zinc deficiency–associated dermatitis was made.

Zinc deficiency is readily treatable and important to consider since it may mimic treatment-refractory atopic dermatitis, impetigo, and other eczematous skin diseases. The underlying cause in this case was not clear, because the mother's serum zinc levels were normal.

Oral supplementation with zinc sulfate was initiated and resulted in almost complete resolution of the rash within 5 days. Oral zinc supplementation was continued, and during follow-up in the year after the initial presentation there was no recurrence of the rash.

INTRESTING READ

Vaginal Transmission of Cancer from Mothers with Cervical Cancer to Infants

Two cases of pediatric lung cancer (in 23-month-old and 6-year-old boys) resulting from mother-to-infant transmission of uterine cervical tumors were incidentally detected during routine next-generation sequencing of paired samples of tumor and normal tissue. Spontaneous regression of some lesions in the first child and slow growth of the tumor mass in the second child suggested the existence of alloimmune responses against the transmitted tumors.

PATIENT 1

Two Cases of Lung Cancer Attributed to Mother-to-Infant Transmission.

A 23-month-old boy (Patient 1) presented to a local hospital with a 2-week history of a productive cough. Computed tomography (CT) revealed multiple masses scattered along the bronchi in both lungs, and a lung biopsy performed by means of video-assisted thoracoscopic surgery (VATS) revealed neuroendocrine carcinoma of the lung with focal glandular differentiation.

A cervical cytologic test performed in the mother 7 months before the birth was negative, and the infant was delivered transvaginally at 39 weeks of gestation.

The 35-year-old mother, who had not received vaccination against human papillomavirus (HPV), received a diagnosis of squamous-cell carcinoma of the cervix 3 months after the infant's birth. After the diagnosis, she underwent radical hysterectomy with pelvic lymphadenectomy, followed by four cycles of adjuvant chemotherapy. At that time, transmission of the tumor to her son was not suspected because the histologic characteristics were thought to be different from those of her son.

In accordance with his parents' wishes, Patient 1 received frequent follow-up but did not receive treatment. One year after the diagnosis of neuroendocrine carcinoma, the lesions progressed. He was referred to our hospital for further treatment at 3 years of age

Surprisingly, some of the lesions had spontaneously regressed by that time. However, round opacities on radiographic images indicated that multiple foci of the tumor were still present in both lungs. CT imaging confirmed that tumor masses were spread along the bronchi. The patient received five cycles of chemotherapy with cisplatin (Some of the tumors shrank, but others subsequently progressed Lung, liver, and bone metastases developed in the mother during 3 years of follow-up after her last treatment.

Histologic examination of the mother's left lung tumor obtained by VATS revealed poorly differentiated carcinoma with neuroendocrine differentiation.

Pathological reexamination of the hysterectomy specimen revealed that the cervical cancer was predominantly poorly differentiated squamous-cell carcinoma with focal neuroendocrine differentiation admixed with a minor component of adenocarcinoma; this histologic picture was similar to the tumor in her lung as well as that in her son's lung .

Gene Profiles of the Tumors in the Mothers and Children.

Next-generation sequencing testing of paired samples of tumor and normal tissue was independently performed in the analysis of DNA from the lung tumor in the child and from the cervical tumor in his mother. Histologic similarities between the tumor samples from the mother and child prompted us to compare the results of their next-generation sequencing tests. The comparison of the gene profiles in the samples of tumor and normal tissue confirmed that transmission of maternal tumor to the child .

Nucleotide polymorphism (SNP) alleles carried by the mother but not inherited in the child's germline were detected in the child's tumor (i.e., the child's tumor was related to the mother's tumor and contained genes that were not in the child's germline genome).

The disease in the child progressed despite two chemotherapy regimens, so he was enrolled in a clinical trial of nivolumab therapy

He received a total of 14 cycles of nivolumab. The response continued for 7 months without the appearance of new lesions. We then performed lobectomy to resect the remaining nodule. This fibrous nodule with tertiary lymphoid formation and calcification without viable tumor cells indicated a pathological complete response. The patient had no evidence of disease recurrence at 12 months after lobectomy.

His mother was enrolled in a phase 2 trial of anti–PD-1 therapy in which nivolumab was administered at a dose of 240 mg every 2 weeks. However, the tumor progressed despite four cycles of nivolumab, and she died 5 months after disease progression.

PATIENT 2

A 6-year-old boy (Patient 2) presented to a local hospital with chest pain on the left side. CT revealed a mass measuring 6 cm in diameter at the hilar region of the left lung; mucinous adenocarcinoma was diagnosed. A cervical polypoid tumor had been detected in the patient's mother during pregnancy; however, since cervical cytologic analysis was negative and the tumor was stable without any intervention, she delivered the boy vaginally at 38 weeks of gestation. Biopsy of the cervical lesion after the delivery revealed adenocarcinoma, and she was referred to a university hospital for radical hysterectomy and bilateral salpingo-oophorectomy 3 months after delivery.

She died of the disease 2 years after the surgery. We did not suspect maternal transmission of the cancer when the child received a diagnosis at 6 years of age.

The tumor in the boy was considered to be inoperable.

He received five cycles of paclitaxel and cisplatin.

He had a partial response, with a reduction in levels of the tumor marker CA19-9 to normal levels.

The treatment was discontinued.

Three months later, the disease recurred in the left lung

After five cycles of chemotherapy, he underwent total left pneumonectomy.

Pathological examination of the lung showed mucinous adenocarcinoma, which is an unusual morphologic finding for a primary lung tumor, but it was similar to the uterine cervical tumor in the mother. He was followed for 15 months after pneumonectomy and was free from disease.

Samples of the cervical tumor from the mother and from the lung tumor of the child were submitted for next-generation sequencing tests. Although the normal samples from the mother and child differed (as expected), the similarity of the gene profiles of the tumor samples from the mother and child indicated mother-to-infant transmission .

SNP alleles that were carried by the mother but not inherited in the child's germline were detected in the tumor sample from the child.

Discussion

Here, we report two cases of lung cancer in children that was caused by transmission of cervical tumors from the children's mothers.

-The transmission was demonstrated by the fact that the tumors in both male children lacked the Y chromosome and shared multiple somatic mutations, an HPV genome, and SNP alleles (which were not inherited in the children's germline) with tumors from the mothers.

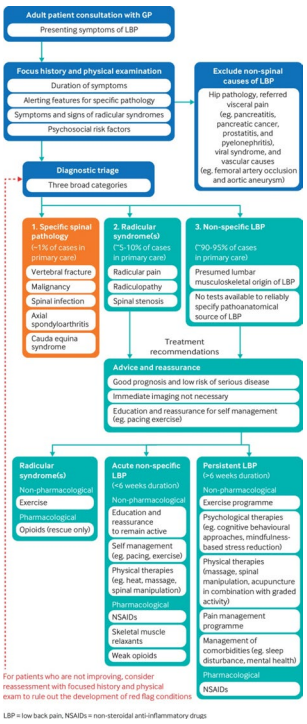
-The peribronchial pattern of tumor growth in both children suggested that the tumors arose from mother-to-infant vaginal transmission through aspiration of tumor-contaminated vaginal fluids during birth.

-In other cases of rare mother-to-fetus transmission of cancer, the offspring present with multiple disseminated metastases in the brain, bones, liver, lungs, and soft tissues; these metastases are consistent with presumed hematogenous spread from the placenta.

-However, in our two patients, tumors were observed only in the lungs and were localized along the bronchi. It is likely that maternal tumor cells were present in the amniotic fluid, secretions, or blood from the cervix and were aspirated by the infants during vaginal delivery.

-These cases indicate that mother-to-infant transmission of uterine cervical cancer is possible during vaginal delivery; therefore, cesarean section should be recommended for mothers with uterine cervical cancer.

5 Do not routinely offer imaging for uncomplicated low back pain



What you need to know

- Less than 5-10% of all low back pain is due to a specific underlying spinal pathology
- The remaining 90-95% has no indication of a serious cause and should be managed with conservative treatments such as advice and reassurance, exercise, physical therapy, chiropractic care, cognitive-behavioural therapy, or pain management
- Diagnostic triage based on clinical history and examination can help distinguish between non-specific or more serious low back pain
- Imaging may do more harm than good when serious conditions are not suspected and is likely to prolong recovery in patients with non-specific low back pain

Patients' primary concerns of whether their pain is caused by something serious and what they should do to aid recovery can be addressed by sound education and reassurance, without the need

for imaging

(a)there are clinical reasons to suspect serious underlying pathology (i.e., red flags), or

- (b) imaging is necessary for the planning and/or execution of a particular evidenced-based therapeutic intervention on a specific spinal condition.
- **Diagnostic triage and management**

Research

Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study

Read our latest coverage of the coronavirus outbreak

Objective To evaluate whether early initiation of prophylactic anticoagulation compared with no anticoagulation was associated with decreased risk of death among patients admitted to hospital with coronavirus disease 2019 (covid-19) in the United States.

Main outcome measures

The main outcome was 30 day mortality.

Secondary outcomes were inpatient mortality,

initiating therapeutic anticoagulation (a proxy for clinical deterioration, including thromboembolic events),

and bleeding that required transfusion.

Conclusions

Early initiation of prophylactic anticoagulation compared with no anticoagulation among patients admitted to hospital with covid-19 was associated with a decreased risk of 30 day mortality and no increased risk of serious bleeding events.

These findings provide strong real world evidence to support guidelines recommending the use of prophylactic anticoagulation as initial treatment for patients with covid-19 on hospital admission.

Practice Guidelines

6 Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline

What you need to know

- The likelihood of developing long term effects of covid-19 is not thought to be related to the severity of the acute infection
- The most common symptoms of long term covid-19 are fatigue and breathlessness. Symptoms may be singular, multiple, constant, transient, or fluctuating, and can change in nature over time
- Offer a chest radiograph by 12 weeks after acute covid-19 if the person has not had one already and has continuing respiratory symptoms

Covid-19 definitions

- Acute covid-19 infection—Signs and symptoms of covid-19 for up to four weeks
- Ongoing symptomatic covid-19—Signs and symptoms of covid-19 present from four weeks and up to 12 weeks
- Post-covid-19 syndrome—Signs and symptoms that develop during or after an infection consistent with covid-19, present for more than 12 weeks and are not attributable to alternative diagnoses

Possible symptoms after acute covid-19

Symptoms are highly variable and wide ranging. The most commonly reported symptoms include (but are not limited to):

Respiratory symptoms

- Breathlessness
- Cough

Cardiovascular symptoms

- Chest tightness
- Chest pain
- Palpitations

Generalised symptoms

- Fatigue
- Fever
- Pain

Neurological symptoms

- Cognitive impairment ("brain fog," loss of concentration or memory issues)
- Headache
- Sleep disturbance
- Peripheral neuropathy symptoms (pins and needles and numbness)
- Dizziness
- Delirium (in older populations)

Gastrointestinal symptoms

- Abdominal pain
- Nausea
- Diarrhoea
- Anorexia and reduced appetite (in older populations)

Musculoskeletal symptoms

- Joint pain
- Muscle pain

Psychological/psychiatric symptoms

- Symptoms of depression
- Symptoms of anxiety

Ear, nose, and throat symptoms

- Tinnitus
- Earache
- Sore throat
- Loss of taste and/or smell

Dermatological

- Skin rashes

- Include in the comprehensive clinical history:
  - history of suspected or confirmed acute covid-19
  - the nature and severity of previous and current symptoms
  - timing and duration of symptoms since the start of acute covid-19
  - history of other health conditions.
- Discuss how the person's life and activities, for example their work or education, mobility, and independence, have been affected by ongoing symptomatic covid-19 or suspected post-covid-19 syndrome.
- Discuss the person's experience of their symptoms and ask about any feelings of worry

or distress. Listen to their concerns with empathy and acknowledge the impact of the illness on their day-to-day life, for example, activities of daily living, feelings of social isolation, work and education, and wellbeing.

- Do not predict whether a person is likely to develop post-covid-19 syndrome based on whether they had certain symptoms (or clusters of symptoms) or were in hospital during acute covid-19.
- When investigating possible causes of a gradual decline, deconditioning, worsening frailty or dementia, or loss of interest in eating and drinking in older people, bear in mind that these can be signs of ongoing symptomatic covid-19 or suspected post-covid-19 syndrome.

Investigation and referral

Covid-19 may cause complications such as myocarditis and postural hypotension. However, not all symptoms will be related to covid-19. Investigations serve to rule out serious or urgent complications, evaluate symptoms secondary to ongoing symptomatic covid-19 or post-covid-19 syndrome, or to look for new, unrelated diagnoses. No one set of investigations and tests would be suitable for everyone because of the wide range of symptoms and severity.

- Offer blood tests, which may include a full blood count, kidney and liver function, C reactive protein, ferritin, B-type natriuretic peptide, and thyroid function.
- Offer a chest radiograph by 12 weeks after acute covid-19 if the person has not had one already and has continuing respiratory symptoms. Chest radiography appearances alone should not determine the need for referral for further care. Be aware that a plain chest radiograph may not be sufficient to rule out lung disease.
- If appropriate, offer an exercise tolerance test suited to the person's ability (for example the 1 minute sit-to-stand test).

During the exercise test, record level of breathlessness, heart rate, and oxygen saturation. Follow an appropriate protocol to carry out the test safely.

- For people with postural symptoms, for example palpitations or dizziness on standing, carry out lying and standing blood pressure and heart rate recordings (3 minute active stand test, or 10 minutes if you suspect postural tachycardia syndrome, or other forms of autonomic dysfunction).
- Refer people with ongoing symptomatic covid-19 or suspected post-covid-19 syndrome urgently to the relevant acute services if they have signs or symptoms that could be caused by an acute or life threatening complication, including (but not limited to):
- severe hypoxaemia or oxygen desaturation on exercise
- signs of severe lung disease
- cardiac chest pain
- multisystem inflammatory syndrome (in children).
- After ruling out acute or life threatening complications and alternative diagnoses, consider referring people to an integrated multidisciplinary assessment service (if available) any time from four weeks after the start of acute covid-19.

Planning care

- After the holistic assessment, use shared decision making to discuss and agree with the person (and their family or carers, if appropriate) what support and rehabilitation they need and how this will be provided. This should include:
- advice on self-management, with the option of supported self-management, and one of the following, depending on clinical need and local pathways:
- support from integrated and coordinated primary care, community, rehabilitation, and mental health services
- referral to an integrated multidisciplinary assessment service
- referral to specialist care for specific complications.

7 Diagnosis and Treatment of Anal Fissures in 2021

Anal fissures can occur in patients of all ages, but most commonly affect younger and middle-aged patients. Anal fissures can be acute or chronic (ie, present for >8 weeks).

*An anal fissure consists of a tear in the anoderm (the epithelial lining of the anal canal under the dentate line) that causes severe, sharp pain associated with defecation that can be debilitating.

*In addition to severe anorectal pain, fissures are associated with bright red rectal bleeding during and shortly after bowel movements because of local trauma to the anus.

* In contrast, **symptomatic** hemorrhoids occur when the veins around the anus become swollen and irritated and can cause mucoid discharge, bleeding, swelling, and/or itching.

*Severe pain with defecation is not usually associated with internal hemorrhoids, except when acute thrombosis is present. *Furthermore, the amount of localized anorectal bleeding and mucoid discharge is highly variable in hemorrhoidal disease, whereas in fissures, bleeding is usually scant and mucoid discharge is usually absent.

*Distinguishing between these entities based on clinical history alone is difficult because patients present with many of the same overlapping symptoms, but it is important because the management of these 2 conditions is very different.

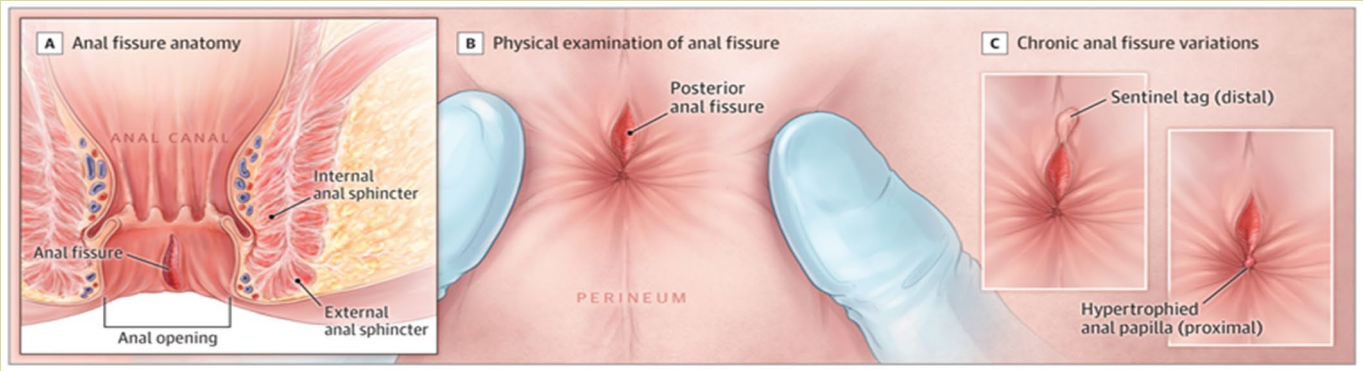
Pathophysiology

The pathophysiology of anal fissures is not entirely known, but is thought to be related to anal trauma, such as passage of hard stools, irritation from diarrhea, and anorectal procedures. A fissure begins as a small tear in the skin of the anal canal, then the exposed internal sphincter muscle spasms. This process increases sphincter tone and compromises blood flow, leading to pressure-induced ischemia that preferentially affects the midline portion of the anus, which receives less blood flow than other areas. The cycle of increased sphincter tone and poor blood flow leads to decreased likelihood of healing and contributes to the development of chronic anal fissures with fibrosed edges.

Diagnosis

Diagnosis based on physical examination findings can be difficult in patients with anal fissures because the severe pain and tenderness preclude performing a complete anorectal examination.

Ideally, patients should be examined in the prone jackknife or left lateral position on the examination table.



In up to 90% of cases, fissures are located in the posterior midline; however, in about 25% of female and 8% of male patients, fissures may be encountered in the anterior midline. Chronic fissures also may be associated with an epithelized skin tag at the distal aspect of fissure, referred to as a sentinel tag, or with a hypertrophied anal papilla proximally.

Differential Diagnoses

Because the diagnosis of anorectal diseases often relies on clinical history and physical examination findings, clinicians should consider alternative diagnoses when assessing patients who have anorectal pain.

Atypical fissures, such as those located laterally, and multiple fissures require special attention because they may be caused by Crohn disease, HIV infection, tuberculosis, syphilis, or malignancies. Patients with these atypical fissures warrant additional evaluation with examination under anesthesia or endoscopy because they may have these disorders.

Perineal infections, such as perianal abscess, also commonly present with severe anal pain with swelling, erythema, and tenderness on examination.

Patients with perineal infections often present with concomitant fever, leukocytosis, and persistent pain lasting more than 24 hours and require prompt diagnosis and treatment to avoid worsening infection. Unlike patients with anal fissures, patients with symptomatic hemorrhoids frequently present with painless rectal bleeding, pruritus ani, or prolapse. Importantly, severe anal pain from hemorrhoids is rare and only occurs in instances when hemorrhoids become thrombosed. Despite the clinical differences among these various disease entities, anal fissure symptoms are frequently misattributed to hemorrhoids by patients and referring physicians (up to 35% of the time).6

Treatment

-Initial management of anal fissure includes measures to avoid further trauma and relax the internal anal sphincter by introducing dietary fiber (25-30 g daily) and increased water intake to augment the bulk of stools, along with sitting in warm-water baths 2 to 3 times a day.

-Following these measures, anal fissure symptoms will resolve in approximately half of patients.

-Opioid medications should be avoided because constipation may exacerbate anal fissure symptoms.

-Medical management includes administration of topical calcium channel blockers (diltiazem, nifedipine) or topical nitrates (nitroglycerin). These agents cause smooth muscle relaxation and vasodilation, which help to promote fissure healing by enhancing blood flow. Diltiazem (2%) cream is applied to the anoderm 3 times a day for at least 8 weeks, with healing rates of 65% to 95%.

- Nitroglycerin ointment (0.2% or 0.4%) is used in a similar manner and can be more affordable for patients.

-Topical calcium channel blockers are efficacious with minor adverse effects, including itching, but these are unlikely to result in discontinuation of therapy.

- Symptomatic improvement may take at least 4 weeks, and there is a lag time from resolution of symptoms to complete fissure healing.

-Botulinum toxin is an exotoxin that binds to presynaptic nerve terminals at the neuromuscular junction, resulting in sphincter relaxation. Injection of botulinum toxin directly into the anal sphincter has similar healing rates compared with topical agents. Although not as effective as surgery in the long term, botulinum toxin may be considered as

an adjunctive therapy to topical calcium channel blockers and for patients who are not appropriate surgical candidates or those who are unwilling to consent to a risk of altered continence from a surgical procedure.

-Surgery is considered for patients with severe or refractory anal pain from anal fissures.

Referral to a specialist should be considered when symptoms do not begin to improve after the first 3 to 4 weeks of medical management, when atypical fissures are noted, or when the diagnosis is in question.

-The mainstay of surgical therapy for the management of anal fissure is lateral internal sphincterotomy (LIS). LIS can be done as an outpatient procedure. After anesthesia is administered, a portion of the internal sphincter muscle is divided to relieve hypertonicity. LIS is highly effective and durable, with long-term healing rates of more than 90%. Important risks of the procedure include disease recurrence and anal incontinence. Recent studies estimated that following LIS, the recurrence rate of anal fissure is 6% and incontinence ranges from 3.4% to 4.4%.

8 A prospective study of type 2 diabetes, metformin use, and risk of breast cancer

***Breast cancer risk associated with type 2 diabetes (T2D) and antidiabetic medication use was studied prospectively in the Sister Study.**

***Time varying information on self-reported diagnoses of T2D and medication use was available for 44 541 women.**

***Compared with no T2D, T2D with metformin use was associated with lower risk of estrogen receptor (ER)-positive breast cancer.**

***By contrast, T2D with metformin use was associated with higher risk of ER-negative and triple-negative breast cancer.**

***Associations between T2D and breast cancer may be altered by metformin use and differ by hormone receptor status.**

Background

Type 2 diabetes (T2D) has been associated with increased breast cancer risk, but commonly prescribed antidiabetic medications such as metformin may reduce risk. Few studies have investigated T2D and medications together in relation to breast cancer.

Patients and methods

Data came from 44 541 Sister Study participants aged 35 to 74 years at enrollment (2003-2009) who satisfied eligibility criteria, followed through 15 September 2017. Information on time-varying, self-reported, physician-diagnosed, prevalent and incident T2D, use of antidiabetic medications, and covariates was obtained from baseline and follow-up questionnaires. Incident breast cancers were confirmed with medical records. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated.

Conclusion

Our findings suggest that associations between T2D and breast cancer may differ by hormone receptor status and that associations between **T2D and ER-positive breast cancer may be reduced by long-term metformin use.**

Summarised / Edited for Internal Circulation:

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