Should there not be an appendix?
Atypical erythema, tinea incognito
Skin-colored papules on the cheeks
Spider nevi in alcoholic liver disease
Pigmented lesion on the nail bed
Skin pigmentation in Carney complex

Appendicitis management: Is it time for a change?
When to evaluate an incidentally detected common bile duct dilation
Dyspnea and cough in a lung transplant recipient
Chronic anal pain: Causes, diagnosis, and treatment
Anticoagulation management of new-onset atrial fibrillation after cardiac surgery
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A clinical trial and another clinical practice bites the dust, or should there not be an appendix?

There are clinical directives that I recall reiterated in multiple settings from medical school onwards. On medical school pediatric rotations, general surgery rotations, and during my time in the emergency ward as a resident and attending physician, the patient with potential acute appendicitis was evaluated by a surgeon and, without an alternative explanation for the symptoms and physical examination findings, the patient was admitted to the surgical service with the expectation of going to the operating room (OR). The dictum was that some patients without appendicitis need to go to the OR to avoid “missing” the opportunity to appropriately surgically treat every patient with acute appendicitis. Perhaps from naivety, it never really struck me to question the general underpinnings of this practice. Yet over the past 2 decades, several studies have assessed an alternative approach to acute appendicitis: treatment with systemic antibiotics and observation.

In this issue of the Journal, DeRoss and Fathalizadeh1 offer a commentary with their perspective on the clinical practice implications of the Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial,2 which demonstrated short-term noninferiority of antibiotic therapy vs surgical therapy for patients diagnosed with acute appendicitis.

Several challenges confront the prospective evaluation of surgical and other physical interventions. There can be significant placebo and “nocebo” effects that can only be teased out with the use of sham procedural interventions, and sometimes only incompletely. These are particularly troublesome when using subjective outcome measures like pain. For instance, there may be a 40% to 50% pain-relief response to intra-articular saline (placebo) injection into the knees of patients with osteoarthritis. This makes it extremely difficult to ascribe great benefit to the intra-articular injection of hyaluronate or corticosteroid when compared with the saline control. But in patients with acute appendicitis, unless there is a marked nocebo response associated with surgery that could muddle the interpretation, this seems not to be an issue with analysis of data from the current study.

Another challenge interpreting surgical studies like CODA is the difficulty of selecting for analysis small subsets of patients who may behave differently from the study mean and derive benefit from early surgical intervention—and detriment from an alternative approach. There have been several randomized clinical trial (RCT) evaluations of (previously) well-accepted, frequently performed surgical procedures over the past few years. These have included arthroscopic intervention for degenerative knee arthritis with or without a “torn” meniscus,1 vertebroplasty for painful vertebral fractures,4 and surgical decompression with or without fusion in patients with degenerative lumbar spondylolisthesis.5 A common reaction from surgeons to the results of these trials, which indicated little if any benefit of the studied procedures, was that patient selection and the clinical acumen and skill of the surgeon truly make a difference. Hence, it is argued that the procedures can still be of benefit in appropriately selected patients. It is tempting to dismiss this as professional hubris, but there is undoubtedly some truth in their critique of the trials.

As internists, we can espouse that we practice based on trial data and evidence-based guidelines, but population practice metrics do not bear this out. And we frequently hark to the limitations of guidelines and RCTs when it comes to individual patient treatment decisions, citing the limited external validity of the clinical trial data when applied to the very specific patient in front of us.

doi:10.3949/ccjm.89b.06022
There is no reason to believe that the same premise would not apply for surgical interventions. And I would offer that surgeons in particular “have a lot of skin in the game” when taking a patient to the OR—ie, they are uniquely and individually associated with the surgical outcome. Their assessment requires more than cursory assessment of imaging, physical examination, and clinical history. Recognition of this supports the argument for publicizing outcome data for individual surgeons.

The CODA trial was reasonably sized and, unlike several earlier studies, was broadly inclusive of a diverse patient population, representative of general practice. Nonetheless, it was not powered to perform discrete subset analysis. The short-term (30-day) results indicating noninferiority of antibiotics vs surgery jibe with older observations and suggest that the fear of imminent appendix perforation, sepsis, and possibly death for the “missed” case of acute appendicitis may have been overblown.

DeRoss and Fathalizadeh discuss details of the CODA trial and the impact they feel it should have on practice. To me, a striking part of the study—an appendix, if you will—is presented in the long-term CODA follow-up, which showed that more patients in the antibiotic-treatment group subsequently visited the emergency room, and nearly 50% of patients in this group ultimately underwent appendectomy, 30% within 90 days.

I wonder if there will ultimately be a way—other than a particularly skilled surgeon’s hand and clinical gestalt—that those 50% could be recognized early on.

But again, trial data cannot yet completely replace clinical judgment.

Brian F. Mandell, MD, PhD
Editor in Chief

CME CALENDAR

2022

JUNE

MEDICAL DERMATOLOGY THERAPY UPDATE
June 1–3
Cleveland, OH

INNOVATIONS IN CEREBROVASCULAR CARE
June 10
Cleveland, OH

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 13–17
Live stream

CLEVELAND CLINIC FLORIDA INTERNAL MEDICINE BOARD REVIEW
June 21–25
Weston, FL

MELLEN CENTER UPDATE IN MULTIPLE SCLEROSIS (MS)
June 24
Live stream

BEHAVIORAL SYNDROMES ACROSS THE NEUROPSYCHIATRIC SPECTRUM
June 25
Virtual live conference

JULY

CLEVELAND SPINE REVIEW: HANDS-ON 2022
July 20–25
Cleveland, OH

HEALTHY BRAINS, HEALTHY COMMUNITIES: CONTINUING EDUCATION CONFERENCE AND COMMUNITY EVENT
July 30
Mesquite, NV

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 5–7
Washington, DC

CLEVELAND BREAST CANCER UPDATE: COLLABORATING FOR A CURE
August 12
Cleveland, OH

SEPTEMBER

INTERPROFESSIONAL APPROACH TO MANAGEMENT OF CRITICALLY ILL LIVER PATIENTS
August 15–16
Cleveland, OH, and live stream

INTENSIVE REVIEW OF CARDIOLOGY
August 19–21
Live stream

SEPTEMBER

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
September 8–9
Cleveland, OH

HOSPITAL MEDICINE
September 8–9
Beachwood, OH, and live stream

SPASTICITY AND NEUROREHABILITATION: PEDIATRIC AND ADULT SYMPOSIUM
September 8–10
Warrensville Heights, OH

GENETICS EDUCATION SYMPOSIUM—GENETICS AND GENOMICS: APPLICATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES
September 15
Cleveland, OH

THE PRACTICE OF ECHOCARDIOGRAPHY AT CLEVELAND CLINIC 2022
September 17
Live stream

OCTOBER

OBESITY SUMMIT
September 22–23
Cleveland, OH, and live stream

RESTORING NEUROLOGICAL FUNCTION: THE CROSSROADS OF NEUROLOGY, PSYCHIATRY, AND NEUROSURGERY
September 23
Warrensville Heights, OH

GLOBAL EP 2022
September 23–24
Cleveland, OH

INTENSIVE REVIEW OF GASTROENTEROLOGY AND HEPATOLOGY
September 23–26
Las Vegas, NV

CLEVELAND CLINIC EPILEPSY UPDATE AND REVIEW COURSE
September 28–30
Cleveland, OH

NOVEMBER

PRECISION CARE IN LUNG DISEASE
November 3
Cleveland, OH

PULMONARY HYPERTENSION SUMMIT
November 4
Cleveland, OH

DECEMBER

MASTERING THE MITRAL VALVE
December 2–3
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SHAPING THE MANAGEMENT OF PARKINSON DISEASE: DEBATING THE MOST CONTROVERSIAL ISSUES AND DISCUSSING THE LATEST BREAKTHROUGHS
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Atypical erythema as a clinical presentation of tinea incognito

A 72-YEAR-OLD WOMAN was referred to the dermatology department with a 1-year history of itchy, erythematous plaques on the flexor aspects of her upper arms. The lesions had been previously diagnosed as contact allergic dermatitis and were treated with systemic and topical corticosteroids. The lesions would initially respond to treatment but would rapidly return after her prescriptions expired.

At presentation in the dermatology department, the patient had annular and polycyclic erythematous plaques with solitary papules on the periphery present on the flexor sides of the forearms (Figure 1). She declined biopsy but consented to skin scrapings. The scrapings showed the presence of hyphae, and mycological culture revealed *Trichophyton rubrum*. These findings and her history of immunosuppressant (ie, corticosteroid) therapy confirmed the diagnosis of tinea incognito, a localized, superficial dermatophyte infection that lacks the classic features of fungal infection as a result of immunosuppressant therapy. The patient received therapy with oral itraconazole 100 mg/day for 2 weeks and with topical miconazole, with full symptom resolution (Figure 2).

**Figure 1.** The patient presented with annular and polycyclic pruritic erythematous plaques localized on the flexor sides of (A) the left forearm and (B) the right forearm.
Tinea incognito is often erroneously treated with corticosteroids, which suppress the local immune response, allowing the fungus to spread easily and creating an atypical clinical presentation.\(^1,2\)

In the setting of nonresolving erythematous lesions treated with corticosteroids, skin scraping for fungal examination is recommended.\(^3\) A blunt scalpel is used to scrape the edges of a well-cleaned lesion. The scrapings are placed onto a slide covered with 10% potassium hydroxide and examined under a microscope.\(^5\) For tinea incognito, examination with low magnification (10 ×) and then higher magnification (40 ×) reveals the presence of fungal spores with or without hyphae.\(^5\)

**Take-home message**

When fungal infection is misdiagnosed and treated with corticosteroids, the normal cutaneous response is blunted, allowing the fungus to spread easily in the absence of significant erythema. The clinical presentation may suggest an infectious, paraneoplastic, allergic or autoimmune etiology.\(^1,2\) Therefore, if the appearance of a skin lesion changes or worsens during treatment with immunosuppressants, a diagnosis of tinea incognito should be considered.\(^1,2\)

**Disclosures**

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

**References**


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**Figure 2.** Complete improvement on both forearms after administration of antifungal agents.
A 43-year-old woman presented to the dermatology department with multiple small skin-colored papules on her cheeks (Figure 1) and acrochordons (“skin tags”) on the axillae (Figure 2). She reported that they had appeared over the past few years. Her personal medical history was unremarkable, but she had a first-degree relative with renal carcinoma.

Biopsy of a papule revealed dermal follicular structures surrounded by a perifollicular fibrous sheath and a densely fibrous stroma, consistent with a fibrofolliculoma (Figure 3), ie, a benign hair follicle tumor pathognomonic for Birt-Hogg-Dubé (BHD) syndrome. Subsequent genetic testing found a mutation in the FLCN gene, confirming the diagnosis.

Computed tomography showed no evidence of lung cysts or kidney tumor. Regular cancer surveillance was instituted.

BHD SYNDROME: SKIN, LUNGS, KIDNEYS

BHD syndrome is an autosomal dominant genetic disorder that predisposes patients not only to characteristic skin lesions but also to the development of lung cysts, spontaneous pneumothorax, and kidney neoplasms. It is caused by inactivating mutations in the gene that codes for folliculin, a protein that likely acts as a tumor suppressor. Most studies suggest that folliculin plays a role in the mammalian target of rapamycin (mTOR) pathway.1,2

Prevalence of BHD syndrome is uncertain. It is likely underdiagnosed, especially as more than 150 pathogenic variants with variable penetrance have been described.3,4 Some studies suggest that BHD syndrome may be the cause of 5% to 10% of cases of apparent primary spontaneous pneumothorax.3

Figure 1. Multiple whitish to skin-colored papules on both cheeks.

Figure 2. Acrochordons on the axillae.
Skin manifestations often arise first

First clinical manifestations tend to appear in the second or third decade. Many patients with BHD syndrome (75% to 90% of White patients, but only 30% to 50% of Asian patients) present with multiple fibrofolliculomas.2,4 They are rarely seen in the general population.

BHD syndrome should be suspected in patients with more than 5 fibrofolliculomas. Histologically, they appear as epithelial cells arranged in rows growing from a central aberrant hair follicle, surrounded by a thick connective-tissue stroma.1

Other dermatologic manifestations may include trichodiscomas, perifollicular fibromas, and acrochordons. These benign tumors, including fibrofolliculomas, are considered hamartomas (ie, abnormal development of normal tissue) of the hair follicle. They may be indistinguishable from each other, and some argue that they are variants of the same lesion.4 Fibrofolliculomas and trichodiscomas present as multiple, small, whitish papules, most commonly on the face, neck, and upper trunk. Acrochordons are small, pedunculated outgrowths of epidermal and dermal tissue in the neck, eyelids, upper chest, and axillae, and they may be reported as fibrofolliculomas on histology.4

Pulmonary involvement commonly develops

Over 80% of patients develop multiple, bilateral pulmonary cysts in the fourth to fifth decades,1,2,4 with up to 38% of patients experiencing at least one pneumothorax.1 Larger number and size of cysts are associated with greater likelihood of spontaneous pneumothorax, but no clear association of BHD syndrome with pulmonary cancers has been found.4

Risk of renal carcinoma is markedly increased

Patients with BHD may have a 7-fold higher risk of renal cell cancer than the general population, with an estimated prevalence between 27% and 34%.1 Frequent histologic subtypes are chromophobe and oncocytic hybrid tumors, but they rarely show sarcomatoid transformation and generally have a favorable prognosis.3 Tumors in the same kidney may also be of different histologic types, but the significance of this for prognosis is not clear.2

### MONITORING

An exact monitoring strategy has not been universally established. Risk of excessive radiation exposure from repeated computed tomography scans must be balanced with the relatively low risk of the slow-growing renal cancers associated with BHD syndrome: 12% to 34% of patients with BHD develop renal tumors.4 Most recommend periodic magnetic resonance imaging of the kidney, with the schedule (1 or 2 years) depending on past findings.6 Routine lung screening is not recommended.7 Periodic monitoring for cancers in other organs that may be associated with BHD syndrome—including the parotid, thyroid, and colon—is also recommended.7

### TAKE-HOME POINTS

- BHD syndrome is a genetic disorder caused by FLCN gene mutations that predispose patients to develop lung cysts, spontaneous pneumothorax, and renal neoplasms.
- Multiple fibrofolliculomas and trichodiscomas are benign cutaneous lesions that provide a clue to BHD.
- Upon diagnosis of BHD, screening with regular imaging is prognostically crucial for these patients, since identification of lung cysts and renal malignancies at early stages significantly improves life expectancy.

### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
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A 44-year-old male was brought to the emergency department after suffering a seizure while undergoing alcohol detoxification. His medical history was notable for liver cirrhosis secondary to excess alcohol consumption and hepatitis C infection.

The physical examination revealed signs of liver cirrhosis including palmar erythema, hepatomegaly, gynecomastia, paucity of chest hair, and red lesions on his arms, back, chest, and neck (Figure 1). The lesions blanched when pressure was applied centrally, and when pressure was released, they refilled from the center outward (Video 1).

**Pathophysiology of Spider Nevi**

Spider nevi are the ends of arterioles from which capillaries radiate outward, resembling the legs of a spider (Figure 2). Patients with chronic liver disease from alcohol consumption commonly have many spider nevi. The nevi are present in up to one-third of patients with cirrhosis, and increasing numbers of lesions correlate with the severity of liver disease and the presence of esophageal and gastric varices.1,2

As in this patient, the nevi are ordinarily distributed in blood vessels supplied by the superior vena cava (eg, in the face, neck, chest, and arms). They may also be found in patients with increased circulating estrogen, such as during pregnancy or when taking hormonal contraceptives. Occasionally, they can be seen in healthy patients with no underlying cause or pathology, and up to 3 lesions is considered normal.

Spider nevi occur due to the failure of sphincteric muscle surrounding a cutaneous arteriole.3 The mechanism of development is unclear, but they are

**Figure 1.** The patient presented with spider nevi on the chest, neck, and upper arms, as well as gynecomastia and paucity of chest hair.

**Video 1.** Spider nevus. When pressure is applied to the central arteriole, the whole lesion blanches. When pressure is released, the “legs” of the nevus refill from the center outward.
thought to be caused by excess circulating estrogen due to pregnancy or insufficient hepatic metabolism, by inadequate metabolism of steroid hormones, by neovascularization from angiogenic growth factors, or by direct vasodilatory effects of alcohol.4

■ MANAGEMENT OF THIS PATIENT

The patient’s blood test results were within normal limits. He was admitted for alcohol detoxification regimen consisting of chlordiazepoxide and tapering doses of lorazepam, titrated to Clinical Institute Withdrawal Assessment for Alcohol-Revised score. His neurologic status improved over the course of an 8-day admission. He was discharged with follow-up with community-based alcohol services.

■ DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

■ REFERENCES


Figure 2. A close-up view of the spider nevi shows a central arteriole with vessels growing outward, resembling the legs of a spider.

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A 39-year-old man was referred to the dermatology clinic for nail bed discoloration on his right thumb. The discoloration had been present since the patient was 14 years old and had not changed in appearance.

Physical examination showed a brown-black linear band with regular borders extending from the proximal nail fold along the entire nail length (Figure 1). The patient reported no significant trauma to his fingers, and his medical history was unremarkable.

Dermatoscopy revealed a linear, regular, brushy-patterned, brown-black band 3 mm wide, with homogeneity of color and thick pigmented parallel lines that were regular in width and spacing. Study of an incisional biopsy of the thumbnail matrix and the affected fold showed hyperpigmentation of the basal layer of the matrix and few melanocyte aggregations, without atypia. These features favored a diagnosis of acral lentiginous nevus.

However, because periungual pigmentation of the nail folds is also a feature of subungual melanoma (Hutchinson sign), immunohistochemical study was requested. Staining was positive for SOX10 in the epidermal melanocytes and for Ki67 in the parabasal epidermal cells. Additionally, the cyclin D1 marker was weakly positive in a few scattered cells in the upper dermis. Considering the results of pathology study, melanoma was excluded, and the diagnosis of acral lentiginous nevus presenting as pseudo-Hutchinson sign was made. The patient was referred to his primary care physician for routine follow-up.

**DIFFERENTIAL DIAGNOSIS OF THE PSEUDO-HUTCHINSON SIGN**

The Hutchinson nail sign, first described in 1886, is a periungual band of brown-black pigmentation extending from the nail matrix onto the surrounding tissue, usually due to progression of subungual melanoma. Pseudo-Hutchinson sign mimics Hutchinson sign but reflects a benign disease process. It is a diagnosis of exclusion, made only after malignancy is ruled out.

Conditions associated with pseudo-Hutchinson sign include Bowen disease, subungual squamous cell carcinoma, fungal infection, ethnic (racial) melanonychia, Peutz-Jeghers syndrome, Laugier-Hunziker syndrome, systemic disease (systemic lupus erythematosus, scleroderma), radiation therapy, AIDS, congenital nevus, drug-induced dyschromia, malnutrition, chronic trauma, and subungual hematoma.

**ASSESSMENT OF NAIL BED DISCOLORATION**

Assessment of a pigmented nail bed lesion should begin with a complete history of the lesion including...
duration, color changes, and trauma, as well as a medical history that includes medication use and a family history of melanoma. Factors that should prompt investigation for melanoma include linear band widths greater than 3 mm, linear bands wider proximally than distally, heterogeneous nail discoloration, irregular border of the discoloration, nail plate dystrophy or ulceration and bleeding, or involvement of high-risk digits (ie, thumb, index finger, great toe). However, malignancy should not be ruled out based solely on the history and physical examination. Other methods such as dermatoscopy can be used.

Dermatoscopy is a principal tool for clinical assessment of skin lesions and should be used routinely for all skin lesions. Studies have shown that compared with examination with the naked eye, dermatoscopy increases the diagnostic accuracy of melanoma. Whereas a linear brushy pattern indicates a benign condition, a diffuse haphazard pattern suggests malignancy. For suspicious lesions, serial monitoring (every 2 to 3 months), biopsy (especially excision of the pigmented lesion), referral to a dermatologist, and a second look by an expert pathologist are highly recommended. Although biopsy even in skilled hands can lead to nail dystrophy, the risk does not outweigh the risk of failing to diagnose a malignant condition such as acral melanoma.

Additional evaluations

When these evaluations fail to confirm the diagnosis of melanoma but there is still suspicion, genetic studies can be used, especially since genetic mutations play a key role in development of cancer. For example, mutations of BRAF and NRAS are the 2 most common in melanoma tumors: 40% to 60% for BRAF, and 15% to 20% for NRAS. Other options for diagnosis include immunohistochemistry screening (to evaluate the rate of mitosis and proliferation), fluorescence in situ hybridization analysis, cytogenetic testing, and comparative genomic hybridization.

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES


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Want to know the symptoms, risk factors and prevalence of OSA? Jessica Vensel Rundo, MD, MS, discusses screening tools that can be used to assess for OSA risk.

**Sleep Apnea and the Heart**
Are you able to identify the physiology of sleep-heart interactions? Reena Mehra, MD, MS, describes the association of OSA and cardiovascular health.

**Beyond Heart Health: Consequences of Obstructive Sleep Apnea**
Ever wondered about the relationship between OSA and metabolic disease, and OSA and cognitive impairment? Harneet K. Walia, MD, presents OSA’s impact on one’s quality of life.

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Spotty skin pigmentation in Carney complex

A 33-year-old man with a known history of Carney complex presented to our hospital. At 18 years of age, he was diagnosed with adrenal Cushing syndrome and acromegaly, for which he had undergone bilateral adrenalectomy and transsphenoidal surgery. Pathological examination revealed primary pigmented nodular adrenocortical disease at that time.

On examination, spotty skin pigmentation was observed on the lower lip (Figure 1) and both thumb tips (Figure 2). Moreover, the patient’s lips were noted to be thick and coarse and his hands were large in size, consistent with acromegaly. Four of his family members had similar areas of pigmentation.

DIFFERENTIAL DIAGNOSIS OF SPOTTY SKIN PIGMENTATION

Physicians commonly encounter patients with facial pigmented macules in daily practice, and this may provide an important clue for diagnosing underlying systemic disease. It should be determined if the patient has other areas of skin pigmentation and if the lesions are congenital or acquired.

In particular, characteristic skin findings and their locations can indicate underlying hereditary lentiginosis syndromes including Peutz-Jeghers syndrome, Carney complex, Noonan syndrome with multiple lentigines, Bannayan-Riley-Ruvalcaba syndrome, and Laugier-Hunziker syndrome.1,2 Among these syndromes, differentiating between Peutz-Jeghers syndrome and Carney complex is clinically important because of similar densities and distributions of lentigines. Patients with Peutz-Jeghers syndrome typically have brown-blue macules found on the lips and oral mucosa, eyes, nares, palms, soles, and perianal region.3 In contrast, patients with Carney complex typically have brown-to-black macules that are mostly found on the lips, eyelids, or canthi, and less frequently on genital mucosa or fingers.4 To assist in differential diagnosis between Peutz-Jeghers syndrome and Carney complex, it is important to note that lentigines are not usually observed on the oral mucosa in Carney complex.4 In addition, thick and coarse lips and large-sized hands are indications of acromegaly associated with Carney complex.
CARNEY COMPLEX

Carney complex is rare, hereditary in 50% of patients. In a large case series, 63% were female and 37% were male. Approximately 80% of patients have spotty skin pigmentation, with lentigines that usually appear before puberty and increase in number and density during and after adolescence. Pigment intensity tends to decrease gradually with advancing age, but lentigines can still be observed in the elderly. Lentigines in genital areas that have not been exposed to sunlight provide important information to diagnose Carney complex.

Mechanisms of skin pigmentation in Carney complex remain unclear. Carney complex is caused by mutations in the protein kinase cyclic adenosine monophosphate (cAMP)-dependent type 1 regulatory subunit alpha (PRKAR1A) gene, and loss of PRKAR1A function leads to increased cAMP activity. In general, pigmentation is regulated by the cAMP signaling pathway. Therefore, the skin pigmentation in Carney complex is probably caused by cAMP pathway activation.

Hyperpigmentation in Cushing disease
Some patients with pituitary Cushing disease or ectopic adrenocorticotropic hormone (ACTH) syndrome may have generalized hyperpigmentation of the skin and oral mucosa, caused by increased ACTH that acts through binding to melanocyte-stimulating hormone receptors. Hyperpigmentation does not occur in patients with adrenal Cushing syndrome because overproduction of cortisol suppresses ACTH secretion.

PATIENT’S TREATMENT
This patient received treatment with cabergoline and octreotide, but blood tests revealed high serum levels of growth hormone and insulin-like growth factor 1. After altering treatment to pegvisomant, at 18-month follow-up, the patient’s serum concentration of insulin-like growth factor 1 had normalized, but the pigmented lesions remained unchanged. The patient declined genetic testing.

CONCLUSION
Recognition of characteristic skin findings associated with familial lentiginosis syndromes is key for early diagnosis and can lead to early detection and treatment of multiple endocrine tumors and life-threatening cardiac myxomas, and thereby curtail disease-specific mortality.

DISCLOSURES
The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

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Acute appendicitis is one of the most common general surgical emergencies, with an estimated lifetime risk of 7% to 9% in the United States. More than 95% of US patients with appendicitis are managed by appendectomy, representing a significant healthcare burden. Although antibiotic therapy has been successfully used as an alternative therapy for more than 60 years, it has not superseded surgical intervention as the primary treatment.

**SURGERY OR ANTIBIOTICS?**

The management of acute appendicitis has been heavily researched and debated over the years. Randomized controlled trials have examined the management of appendicitis in adults, but many of these had small sample sizes and excluded patients with appendicolith, thus limiting the generalizability of study results.

The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial recently shed new light on the management of appendicitis with a larger study size and broader inclusion criteria than in previous trials. The study concluded that antibiotics were noninferior to appendectomy, based on a validated quality-of-life questionnaire.

But other aspects of management should be considered. Ultimately, the approach should be based on shared decision-making between the surgeon and the patient. Surgical appendectomy remains our general preference and our continued recommendation. However, in situations such as the COVID-19 pandemic, when hospital resources may be strained, management with antibiotics may be the best option for good stewardship of resources. Also, the effects of surgery and anesthesia in patients who may have COVID-19 are not completely understood, possibly favoring management with antibiotics at such times.

**THE CODA TRIAL: WHAT DID IT SHOW?**

The CODA trial was a nonblinded, noninferiority, randomized trial that compared antibiotic therapy (10-day course) with appendectomy at 25 US centers. Antibiotics were not standardized among centers, but the most common regimens were reported:

- Therapies for initial intravenous use of least 24 hours were ertapenem, cefoxitin, or metronidazole plus intravenous ceftriaxone, cefazolin, or levofloxacin
- Medications for oral use (remainder of 10 total days) were metronidazole plus ciprofloxacin or cefdinir.

The primary outcome focused mostly on the 30-day health status of the patient, assessed using a validated health status survey, the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. Secondary outcomes recorded were the rate of eventual appendectomy in the antibiotics group and the rate of patient complications at up to 90 days.

CODA study participants included 1,552 adults randomized to antibiotic therapy or appendectomy, with 776 in each arm of the study. The sample size in the CODA trial was larger than in previous studies and included patients with appendicolith.

**EVIDENCE FOR ANTIBIOTICS**

Based on the 30-day EQ-5D scores, the CODA trial concluded that antibiotics were noninferior to appendectomy for adults with appendicitis, and this conclusion also applied to patients who had appendicolith. Resolution of symptoms such as pain, tenderness, and fever was similar for both groups at 7, 14, and 30 days. Nearly half of patients assigned to the antibiotics group were not hospitalized. Among patients who were admitted from the emergency department, the mean time from admission to discharge was comparable for both groups. However, subsequent
emergency department visits were more common in the antibiotics group. Overall, patients receiving antibiotics missed fewer work days than those undergoing appendectomy (5.26 days with antibiotics vs 8.73 days with appendectomy).6 The largest previous randomized trial, Appendicitis Acuta,9 also demonstrated fewer missed work days in patients treated with antibiotics.

Although the rate of serious adverse events was comparable for the 2 groups in the CODA trial, the rate of surgical complications as defined by the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) criteria was higher in those in the antibiotics group who eventually underwent surgery.6 The difference was attributable to patients with appendicolith, which has been linked to higher rates of complications in other studies.5,6 A recent meta-analysis of 5 randomized controlled trials also showed lower complication rates and shorter disability with antibiotic treatment than with appendectomy.10

■ THE CASE FOR APPENDECTOMY

Although the patients in the CODA antibiotics arm had comparable initial hospital visit times, they subsequently required 3 times more emergency department visits and had twice as many NSQIP-defined complications than those who underwent appendectomy.6 Percutaneous drainage procedures were also more common in the antibiotics group.6

About one-third of the patients assigned to receive antibiotics ultimately underwent appendectomy within 90 days. About 11% of patients in the antibiotics group required a redosing of antibiotics, and 10% were noncompliant with their medications. A few patients had adverse reactions to antibiotic therapy, including one that was life-threatening.6 Longer-term outcomes were reported subsequently by the CODA Collaborative for patients as far as 4 years out from treatment.8 In the antibiotics groups, the percentage of patients who underwent subsequent appendectomy was 40% at 1 year, 46% at 2 years, and 49% at 3 and 4 years.8

Appendectomy permits pathologic examination of the specimen. Neoplasms were identified on subsequent pathologic examinations in 9 patients (7 in the appendectomy group and 2 in the antibiotics group who eventually underwent appendectomy), all of whom were excluded from the study. These might have been missed with antibiotics-only management.6

■ CONCLUSIONS FOR ADULT PATIENTS

In the CODA trial, 3 in 10 patients in the antibiotic therapy group ultimately required surgery. But from the other perspective, 7 in 10 avoided surgery and missed less work time.6 The EQ-5D outcome established noninferiority of treatment with antibiotics alone compared with surgery in terms of resolution of symptoms and incidence of serious adverse events. Because quality-of-life measures were comparable between study groups, the secondary outcomes (eg, need for eventual appendectomy, percutaneous drainage, and repeat courses of antibiotics) become arguably more important when deciding between therapies.

Selection bias may have been introduced into the process because of 3,987 patients excluded due to language barriers, clinical reasons, or refusal to participate (2,629 did not agree to undergo randomization). Still, the overall trial population is likely representative of most patients being treated for appendicitis. Patients with appendicolith were associated with an increased risk of need for appendectomy and NSQIP-defined complications. These patients may be better treated with surgery initially. Although inpatient hospitalization rate is important, presentation to the emergency department is equally significant, especially in the COVID-19 era.

The optimal timing for follow-up to evaluate patients treated with antibiotics alone is undetermined. Until lifetime data are available for nonsurgical treatment of appendicitis, each patient’s case should be considered carefully. Decisions regarding therapy should be based on thorough discussion between the patient and physician.

Recommendation

We believe that compared with antibiotic therapy, appendectomy is the more definitive solution, as it limits the risk of further emergency department visits, hospitalizations, or interventions. Additionally, during times such as the COVID-19 pandemic or other public health emergency that can strain healthcare resources, it may be valuable and often necessary to reconsider treatment paradigms, as with appendectomy vs antibiotic therapy, to optimize patient care and maximize resources.

■ APPENDICITIS IN CHILDREN

Appendicitis affects approximately 250,000 people in the United States annually, with the highest incidence in children and young adults age 10 to 19.1 It accounts for approximately one-third of pediatric
hospital admissions for abdominal pain and for nearly one-third of the total cost of all pediatric general surgical conditions.11,12 A body of research is emerging to investigate antibiotic therapy as a safe and effective alternative to surgery for treatment of appendicitis in pediatric patients.

Most studies of antibiotic treatment of appendicitis in children and young adults are retrospective and involve relatively small numbers of patients.13–17 Other trials have been prospective but nonrandomized, patient-preference cohort trials comparing nonoperative management with surgical control.10,18–21 Most patients had nonperforated appendicitis.

**Less disability and cost, but risk of recurrence**

Antibiotic regimens vary in studies of children, but typically involve broad-spectrum intravenous agents during the initial hospitalization, with a course of oral amoxicillin-clavulanate or ciprofloxacin and metronidazole after discharge. Follow-up intervals of at least 1 year are common. From 20% to 36% of patients initially treated with antibiotics undergo subsequent appendectomy for persistent or recurrent symptoms. The presence of appendicolith in the appendix is associated with increased risk of failed nonoperative management.10,13,19,20 Compared with appendectomy, the nonoperative groups have significantly fewer disability days18 and lower hospital costs.22

In a meta-analysis that included many of these studies, complication-free success was higher with operative than with nonoperative management.23 Among the authors’ conclusions were the following:

- Nonoperative management for uncomplicated appendicitis does not increase the perforation rate significantly in those receiving antibiotics
- Nonoperative management may fail during the initial hospitalization in 8% of cases
- An additional 20% of patients may need a second hospitalization for recurrent appendicitis.

A meta-analysis by Maita et al24 looked at 21 studies of nonoperative management in children with appendicitis. They concluded that 92% of patients had initial resolution of symptoms, and 16% of patients underwent appendectomy after discharge from the initial hospital stay. Complications and length of hospital stay did not differ significantly between those patients treated with antibiotics alone and those treated with surgery.

A randomized controlled pilot trial studied 50 patients age 5 to 15 who had imaging-confirmed nonperforated appendicitis.25 Of these, 24 patients received antibiotic therapy alone with meropenem and metronidazole intravenously followed by ciprofloxacin and metronidazole orally. Treatment was initially successful in 22 patients (92%). At 1 year, however, the success rate had decreased to 62%, with appendectomy classified as failed management. A subsequent follow-up study showed that 46% of the patients treated with antibiotics for acute nonperforated appendicitis underwent appendectomy within a 5-year period, although only 17% of pathology specimens confirmed appendicitis histologically.26

**The Midwest Pediatric Surgery Consortium studies**

The Midwest Pediatric Surgery Consortium27 designed and executed one of the most comprehensive studies for the nonoperative management of acute appendicitis in children, using a prospective controlled intervention design. Eligibility criteria included children between ages 7 and 17 diagnosed with uncomplicated appendicitis confirmed by imaging with the following specifications27:

- Ultrasonography showing hyperemia, appendix less than or equal to 1.1 cm in diameter, compressible or noncompressible, no abscess, no appendicolith, no phlegmon
- Computed tomography or magnetic resonance imaging showing hyperemia, fat-stranding, size less than or equal to 1.1 cm in diameter, no abscess, no appendicolith, no phlegmon
- White blood cell count greater than 5.0 × 10⁹/L and less than or equal to 18.0 × 10⁹/L
- Abdominal pain starting 48 hours or less prior to the start of antibiotics.27

Patients were excluded from the study if they had any of the following:

- History of chronic intermittent abdominal pain
- Diffuse peritonitis on physical examination by the surgical team
- Positive urine pregnancy test at time of diagnosis
- Appendicolith on imaging
- Evidence on imaging of evolving perforated appendicitis including abscess or phlegmon
- Difficulty communicating (eg, due to severe developmental delay).

Nonoperative management included hospital observation with a minimum of 24 hours of intravenous antibiotics—piperacillin-tazobactam or, in the presence of penicillin allergy, ciprofloxacin and metronidazole. Patients who tolerated a regular diet were switched to oral amoxicillin and clavulanate or, in the event of penicillin allergy, ciprofloxacin and metronidazole. Patients who tolerated a regular diet and oral therapy with minimal pain were discharged.
Nonoperative management was determined to be a failure in patients who had persistent or worsening clinical or symptomatic status after receiving 24 hours of intravenous antibiotics or who returned after discharge with abdominal pain and a clinical evaluation consistent with appendicitis.

Of the 1,068 patients who participated, 370 (35%) chose nonoperative management. The success rate for nonoperative management at 1 year was 67%. There was a statistically significant decrease in patient disability days at 1 year for patients who underwent nonoperative management compared with patients who underwent surgery (6.6 vs 10.9 days). The authors noted a 19% loss to follow-up at 1 year as a limitation, along with the nonrandomized study design.

### APPENDICITIS IN THE COVID-19 ERA

COVID-19 has raised new questions about the treatment of appendicitis. Numerous reports have identified multisystem inflammatory syndrome in children as a condition that mimics appendicitis and occurs with appendicitis. Early in the pandemic, lockdown restrictions were associated with changes in the incidence of appendicitis. One study found a dramatic decrease in the number of patients presenting with appendicitis in 2020, with the authors considering whether the decrease could be attributed to altered social factors or environmental influences.

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**COVID-19 outbreaks can affect appendicitis treatment decisions**

Limited inpatient resources during COVID-19 outbreaks resulted in some centers shifting to nonoperative management of appendicitis. In a multicenter study, pediatric patients presenting with appendicitis in a major metropolitan area from March through May 2020, corresponding with a peak COVID-19 outbreak in that region, were compared with historical control patients. Control variables were collected from the same institutions for the preceding 5 years. In 55 children presenting with acute appendicitis over the 10 weeks in 2020, the perforation rate was 45% compared with a rate of 27% in the controls. There were no differences in perforation rates or length of stay between COVID-positive and COVID-negative children. Investigators postulated that disruption of local healthcare delivery systems by the pandemic may continue to impact conditions for which outcomes reflect the timeliness of care.

A separate retrospective study evaluated nonoperative management of acute appendicitis during the same spring 2020 COVID-19 peak. The investigators used the protocol established by the Midwest Pediatric Surgery Consortium, but they expanded inclusion criteria to include all patients with acute appendicitis. Patients who demonstrated improvement were discharged home promptly on oral antibiotics. The authors found that 78.2% of patients treated outside the Midwest Pediatric Surgery Consortium guidelines for inclusion, but 45.5% (25/55) were treated successfully with antibiotics within a short-term follow-up interval.

### CONCLUSIONS AND RECOMMENDATIONS FOR PEDIATRIC PATIENTS

Recent studies of appendicitis management in pediatric patients show that pediatric patients with appendicitis can be treated safely with antibiotics alone, but that nonoperative management will fail within 1 year in up to one-third of patients. The presence of appendicolith is associated with increased risk of failure of nonoperative management.

In our view, appendectomy should remain the routine choice of therapy for appendicitis in pediatric patients. At the time of diagnosis, pediatric patients have a longer life expectancy than adult patients and therefore an increased likelihood of developing recurrent appendicitis if treated nonoperatively at the initial presentation.

Questions that need to be addressed in clinical studies include the risks associated with repeated radiologic studies in patients whose nonoperative management was unsuccessful and whose symptoms recur, and the possibility that a neuroendocrine tumor within the appendix is causing acute appendicitis. Surgeons and patients together will continue to decide whether the risk for recurrent appendicitis with nonoperative management outweighs the risks of surgery, and whether the benefit of fewer disability days and decreased hospital costs seen in nonoperative management is great enough to influence how appendicitis is managed in the future.

### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
REFERENCES


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Q: Does incidentally detected common bile duct dilation need evaluation?

A: It depends. If dilation of the common bile duct is detected incidentally with ultrasonography or computed tomography (CT) and the patient has clinical signs (e.g., jaundice, pruritus, fever, weight loss), concerning laboratory test results (e.g., elevated total bilirubin), or additional concerning imaging findings (Table 1), then further evaluation is indicated with magnetic resonance cholangiopancreatography (MRCP) with contrast, endoscopic ultrasonography (EUS), or endoscopic retrograde cholangiopancreatography (ERCP). If the patient does not have clinical signs or concerning laboratory test results but does have risk factors for nonobstructive dilation such as age over 60, previous cholecystectomy, or opioid use, then the dilation is likely benign, and further investigation is not warranted.

To avoid unnecessary testing and imaging, a patient-centered approach integrating the clinical history, liver biochemistries, and knowledge of the diagnostic yield of further testing can help clinicians determine appropriate management for incidentally detected common bile duct dilation.

What Constitutes Bile Duct Dilation?

There is no absolute measurement that defines common bile duct dilation, but a dilation of 7 mm or greater is generally accepted as the cutoff for clinical and research purposes. It is important to note that measurement ranges for dilation vary based on the imaging modality, site of measurement along the duct, and patient factors (e.g., age, history of cholecystectomy). The upper limit of normal for common bile duct diameter is 6 to 8 mm when measured with transabdominal ultrasonography, and 8 to 10 mm with CT. To adjust for age, adding 1 mm to the mea-

| TABLE 1 Clinical considerations and red flags for incidental bile duct dilation |
|---------------------------------|-------------------|
| Clinical signs of bile obstruction |                      |
| Jaundice                        | Steatorrhea        |
| Acholic stools                   | Dark urine         |
| Pruritus                         | Weight loss (concern for malignancy) |
|                                 | Fever, right upper quadrant abdominal pain, and jaundice (concern for ascending cholangitis) |
| Relevant findings on laboratory testing |                     |
| Elevation of any of the following: |                       |
| • Total or direct serum bilirubin |                         |
| • Alkaline phosphatase           | Aspartate aminotransferase |
| • Alanine aminotransferase       |                         |
| Abnormal imaging findings        | Concurrently dilated pancreatic duct ("double-duct" sign) |
| Intraductal stone or lesion      | Intrahepatic duct dilation |
| Moderate to severe extrahepatic duct dilation (≥ 10 mm) | Abrupt cutoff in common bile duct dilation |
| New or progressive dilation compared with prior imaging |                     |

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measurement per decade of life after age 60 or 0.4 mm for each decade of life has been proposed, although the evidence varies. After cholecystectomy, asymptomatic common bile duct dilation of up to 10 mm has been reported to be within normal range. Given the challenges to defining specific dilation values, the decision to pursue further diagnostic testing should be based on the likelihood of underlying obstructive vs nonobstructive causes.

Obstructive vs nonobstructive causes
Obstructive causes of common bile duct dilation include choledocholithiasis, malignancy (eg, pancreatic cancer, cholangiocarcinoma, ampullary carcinoma), extrinsic compression (eg, Mirizzi syndrome, lymphadenopathy, fluid collections), chronic pancreatitis stricture, periampullary diverticulum, primary sclerosing cholangitis, papillary stenosis, and parasitic worm infection (uncommon in the United States). A nonobstructive dilation can be related to age over 60, previous cholecystectomy (or other bile surgery), and opioid use, and dilation in patients with these risk factors is considered benign. Rarely, bile duct dilation is caused by cysts (eg, choledochal cysts), which typically have a distinct appearance on imaging.

■ CLINICAL EVALUATION
Specific elements of the patient’s history, physical examination, and biochemical markers can help determine if biliary obstruction warrants further investigation (Table 1). Clinical symptoms such as jaundice, steatorrhea, acholic stools, dark urine, pruritus, and weight loss can reflect obstructive causes, which may include malignancy. The combination of fever, abdominal pain, and jaundice (Charcot triad) suggests ascending cholangitis, which occurs more commonly with choledocholithiasis than with malignancy in the absence of a previous biliary procedure such as ERCP. Acute onset of symptoms including pain is typical of choledocholithiasis, whereas gradual weight loss and jaundice (often painless) suggest a malignant process.

Abnormal liver biochemistry results including elevation of total or direct serum bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase can indicate an obstructive cause and should be evaluated. To some degree, these levels can be elevated in the setting of common bile duct obstruction, depending on the cause, extent, and chronicity of disease. Moreover, imaging with EUS is more likely to reveal a cause for dilated common bile duct in patients with elevated liver biochemistries than in those without (53% vs 6%), highlighting the importance of testing for these abnormalities. Although this article focuses on evaluating incidental common bile duct dilation, if abnormal liver biochemistries persist after an appropriate workup for bile duct dilation (see discussion below), further assessment is needed in accordance with published guidelines and in consultation with gastroenterology and hepatology specialists.

Given the challenges to defining specific dilation values, further diagnostic investigation is primarily based on obstructive vs nonobstructive causes
If there are no concerning clinical or biochemical findings for obstruction and there is no explanation for nonobstructive dilation such as older age, previous cholecystectomy, or opioid use, imaging should be done to exclude features suggestive of an infrequently encountered subclinical or impending obstructive process. These include a concurrently dilated pancreatic duct (the “double-duct sign”), which could indicate a pancreatic or ampullary tumor; an appreciable intraductal biliary stone or lesion suggesting choledocholithiasis; intrahepatic duct dilation (≥ 1–2 mm); moderate to severe extrahepatic bile duct dilation (≥ 10 mm), or an abrupt cutoff of the common bile duct dilation. If available, prior imaging (including an intraoperative cholangiogram performed during cholecystectomy) should also be reviewed as a new or progressive dilation may be more concerning than a chronic stable dilation.

In the absence of the above findings, mild ductal dilation may be benign, especially in patients who are over age 60, have undergone cholecystectomy, or use opioids, and does not warrant further evaluation. Studies have shown that further diagnostic testing of incidentally found asymptomatic ductal dilatations without clinical or biochemical abnormalities has very low diagnostic yield, but it is a potential area for research.

■ IMAGING OPTIONS FOR WORKUP
If a common bile duct dilation is identified and the decision is made to pursue further workup, the next step is to determine which imaging modality to use. The most commonly used options are described below.
MRCP with contrast
MRCP with contrast detects the cause of bile duct obstruction more accurately than transabdominal ultrasonography and CT. Its sensitivity for detecting choledocholithiasis is 92% and its specificity is 97%, depending on stone size; the sensitivity for malignancy is 88%, and the specificity is 95%.1 Because MRCP is noninvasive and does not require ionizing radiation, it can be a useful first tool for evaluation of bile duct dilatation. However, its reported accuracy in distinguishing benign from malignant causes of obstruction varies widely, from 30% to 98%.1 The cost of the procedure is high compared with transabdominal ultrasonography and CT. In addition, some patients may suffer from severe claustrophobia or have difficulty holding their breath or lying still during the scan, potentially causing motion artifact and decreasing sensitivity of the imaging for smaller stones.1

Endoscopic ultrasonography
EUS provides high-resolution images of the pancreaticobiliary system, detecting choledocholithiasis with greater than 90% sensitivity and up to 100% specificity, and pancreatic neoplasms such as carcinoma and cysts with sensitivity of 90% or greater.1 If abnormalities are identified, diagnostic biopsy via fine-needle aspiration or fine-needle (core) biopsy can be performed as well. Visualization can be limited by pancreatic calcifications, inflammation from acute pancreatitis, altered anatomy of the stomach and proximal duodenum, and pneumobilia (most commonly resulting from previous instrumentation).1 Due to the cost and the need for sedation, EUS is typically performed in patients with a high probability of bile duct obstruction and with an anticipated need for tissue acquisition or intervention, or in patients for whom MRCP with contrast is not possible or is contraindicated.

Cholangiopancreatography
ERCP is primarily a therapeutic intervention when obstruction is probable (ie, there are signs of ascending cholangitis) rather than for purely diagnostic purposes, and it is typically preferred over percutaneous or surgical methods.11 This shift toward its use as a therapeutic modality is partly due to advances in noninvasive imaging (MRCP with contrast, EUS) that obviate the need for diagnostic ERCP and its related adverse events such as post-ERCP pancreatitis. In patients with bile duct obstruction, ERCP can provide decompression via sphincterotomy, stone extraction, or stent placement. If indicated, it can be performed immediately after EUS during a single session of anesthesia.12

In patients with bile duct obstruction, ERCP can provide decompression via sphincterotomy, stone extraction, or stent placement

CLINICAL APPROACH TO THE EVALUATION
For a patient with potential incidental bile duct dilation, there are 4 general clinical decision-making pathways, as follows (Figure 1)13:

- Common bile duct dilation (ie, ≥ 7 mm on ultrasonography or ≥ 10 mm on CT) with clinical or biochemical features of obstruction warrants further investigation. ERCP is the initial choice if there are signs of ascending cholangitis. If there are no signs of ascending cholangitis, MRCP with contrast or EUS is indicated, and if these imaging results are positive for obstruction, EUS for biopsy with or without ERCP for drainage is needed.
- If there is dilation but no clinical or biochemical signs of obstruction, and if the patient has risk factors for nonobstructive dilation (eg, older age, previous cholecystectomy, opioid use), no further workup is warranted. But if the patient has no risk factors for nonobstructive dilation, then pursue MRCP with contrast or EUS.
- If the common bile duct diameter is normal (ie, < 7 mm on ultrasonography or < 10 mm on CT) but there are clinical or biochemical signs of obstruction, further evaluation is warranted. If there are signs of ascending cholangitis, an ERCP is indicated. If there are no signs of ascending cholangitis, MRCP with contrast or EUS is indicated. If either imaging test shows an obstruction, EUS for biopsy with or without ERCP for drainage is needed.
- If the bile duct diameter is normal and there are no clinical or biochemical characteristics of obstruction, further evaluation is not indicated. If EUS or ERCP is warranted or if there is uncertainty regarding the workup of bile duct dilation, the patient should be referred to a gastroenterologist.

TAKE-HOME POINTS
Once identified, incidental common bile duct dilation can be categorized as nonobstructive or obstructive. Clinical, biochemical, and imaging findings should guide the decision-making regarding further evaluation or intervention. MRCP with contrast and
COMMON BILE DUCT DILATION

EUS can provide an accurate and minimally invasive diagnostic evaluation, while ERCP is best reserved for patients who require therapeutic intervention.

DISCLOSURES
Dr. Sethi has disclosed consulting for Boston Scientific, Fujifilm, Interscope, Medtronic, and Olympus America. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
REFERENCES


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A 62-year-old woman presented to the emergency department after suddenly becoming short of breath at rest. Over the past 24 hours she had also noticed a decline in her home spirometry values, and dry cough and fatigue. She had not experienced any fever, chills, weight loss, lymphadenopathy, rhinorrhea, chest pain, or palpitations. She had not traveled recently and had not been in contact with anyone who was sick.

Six years earlier, she had undergone bilateral lung transplantation for chronic respiratory failure due to usual interstitial pneumonitis. Of note, prior to transplant, both this patient and the donor had tested positive for Epstein-Barr virus and cytomegalovirus. Her medications included low-dose aspirin, trimethoprim-sulfamethoxazole, azithromycin, and an immunosuppressive regimen of tacrolimus, prednisone, and mycophenolate. She said she took her medications faithfully and did not use tobacco, electronic cigarettes, alcohol, or recreational drugs, including intravenous ones.

**PHYSICAL EXAMINATION NORMAL, BUT AN OPACITY IN HER LUNG**

On admission, the patient was hemodynamically stable and had an oxygen saturation of 97% while breathing room air. She did not appear to be in acute distress and could converse in full sentences without difficulty.

Her heart, lungs, and abdomen were normal on examination, with no rales, rhonchi, wheezes, or decreased breath sounds. While in the emergency department, her temperature went up to 38.1°C (100.6°F) without any other significant changes in her vital signs. She was given acetaminophen, and her temperature came back down.

Initial blood test results were as follows:

- White blood cell count 10.6 × 10⁹/L (reference range 3.4–9.6); a differential count was not done
- Procalcitonin below the limit of detection, ie, less than 0.06 ng/mL
- Tacrolimus 4.3 ng/mL (reference range 5.0–15.0, goal 6.0–8.0)
- Human leukocyte antigen class I and II antibodies, negative
- Aspergillus (galactomannan) antigen, negative
- Epstein-Barr virus and cytomegalovirus viral load undetectable.

Arterial blood gases were not measured, as the patient was clinically stable without tachypnea or oxygen desaturation. All other laboratory results were within normal limits.

Chest radiography revealed a new, ill-defined opacity superior to the right hilum (Figure 1). Although her seemingly benign symptoms could have been due to a self-limiting illness, in view of her immunosuppressed state, she was admitted for further workup and management.

**DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA IS WIDENED**

1. What is the most likely cause of this patient’s symptoms?
   - Respiratory tract infection
   - Pulmonary embolism
   - Lung transplant rejection and dysfunction
   - Posttransplant lymphoproliferative disorder
For patients presenting with acute onset of dyspnea and cough, the differential diagnosis is relatively broad and includes pulmonary embolism, myocardial infarction, and respiratory tract infections such as pneumonia or bronchitis. However, in this patient who has a lung transplant, it is important to also consider primary lung graft dysfunction, acute lung transplant rejection, and chronic lung allograft dysfunction, specifically bronchiolitis obliterans syndrome and restrictive allograft syndrome. And in view of her immunosuppressed state, it is also important to consider opportunistic infections, lymphoma, and iatrogenic injury due to the toxic effects of the immunosuppressive regimen.

**Chronic lung allograft dysfunction is a leading cause of long-term morbidity and mortality in lung transplant recipients**

**Respiratory tract infection**
Respiratory tract infection can include pneumonia, bronchitis, or bronchiolitis. It must be strongly suspected in immunocompromised patients, since they are prone to rapid deterioration and are at high risk of infection from a broad array of pathogens, many of which may not affect immunocompetent patients.

The most common pathogens, in order of greatest incidence, include bacteria (eg, *Staphylococcus aureus*, *Pseudomonas* species, Enterobacteriaceae, enterococci, *Haemophilus influenzae*, mycobacteria), viruses (eg, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, coronavirus), and fungi (eg, *Pneumocystis jirovecii*, *Aspergillus*).

Respiratory tract infection is the most likely diagnosis in our immunocompromised patient with dyspnea, cough, and fever with leukocytosis and chest radiography positive for a perihilar opacity.

**Pulmonary embolism**
Pulmonary embolism classically presents with pleuritic chest pain and dyspnea at rest with a physical examination notable for tachycardia, hypoxia, or both. Although our patient’s presentation with dyspnea at rest, cough, fever, and leukocytosis could be explained by pulmonary embolism, her pretest probability of pulmonary embolism was zero based on the absence of hereditary and acquired risk factors (eg, clinical signs or symptoms of deep vein thrombosis, hemoptysis, immobilization). Therefore, additional evaluation for pulmonary embolism was not warranted.

**Lung transplant rejection or dysfunction**
Transplant rejection or dysfunction should be high on the list of differential diagnoses when a recipient presents with new or worsening respiratory symptoms or a decline in spirometric values. Determining how long after transplant the symptoms began can help establish the type of rejection.

**Primary lung graft dysfunction** is not a consideration in our patient, as it presents within 72 hours of transplant with hypoxemia and evidence of diffuse alveolar infiltrates on chest radiography.

**Acute rejection** typically occurs within the first 6 months after lung transplantation and can be subdivided into cellular and antibody-mediated rejection. Our patient received her lung transplant 6 years ago and has no history of rejection, making this diagnosis less likely, even though her serum tacrolimus level was subtherapeutic on admission. The absence of serum human leukocyte antigen antibodies during initial laboratory testing was also reassuring.

**Chronic lung allograft dysfunction** is a leading cause of long-term morbidity and mortality in lung transplant recipients and is a major reason the 5-year survival rate is only about 55%. It typically occurs more than 6 months after lung transplant and is char-
characterized by an obstructive (ie, bronchiolitis obliterans syndrome) or restrictive phenotype.7 Our patient reported a decrease in her home spirometry values, but it was an acute decrease, occurring over less than 3 weeks, making chronic lung allograft dysfunction less likely. Also, our patient has been taking azithromycin prophylactically, which has demonstrated effectiveness in preventing bronchiolitis obliterans syndrome.5,7 However, if other possible causes of her acute symptoms are excluded, then additional evaluation may be warranted.

Posttransplant lymphoproliferative disorder occurs in 3% to 10% of lung transplant recipients, who are the group of transplant recipients with the second highest incidence rate of this disorder (after multiorgan and intestinal transplant recipients).8 Its presentation is nonspecific, but it should be considered in lung transplant recipients presenting with a mononucleosis-like syndrome (fever, malaise, tonsillitis, pharyngitis) or fever of unknown origin.9 It is strongly associated with Epstein-Barr virus. Our patient had no constitutional symptoms such as weight loss or fever, no asymmetric lymphadenopathy on examination, and no detectable Epstein-Barr virus in peripheral blood, making this diagnosis less likely. However, as noted, both the patient and the donor were seropositive for Epstein-Barr virus.

Our patient had no constitutional symptoms such as weight loss or fever, no asymmetric lymphadenopathy on examination, and no detectable Epstein-Barr virus in peripheral blood, making this diagnosis less likely. However, as noted, both the patient and the donor were seropositive for Epstein-Barr virus before transplant.

■ THE NEXT STEP

2 What should be the next step in this patient’s management?

☐ Obtain a viral respiratory pathogen panel, including urine, sputum, and blood cultures
☐ Empirically start broad-spectrum intravenous antimicrobials
☐ Perform bronchoscopy with bronchoalveolar lavage and transbronchial biopsy
☐ Obtain serial chest radiographs and treat her symptoms only

Because infection is very strongly suspected in our patient, the next step should be a viral respiratory pathogen panel, sputum Gram stain and cultures, and blood cultures, and empirical antimicrobial therapy should be started.

Identifying a culprit microbe early will help in forming an appropriate treatment plan.9 Although the cost, appropriateness, and usefulness of each diagnostic test must be carefully weighed, these tests are necessary in an immunocompromised patient.

Our patient’s presentation also coincided with the ongoing COVID-19 pandemic, so based on the US Centers for Disease Control and Prevention testing criteria,10 she was tested for SARS-CoV-19 infection.

Starting broad-spectrum intravenous antimicrobials empirically is recommended before the organism responsible for the suspected infection is identified in patients at high risk of severe infection, such as solid-organ transplant recipients. These should be started right away and not delayed for specimen collection if the patient is hemodynamically unstable. The likely type of infection (bacterial, viral, or fungal) and therefore the microorganisms to consider when selecting empiric antimicrobial coverage depends on the time elapsed since the transplant procedure: the postsurgical phase (< 4 weeks), the period of maximum immunosuppression (1 to 6–12 months), or beyond 6 to 12 months.11,12

It is also important to consider environmental exposures (eg, recent travel); bacterial colonization history, including Pseudomonas, methicillin-resistant S aureus, or multidrug-resistant organisms, particularly in patients with cystic fibrosis; and whether the patient has been taking antimicrobials prophylactically.11

We selected antimicrobials for our patient to cover community-acquired bacterial pathogens, the most common causes of infection in the period beyond 6 months after transplant. We started intravenous cefepime and vancomycin because they have a broad spectrum of antimicrobial activity and because our patient had a history of allergy to fluoroquinolones and penicillin. Prophylactic trimethoprim-sulfamethoxazole for P jiroveci pneumonia and azithromycin for bronchiolitis obliterans syndrome were also continued.

Bronchoscopy with bronchoalveolar lavage and biopsy is invasive but is a reasonable next step in a lung transplant recipient in whom infection or rejection is a concern if the etiology or causative agent or agents remain unclear in the next 24 to 48 hours from the time of initial testing.1

Our patient had undergone surveillance bronchoscopy with bronchoalveolar lavage after receiving her lung transplant, and the findings were unremarkable. During her hospital stay (lasting 4 days), her oxygen requirements remained unchanged and her clinical condition improved, even though her cough changed from nonproductive to productive. We still strongly suspected infection or rejection, or both, despite unremarkable Gram stain and culture results for blood and
sputum, including a negative result for COVID-19, and we therefore went ahead with bronchoscopy with bronchoalveolar lavage and transbronchial biopsy.

**Serial chest radiographs** can help find an explanation for new or worsening signs and symptoms such as a productive cough, which our patient developed during her hospital course. Certain findings on imaging can suggest particular types of infectious or noninfectious etiologies.

In our patient, the acute finding of a focal air-space opacity may suggest a bacterial cause. If this finding is subacute or chronic, resistant bacterial infection, fungi, *Nocardia*, and mycobacterial infection may be more likely, including atypical *P. jirovecii* pneumonia or bronchiolitis obliterans organizing pneumonia.

High-resolution computed tomography after chest radiography can be useful if the radiographs appear normal. In cases of suspected acute rejection, it typically shows ground-glass opacities, interlobular septal thickening, nodules, consolidation, and volume loss, whereas in patients with suspected chronic rejection, such as bronchiolitis obliterans syndrome, it may show bronchial dilation, bronchial wall-thickening, and mosaic attenuation primarily in the lower lobes. High-resolution computed tomography was not deemed necessary in view of our patient’s abnormal results on radiography, and the inpatient team decided that bronchoscopy with bronchoalveolar lavage and transbronchial biopsy would be more definitive in diagnosing her illness.

However, most findings on imaging studies are nonspecific, and therefore microbial identification and histopathologic analysis would be more useful. Also, treating the symptoms alone would be inadequate in our immunocompromised patient.

## Hospital Course

In our patient, bronchoscopy was overall unremarkable, with minimal secretions noted. Bronchoalveolar lavage samples were obtained near the site of the focal opacity identified on imaging and tested for the following:

- *Aspergillus* antigen
- Bacteria, including *Legionella* and methicillin-resistant *S. aureus*, by Gram stain and culture
- Fungi by a smear and culture
- Mycobacteria by acid-fast smear and culture
- *P. jirovecii* by a smear
- *Bordetella pertussis*, *B parapertussis*, *B bronchiseptica*, and *B holmesii*
- Viral respiratory pathogen panel with a polymerase chain reaction assay.

The viral pathogen panel included the following organisms:

- Adenovirus
- Cytomegalovirus by polymerase chain reaction
- Herpes simplex virus 1 and 2 by polymerase chain reaction
- Human metapneumovirus (HMPV)
- Influenza AH1, AH3, and B
- Parainfluenza virus 1, 2, 3, and 4
- Respiratory syncytial virus A and B
- Rhinovirus.

Testing did not include polymerase chain reaction assays for *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* since the patient was receiving azithromycin prophylactically, but these assays should be performed if available because these are common community-acquired pathogens.

Transbronchial biopsy obtained 5 samples for histopathologic analysis. These contained lung parenchymal tissue and, in at least 3 samples, lung wall tissue. Histopathologic analysis found no evidence of acute rejection such as perivascular or interstitial mononuclear cell infiltrates.

Our patient stayed in the hospital a total of 4 days. Before her discharge, results from the viral panel from bronchoalveolar lavage were returned and were positive for HMPV. We therefore diagnosed acute or infectious bronchitis.

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**Figure 2.** Chest radiograph on day 4 showing interval improvement in opacity superior to the right hilum (circle).
HUMAN METAPNEUMOVIRUS, AN EMERGING PATHOGEN

HMPV is an emerging pathogen responsible for respiratory tract infections, which are a significant cause of morbidity and death in immunocompromised patients. HMPV infection can present with clinical symptoms as benign as a self-limiting cough and rhinorrhea, or as severe as respiratory failure and death.

Nucleic acid amplification testing of respiratory secretions with reverse transcriptase polymerase chain reaction is the gold standard for HMPV diagnosis. A higher level of suspicion is warranted for secondary bacterial pneumonia, which is associated with increased mortality in immunocompromised patients.

No guidelines or licensed antivirals currently exist, so treatment primarily consists of supportive care. Although ribavirin and intravenous immunoglobulin have been used in individual patients and series, randomized clinical trials have yet to be published. Unfortunately, infection does not provide long-term immunity, and no antivirals have been licensed for prevention, and vaccine development is still in preclinical stages.

HMPV infection can present with clinical symptoms as benign as a self-limiting cough and rhinorrhea, or as severe as respiratory failure and death.

FURTHER MANAGEMENT

Given our patient’s diagnosis of HMPV bronchitis, which of the following is the best next step in her management?

- Transition to oral antibiotics
- Decrease her immunosuppression
- Repeat chest imaging
- Supportive care only

Transitioning to oral antibiotics is appropriate in our immunocompromised patient, even though a viral pathogen has been identified, in view of her risk of developing secondary bacterial pneumonia. No high-quality evidence is available yet to guide the duration of treatment in immunocompromised patients, but our patient was discharged on a 3-day course of azithromycin at a higher dose to treat her acute infection, followed by continuation of a lower dose to prevent bronchiolitis obliterans syndrome. She was also instructed to continue using her home spirometer to monitor and ensure continuous improvement.

In an otherwise healthy patient, antibiotic treatment of acute bronchitis, which is most often of viral etiology, is not recommended, as outlined in clinical guidelines from the American College of Physicians and the Centers for Disease Control and Prevention.

Procalcitonin, a serum marker of bacterial infections, has received interest as a tool to help decide whether to start or stop antibiotics. A Cochrane review found that measuring procalcitonin resulted in a lower risk of death and a shorter duration of antibiotic use, resulting in a lower risk of antibiotic-associated side effects. However, evidence is scarce regarding its utility in immunocompromised patients. Our patient’s procalcitonin level was low and thus could not be used to support the use of antibiotics.

Decreasing immunosuppression may be a useful adjunct to antimicrobial therapy, but this benefit may be outweighed by the risks of graft rejection and increased inflammation due to immune reconstitution syndromes. Current guidelines do not provide clear direction, and the decision to decrease immunosuppression should be made on a case-by-case basis by the transplant team.

Repeat chest imaging should be done based on clinical judgment. Because our patient was immunosuppressed and had developed a productive cough while in the hospital, a repeat chest radiograph was obtained before discharge. It showed that the focal opacity in her right lung had gotten smaller (Figure 2).

Supportive care only is recommended for an otherwise healthy patient with acute bronchitis. But in an immunocompromised patient, close follow-up with repeat blood testing and imaging and consideration of antibiotic therapy are important. Of note, high-dose corticosteroids are a risk factor for progression of respiratory tract infection in immunocompromised patients with HMPV infection, so their therapeutic use is not recommended. Antileukotrienes and antihistamines may also in theory be therapeutic based on their anti-inflammatory properties, but this has not yet been demonstrated clinically.

Posthospitalization follow-up

Routine follow-up is important in the care of transplant patients, particularly after recent hospitalization.

Less than 1 week after going home, our patient had a complete blood cell count with differential, basic metabolic panel, serum phosphorus and magnesium, serum cytomegalovirus viral load, and serum
human lymphocyte antigen antibody screen: all were negative or within normal limits. Pulmonary function testing was also performed, and the results were deemed stable overall compared with earlier results. At an outpatient clinic visit with the lung transplant team, she was found to have completely recovered.

■ TAKE-HOME POINTS

- The differential diagnosis must be broad in transplant recipients when they present with even minor symptoms.
- Although a self-limiting illness is possible, a high level of clinical suspicion is warranted in immunosuppressed patients such as transplant recipients, who are at great risk of rapid deterioration.
- Early and comprehensive evaluation of transplant recipients is essential to determine appropriate treatment, as the choice of intervention may vary widely based on the diagnostic workup.
- Serial radiographic imaging may not be appropriate unless new symptoms arise or symptoms worsen.
- Community-acquired viral respiratory tract infections are common and can cause severe illness and death in solid-organ transplant recipients.

■ REFERENCES


■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.


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Unilateral pulmonary edema

To the Editor: We appreciate the article, “Unilateral pulmonary edema,” by Harano and Nakajima in the March issue (Harano Y, Nakajima M. Unilateral pulmonary edema. Cleve Clin J Med 2022; 89(3):124–125. doi:10.3949/ccjm.89a.21046). It was a very interesting discussion of the potential manifestations of unilateral pulmonary edema after COVID-19 infection. One key aspect we would like to bring to the discussion is to include multisystem inflammatory syndrome in adults (MIS-A) in the differential diagnosis. The evaluation includes fever at or before presentation, severe cardiac illness, rash with nonpurulent conjunctivitis, abdominal pain, vomiting, diarrhea, and thrombocytopenia. The recommended laboratory evaluation includes C-reactive protein, ferritin, interleukin-6, erythrocyte sedimentation rate, and procalcitonin. If indeed the patient had MIS-A, the treatment would have included steroids, intravenous immunoglobulin, and supportive care. The reason to include this in the differential is that the therapy required for the treatment of MIS-A is different than what was discussed. Given the emergence of MIS-A with COVID-19, healthcare providers would benefit from further discussion to ensure this diagnosis is contemplated especially in the 2 to 12 weeks after diagnosis of COVID-19. The patient presented by Harano and Nakajima met the criteria for severe cardiac illness, and further discussion regarding the above evaluation would be useful to know if this diagnosis was considered, because treatment would have included those we mentioned above.

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In Reply: We thank Drs. Joseph and Rohde for their insightful comments. We enthusiastically concur that practitioners should maintain a broad differential. This is particularly true in the COVID-19 era. In our article, the patient presented with unilateral pulmonary edema post-COVID-19, warranting inclusion of multisystem inflammatory syndrome in adults (MIS-A) in the differential diagnosis. However, after dissecting the case at the fine-scale level, we identified 3 critical precluding factors that effectively ruled out MIS-A:

First, although the patient presented with impairments in cardiac function, other primary and secondary clinical criteria indicative of MIS-A, such as fever, rash, nonpurulent conjunctivitis, neurologic impairments, abdominal pain, vomiting, diarrhea, and thrombocytopenia were not documented. If indeed the patient had MIS-A, the treatment would have included steroids, intravenous immunoglobulin, and supportive care. The reason to include this in the differential is that the therapy required for the treatment of MIS-A is different than what was discussed. Given the emergence of MIS-A with COVID-19, healthcare providers would benefit from further discussion to ensure this diagnosis is contemplated especially in the 2 to 12 weeks after diagnosis of COVID-19. The patient presented by Harano and Nakajima met the criteria for severe cardiac illness, and further discussion regarding the above evaluation would be useful to know if this diagnosis was considered, because treatment would have included those we mentioned above.

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REFERENCES
doi:10.3949/ccjm.89c.06001

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Anticoagulation management of post-cardiac surgery new-onset atrial fibrillation

ABSTRACT

New-onset post-cardiac surgery atrial fibrillation (PCSAF) is a frequent complication with estimated incidence of 17% to 64%, depending on type of surgery. It is associated with higher mortality, morbidity, and predisposition to stroke and systemic embolism postoperatively. Standard care involves rate or rhythm control, in addition to antithrombotic therapy in those with history of stroke, transient ischemic attack, or high risk of systemic thromboembolism. However, risk of bleeding is not negligible, and treating physicians should weigh the risks and benefits before committing to postoperative anticoagulation therapy. More investigations are warranted to explore antithrombotic therapy benefit, particularly postoperative anticoagulation, considering the potentially self-limited nature of the arrhythmia and high risk of postoperative bleeding.

KEY POINTS

Anticoagulation should be weighed against potential risk of postoperative bleeding for patients with new-onset PCSAF as it is potentially transient and self-limited.

Avoid anticoagulation therapy for transient atrial fibrillation < 48 hours.

Anticoagulation is usually recommended for 4 to 6 weeks after atrial fibrillation conversion owing to enhanced risk of thrombosis resulting from persistent weak atrial contraction.

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erative day 3. Few patients develop new-onset atrial fibrillation in the very early postoperative period or 4 days or more after surgery. In patients who have no prior history of atrial fibrillation, new-onset PCSAF is usually transient in nature, as up to 80% revert to sinus rhythm within 24 hours, and the majority of patients (90%) are in sinus rhythm 6 to 8 weeks after discharge.

**THE IMPACT OF NEW-ONSET POST-CARDIAC SURGERY ATRIAL FIBRILLATION**

Potential adverse events following new-onset PCSAF include thromboembolic complications, worsening of comorbid medical conditions, and increased mortality. Of interest, is the potentially increased rate of postoperative thromboembolic complications including stroke leading to the potential role of anticoagulation therapy in their prevention.

**Short-term complications**

In multiple series, new-onset PCSAF had been associated with increased in-hospital postoperative stroke and increased mortality. These findings were similar in both on-pump (with cardiopulmonary bypass) and off-pump (without cardiopulmonary bypass) CABG surgery, and with and without valve surgery.

There is considerable debate as to whether new onset atrial fibrillation has a high risk of recurrence after discharge.

On the other hand, other single-center studies failed to find an association between new-onset PCSAF and increased risk of in-hospital stroke. In one study, more than half of strokes occurred postoperatively rather than intraoperatively, and new-onset PCSAF was not associated with increased risk of stroke. However, older age and variables indicative of arteriosclerotic burden were risk factors for both intraoperative and postoperative stroke.

**Long-term complications**

In most reports, new-onset PCSAF has been associated with worse long-term survival and increased thromboembolic complications. For instance, in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial of patients with left main coronary artery disease who underwent revascularization with either CABG or percutaneous coro-

nary intervention, new-onset atrial fibrillation was an independent stroke predictor at three years in CABG patients.

In another cohort study of patients who had undergone CABG surgery, risk of thromboembolism was lower in the PCSAF group than in the group with atrial fibrillation that was not valvular. Anticoagulation was associated with a lower risk of thromboembolic events in both groups, and thromboembolism was not significantly higher in patients with new-onset PCSAF compared with those who did not develop new-onset atrial fibrillation after surgery.

**Risk of recurrence**

There is considerable debate as to whether atrial fibrillation developing after cardiac surgery has a high risk of recurrence and thus whether extended anticoagulation therapy to prevent thromboembolism can be beneficial. A recent meta-analysis analyzed 8 studies with a total of 1,157 participants monitored for new-onset PCSAF recurrence after discharge, all of whom were discharged in sinus rhythm and subsequently monitored by both noninvasive and invasive devices. Monitoring identified recurrence in 28.3 per 100 persons screened in the first 2 to 4 weeks after discharge using noninvasive techniques. Implanted devices identified recurrence in 61% to 100% of cases, suggesting that in-hospital PCSAF episodes are not transient. Most recurrences were asymptomatic and thus likely to be overlooked without the use of monitoring after hospital discharge.

**ANTICOAGULATION THERAPY FOR POST-CARDIAC SURGERY ATRIAL FIBRILLATION**

**Evidence behind anticoagulation and benefits**

In medical patients with chronic or recurrent atrial fibrillation, the cause-and-effect relationship between atrial arrhythmias and thromboembolic events has been thoroughly examined; however, this relationship has not been evaluated in the post-cardiac surgery setting. Current recommendations from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) 2014 and 2019 updated guidelines is to use warfarin (to target an international normalized ratio [INR] 2–3) and novel oral anticoagulants in patients with history of stroke, transient ischemic attack, or CHA2DS2-VASc score ≥ 2, defined as patients with congestive heart failure, hypertension, age ≥ 75, diabetes, stroke, vascular disease, age 65 to 74, and female.
The question remains whether these guidelines are applicable to new-onset PCSAF in the postoperative period, taking into account the following facts:

- Risk of bleeding may be significant in the postoperative period
- CHA₂DS₂-VASc is a risk stratification tool that assesses annual stroke risk, however, has not been studied as an instrument for predicting postoperative stroke and embolic phenomena
- In current literature, high-quality evidence of early postoperative antithrombotic therapy benefits in thromboembolic complications is lacking.

Kollar and colleagues described a retrospective study regarding benefits of anticoagulation in the postoperative period of 2,960 patients after CABG with 32 patients having had a postoperative stroke. The study was unique in that it examined the temporal relationship between postoperative atrial fibrillation and stroke. Seventeen of these patients continued to maintain sinus rhythm during their hospitalization. Of the remaining 15 patients, 9 had neurologic deficits before the first episode of atrial fibrillation. Of the 6 patients with atrial fibrillation preceding neurologic events, three strokes occurred within 1 week after spontaneous conversion to normal sinus rhythm. One patient with preoperative as well as intraoperative atrial fibrillation underwent emergency CABG surgery and woke up with a stroke. In the remaining two cases, the atrial fibrillation or atrial flutter episodes lasted less than 6 hours each before the onset of neurologic events. Authors concluded that aggressive anticoagulation as suggested in current guidelines could not have decreased the already low incidence of postoperative stroke. The study, however, was underpowered making it difficult to draw a conclusion that is generalizable to a large cohort. An adequately powered prospective registry evaluating the benefits of anticoagulation in the early postoperative period is warranted.

**Risk of postoperative bleeding with anticoagulation**

The questionable rationale of early anticoagulation in reducing postoperative stroke is impacted by the risk of associated bleeding in the postoperative period. For instance, there was a significant increase in large pericardial effusions and tamponade occurring one week or more after surgery in a study of patients treated with warfarin compared with the antiplatelet control group, especially when excessively anticoagulated (INR above therapeutic target).

Bleeding other than at the surgical site might be relevant when determining use of anticoagulants, particularly with gastrointestinal hemorrhage. In a single-center, retrospective analysis of 9,017 patients undergoing cardiac surgery, the incidence of endoscopy-requiring gastrointestinal hemorrhage was 1.01%, and 30-day mortality was higher in patients who bled compared with patients who did not. The study was limited in that only bleeding events requiring intervention were included.

HAS-BLED is a risk score, defined as hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile INR, elderly (age > 65), and drugs or alcohol concomitantly, that is often used to determine use of anticoagulation therapy by evaluating risks and benefits in the general population with atrial fibrillation that is not valvular. However, validity in patients after surgery has not been evaluated. Thus, a high-quality risk stratification tool to identify bleeding in surgical patients would be of great clinical value.

**Recommendations of professional societies**

The AHA/ACC/HRS guidelines recommend considering using anticoagulation medication for patients who develop new-onset postoperative atrial fibrillation as administered for nonsurgical patients. The American College of Chest Physicians suggests weighing the AHA/ACC/HRS recommendations in the context of the usually transient and self-limited duration of new-onset PCSAF against the potential risk of bleeding and recommends starting anticoagulation therapy if atrial fibrillation persists 48 hours and beyond. They further state that therapy should be continued for 30 days after the return to normal sinus rhythm because of persistent atrial contraction impairment and possible enhanced risk of thrombosis following cardioversion to sinus rhythm. The Canadian Cardiovascular Society Atrial Fibrillation Guidelines recommend continuing anticoagulation for new-onset PCSAF for a minimum of 6 weeks, although the American College of Chest Physicians and AHA/ACC/HRS did not provide details regarding timing of initiation of antithrombotic therapy. A report from the European Association for Cardio-Thoracic Surgery does not recommend immediate full antithrombotic therapy when new-onset atrial fibrillation develops within 48 hours of cardiac surgery, due to increased risk of cardiac tamponade. Table 1 provides a summary of these recommendations, and Figure 1 shows our proposed algorithm for management of new-onset PCSAF.
Selection of drugs
The American College of Chest Physicians and AHA/ACC/HRS recommend anticoagulation therapy with warfarin, with or without heparin for atrial fibrillation.22,28 Novel oral anticoagulants have been included in the 2014 and 2019 updated AHA/ACC/HRS guidelines.22,23 More recently, the 2019 report added idarucizumab and andexanet alfa for the reversal of direct thrombin and activated factor Xa inhibitors, respectively.23

In one retrospective review, patients were administered anticoagulation with either warfarin or novel oral anticoagulants for new-onset PCSAF in the postoperative period; both drug classes were found to be safe and effective methods of anticoagulation with no significant difference between outcomes of strokes,
postoperative hemorrhage, and hospital length of stay. The study was small and limited to the hospital postoperative period. Two other small pilot studies compared edoxaban and apixaban to warfarin for new-onset PCSAF and demonstrated safety and efficacy while suggesting larger scale clinical trials for further evaluation. A randomized clinical trial comparing rivaroxaban and warfarin for new-onset PCSAF is currently under way.

Monitoring of therapy and discontinuation of anticoagulants
There is a lack of evidence regarding monitoring following discharge for new-onset PCSAF patients who revert to sinus rhythm before discharge. Consequently, some hospitals have developed institutional policies regarding follow up and monitoring of patients that relies on expert opinion. For instance, a feasibility cross-sectional study with a unique idea of self-monitoring assessed 42 patients who had undergone cardiac surgery (CABG, valve surgery, or combination) for new-onset PCSAF recurrence using smart phone handheld electrocardiogram devices. Study participants were instructed to record rhythm for 30 seconds, 4 times daily, for 4 weeks after discharge. Owing to the feasibility of the study, there was no control group, randomization, or blinding. Self-monitoring identified 24% with atrial fibrillation recurrence within 17 days of hospital discharge. Owing to the feasibility of the study, there was no control group, randomization, or blinding. Self-monitoring identified 24% with atrial fibrillation recurrence within 17 days of hospital discharge.

Figure 1. Proposed algorithm for management of new-onset atrial fibrillation following cardiac surgery.
AF = atrial fibrillation; CHA2DS2-VASc = congestive heart failure, hypertension, age ≥ 75, diabetes, stroke, vascular disease, age 65 to 74, and female; PCSAF = post-cardiac surgery atrial fibrillation
tion owing to the small sample size, infrequent self-monitoring, and study duration. Additional atrial fibrillation episodes may have been detected with a larger sample size and longer daily monitoring.

**CONCLUSIONS**

Adequately powered, large prospective studies are needed to investigate the relationship between transient atrial fibrillation and subsequent thromboembolic events in the postoperative period. Assessment of risk of hemorrhage in the immediate (first 48 hours) and later (≥ 48 hours to 7 days) postoperative period must be validated for cardiac surgery patients in large scale settings and may help to predict bleeding risk and allow for evaluation of postoperative anticoagulants. It is important to identify risk assessment models other than CHA2DS2-VASc score while considering operative technique to help identify patients at high risk in the setting of cardiac surgery. Finally, multicenter randomized trials investigating the benefits and risks of anticoagulation therapy indicated for transient atrial fibrillation early after cardiac surgery are warranted.

**DISCLOSURES**

The authors report no relevant financial relationships, which, in the context of their contributions, could be perceived as a potential conflict of interest.


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Chronic anal pain: A review of causes, diagnosis, and treatment

ABSTRACT

Chronic anal pain is difficult to diagnose and treat, especially with no obvious anorectal cause apparent on clinical examination. This review identifies 3 main diagnostic categories for chronic anal pain: local causes, functional anorectal pain, and neuropathic pain syndromes. Conditions covered within these categories include proctalgia fugax, levator ani syndrome, pudendal neuralgia, and coccygodynia. The signs, symptoms, relevant diagnostic tests, and main treatments for each condition are reviewed.

KEY POINTS

Local causes of chronic anal pain can be identified by clinical examination based on index of suspicion and with or without adjunctive diagnostic testing.

Functional anorectal pain syndromes can be subdivided into 3 diagnoses with management individualized for each, albeit with a limited evidence base.

Neuropathic pain syndromes are rare but can be positively diagnosed to allow specific management.

CHRONIC ANAL PAIN IS A RELATIVELY COMMON PROBLEM AFFECTING UP TO 11.6% OF THE US POPULATION. 1 Although many adults have self-limiting symptoms that do not lead to specialist consultation, there is a subgroup of patients with refractory or severe symptoms who do visit surgical clinics. Such patients may see several specialists, such as a colorectal surgeon, urologist, and gynecologist, and may undergo numerous diagnostic or even surgical procedures. It is a sad reality that patients with chronic anal pain commonly feel resigned to defeat when being evaluated by a clinician whose training fails to cover painful anal conditions beyond fissure, fistula, prolapsed hemorrhoids, and other conditions caused by overt disease.

But this need not be so. Clinicians armed with a relatively basic knowledge of possible diagnoses and treatments for chronic anal pain can make a specific diagnosis and initiate treatment even without a complex evaluation.

DIAGNOSTIC APPROACH AND COMMON PITFALLS

Anal pain can conveniently be grouped into 3 main categories, each with individual diagnoses, causes, and symptoms, which provide a starting point for the examination (Table 1).1,2 The most common category is local anorectal causes and includes a textbook list of anal conditions that, if persistent, can cause chronic anal pain. These include anal fissure, anal and perineal sepsis (eg, inter-sphincteric fistula or abscess), various ulcerations, and anal tumor.
Pitfalls to avoid in the diagnosis of chronic anal pain due to local anorectal conditions include the following:

- Attributing the anal pain to hemorrhoids (only thrombosed external hemorrhoids cause significant pain)
- Attributing the pain to a fissure without clear proof of a chronic fissure on examination (under anesthesia, if required), even if this has been “diagnosed” in the past

- Failing to consider less common diagnoses such as ulcers due to Crohn disease, tuberculosis, human immunodeficiency virus, syphilitic chancre, herpes, the vasodilator drug nicorandil (used globally but not approved by the US Food and Drug Administration), proctitis (including pelvic radiation disease), tumor, or solitary rectal ulcer.

These pitfalls may lead to a nonselective approach to diagnosis and to an extensive workup including endoscopy, anorectal physiologic testing, endoanal

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Diagnosis or syndrome</th>
<th>Assumed etiology</th>
<th>Main symptoms</th>
<th>Examination findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anorectal conditions</td>
<td>Fissure, perianal sepsis, tumor, ulcers, thrombosed hemorrhoids, severe proctitis</td>
<td>Specific to disorder</td>
<td>Common symptoms: Bleeding, discharge, lump, pruritis ani</td>
<td>Overt findings (may require EUA)</td>
</tr>
<tr>
<td>Functional anorectal conditions</td>
<td>Proctalgia fugax</td>
<td>Unknown</td>
<td>Short-lasting (seconds or minutes) sharp deep rectal stabbing or cramping. No radiation. No anorectal pain between episodes</td>
<td>No findings</td>
</tr>
<tr>
<td>Levator ani syndrome</td>
<td>Pelvic floor muscle tension or spasm</td>
<td>Chronic (&gt; 30 minutes) dull rectal ache or pressure sensation. Radiation to buttock, vagina, thigh. Other functional diagnoses common (eg, IBS, FDD, fibromyalgia)</td>
<td>Tender puborectalis, replicates pain (usually left side)</td>
<td></td>
</tr>
<tr>
<td>Unspecified functional anorectal pain</td>
<td>Unknown</td>
<td>Chronic (&gt; 30 minutes) dull rectal ache or pressure sensation. Other functional diagnoses very common (eg, IBS, FDD, fibromyalgia)</td>
<td>No findings</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain syndromes</td>
<td>Coccygodynia</td>
<td>Coccyx trauma leading to peripheral sensitisation</td>
<td>Perineal pain triggered by sitting</td>
<td>Tender on pressure or manipulation of coccyx</td>
</tr>
<tr>
<td>Pudendal neuralgia</td>
<td>Pudendal nerve entrapment: peripherally generated or neuropathic pain</td>
<td>Unilateral perineal pain with paresthesia. Worse on sitting. Nantes criteria²</td>
<td>Pain on transvaginal pressure on ischial spine</td>
<td></td>
</tr>
<tr>
<td>Phantom rectum syndrome</td>
<td>Neuropathic pain (deafferentation)</td>
<td>Specific to disorder</td>
<td>Specific to disorder</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal extreme pain disorder</td>
<td>Neuropathic pain (genetic)</td>
<td>Specific to disorder</td>
<td>Specific to disorder</td>
<td></td>
</tr>
</tbody>
</table>

EUA = examination under anesthesia; FDD = functional defecation disorder; IBS = irritable bowel syndrome
ultrasonography, or pelvic magnetic resonance imaging (MRI), with the goal of excluding other diagnoses. While this broad approach with extensive testing can allay anxiety in an anxious patient and possibly set a starting point for treatment, it is costly and may commit the patient to a series of investigations that are invasive, embarrassing, and not cost-effective.

Thus, a selective approach is generally recommended based on suspicion from the patient’s history and examination findings of past or present structural disease. For example, symptoms of covert perianal sepsis (discharge or swelling as well as pain) or a past history of abscess or anal fistula surgery should prompt MRI even if a fistula is not clinically evident. Similarly, symptoms of obstructed defecation or concomitant fecal incontinence would promote consideration of anorectal physiologic testing and endoanal ultrasonography. Figure 1 shows an algorithm for the diagnosis and management of chronic anal pain.

Chronic perineal pain

This review excludes discussion of chronic perineal pain, defined as pain felt between the posterior fourchette (posterior lip of the introitus) and the anus and, in males, between the scrotum and the anus. The diagnosis of perineal pain syndrome requires the occurrence of persistent or recurrent episodic pain that is either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction. Although some conditions that cause chronic anal pain can also lead to pain in the perineum, patients meeting the definition of chronic perineal pain should be managed by appropriate specialists (gynecology, urology) to examine for urogenital causes such as episiotomy pain and prostatodynia.

FUNCTIONAL ANORECTAL PAIN SYNDROMES

If a careful history and digital and rigid endoscopic examination of the anorectum exclude local anorectal conditions, the next most common diagnostic category is functional anorectal pain syndrome. The term functional denotes that structural or biochemical causes are absent on routine evaluation, and it should not be considered pejorative (eg, symptoms are all in the patient’s mind). In fact, of the 3 defined syndromes—proctalgia fugax, levator ani syndrome, and unspecified—the first 2 can be positively diagnosed by conducting a careful pain history and examination. The key diagnostic criteria relate to the character and duration of pain and to findings on examination of the levator ani muscle (Table 1). Proctalgia fugax

This syndrome was described back in 1962 as a condition that is “harmless, unpleasant, and incurable.” Diagnosis is based on a history of sudden-onset pain in the rectal area lasting for only seconds or minutes
(mean 15 minutes in 1 study7) then disappearing completely.7,8 The pain can occur night or day and vary in severity from uncomfortable to unbearable.

From a treatment perspective, the problem with diagnosing proctalgia fugax is that symptoms are generally too brief or infrequent to treat. Thus, the key is patient reassurance and explanation, such as describing the condition as a “cramp in your bottom” that is harmless and not indicative of any serious bowel disease. For severe cases, several drugs have been tested including clonidine, nifedipine, diltiazem, nitroglycerine, and even (historically) chloroform.8,9 However, only inhaled salbutamol (albuterol), a beta-adrenergic agonist, has been investigated in a randomized controlled clinical trial.9,10 Antidepressants such as amitriptyline or antianxiolytics are sometimes used but have no evidence base as to their efficacy. Table 2 lists the treatments for chronic anal pain investigated in randomized clinical trials.10–15

### TABLE 2
Randomized, controlled clinical trials of treatments for chronic anal pain

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Diagnosis</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckardt et al 199610</td>
<td>Proctalgia fugax</td>
<td>Inhaled salbutamol</td>
<td>Placebo</td>
<td>Salbutamol shortened duration of severe pain vs placebo (P = .019); effect most marked in patients having prolonged attacks</td>
</tr>
<tr>
<td>Abbott et al 200611</td>
<td>Pelvic floor myofascial pain</td>
<td>Botulinum toxin A; pelvic floor injection</td>
<td>Placebo: saline injection</td>
<td>Significant reductions in dyspareunia and pelvic floor pressure with both botulinum toxin and placebo</td>
</tr>
<tr>
<td>Dessie et al 201912</td>
<td>Myofascial pelvic pain</td>
<td>Botulinum toxin A; pelvic floor injection</td>
<td>Placebo: saline injection</td>
<td>No significant clinical effect</td>
</tr>
<tr>
<td>Rao et al 200913</td>
<td>Levator ani syndrome</td>
<td>Botulinum toxin A; transanal injection</td>
<td>Placebo</td>
<td>No effect of either botulinum toxin or placebo</td>
</tr>
<tr>
<td>Chiarioni et al 201014</td>
<td>Levator ani syndrome</td>
<td>Biofeedback</td>
<td>EGS; levator muscle massage</td>
<td>12-month results</td>
</tr>
<tr>
<td>Zoorob et al 201515</td>
<td>Levator ani syndrome</td>
<td>Steroid injections in levator ani trigger points</td>
<td>Pelvic floor physiotherapy</td>
<td>Both groups improved equally (60% achieved 50% reduction in symptoms)</td>
</tr>
</tbody>
</table>

---

**Levator ani syndrome**

Levator ani syndrome—also called pelvic myalgia, pelvic floor myofascial pain, and pelvic floor muscle spasm—is chronic anal pain resulting from tension or spasms in the levator muscles leading to compression of nerve endings and pain via peripheral sensitization. Patients often describe a dull ache or pressure sensation in the rectum that is exacerbated by prolonged sitting and relieved by standing or lying down.5 Some patients describe the feeling as like sitting on a ball or having a ball inside their rectum. The pain commonly lasts for hours but may be continuous, with sudden exacerbations.16,17

Levator ani syndrome rarely occurs at night. Instead, the pain usually begins in the morning and increases in severity throughout the day. It can radiate into the vagina, the gluteal area, or the thigh. The pain may be precipitated by apparently unrelated factors such as long-distance car travel, stress, sexual
intercourse, or normal defecation that can potentially lead to stool-withholding.\textsuperscript{16,17} Tenderness (reproducing pain) on palpation of the levator muscle (usually the left side, for unknown reasons) is diagnostic.

The overlap of levator ani syndrome with functional defecation disorder\textsuperscript{5,16} brings into play several well-established risk factors for the latter that may be determined from the history including anxiety, depression, and a history of sexual abuse.\textsuperscript{17–19}

Treatments. Of the various treatments that have been studied for levator ani syndrome (Table 3),\textsuperscript{11–15} the best evidence is for behavioral training with biofeedback. In a randomized controlled trial of 157 patients, Chiarioni et al\textsuperscript{14} compared behavioral training against electrogalvanic therapy (ie, transvaginal or transanal direct neuromuscular stimulation using low-voltage electric charge from a probe) and massage. An intent-to-treat analysis showed that 87% of patients reported adequate relief of rectal pain with biofeedback vs 45% of patients with electrical stimulation and 22% with massage. The improvement was maintained at 12 months.\textsuperscript{14}

However, behavioral training with biofeedback is not universally available, and most patients with levator ani syndrome are referred for a comprehensive program of pelvic floor physical therapy focused on pain management. These programs are different from standard pelvic floor physical therapy for prolapse or incontinence that focus on muscle training to strengthen the pelvic floor. Programs for levator ani syndrome include techniques that focus on myofascial release, muscle-stretching, and posture improvement. Most treatment programs are poorly standardized and may include an adjunct such as electrogalvanic stimulation.\textsuperscript{20,21} Other attempts at pain management include the Stanford pelvic pain protocol (the Wise-Anderson protocol), which includes relaxation therapy and use of a wand-like device that patients can use to massage internal pelvic myofascial trigger points. The wand was approved by the US Food and Drug Administration in 2012 based on results of a 4-year clinical trial.\textsuperscript{22} Local anesthetic injections also have shown efficacy when administered as an adjunct by trained clinicians.\textsuperscript{15,23}

Coexisting and overlapping conditions. Patients with levator ani syndrome commonly have symptoms of obstructed defecation, and there is a well-acknowledged overlap with functional defecation disorders such as dyssynergic defecation.\textsuperscript{5} Biofeedback to improve rectoanal coordination (which includes pelvic floor relaxation) should be the first-line treatment for dyssynergic defecation.\textsuperscript{24} Other functional and chronic pain disorders may coexist such as irritable bowel syndrome and fibromyalgia. Attention should be paid to holistic management, especially if depression and anxiety appear to be causing symptoms.

\textbf{Botulinum toxin.} If symptoms persist after biofeed-

\begin{table}[h]
\centering
\caption{Treatments for levator ani syndrome}
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Category} & \textbf{Examples} & \textbf{Level of Evidence} & \textbf{Comments} \\
\hline
Behavior therapy & Biofeedback to improve defecation dynamics & B & Most effective treatment for LAS in single RCT\textsuperscript{14} \\
\hline
Muscle relaxant & Electrogalvanic stimulation & B & More effective than massage in single RCT\textsuperscript{14}; benefits decrease in long-term \\
\hline
Muscle relaxant & Diazepam & C & Poorly effective in the long-term; addictive potential \\
\hline
Muscle relaxant & Digital massage of puborectalis muscle & D & No standardized methodology; often provided with sitz bath \\
\hline
Anticholinergic & Botulinum toxin A injection & B & Ineffective as transvaginal or transanal injection in three RCTs\textsuperscript{11–13} \\
\hline
Anti-inflammatory & Pelvic floor muscle steroid injection & D & Equally effective as physiotherapy in pilot RCT\textsuperscript{15} \\
\hline
Antidepressants & Amitriptyline & D & Unclear mechanism of action; diverse dosage \\
\hline
Neuromodulation & Sacral neuromodulation & D & Conflicting results in small observational studies \\
\hline
\end{tabular}
\end{table}

LAS = levator ani syndrome; RCT = randomized controlled trial
back or pelvic floor physiotherapy, a high dose (total 200 units) of botulinum toxin A (onabotulinumtoxin A) may be injected into the levator (unilaterally or bilaterally). Although the supporting evidence is poor,11–13,25,26 it is a common practice. It should generally be considered an adjunct to ongoing physical or biofeedback therapy.

### NEUROPATHIC PAIN SYNDROMES

Neuropathic pain syndromes in chronic anal pain are rare compared with local and functional anorectal syndromes. They include coccygodynia and pudendal neuralgia, in which the pain in part has a structural origin, and two overtly neuropathic syndromes, ie, phantom rectum syndrome and paroxysmal extreme pain disorder (Table 1).

#### Coccygodynia

Coccygodynia is pain arising in or around the coccyx depending on its position.27 The pain is considered to arise from instability of the coccyx with or without pelvic floor spasm.28 There is usually a history of trauma including childbirth and epidural anesthesia.29 Risk factors include female sex, obesity, anxiety, depression, and chronic pain elsewhere. Examination will reveal any instability, and movement of the coccyx should reproduce the pain. Rectal examination will often demonstrate coexistent levator ani syndrome.

**Dynamic digital radiography** of the coccyx will show coccygeal instability in about 50% of patients with a clinical diagnosis of coccygodynia.28 Radiologically, the 2 main patterns of instability are hypermobility (on flexion) and posterior subluxation.

**Management** involves treatment of levator ani syndrome, if present, manipulation of the coccyx, and injection of local anesthetic and steroid into the affected segment. If this fails, an orthopedic referral for coccygectomy may be relevant in selected patients, but this should be done in recognition that outcomes are supported only by retrospective observational data and complications such as infection are common.29

#### Pudendal neuralgia

Pudendal neuralgia (or pudendal nerve entrapment syndrome) occurs when the pudendal nerve is compressed by the obturator fascia as it forms the Alcock canal.30 Diagnosis is challenging and requires use of the Nantes criteria, a series of essential, complementary, and exclusion criteria (Table 4). Of these, the essential criteria are most useful as a screening tool. These can be divided into symptom-based and examination-based criteria plus the important confirmatory criterion that pain is relieved by pudendal nerve block. Although this can be accomplished by any trained clinician, it is usual practice to refer the patient to a pain service with neurophysiologic testing expertise so that the pudendal nerve block can be performed under electrophysiologic guidance.

The pain of pudendal neuralgia may be unilateral or bilateral and may radiate to the pelvis and thighs and cause deep pelvic discomfort.30 A burning sensation and numbness or paresthesia in the gluteal, perineal, and genital areas are commonly reported in association with the pain. Patients with pudendal neuralgia often suffer for several years before being diagnosed.

**Treatments.** Pharmacologic treatments for pudendal neuralgia include use of transcutaneous electrical nerve stimulation (TENS), self-administered ice packs, and pudendal nerve blocks. If failed, pudendal nerve decompression or neurolysis may be considered. If these methods fail, surgical intervention such as a pudendal neurectomy or pudendal nerve neurotomy may be considered.31,32 Reprinted with permission from John Wiley & Sons. From Labat JJ, Riant T, Robert R, Amarenco G, Lefaucheur JP, Rigaud J. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). Neurourol Urodyn 2008; 27(4):306–310. doi:10.1002/nau.20505.
Phantom rectum syndrome and paroxysmal extreme pain disorder

Phantom rectum syndrome (postproctectomy pain) and paroxysmal extreme pain disorder (previously known as familial rectal pain syndrome) are rare causes of chronic anal pain.\textsuperscript{13}

Phantom rectum syndrome is a possible diagnosis when an organic source for pain such as perineal hernia or pelvic sepsis is excluded after proctectomy.

Paroxysmal extreme pain disorder is a genetic disorder caused by a mutation in the SCN9A gene. The patient usually has a family history and onset in the neonatal period or during infancy.\textsuperscript{14} It persists throughout life, with autonomic manifestations such as harlequin skin flushing and episodes of syncope with bradycardia. Later in life, the disorder is characterized by attacks of excruciating, deep, burning pain often in the rectal, ocular, or jaw areas. Rectal pain may be triggered by defecation. Management includes use of carbamazepine and needs to be guided by an expert neurologist.

\section*{REFERENCES}


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