Taylor & Francis
Taylor & Francis Group

Expert Review of Respiratory Medicine

ISSN: 1747-6348 (Print) 1747-6356 (Online) Journal homepage: http://www.tandfonline.com/loi/ierx20

Acute and chronic non-pulmonary complications in adults with cystic fibrosis

Lucile Regard, Clémence Martin, Guillaume Chassagnon & Pierre-Régis Burgel

To cite this article: Lucile Regard, Clémence Martin, Guillaume Chassagnon & Pierre-Régis Burgel (2018): Acute and chronic non-pulmonary complications in adults with cystic fibrosis, Expert Review of Respiratory Medicine, DOI: 10.1080/17476348.2019.1552832

To link to this article: https://doi.org/10.1080/17476348.2019.1552832

Accepted author version posted online: 24 Nov 2018.
Published online: 30 Nov 2018.

EXPERT REVIEW OF RESPIRATORY MEDICINE
https://doi.org/10.1080/17476348.2019.1552832

Taylor & Francis
Taylor & Francis Group

REVIEW

Acute and chronic non-pulmonary complications in adults with cystic fibrosis

Lucile Regard[a,b], Clémence Martin[a,b], Guillaume Chassagnon[a,c] and Pierre-Régis Burgel[a,b]

[a]Faculté de Médecine, Paris Descartes University, Sorbonne Paris Cité, Paris, France; [b]Pulmonology Department, Cochin Hospital, AP-HP, Paris, France; [c]Radiology Department, Cochin Hospital, AP-HP, Paris, France

ABSTRACT

Introduction: Cystic fibrosis (CF) is a genetic disease that primarily affects the respiratory system and often leads to respiratory failure and premature death. Although pulmonary complications contribute to 85% of deaths, non-pulmonary complications are responsible for significant morbidity and mortality in adults with CF.

Areas covered: This review summarizes acute and chronic non-pulmonary complications in CF patients, with emphasis on emerging complications and in the context of the current growth and aging of the CF adult population. It also addresses the potential benefits of CF transmembrane conductance regulator modulator therapy. Complications that occur after solid organ (e.g. lung and/or liver) transplantation have been excluded. The review is based on an extensive search of the available literature, using PubMed and international guidelines, and on the authors' clinical experience.

Expert commentary: Acute non-pulmonary complications have been well described but should be recognized and managed carefully. Managing chronic non-pulmonary complications is an important and changing aspect of CF patient care, particularly with the emergence of novel complications in adults. Early detection of non-pulmonary complications is essential to the development of prevention and treatment strategies that aim to further improve the survival and health status of adult CF patients.

ARTICLE HISTORY
Received 3 July 2018
Accepted 23 November 2018

KEYWORDS
Cancer; chronic kidney disease; diabetes

1. Introduction

Cystic fibrosis (CF) is the most common genetic disease in Caucasian populations, affecting at least 70,000 individuals worldwide [1]. It is a multisystem disease affecting the lungs, pancreas, intestine, liver, and reproductive organs. Significant improvements in survival have been achieved in the past six decades [2], but CF remains associated with premature death secondary to respiratory failure [3]. The demographic characteristics of the CF population have dramatically changed over the past decades and more than half of CF patients are now 18 years or older in many countries [1]. Recent studies predict a 50% increase in the overall number of CF patients, with a 75% increase in the European adult CF population between 2010 and 2025 [4,5]. These figures, which reflect both reduced pediatric mortality and increased life expectancy in adults, suggest that the CF adult population will continue to grow and age over the next decade. Because CF is a progressive disease in which the risk of pulmonary and non-pulmonary complications increases with age, one can expect that the incidence and severity of non-pulmonary complications will increase because of rising life expectancy. Table 1 summarizes the main acute and chronic non-pulmonary complications that have been observed in adults with CF.

The objectives of this review are to (1) provide a comprehensive review of non-pulmonary complications in adults with CF, distinguishing between acute versus chronic complications; (2) describe emerging and classical chronic complications; (3) review current international guidelines – when available – on the management of these comorbidities; (4) suggest screening and prevention strategies for selected complications; and (5) review the impact of CF transmembrane conductance regulator (CFTR) modulators, which bind to defective CFTR proteins and partially restore their function [6], on non-pulmonary complications. The management of pediatric CF patient care has been described [7–9] and will not be examined here. Likewise, non-pulmonary complications that occur after lung transplantation have been the subject of a recent review [10] and will not be discussed here as they can be attributed to both CF and immunosuppressive therapy.

2. Acute non-pulmonary complications in adult patients with CF

2.1. Acute hyponatremic dehydration

Acute hyponatremic dehydration (AHD) is a common complication in CF and has been described as a major feature of CF disease [11,12]. Although it is more prevalent in the pediatric population, CF adults are also at risk [13]. AHD occurs secondary to sodium loss through perspiration – CF patients have much higher sweat concentrations of sodium and chloride than the general population. Symptoms are nonspecific and can include fatigue, nausea, vomiting, rapid weight loss, cramps, headaches, hypotension, and/or fever. In most cases, AHD is associated with the following contributing factors: hot and dry weather conditions [13], exercise, and/or fever. The classical laboratory findings are hyponatremia, hypochloremia, and metabolic alkalosis. AHD

CONTACT Pierre-Régis Burgel pierre-regis.burgel@aphp.fr 27, rue du Faubourg Saint Jacques, Paris 75014, France

Table 1. Acute and chronic non-pulmonary complications in adults with CF.

Acute complications	Chronic complications		
Acute hyponatremic dehydration	**Pancreas**	**Genito-urinary tract**	**Sinus**
	Exocrine pancreatic insufficiency	Male infertility (absence of vas deferens)	Rhinosinusitis
	CF-related diabetes	Female hypofertility	Nasal polyposis
	Pancreatic cysts	Amenorrhea	
	Liver	Urinary stress incontinence	**Kidney**
Pancreas	Elevation of serum liver enzymes	**Bone/joint**	Metabolic alkalosis
Acute pancreatitis	Steatosis	Osteopenia/Osteoporosis	Chronic kidney disease
Gall bladder	Cirrhosis	CF-related arthropathy	Diabetic nephropathy
Biliary lithiasis (colic, cholecystitis, cholangitis)		Hypertrophic pulmonary osteoarthropathy	Nephrolithiasis, nephrocalcinosis
			Amyloidosis
Gastrointestinal tract	**Gastrointestinal tract**	**Drug induced/device-related**	**Malignancies**
Distal intestinal obstruction syndrome	Gastroesophageal reflux disease	Adrenal insufficiency (corticosteroids, azoles)	Colorectal
Intussusception	Constipation	Hearing loss (aminoglycosides)	Digestive tract (small bowel, esophagogastric junction, biliary tract, pancreatic)
Appendicitis	Inguinal hernia	Chronic kidney disease (aminoglycosides)	Testicular
Kidney		Superior vena cava stenosis/syndrome (central venous catheter)	Lymphoid leukemia
Symptomatic nephrolithiasis	**Nutrition**	**Skin**	**Psychiatric**
Drug-induced/device-related	Malnutrition	Aquagenic palmoplantar keratoderma	Anxiety
Acute kidney injury (aminoglycosides)	Obesity		Depression
Allergy and adverse drug reaction			
Clostridium difficile colitis (antibiotics)			
Central venous catheter			
Thrombosis			
Infection			

symptoms should be recognized promptly by patients and caregivers as dehydration can evolve into hypovolemia and hypovolemic shock, acute renal failure and ultimately death, if not rapidly treated [13]. Patients presenting with AHD should be hospitalized and closely monitored. Treatment involves rehydration with intravenous isotonic saline. Patients should be advised to increase water and sodium intake when exercising and during hot weather conditions.

2.2. Acute pancreatitis

Acute pancreatitis (AP) occurs in 10–22% of CF patients that otherwise show no pancreatic insufficiency (PI) [14–16] and whose CFTR mutations are associated with residual CFTR function [16–18]. This complication may be the consequence of ductal obstruction secondary to semi-viscous pancreatic secretions and/or gallstone migration. AP recurrence is frequent (75%) and sometimes results in impaired exocrine pancreatic function, leading to PI. Since presentation is often characterized by non-specific abdominal pain, AP should be suspected in pancreatic-sufficient patients presenting with recurrent abdominal pain, nausea and vomiting. Laboratory findings include elevated lipase and/or amylase. Imaging evidence of AP shows pancreatic edema or the presence of peripancreatic fluid (Figure 1(a)) and, rarely, hemorrhage and necrosis. The preferred imaging techniques are ultrasonography or magnetic resonance imaging (MRI), as they expose patients to less radiation than computed tomography (CT) scans. Physicians should search for additional risk factors, such as alcohol use, that can trigger AP [19,20]. AP management in CF and non-CF patients is similar and recent international guidelines now recommend early (within 24 h) food intake (as tolerated) rather than fasting [21]. However, the associated dehydration is likely to be more severe in the CF population; therefore, particular attention should be given to rehydration and electrolyte monitoring [22]. Antibiotics should not be prescribed systematically and are indicated only in complicated AP cases (abscess, necrosis) or if the patient presents with a concurrent respiratory exacerbation.

2.3. Acute complications of gallstones: symptomatic cholelithiasis, cholecystitis, and acute cholangitis

Gallbladder abnormalities are reported in 24–50% of CF patients and include a small or absent gallbladder, gallbladder dysfunction, symptomatic cholelithiasis, and malignancy [23,24]. Calcium bilirubinate gallstones, which arise from insufficient bile acidification secondary to bile stasis, are frequent in CF patients, although their prevalence has not been estimated recently. Symptomatic gallbladder disease occurs in up to 4% of CF patients [25]. Biliary colic usually occurs secondary to symptomatic cholelithiasis or gallbladder dyskinesia [23]. Typically, patients present with a gradual onset of postprandial squeezing right upper quadrant pain. Ultrasonographic examination should be performed to visualize the gallstones (Figure 2(a)) and to rule out more severe complications, such as cholecystitis or acute cholangitis. Cholecystitis should be suspected in patients presenting with sustained right upper quadrant pain, along with fever and chills, and acute

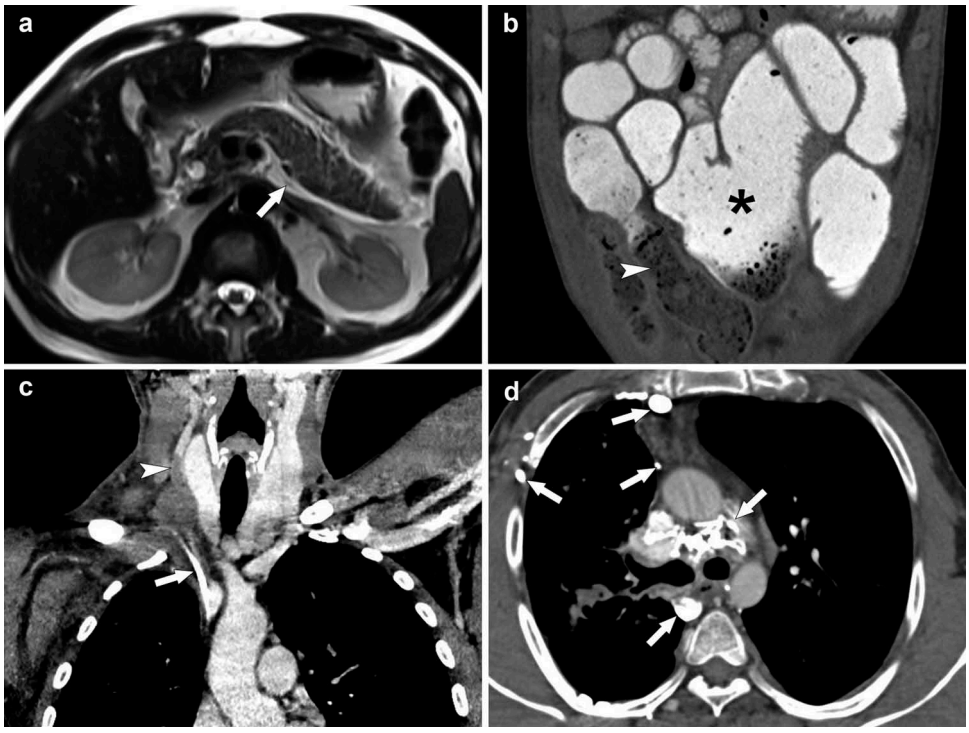

Figure 1. Acute non-pulmonary complications in adults with CF.

(a) *Acute pancreatitis in a 26-year-old pancreatic sufficient patient presenting with acute abdominal pain.* Axial T2-weighted magnetic resonance image of the abdomen showing an edematous pancreatitis with peripancreatic hyperintensity corresponding to peripancreatic fluid (arrow). **(b) *Distal intestinal obstruction syndrome (DIOS) in a 32-year-old patient presenting with recurrent episodes of DIOS***. Coronal non-enhanced computed tomography image of the abdomen with oral opacification showing significant jejunal dilation (*) with inspissated fecal material in the distal ileum (arrowhead). **(c) *Acute venous thrombosis resulting from central venous catheter in a 59-year-old CF patient.*** Coronal contrast-enhanced computed tomography image showing jugular thrombosis (arrowhead) in a CF patient with a central venous catheter (arrow). **(d) *Superior vena cava syndrome in a 30-year-old CF patient***. Axial contrast-enhanced computed tomography image showing major collateral circulation (arrows) in a CF patient presenting with acute venous thrombosis caused by a central venous catheter.

cholangitis in those who also show signs of jaundice. Symptomatic cholelithiasis, cholecystitis, or acute cholangitis management in CF and non-CF patients is similar (Table 2). For those presenting with symptomatic cholelithiasis, a laparoscopic cholecystectomy should be discussed after the first acute episode to prevent recurrence and complications. This surgical procedure is usually safe in CF patients unless pulmonary function is severely impaired [23]. The effectiveness of conservative treatment, such as ursodeoxycholic acid (UDCA) or lithotripsy, has not been demonstrated in the management of symptomatic gallstones [26]. Cholecystitis treatment should include antibiotic administration and delayed laparoscopic cholecystectomy. For acute cholangitis, treatment consists of antibiotics, stone removal through endoscopic retrograde cholangiopancreatography if accessible, percutaneous drainage of the biliary tract, and/or surgery [23]. Patient management should be multidisciplinary, involving anesthesiologists, gastroenterologists, surgeons, and CF physicians [23].

2.4. Acute gastrointestinal complications: distal intestinal obstruction syndrome, intussusception, and appendicitis

2.4.1. Distal intestinal obstruction syndrome

Distal intestinal obstruction syndrome (DIOS) is a frequent complication in CF patients and is brought on by the accumulation of viscous fecal material and sticky mucous secretions in the distal ileum and cecum [27]. In a recent study, DIOS incidence in the adult CF population was estimated at 7.8 episodes/1000 patient-years [27]. DIOS diagnosis can be challenging because symptoms might not be specific (abdominal pain, nausea, vomiting). Differential diagnoses include constipation, appendicitis, appendicular abscess, mucocele of the appendix, intussusception, or malignancy. In 2011, an international consensus introduced the differentiation between Complete DIOS (C DIOS) and Impending DIOS (I DIOS) [28]. A CT scan is the gold standard for diagnosis and usually shows intestinal wall thickening, inspissated fecal material in the distal ileum, and small bowel dilation [29] (Figure 1(b)). Risk factors for DIOS include severe CFTR genotype, history of meconium ileus, PI, previous DIOS, CF-related liver disease (CFLD), CF-related diabetes (CFRD), airway colonization with *P. aeruginosa*, and dehydration [27,30]. Delayed diagnosis and treatment are both associated with significant morbidity [22]. For I DIOS, oral rehydration combined with oral osmotic laxatives (containing polyethylene glycol (PEG) or sodium meglumine diatrizoate [Gastrografin®]) is almost always sufficient.

For C DIOS, patients should be hospitalized and treated in a stepwise approach [30]. In those presenting with moderate obstruction and no vomiting, an oral osmotic laxative is the first line of treatment (PEG or Gastrografin®), followed by intravenous hydration, fasting, nasogastric aspiration, and pain relief if the patient presents with bilious vomiting. A Gastrografin® enema can be administered but should be performed by an experienced radiologist to prevent the

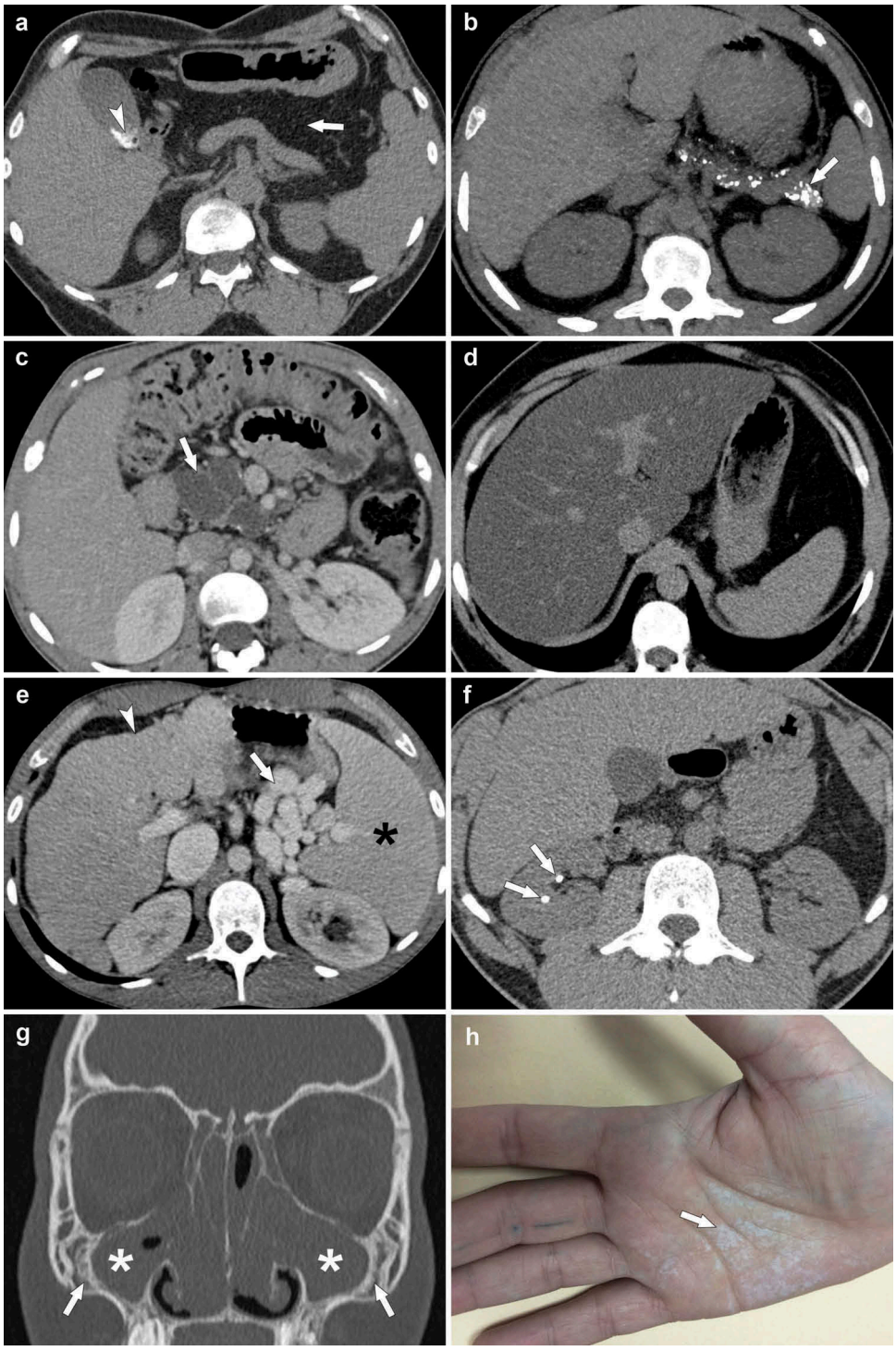

Figure 2. Chronic non-pulmonary complications in adults with CF.

(a) ***Complete fatty atrophy of the pancreas and cholelithiasis in a CF patient presenting with pancreatic insufficiency***. Axial non-enhanced computed tomography image of the abdomen showing the typical appearance of end-stage pancreatic disease with complete fatty replacement: diffuse fatty attenuation with no discernable residual pancreatic tissue (arrow). Arrowhead shows lithiasis in the gallbladder. (**b)** ***Chronic pancreatitis***. Axial non-enhanced computed tomography image of the abdomen showing extensive pancreatic calcifications (arrow). (**c)** ***Pancreatic cysts in a 28-year-old patient with CF***. Axial contrast-enhanced computed tomography image of the abdomen showing small and large cephalic pancreatic cysts (arrow). (**d)** ***Hepatic steatosis***. Axial non-enhanced computed tomography image of the abdomen showing low hepatic attenuation compared with the spleen and accentuation of vascular structures. (**e)** ***Cirrhosis in a 27-year-old patient***. Axial contrast-enhanced computed tomography image of the abdomen showing a lobular cirrhotic liver (arrowhead), stigmata of portal hypertension including splenomegaly (asterisk) and porto-systemic collateral pathways (arrow). (**f)** ***Asymptomatic renal lithiasis***. Axial non-enhanced computed tomography image of the abdomen showing two renal stones in the right kidney (arrows). (**g)** ***Chronic sinusitis***. Coronal non-enhanced computed tomography image of the head showing osseous thickening (arrow) and opacification of the maxillary sinuses (asterisk). (**h)** ***Aquagenic palmoplantar keratoderma***. Picture of the right hand of a CF patient presenting typical features of aquagenic palmoplantar keratoderma: small whitish papules (arrow) gathering into edematous plaques and associated to erythematous areas of the palms.

severe complications (shock, perforation, necrotizing enterocolitis) that may result from a fluid shift from the circulation to the bowel [30]. If conservative treatment fails, surgery should be discussed [27]. DIOS prevention consists of adequate hydration, regular physical activity and, in patients with a history of DIOS, *p.o.* osmotic laxatives. Since poorly controlled fat absorption increases the risk of DIOS (via impaired luminal content viscosity and ileal brake activation), the dose

Table 2. Suggested or recommended interventions to prevent/manage selected acute non-pulmonary complications in adults with CF.

Complications	Suggested/recommended prevention	Management guidelines	Ref
Acute hyponatremic dehydration	- Avoid exercise during hot weather - Increased water and salt intake when exercising and/or hot weather	None	-
Acute pancreatitis	- Discourage alcohol use in pancreatic sufficient patients, especially if there is a previous history of acute pancreatitis	Yes, nonspecific to CF	[24]
Acute lithiasic cholecystitis	- Perform early cholecystectomy in patients with symptomatic gallbladder disease	Yes, nonspecific to CF	[1,2]
Distal intestinal obstruction syndrome	- Adequate hydration - Long-term oral laxatives if prior episode of DIOS - Proactive initiation of a scheduled bowel regimen - Pancreatic enzyme replacement therapy reevaluation if prior episode of DIOS	Yes, specific to CF	[32]
Symptomatic nephrolithiasis	- High fluid intake - Low-oxalate and high-calcium diet	Yes, nonspecific to CF	[3]
Acute kidney injury	- Follow recommended treatment dosing - Therapeutic drug monitoring when using aminoglycosides or glycopeptides - Avoid gentamicin (prefer tobramycin or amikacin) when using aminoglycosides - Avoid co-administration of nephrotoxic drugs (e.g. aminoglycosides and NSAID's) - Plasma creatinine measurements during IV antibiotics in patients at higher risk (CFRD, chronic kidney disease)	Yes, specific to CF	[47]
Type I hypersensitivity reaction to antibiotics	- Written instructions for emergency treatment in case of allergic reactions during outpatient IV antibiotic courses - Desensitization procedure for important drugs with no other treatment option - Hospitalization to start new antibiotic treatment in patients at risk	Yes, specific to CF	[23]

of pancreatic enzymes prescribed should be adjusted and regularly evaluated [22]. If a patient has recurrent episodes of DIOS, the introduction of a scheduled bowel regimen using PEG-based solution can be considered [31].

2.4.2. Intussusception

Intussusception is rarely seen in adult CF patients [32,33]. It usually involves the ileocecum and can resolve spontaneously [32]. Intussusception can also occur as a complication of DIOS [30] or colorectal cancer. Treatment should be conservative and consists of water-soluble contrast enema [34]. A colonoscopy is indicated after the first episode to rule out malignancy [33].

2.4.3. Appendicitis

In CF patients, appendiceal disease ranges from simple mucous distension to appendiceal mucocele and acute appendicitis [35]. The incidence of appendicitis is lower in CF patients (1–2%) than in the general population [36]. In CF, nonspecific presentation and symptom attenuation – due to frequent antibiotic treatment for pulmonary exacerbations – often delay diagnosis. As a consequence, CF patients are at higher risk developing complications (appendiceal abscess or mass, perforation) [37]. Radiological diagnosis can be challenging due to the mucous distension of the appendix observed in CF patients [38]. Management is based on antibiotics and appendectomy as in the non-CF population.

2.5 Symptomatic nephrolithiasis

With a prevalence of 2.0–6.3% [39], nephrolithiasis is more frequent in CF patients than in the general population (Figure 2(f)). Risk factors associated with stone formation include decreased urine output, hyperoxaluria, and hypocitraturia [40]. Hyperoxaluria is the consequence of a reduction in enteric colonization by *Oxalobacter formigenes* (an oxalate-degrading bacterium) secondary to PI and recurrent courses of antibiotics [41]. Although nephrolithiasis can be asymptomatic, acute symptomatic nephrolithiasis can occur in CF adults who show the classical symptoms of renal colic and hematuria. Management should involve pain relief and hydration. For recurrent or complicated nephrolithiasis, lithotripsy or surgery should be considered [39]. Prevention includes increased fluid intake, and a low-oxalate/high-calcium diet [22].

2.6 Drug-induced and catheter-related acute complications

2.6.1. Acute kidney injury

In CF patients, acute kidney injury (AKI) is usually the result of intravenous (IV) aminoglycoside treatment, with a higher risk of developing AKI with gentamicin than with tobramycin [42]. In addition to aminoglycoside exposure, patients often have additional risk factors, including CFRD, preexisting renal failure, dehydration, and concurrent use of another nephrotoxic drug. Other drugs may be involved in the development of AKI: cephalosporins, colistin, nonsteroidal anti-inflammatory drugs (NSAIDs), amphotericin and ciprofloxacin. To prevent drug-induced AKI, a once daily tobramycin regimen, regular benefit/risk monitoring and avoiding other concurrent nephrotoxic

drugs are recommended [22]. Attention should be given to patients with a history of CFRD and/or preexisting chronic renal failure. The UK's Cystic Fibrosis Trust Antibiotic Working Group recommends creatinine monitoring before the first dose and again before the eighth dose [43]. Given that the CF population is aging and presenting with more comorbidities, the risk of developing AKI secondary to IV aminoglycoside treatment (or other nephrotoxic drugs like glycopeptides) is likely to increase in coming years.

2.6.2. Allergy

In CF patients, the incidence of hypersensitivity reactions (HSRs) to IV antibiotics has been reported to be up to three times higher than in the general population [44,45]. This higher risk is thought to be related to higher cumulative antibiotic exposure and to the high immunogenic nature of the antibiotics (e.g. beta-lactams) prescribed for pulmonary exacerbations. However, it is worth noting that various clinical manifestations have been reported as HSRs even though a proportion would probably not meet immune-mediated HSR criteria [46]. The majority of HSRs reported in CF patients are delayed [47] and true type 1 HSRs to antibiotics may have been overestimated in patients with CF [48,49]. If a patient has a type 1 HSR and if no other treatment option is available, clinicians should prescribe a desensitization protocol [50], which has been reported to be successful in up to 65% of cases in a recent study [45].

2.6.3. Clostridium difficile infection

CF patients are at high-risk of acquiring *Clostridium difficile* (*C. difficile*) due to frequent antibiotic exposure, frequent hospitalizations, and decreased gastric acid secretions [51]. A recent study reported a 50% asymptomatic carriage rate in CF patients compared with 2% in a healthy control group (stools positive for *C. difficile* in the absence of clinical symptoms) [52]. Yet *C. difficile* infection (colitis symptoms and positive stool culture for toxin-producing *C. difficile*) rates remain low in the CF population [53], probably due to a superior ability to generate robust humoral immunity against *C. difficile* toxins [54]. In CF patients, the clinical presentation of a *C. difficile* infection can be atypical [55] leading to delayed diagnosis and treatment. International guidelines for the management of *C. difficile* infection in the general population should be followed for CF patients [56]. First-line treatment should include oral vancomycin or fidaxomicin. Metronidazole should be used only if vancomycin or fidaxomicin are not available or when IV treatment becomes necessary. For recurrent *C. difficile* infection, fecal transplantation may be considered although only one case of successful fecal transplantation in a CF patient has been reported in the literature [57]. The effectiveness of probiotics has not been evaluated.

2.6.4. Central venous access complications

Over time, peripheral venous access can become challenging in adults with CF who have received repeated courses of IV antibiotics. Central venous catheters (CVCs), including peripherally inserted central catheters (PICC) and totally implantable central venous catheters (TICVC), are frequently used in this population. Both PICCs and TICVCs can lead to local or systemic complications although complication rates remain low in the CF adult population: 13.1–21.0% for PICC lines and 0.337 to 0.905 per 1000 catheter days for TICVC have been reported [58–63]. The most frequent complications for PICC lines include occlusion (18–21%) and pain (18%) [59,64]. Symptomatic deep vein thrombosis has been reported in 2–8% of PICC carriers [59,65] and infectious complication rates are very low (0–0.8%) [59,61]. A recent multicenter study identified several risk factors for PICC line complications, including larger catheter diameter, multiple lumens, poor nutritional status, *Burkholderia cepacia spp*., infection and having ≥5 PICCs inserted during the study period [61]. TICVCs can lead to complications such as thrombosis (Figure 1(c)), embolism, superior vena cava (SVC) syndrome (Figure 1(d)), occlusion, stenosis, sepsis, and pneumothorax [62].

Infection rates remains low, with an incidence of 0–9% per catheter inserted [62,66]. The most common organism cultured from the bloodstream of these patients are fungi (particularly *Candida species*) [62,66]. Prevention and management strategies for intravascular catheter related infections should follow published guidelines [67,68]. Symptomatic thrombosis rates vary from 3.5% to 16.4% [69,70]. SVC syndrome symptoms include dyspnea, venous distension in the neck, facial swelling, chest wall edema, and, occasionally, cyanosis [71]. The mechanisms of CVC occlusion include (1) fibrin sheath formation; (2) CVC lumen occlusion; (3) Ball valve occlusion preventing aspiration but not infusion; and (4) mural thrombosis leading to catheter-related thrombosis.

There are no CF-specific recommendations for the management of PICC- or TICVC-associated occlusion. Current general guidelines recommend that: (1) catheters should be removed only if not needed or nonfunctional and (2) anticoagulant therapy should be the first line treatment, using low molecular weight heparin, although vitamin K antagonists can also be used (lack of comparative studies) [72]. The duration of anticoagulation therapy should be discussed on a case-by-case basis since patients with CF are at high risk of hemoptysis. IV thrombolysis should only be used in patients with a high thrombotic risk (severe SVC despite systemic anticoagulation) [72]. Catheter-directed thrombolysis, angioplasty, or percutaneous stenting [60,69] have also been reported to be successful in CF patients. PICC line occlusions can be resolved with saline or urokinase injection [59]. Table 2 summarizes suggested interventions to prevent and/or manage selected acute non-pulmonary complications in adults with CF.

3 Classical chronic non-pulmonary complications in adults with CF

This section reviews chronic non-pulmonary, symptomatic complications that are classically associated with CF and can lead to increased treatment burden in adults.

3.1. Exocrine PI

Pancreatic exocrine disease is the earliest manifestation of CF: it has been reported to start during fetal life [73] and 80–85% of CF patients develop PI before age one [74]. PI is also the most frequent extrapulmonary complication of CF with a prevalence reaching 90% in the adult population [75]. It is

correlated with genotype: patients with two severe CFTR mutations (Classes I to III and class VI) are more likely to present with early PI (often at birth), while patients with one mild (Class IV or V) mutation are usually pancreatic sufficient (PS) at birth, presenting with milder lung disease and greater life expectancy than patients born with PI [74,76]. PI is characterized by fatty infiltration, atrophy, and destruction of both the ductal and the acinar tissue in the pancreas [77] (Figure 2(b)). PI symptoms in CF adults are related to poor protein and fat absorption and include weight loss, steatorrhea, diarrhea, bloating, abdominal pain, gas, and dyspepsia. Most adults with CF are diagnosed with PI during infancy. Patients who reach adulthood and are still PS should be reevaluated annually (nutritional assessment) and fecal pancreatic elastase-1 (FE1) should be measured if PI symptoms are present. FE1 measurements should also be performed in adults who are newly diagnosed with CF [22,75,78]. Fat-soluble vitamins (A, D, E, K) should be measured at diagnosis and at least annually or 3–6 months after a change in vitamin therapy [78]. Vitamin K levels are usually not measured directly but estimated using prothrombin time (PT). International recommendations for screening and management of fat-soluble vitamin deficiency in patients with CF have been published [78].

Management of PI in adults with CF should include education (explaining the importance of good nutrition in improving survival in CF) with the help of a specialized CF dietician, high calorie and high fat diet, pancreatic enzyme replacement therapy (PERT), and fat-soluble vitamin supplementation [78]. In the future, CFTR modulation therapy may change the face of pancreatic exocrine disease. The KIWI study evaluated the safety and efficacy of ivacaftor (a CFTR potentiator) in children with CF aged 2–5 and carrying the G551D mutation, 93% of which were pancreatic insufficient (FE-1 < 50 mg/g). After 24 weeks of ivacaftor, a 99.8 mg/g mean increase in FE-1 was observed, suggesting an improvement of exocrine pancreatic function [79]. Another report also suggested a positive effect of ivacaftor in older patients with CF [80]. More recently, a phase 3 study evaluating the safety and efficacy of ivacaftor in patients <2 years of age with a CFTR gating mutation showed a significant improvement in FE1 in treated patients. These findings suggest there may be a window of opportunity in early life for improving pancreatic function [81].

3.2. CF-related diabetes

CFRD is the third most frequent complication in the CF adult population after respiratory insufficiency and exocrine pancreatic disease, with an estimated prevalence of 30–50% [82,83], and occurs almost only in patients with PI. The pathophysiology of CFRD is complex and involves (a) decreased insulin production due to β cell dysfunction (CFTR defect) and/or β cell loss; (b) decreased insulin sensitivity (secondary to corticosteroids, chronic infection, and inflammation); and (c) increased glucagon secretion [84]. CFRD is different from type 1 and type 2 diabetes and is characterized by a reduced and delayed insulin response despite normal basal insulin secretion. As a result, at the early stages of the disease, fasting blood glucose levels often fall within the normal range and postprandial glucose levels are high. Mortality rates among CF patients are higher in those with CFRD than in those without diabetes [83,85,86] and increase with lower lung function and more frequent exacerbations [87,88]. Clinical decline (weight loss, lung function decline, pulmonary exacerbations) in the years prior to CFRD diagnosis has been reported, as has an improvement in these clinical markers after insulin therapy initiation [89–91]. An annual oral glucose tolerance test (OGTT) when the patient is stable is recommended for all patients with CF over the age of 10 [22,92]. Because OGTT may fail to detect some glycemic abnormalities in CF, continuous glucose monitoring has been evaluated in several studies and was approved by the FDA to help diagnose CFRD in children and adolescents [93–96]. The value of HbA1c as a screening tool for the diagnosis of CFRD is controversial although it is commonly used to monitor glycemic control [93]. Diabetes screening should be more frequent in patients receiving corticosteroid treatment and enteral nutrition as well as during pregnancy [22]. All individuals with CF who meet the diagnostic criteria for diabetes should be treated [22]. Treatment should also be considered in patients with glucose level abnormalities associated with clinical deterioration [88].

Treatment of CFRD relies on insulin therapy. Though oral treatment is not recommended in patients with CFRD [22], a single study suggested that repaglinide could be effective in some patients [97]. These results need to be confirmed in long-term studies and with a larger population sample, however. High-calorie food intake must be maintained [92] and physical activity should be promoted. Because their life expectancy is increasing, adults with CF become more likely to develop complications of CFRD. Microvascular complications comparable to those seen in patients with type 1 diabetes (neuropathy, retinopathy, and nephropathy) have been reported in patients with CFRD, especially in the context of poor glycemic control [98–101]. Thus, screening for retinopathy (dilated eye examination), neuropathy (clinical evaluation), and nephropathy (microalbuminuria screening) should be performed at least annually and foot issues should be closely monitored [22,88]. Macrovascular complications have so far been rare and only a few cases of coronary disease have been reported in patients with CFRD [102,103]. However, it seems likely that these complications will become more frequent in the future because of long-standing diabetes in aging CF adults.

The impact of CFTR modulators on CFRD has not been fully established: ivacaftor may improve insulin response after oral glucose stimulation [104,105] and could even reverse CFRD in adult CF patients [106]. However, the impact of lumacaftor/ivacaftor on glucose tolerance or insulin secretion was not consistent in a small number of patients with CF [107]. These results need to be confirmed in larger studies.

3.3. Pancreatic cysts

Pancreatic cystosis is rare in CF adults [108]. Patients are usually asymptomatic and diagnosis is often made during routine abdominal imaging. When present, clinical manifestations are not specific – mainly due to the mass effect – and include abdominal pain, nausea, and early satiety [109,110]. CT scans usually show numerous large hypodense lesions (Figure 2(c)),

Table 3. Suggested screening and management of selected chronic non-pulmonary complications in adults with CF.

Complications	Suggested screening/assessment	Suggested intervention	Management guidelines	Ref.
Colorectal cancer (non-transplanted patients)	Start screening at age 40 years Colonoscopy every 5 years Colonoscopy at 3 years if adenomatous polyps found on the latest endoscopic examination	Polyp removal	**Yes, specific to CF**	[174]
CF-related liver disease (CFLD)	**Annual screening** Abdominal examination by a gastroenterologist; Biochemical evaluation (AST, ALT, GGT, ALP, Prothrombin time, platelets). Abdominal ultrasound imaging	Start ursodeoxycholic acid when CFLD is diagnosed Start with daily dose of 20 mg/kg	**Yes, specific to CF**	[126]
Chronic kidney disease	**Annual screening** Serum creatinine Microalbuminuria in patients with CF-related diabetes	Diabetes treatment Reduce exposure to aminoglycosides and other nephrotoxic drugs	**None**	-
Osteopenia/ osteoporosis	**Regular evaluation** of bone mineral density by Dual Energy X-ray Absorptiometry (every 1–5 years) Annual measurement of serum 25-hydroxyvitamin D, serum calcium, serum phosphorus and parathyroid hormone concentrations	Achieve adequate nutritional status (normal body mass index and lean mass) Promote physical activity Calcium and vitamin D supplementation Consider bisphosphonates	**Yes, specific to CF**	[146]
Anxiety/depression	**Annual screening with questionnaires** Patient Health Questionnaire 9 (PHQ-9) for depression Generalised Anxiety Disorder 7-item (GAD-7) for anxiety	Referral for evidence-based psychological interventions ± treatment	**Yes, specific to CF**	[189]
CF-related diabetes	**Annual screening in pancreatic insufficient patients** Oral glucose tolerance test (OGTT) Possibly continuous glucose monitoring (CGM)	Insulin therapy Regular follow-up by a diabetologist	**Yes, specific to CF**	[[23–97]]
Ototoxicity	**Annual audiometric assessment** for patients with repeated IV aminoglycoside courses	Reduce exposure to aminoglycosides	**None**	-

although MRI is the most accurate method for cyst evaluation and follow-up [111]. Infectious or hemorrhagic complications are rare with only one reported case of intracystic bleeding [108]. To our knowledge, no malignancy has been reported. Surgery or endoscopic cyst gastrostomy are to be discussed on a case-by-base basis if the patient has chronic pain or complications [112].

3.4. CF-related liver disease

CFLD is the third most frequent cause of mortality in the CF population after lung disease and transplantation complications, accounting for 2.5–5% of the overall mortality [3,82,113,114]. CFLD is considered to be the consequence of CFTR dysfunction in the biliary epithelium leading to abnormally viscous biliary secretion, ductal obstruction, inflammation, and subsequent hepatic cirrhosis [115]. In an autopsy study, up to 70% of patients with CF presented with focal biliary cirrhosis [116], and 5–8% had multilobular biliary cirrhosis [117,118], though the progression to multilobular cirrhosis occurs only in 5–10% of patients [119]. CFLD usually appears during the first decade of life [120] though a recent study suggested a possible case of adult-onset CFLD [118]. Patients are frequently asymptomatic and the spectrum of CFLD manifestations is wide and heterogeneous, leading to challenges in diagnosis and management [114]. CFLD manifestations range from a simple asymptomatic elevation in aminotransferases to end-stage cirrhosis and portal hypertension. There is no consensus for the definition of CFLD, which makes its prevalence difficult to estimate. European guidelines recommend considering CFLD diagnosis if at least two of the following variables are present: (a) hepatomegaly on physical examination; (b) elevated liver enzymes in at least 3 consecutive measurements over 12 months and after ruling out other causes of liver disease; (c) ultrasonographic evidence of liver disease, portal hypertension, or biliary abnormalities [121] (Figure 2(e)). Contrary to European guidelines, North American guidelines define CFLD as the presence of both liver cirrhosis and portal hypertension, and liver involvement as persisting or intermittent liver enzyme elevation, steatosis, fibrosis, cholangiopathy, and/or ultrasound abnormalities [24]. Steatosis can be detected through imaging or biopsy and is the most frequent hepatic manifestation in patients with CF, with a prevalence of 20–60% [122] (Figure 2(d)). This manifestation appears to be distinct from CFLD and patients presenting with hepatic steatosis tend to have a higher body mass index (BMI) and better lung function than patients with no steatosis [122].

Current guidelines recommend annual screening for CFLD (Table 3) [121]. Although an abdominal ultrasound is recommended, the positive predictive value of a normal ultrasound has been shown to be only 33%, with a sensitivity of 57%. Moreover, a normal ultrasound does not preclude significant liver fibrosis. Therefore, diagnosis of early liver disease cannot reliably be made on the basis of ultrasound findings alone. If a diagnosis is hard to reach, elastography can be used to assess liver function in patients with CF and a liver biopsy can be considered if noninvasive tests are inconclusive [121]. Risk factors associated with CFLD include male gender, meconium ileus, environmental factors, and the Z allele of Serpina1

[120,123]. Treatment options are limited: UDCA has been recommended [121], but its role in improving the progression of established CFLD remains unproven [124]. Screening for esophageal varices by gastrointestinal endoscopy should be performed in patients with cirrhosis or hypersplenism and should be treated endoscopically if necessary. PT and coagulation factors should be measured at least once a year to detect early signs of liver failure. In patients presenting with cirrhosis, an annual liver ultrasound and blood alpha-fetoprotein monitoring are indicated in order to screen for hepatocellular carcinoma [121]. Liver transplantation must be considered if patients develop progressive hepatic dysfunction, ascites and jaundice, variceal bleeding that is not controlled by conventional management, hepatopulmonary and portopulmonary syndromes, severe malnutrition, or deteriorating pulmonary function [121]. A case report suggested a possible beneficial effect of CFTR modulation on CFLD, with a reversal of hepatic steatosis on abdominal CT imaging in a 17-year-old female after treatment with ivacaftor [125].

3.5. Other chronic gastrointestinal complications

Gastroesophageal reflux disease (GERD) is frequent among adults with CF and 24–39% report heartburn, acid reflux, or dysphagia [126]. GERD diagnosis is symptoms based and should be confirmed with impedance or pH monitoring. Endoscopy is used to assess inflammation (i.e. erosive esophagitis) and to identify an additional etiology of epigastric pain (ulcer) [127]. GERD management includes diet-related measures (limiting acidic and spicy food, caffeine, and chocolate) [128] and treatment with acid blockers (pump proton inhibitors) and pro-kinetic agents if symptoms persist. Surgical fundoplicature may be considered in symptomatic GERD that is not controlled with medical treatment.

Constipation is also a frequent symptom among adults with CF. In 2010, diagnostic criteria for constipation were defined to differentiate it from DIOS and included abdominal pain/distension, or reduced frequency/hard stools in the last weeks/months, that are relieved with laxative use [28]. Management of constipation includes adequate hydration, increased salt and fiber intake, physical activity, adequate PERT, and laxatives.

3.6. Infertility

Congenital bilateral absence of the vas deferens (CBAVD) affects up to 99% of male patients with CF and is responsible for male infertility [129]. In women with CF, fertility is less compromised although up to 50% will have difficulty conceiving because of poor general health/nutritional status, thickened cervical mucus, or diabetes [130]. Recently, two cases of improved fertility were reported in female patients treated with ivacaftor, which could have led to an improvement in general health, nutritional status, or cervical mucus consistency secondary [129]. All patients with CF should receive counseling regarding conception options including assisted reproductive technology [22,131].

3.7. Sinonasal manifestations

Nearly all CF patients will present with sinonasal abnormalities on clinical and/or radiographic examination [132]. The sinuses serve as a reservoir for pathogens that may contribute to lower airway colonization and to lower airway disease progression. In CF patients, nasal polyposis prevalence is estimated at 32–44% [133] and chronic rhinosinusitis (CRS) prevalence at 30–65% [134]. CRS diagnosis is based on a combination of clinical symptoms (nasal obstruction or congestion, mucopurulent discharge), endoscopic evidence (nasal polyps), and/or CT findings (sinus opacification, osseous thickening) [135] (Figure 2(g)). Management guidelines for CRS are not specific to the CF population [135] and should be conservative. First-line management includes saline irrigation and/or topical corticosteroids. Some studies suggest that topical antibiotics could improve CF-related CRS symptoms and/or complications [132,136]. Dornase alfa, a mucolytic agent has also been shown to improve CRS, but its availability is currently limited by cost [137]. Surgical treatment should be offered when medical management has failed and patients should be referred to surgeons that are familiar with CF-related sinus disease. CFTR modulators may be beneficial [138] but further research is necessary.

3.8. CF-related bone and joint diseases

Low bone mineral density (BMD) and increased fracture risk have been reported in adults with CF, with a prevalence of 38% for osteopenia and 23% for osteoporosis [139]. Contributing factors include PI, pulmonary infections, poor nutritional status, delayed puberty, corticosteroids, hypogonadism, and vitamin D, calcium and vitamin K deficiencies [140]. Regular screening for reduced BMD using dual energy X-ray absorptiometry is recommended in patients > 8–10 years old (Table 3) [141]. Management of low BMD includes adequate nutrition, vitamin D and calcium supplementation, and weight bearing physical exercise [141]. When corticosteroids are necessary (e.g. for the treatment of allergic bronchopulmonary aspergillosis), the dose and duration prescribed should be minimized [141]. The use of bisphosphonates is not universally agreed upon and should be considered on an individual basis with the help of an endocrinologist [22]. CFTR modulators may improve BMD: a recent study reported an improvement in the Z-score of seven patients treated with ivacaftor [142].

Hypertrophic pulmonary osteoarthropathy is a rare complication of CF and is usually seen in adults with severe lung disease. Symptoms include clubbing and pain at the distal end of long bones [64]. Treatment is symptomatic and should include NSAIDs and management of pulmonary exacerbations. Bisphosphonates may be considered if initial management fails [143].

CF-related arthropathy usually occurs in 2–8.5% of adults with CF and consists of recurrent acute episodes of mono- or poly-arthritis (joint swelling, pain, stiffness) [143]. Symptoms usually resolve spontaneously in 1–5 days. Treatment is essentially symptomatic and consists of NSAIDs or corticosteroids [64]. Refractory cases should be referred to a rheumatologist to rule out or treat other rheumatologic diseases [22].

3.9. Aquagenic palmoplantar keratoderma

Aquagenic palmoplantar keratoderma (APK) is a dermatosis characterized by edema, translucent or whitish papules, and excessive wrinkling of the palms after exposure to water (Figure 2(h)) [144]. This condition is known to be associated with CF with a prevalence ranging from 35% to 78%, suggesting CFTR involvement. A correlation between APK and palmoplantar hyperhidrosis has been noted [144]. One case of APK improvement with ivacaftor has been reported in the literature [145].

3.10. Drug-induced chronic complications

3.10.1. Secondary adrenal insufficiency

Secondary adrenal insufficiency (AI) may occur in patients with CF treated with long-term systemic glucocorticoids or with inhaled glucocorticoids (ICS) and might lead to adrenal crisis in some patients. Prevalence of AI in the CF population has never been assessed. However, several studies reported adrenal suppression in patients treated with ICS and azole antifungal treatment (i.e. itraconazole, voriconazole, and posaconazole) [146]. The interaction between azoles and glucocorticoids, inhaled or systemic, can lead to increased serum concentrations of both methylprednisolone or dexamethasone and budesonide or fluticasone [146]. A study reported abnormal ACTH blood levels in 100% (12/12) of patients with CF receiving itraconazole and inhaled fluticasone [147]. Other reports also suggested similar interactions with voriconazole or posaconazole [148,149]. A recent Canadian single center retrospective study estimated the prevalence of AI at 8–9%, although these results are probably an underestimate since ACTH testing was not systematic. In this study, the authors reported that patients with AI had a higher frequency of *Aspergillus* colonization and were more likely to be treated with ICS or systemic corticosteroids [150]. Patients at risk of AI, especially those treated with azoles and ICS, should be tested for adrenal suppression and supplemented as needed.

3.10.2. Ototoxicity

Frequent use of aminoglycosides can lead to ototoxicity, including vestibular dysfunction and hearing loss. Hearing loss is well documented and its prevalence ranges from 17% to 23% [151,152]. It should be screened for annually in patients who receive frequent IV or inhaled aminoglycoside courses. Screening consists of clinical audiometry and/or otoacoustic emission testing [153]. Vestibular dysfunction secondary to aminoglycoside exposure is less well characterized: symptoms include dizziness, motion sickness, unsteadiness when standing/walking and disturbed vision with head motion. A recent study reported a prevalence of 79% of vestibular system dysfunction in a cohort of 71 patients with CF receiving aminoglycosides [151,152]. This high prevalence needs to be confirmed by larger studies. Routine screening for vestibular dysfunction is not recommended at this time, although the European CF society recommends that CF centers have access to a clinician experienced in vestibular assessment [22].

4. Emerging chronic non-pulmonary complications in adult patients with CF

This section describes important chronic non-pulmonary complications that have emerged in recent years due to the aging of the CF adult population.

4.1. Malignancies

Numerous case reports of cancer in CF patients can be found in the literature [154–157]. Between 1993 and 2013, several studies demonstrated an increased risk of neoplasms of the gastrointestinal tract (GI tract) [158–161] but the pathophysiological mechanism behind this increased risk remains unclear. Chronic inflammation and chronic infection are common features of CF and are known to contribute to cancer [162,163]. Gut dysbiosis (i.e. any change to the composition of an individual's gut microbiota) is now a well-established consequence of the CFTR defect [164] and has been shown to be associated with an increased risk of GI tract cancer, especially colorectal cancer [165]. The existence of CFTR-dependent cancer formation mechanisms is another possible hypothesis since CFTR has recently been identified as an emerging regulator of cancer [166].

The largest registry study to evaluate the risk of cancer in CF patients was published in 2013 [167]. In the non-transplanted patient group, data from 344,114 patients-years of follow-up showed that the global risk of cancer in CF was no different from that of the general population (standardized incidence ratio [SIR]: 1.1, 95% confidence interval [CI] = 1.0 to 1.3). However, the authors reported an increased risk of GI tract cancer (SIR 3.5, 95% CI = 2.6 to 4.7) with the highest risk in the small intestine (SIR 11.5, 95% CI = 4.2 to 25.4), biliary tract (SIR 11.4, 95% CI = 3.6 to 27.4), and colon (SIR 6.2, 95% CI = 4.2 to 9.0). Non-transplanted CF patients were also at higher risk for testicular cancer and lymphoid leukemia (SIR 1.7, 95% CI = 1.02 to 2.7, and SIR 2.0, 95% CI = 1.2 to 3.1, respectively). Bowel cancer risk was notably elevated in men, patients with severe CFTR mutations and those with a history of DIOS. In the transplanted group, overall cancer risk was higher than expected (SIR 2.7, 95% CI = 1.8 to 3.9) with a particularly high GI tract cancer risk (SIR 17.3. 95% CI = 10.7 to 26.5).

Subsequent studies have evaluated the benefit of screening CF patients for colorectal cancer and suggest that it may be beneficial and cost-effective [168,169]. Consensus recommendations for colorectal cancer screening in non-transplanted CF patients were recently published (Table 3) [170]. Recent findings suggest an increased relative risk of GI tract cancer in non-transplanted CF patients, although the absolute risk remains low. One can expect the number of cancer cases to rise in the coming years as the number of patients over 40 years continues to increase.

4.2. Chronic kidney disease

Chronic kidney disease (CKD) has recently emerged as a new comorbidity in adults with CFRD and/or repeated and prolonged exposure to aminoglycosides. The prevalence of CKD

in patients with CF has not been reliably estimated but a recent Danish study, showed that the prevalence of moderate CKD (GFR < 60 ml/min/1.73 m^2) was higher in adults with CF (2.7%) than in the general population [171] and a larger American study found a prevalence of 2.3% (GFR < 60 ml/min/1.73 m^2) [172]. The pathophysiology of CKD is not well understood. CFTR is expressed in several segments of the nephron and its function is known to be impaired in CF animal models and in CF patients, although no clear renal phenotype is known to be associated with its mutation [173]. The role of aminoglycosides in CKD development is debated: CKD might arise from repeated episodes of AKI during IV antibiotic courses in addition to cumulative antibiotic treatment [172,174]. The prevalence of CKD associated with CFRD has not been estimated, although one can expect an increase in CFRD-associated CKD since patients are living longer with CFRD. Microalbuminuria is frequent and affects up to 50% of patients [174] and proteinuria was recently found in 11% of patients in a single center cohort [175]. Yahiaoui *et al*. examined the renal biopsies of 13 CF patients and reported a wide spectrum of renal diseases with the 2 most frequent being amyloidosis and diabetic glomerulopathy [173]. Chronic infection and inflammation could promote AA amyloidosis or IgA nephropathy in this population, both of which are associated with poor prognosis in patients with CF [176,177].

4.3. Metabolic syndrome and cardiovascular diseases

With the improvement of nutritional management and prolonged life expectancy, patients with CF are at risk of excessive weight gain and obesity. Recent studies show that 6–18% of CF patients are overweight and 1–8% obese [178,179]. Although overweight and obese patients with CF are often considered to have better lung function, a recent study found no evidence of an association [179]. A recent study also suggested that excessive adiposity could be inversely associated with lung function in CF [180]. Overweight and obese patients have higher rates of hypercholesterolemia and lower levels of 25 OH vitamin D. Weight gain might become an issue for patients with CF since it could accelerate the onset of CFRD and the consequent macrovascular complications. Overweight and obese patients should receive dietary counseling to improve their nutritional status and avoid complications, such as dyslipidemia and diabetes. Treatment with CFTR modulators can induce weight gain, which suggests that the high fat/high calorie intake that is usually recommended in CF may need to be changed when CFTR function is improved.

4.4. Anxiety and depression

Studies evaluating psychological complications in adults with CF have found a high prevalence of depression and anxiety (13–33%) [181], the symptoms of which can have a negative impact on the course of CF, with worse lung function, lower BMI and treatment compliance, worse quality of life, more frequent hospitalizations, and increased healthcare costs [182]. International guidelines recommend screening for depression and anxiety in patients with CF that are over 12 years old (Table 3) [182]. Prevention is recommended and consists of stress management and coping skills training. Management should include evidence-based interventions, cognitive behavioral therapy (for severe anxiety), and selective serotonin reuptake inhibitors (citalopram, paroxetine) as first-line agents in patients over 12 years old [182].

4.5. Urinary incontinence

In women with CF, the prevalence of urinary incontinence seems to be higher than in the general population (30–76%) [183] and increases with declining FEV1 and age [64]. In the CF population, urinary stress incontinence (i.e. involuntary urination when sneezing, coughing and physical strain) is most common [64]. Physicians should be aware of this frequent yet unreported complication since coughing and physiotherapy might worsen urinary incontinence and lead to the avoidance of chest physiotherapy [183]. Management includes patient education, pelvic floor muscle exercises, optimizing airway clearance techniques, treatment of constipation if present, and referral as needed. Urinary incontinence in men with CF has not been well documented although a recent study reported a prevalence up to 15% and an association between incontinence and increased rates of anxiety and depression [184].

5. Conclusion

The life expectancy of the CF adult population is expected to further increase in future years thanks to improvements in multidisciplinary care and with the development of effective CFTR modulators [5,185]. As a result, the spectrum of CF-related complications is likely to evolve. Regular monitoring for chronic non-pulmonary complications in adults with CF is paramount and should aim for early management and prevention. Suggested screening and management strategies for selected chronic non-pulmonary complications in adults with CF are provided in Table 3. These suggestions will no doubt evolve in future years as our understanding of CF complications improves and as the phenotype of CF patients changes with novel treatment options such as effective CFTR modulators.

6. Expert commentary

Non-pulmonary complications are highly prevalent in adults with CF and are sometimes responsible for acute episodes that pose specific challenges to the adults with CF and their caregivers. The spectrum of classical chronic complications (e.g. diabetes, liver disease, osteoporosis) is evolving, and novel complications (e.g. digestive cancers, CKD, metabolic syndrome) are emerging. Because non-pulmonary complications represent a significant burden in adults with CF, effective strategies for screening and/or preventing these comorbidities should be developed. Unfortunately, current screening strategies are often not evidence-based and sometimes are not fully acceptable for CF adults, leading to ineffective screening. Thus, there is a major interest in developing tools for effective screening of non-pulmonary complications/comorbidities without increasing the burden of care in adults with CF.

Two significant changes impact the prevalence and severity of non-pulmonary complications in adults with CF. First, the CF adult population is aging; thus, problems that did not exist before (e.g. digestive cancer, long-term microangiopathic and macroangiopathic complications of CFRD) are becoming more prevalent. Second, although there is hope that recently-released CFTR modulators will have significant beneficial effects on non-pulmonary complications (e.g. by reducing malnutrition and improving pancreatic function), there is also a possibility that they may lead to excessive weight gain/obesity and metabolic syndrome in adults with CF that are used to a high fat/high calorie diet. Furthermore, the possible roles of CFTR modulators in preventing other complications (e.g. osteoporosis, digestive cancer) will have to be carefully monitored. CFTR modulators may have indirect beneficial effects on non-pulmonary complication by reducing drug-induced complications (e.g. by reducing exposure to aminoglycosides in relation with the reduction of pulmonary exacerbation rates), although their long-term safety profile is not well established.

As the prognosis of CF keeps improving, the number of adults is increasing, and the CF adult population will continue to grow in number and age in the next 5 years. Current evidence also suggests that most CF patients will be treated with combinations of CFTR modulators, which will have beneficial effects on the pulmonary and (at least some) non-pulmonary complications. The spectrum of non-pulmonary complications will likely evolve with the decrease in some complications due to better prevention and treatment but there are also concerns that emerging complications (e.g. cancer, metabolic syndrome) will constitute significant threats for the adults with CF. Thus, adult CF centers will likely face large cohorts of adults with CF with a high burden of non-pulmonary complications that will be important to address. This will require not only developing screening/caring strategies but also ensuring that adequate knowledge exists in CF centers on the care of specific comorbidities by attracting novel specialists (e.g. oncologists) and by providing appropriate training to physicians and allied professionals working in CF centers.

7. Five-year view

As the CF population ages, rates of long-term extrapulmonary complications are expected to increase. Concerns exist on long-term complications of diabetes and emergence of digestive cancers. Roles of CFTR modulators on reducing long-term extrapulmonary complications in CF patients remain to be establish. These drugs may result in direct effects on complications directly related to defective ion transport or have beneficial effects related to reduction in the use of drugs (e.g. aminoglycosides) that induce significant adverse effects in CF patients. Establishing guidelines for prevention, diagnosis, and treatment of extrapulmonary complications will contribute to decrease disease burden in CF adults.

Key issues

- Life expectancy has markedly increased over the past 20 years and forecasts suggest that the adult CF population will keep expanding and aging in the next decade.
- CF adults are at risk of acute non-respiratory complications (e.g. digestive complications, nephrolithiasis, and drug-induced complications).
- Classical chronic non-pulmonary complications (e.g. diabetes, osteoporosis, liver disease) are highly prevalent and constitute a considerable burden to the patients.
- Emerging complications (e.g. colorectal cancer, CKD, metabolic syndrome) are now recognized and their burden is likely to increase in future years.
- Recently commercialized CFTR modulators may reduce some non-pulmonary complications but their long-term effects on other complications (e.g. digestive cancer) remains to be established.
- A challenge for CF caregivers will be to develop effective strategies for screening and treating major non-pulmonary complications without increasing the burden of care in CF adults.

Funding

This paper was not funded.

Declaration of interest

Pierre-Régis Burgel has received personal fees (advisory boards, lecturing) from Astra-Zeneca, Chiesi, GSK, Novartis, Teva, Vertex and Zambon. Clémence Martin received personal fees (advisory boards, lecturing) from Chiesi and Zambon. The remaining authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewers disclosure

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Stephenson AL, Stanojevic S, Sykes J, et al. The changing epidemiology and demography of cystic fibrosis. Presse Med. 2017;46(6 pt 2):e87–e95.
2. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519–2531.
•• **A recent review on current aspects of cystic fibrosis.**
3. Martin C, Hamard C, Kanaan R, et al. Causes of death in French cystic fibrosis patients: the need for improvement in transplantation referral strategies! J Cyst Fibros. 2016;15(2):204–212.
4. Burgel P-R, Bellis G, Elborn JS. Modelling future trends in cystic fibrosis demography using the French Cystic Fibrosis Registry: update and sensitivity analysis. Eur Resp J. 2017;50(2):1700763.
5. Burgel P-R, Bellis G, Olesen HV, et al. Future trends in cystic fibrosis demography in 34 European countries. Eur Resp J. 2015;46 (1):133–141.
6. Fajac I, Wainwright CE. New treatments targeting the basic defects in cystic fibrosis. Presse Med. 2017;46(6):e165–e175.
7. Kim RJ. Cystic fibrosis-related diabetes in children: an update. Pediatr Ann. 2016;45(9):e321–e326.
8. Debray D, Mas E, Munck A, et al. Atteinte hépatique digestive, prise en charge nutritionnelle et troubles de l'oralité chez l'enfant atteint de mucoviscidose. Arch Pediatr. 2016;23(12):12S15–12S20.

9. Vandenplas Y, Hauser B. An updated review on gastro-esophageal reflux in pediatrics. Expert Rev Gastroenterol Hepatol. 2015;9 (12):1511–1521.
10. Snell G, Reed A, Stern M, et al. The evolution of lung transplantation for cystic fibrosis: A 2017 update. J Cyst Fibros. 2017;16(5):553–564.
11. Gilchrist FJ, Samuels M, Klafkowski G, et al. Pneumomediastinum and hyponatraemic dehydration as presenting features of cystic fibrosis. Eur Resp J. 2013;42(6):1760–1762.
12. Rendle-Short J. Fibrocystic disease of the pancreas presenting with acute salt depletion. Arch Dis Child. 1956;31(155):28.
13. Desmazes-Dufeu N, Hubert D, Burgel P-R, et al. Déshydratation sévère, consequence de la canicule d'août 2003 sur une cohorte d'adultes atteints de mucoviscidose. Presse Med. 2005;34(9):647–648.
14. Durno C, Corey M, Zielenski J, et al. Genotype and phenotype correlations in patients with cystic fibrosis and pancreatitis. Gastroenterology. 2002;123(6):1857–1864.
15. Dray X, Marteau P, Bienvenu T, et al. Discussion on genotype and phenotype correlations in patients with cystic fibrosis and pancreatitis. Gastroenterology. 2003;125(4):1286.
16. Ooi CY, Dorfman R, Cipolli M, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology. 2011;140(1):153–161.
17. Walkowiak J, Lisowska A, Blaszczynski M. The changing face of the exocrine pancreas in cystic fibrosis: pancreatic sufficiency, pancreatitis and genotype. Eur J Gastroenterol Hepatol. 2008;20(3):157–160.
18. De Boeck K, Weren M, Proesmans M, et al. Pancreatitis among patients with cystic fibrosis: correlation with pancreatic status and genotype. Pediatrics. 2005;115(4):e463–e469.
19. Maléth J, Balázs A, Pallagi P, et al. Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis. Gastroenterology. 2015;148(2):427–439.e416.
20. Kadiyala V, Lee LS, Banks PA, et al. Cigarette smoking impairs pancreatic duct cell bicarbonate secretion. JOP. 2013;14(1):31–38.
21. Crockett SD, Wani S, Gardner TB, et al. American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. Gastroenterology. 2018;154 (4):1096–1101.
22. Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros. 2018;17(2):153–178.
•• **European guidelines on cystic fibrosis.**
23. Assis DN, Debray D. Gallbladder and bile duct disease in cystic fibrosis. J Cyst Fibros. 2017;16:S62–S69.
24. Flass T, Narkewicz MR. Cirrhosis and other liver disease in cystic fibrosis. J Cyst Fibros. 2013;12(2):116–124.
25. Curry MP, Hegarty JE. The gallbladder and biliary tract in cystic fibrosis. Curr Gastroenterol Rep. 2005;7(2):147–153.
26. Colombo C, Bertolini E, Assaisso ML, et al. Failure of ursodeoxycholic acid to dissolve radiolucent gallstones in patients with cystic fibrosis. Acta Paediatrica. 1993;82(6–7):562–565.
27. Munck A, Alberti C, Colombo C, et al. International prospective study of distal intestinal obstruction syndrome in cystic fibrosis: associated factors and outcome. J Cyst Fibros. 2016;15(4):531–539.
28. Houwen RH, van der Doef HP, Sermet I, et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Pediatr Gastroenterol Nutr. 2010;50(1):38–42.
29. Robertson MB, Choe KA, Joseph PM. Review of the abdominal manifestations of cystic fibrosis in the adult patient. RadioGraphics. 2006;26(3):679–690.
30. Colombo C, Ellemunter H, Houwen R, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros. 2011;10:S24–S28.
31. Abraham JM, Taylor CJ. Cystic fibrosis & disorders of the large intestine: DIOS, constipation, and colorectal cancer. J Cyst Fibros. 2017;16:S40–S49.
32. Artul S, Artoul F, Habib G, et al. Transient intussusception: rare cause of abdominal pain in cystic fibrosis. BMJ Case Rep. 2013; pii: bcr2013201259.
33. Nash EF, Stephenson A, Helm EJ, et al. Intussusception in adults with cystic fibrosis: a case series with review of the literature. Dig Dis Sci. 2011;56(12):3695–3700.
34. Thorsteinsson M, Burgdorf SK, Penninga L. Intussusception in an adult with cystic fibrosis successfully reduced with contrast enema. BMJ Case Rep. 2015;bcr2015209466.
35. Al-Abed Y, Al Abed Y, Hameed W, et al. Appendicitis in an adult patient with cystic fibrosis: a diagnostic challenge. Gut. 2007;56 (12):1799–1800.
36. Shields MD, Levison H, Reisman JJ, et al. Appendicitis in cystic fibrosis. Arch Dis Child. 1991;66(3):307–310.
37. Canny JD, Brookes A, Bowley DB. Distal intestinal obstruction syndrome and colonic pathologies in cystic fibrosis. Br J Hosp Med. 2017;78(1):38–43.
38. Keyzer C, Knoop C, Van Wettere M, et al. Cystic fibrosis: unenhanced CT description of the appendix in asymptomatic adults. AJR Am J Roentgenol. 2014;202(4):759–764.
39. Wilcock MJ, Ruddick A, Gyi KM, et al. Renal diseases in adults with cystic fibrosis: a 40 year single centre experience. J Nephrol. 2015;28(5):585–591.
40. Terribile M, Capuano M, Cangiano G, et al. Factors increasing the risk for stone formation in adult patients with cystic fibrosis. Nephrol Dialysis Transplantation. 2006;21(7):1870–1875.
41. Perez-Brayfield MR, Caplan D, Gatti JM, et al. Metabolic risk factors for stone formation in patients with cystic fibrosis. J Urol. 2002;167 (2):480–484.
42. Smyth A, Lewis S, Bertenshaw C, et al. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. Thorax. 2008;63(6):532–535.
43. UK Cystic Fibrosis Trust Antibiotic Working Group. 2009. Antibiotic treatment for cystic fibrosis. 3rd ed. Available at https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-care/consensus-documents (accessed on November 27th 2018).
44. Burrows JA, Nissen LM, Kirkpatrick CMJ, et al. Beta-lactam allergy in adults with cystic fibrosis. J Cyst Fibros. 2007;6(4):297–303.
45. Roehmel JF, Schwarz C, Mehl A, et al. Hypersensitivity to antibiotics in patients with cystic fibrosis. J Cyst Fibros. 2014;13(2):205–211.
46. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5(4):309–316.
47. Whitaker P, Naisbitt D, Peckham D. Nonimmediate β-lactam reactions in patients with cystic fibrosis. Curr Opin Allergy Clin Immunol. 2012;12(4):369–375.
48. Caimmi S, Sanfiorenzo C, Caimmi D, et al. Comprehensive allergy work-up is mandatory in cystic fibrosis patients who report a history suggestive of drug allergy to beta-lactam antibiotics. Clin Transl Allergy. 2012;2(1):10.
49. Petroni DH, Aitken ML, Ham E, et al. Approach to the evaluation of adverse antibiotic reactions in patients with cystic fibrosis. Ann Allergy Asthma Immunol. 2016;117(4):378–381.
50. Legere HJ, Palis RI, Bouza TR, et al. A safe protocol for rapid desensitization in patients with cystic fibrosis and antibiotic hypersensitivity. J Cyst Fibros. 2009;8(6):418–424.
51. Egressy K, Jansen M, Meyer KC. Recurrent clostridium difficile colitis in cystic fibrosis: an emerging problem. J Cyst Fibros. 2013;12 (1):92–96.
52. Burke DG, Harrison MJ, Fleming C, et al. Clostridium difficile carriage in adult cystic fibrosis (CF); implications for patients with CF and the potential for transmission of nosocomial infection. J Cyst Fibros. 2017;16(2):291–298.
53. Pant C, Sferra TJ, Deshpande A, et al. Clostridium difficile infection in hospitalized patients with cystic fibrosis. Infect Control Hosp Epidemiol. 2014;35(12):1547–1548.
54. Monaghan TM, Negm OH, MacKenzie B, et al. High prevalence of subclass-specific binding and neutralizing antibodies against Clostridium difficile toxins in adult cystic fibrosis sera: possible mode of immunoprotection against symptomatic C. difficile infection. Clin Exp Gastroenterol. 2017;10:169–175.
55. Piccolo F, Tai AS, Ee H, et al. Clostridium difficile infection in cystic fibrosis: an uncommon but life-threatening complication:

Clostridium difficile colitis in CF. Respirol Case Rep. 2017;5(1): e00204.
56. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):987–994.
57. Dunwoody R, Steel A, Landy J, et al. Clostridium difficile and cystic fibrosis: management strategies and the role of faecal transplantation. Paediatr Respir Rev. 2018;26:16–18.
58. Royle TJ, Davies RE, Gannon MX. Totally implantable venous access devices – 20 years' experience of implantation in cystic fibrosis patients. Ann R Coll Surg Engl. 2008;90(8):679–684.
59. Dupont C, Gouya H, Panzo R, et al. Complications of peripherally inserted central catheters in adults with cystic fibrosis or bronchiectasis. J Vasc Access. 2015;16(3):245–249.
60. Deerojanawong J, Sawyer SM, Fink AM, et al. Totally implantable venous access devices in children with cystic fibrosis: incidence and type of complications. Thorax. 1998;53(4):285–289.
61. May TL, Gifford AH, Lahiri T, et al. Complications of long and intermediate term venous catheters in cystic fibrosis patients: a multicenter study. J Cyst Fibros. 2018;17(1):96–104.
62. McCarthy C, O'Carroll O, O'Brien ME, et al. Risk factors for totally implantable venous access device-associated complications in cystic fibrosis. J Ir Med Sci. 2018;187(2):429–434.
63. Rodgers HC, Liddle K, Nixon SJ, et al. Totally implantable venous access devices in cystic fibrosis: complications and patients' opinions. Eur Resp J. 1998;12(1):217–220.
64. Ronan NJ, Elborn JS, Plant BJ. Current and emerging comorbidities in cystic fibrosis. Presse Med. 2017;46(6):e125–e138.
65. Mermis JD, Strom JC, Greenwood JP, et al. Quality improvement initiative to reduce deep vein thrombosis associated with peripherally inserted central catheters in adults with cystic fibrosis. Ann Am Thorac Soc. 2014;11(9):1404–1410.
66. Munck A, Malbezin S, Bloch J, et al. Follow-up of 452 totally implantable vascular devices in cystic fibrosis patients. Eur Resp J. 2004;23(3):430–434.
67. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):e162–e193.
68. Mermel Leonard A, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1–45.
69. Aitken ML, Tonelli MR. Complications of indwelling catheters in cystic fibrosis: a 10-year review. Chest. 2000;118(6):1598–1602.
70. Kariyawasam HH, Pepper JR, Hodson ME, et al. Experience of totally implantable venous access devices (TIV ADs) in adults with cystic fibrosis over a 13-year period. Respir Med. 2000;94(12):1161–1165.
71. Garwood S, Flume PA, Ravenel J. Superior vena cava syndrome related to indwelling intravenous catheters in patients with cystic fibrosis. Pediatr Pulmonol. 2006;41(7):683–687.
72. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines. Chest. 2012;141(2Suppl):e419S–e496S.
73. Abu-El-Haija M, Ramachandran S, Meyerholz DK, et al. Pancreatic damage in fetal and newborn cystic fibrosis pigs involves the activation of inflammatory and remodeling pathways. Am J Pathol. 2012;181(2):499–507.
74. Wilschanski M, Durie PR. Pathology of pancreatic and intestinal disorders in cystic fibrosis. J R Soc Med. 1998;91(34_suppl):40–49.
75. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in cystic fibrosis. J Cyst Fibros. 2017;16:S70–S78.
76. Gaskin K, Gurwitz D, Durie P, et al. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. J Pediatr. 1982;100(6):857–862.
77. Durie PR, Forstner GG. Pathophysiology of the exocrine pancreas in cystic fibrosis. J R Soc Med. 1989;82(Suppl 16):2–10.
78. Turck D, Braegger CP, Colombo C, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr. 2016;35(3):557–577.
79. Davies JC, Cunningham S, Harris WT, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. Lancet Respir Med. 2016;4(2):107–115.
•• **Effects of ivacaftor on pulmonary and extrapulmonary manifestation of CF in young children.**
80. Howlett C, Ronan NJ, NiChroinin M, et al. Partial restoration of pancreatic function in a child with cystic fibrosis. Lancet Respir Med. 2016;4(5):e21–e22.
81. Rosenfeld M, Wainwright CE, Higgins M, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. Lancet Respir Med. 2018
82. Vaincre la Mucoviscidose I. Registre français de la mucoviscidose–bilan des données 2016. http://www.vaincrelamuco.org, (2017). (accessed on November 27th 2018).
83. Moran A, Dunitz J, Nathan B, et al. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;32(9):1626–1631.
84. Kayani K, Mohammed R, Mohiaddin H. Cystic fibrosis-related diabetes. Front Endocrinol (Lausanne). 2018;9:20.
85. Chamnan P, Shine BSF, Haworth CS, et al. Diabetes as a determinant of mortality in cystic fibrosis. Diabetes Care. 2010;33(2):311–316.
86. Lewis C, Blackman SM, Nelson A, et al. Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. Am J Respir Crit Care Med. 2015;191(2):194–200.
87. Sims EJ, Green MW, Mehta A. Decreased lung function in female but not male subjects with established cystic fibrosis-related diabetes. Diabetes Care. 2005;28(7):1581–1587.
88. Bridges N, Rowe R, Holt RIG. Unique challenges of cystic fibrosis-related diabetes. Diabetic Med. 2018;35:1181–1188.
89. Rolon MA, Benali K, Munck A, et al. Cystic fibrosis-related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. Acta Paediatrica. 2001;90(8):860–867.
90. Lanng S, Thorsteinsson B, Nerup J, et al. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. Eur J Pediatr. 1992;151(9):684–687.
91. Terliesner N, Vogel M, Steighardt A, et al. Cystic-fibrosis related-diabetes (CFRD) is preceded by and associated with growth failure and deteriorating lung function. J Pediatr Endocrinol Metab. 2017;30:8.
92. Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care. 2010;33(12):2697–2708.
• **US recommendation on diabetes.**
93. Moran A, Pillay K, Becker DJ, et al. ISPAD clinical practice consensus guidelines 2014. Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes. 2014;15(Suppl 20):65–76.
94. Frost F, Dyce P, Nazareth D, et al. Continuous glucose monitoring guided insulin therapy is associated with improved clinical outcomes in cystic fibrosis-related diabetes. J Cyst Fibros. 2018;17:798–803.
95. Zorrón Mei Hsia Pu M, Gonçalves AC, Minnicucci WJ, et al. Continuous glucose monitoring to evaluate glycaemic abnormalities in cystic fibrosis. Arch Dis Child. archdischild-2017-314250. 2018;103:592–596.
96. Clemente León M, Bilbao Gassó L, Moreno-Galdó A, et al. Oral glucose tolerance test and continuous glucose monitoring to assess diabetes development in cystic fibrosis patients. Endocrinol Diabetes Nutr. 2018;65(1):45–51.
97. Ballmann M, Hubert D, Assael BM, et al. Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis:

a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6(2):114–121.
98. Schwarzenberg SJ, Thomas W, Olsen TW, et al. Microvascular complications in cystic fibrosis-related diabetes. Diabetes Care. 2007;30(5):1056–1061.
99. Roberts R, Speight L, Lee J, et al. Retinal screening of patients with cystic fibrosis-related diabetes in Wales – a real eye opener. J Cyst Fibros. 2015;14(2):282–284.
100. van Den Berg JMW, Morton AM, Kok SW, et al. Microvascular complications in patients with cystic fibrosis-related diabetes (CFRD). J Cyst Fibros. 2008;7(6):515–519.
101. Andersen HU, Lanng S, Pressler T, et al. Cystic fibrosis-related diabetes: the presence of microvascular diabetes complications. Diabetes Care. 2006;29(12):2660–2663.
102. Perrin FMR, Serino W. Ischaemic heart disease–a new issue in cystic fibrosis? J R Soc Med. 2010;103(Suppl 1):S44–S48.
103. Onady GM, Farinet CL. An adult cystic fibrosis patient presenting with persistent dyspnea: case report. BMC Pulm Med. 2006;6:9.
104. Bellin MD, Laguna T, Leschyshyn J, et al. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study: insulin secretion following CFTR correction. Pediatr Diabetes. 2013;14(6):417–421.
105. Tsabari R, Elyashar HI, Cymberknowh MC, et al. CFTR potentiator therapy ameliorates impaired insulin secretion in CF patients with a gating mutation. J Cyst Fibros. 2016;15(3):e25–e27.
106. Hayes D, McCoy KS, Sheikh SI. Resolution of cystic fibrosis-related diabetes with ivacaftor therapy. Am J Respir Crit Care Med. 2014;190(5):588–590.
107. Thomassen JC, Mueller MI, Alejandre Alcazar MA, et al. Effect of lumacaftor/ivacaftor on glucose metabolism and insulin secretion in Phe508del homozygous cystic fibrosis patients. J Cyst Fibros. 2018;17(2):271–275.
108. Feigelson J, Pécau Y, Poquet M, et al. Imaging changes in the pancreas in cystic fibrosis: a retrospective evaluation of 55 cases seen over a period of 9 years. J Pediatr Gastroenterol Nutr. 2000;30(2):145–151.
109. Freeman AJ, Giles HW, Nowicki MJ. Pancreatic cystosis complicating cystic fibrosis. Clin Gastroenterol Hepatol. 2010;8(2):e18–e19.
110. Burt H, Andronikou S, Langton-Hewer S. Pancreatic cystosis in cystic fibrosis. BMJ Case Rep. 2016;pii: bcr2015214288.
111. Berrocal T, Pajares MP, Zubillaga AF. Pancreatic cystosis in children and young adults with cystic fibrosis: sonographic, CT, and MRI findings. Am J Roentgenol. 2005;184(4):1305–1309.
112. Freeman AJ, Ooi CY. Pancreatitis and pancreatic cystosis in cystic fibrosis. J Cyst Fibros. 2017;16:S79–S86.
113. Chryssostalis A, Hubert D, Coste J, et al. Liver disease in adult patients with cystic fibrosis: a frequent and independent prognostic factor associated with death or lung transplantation. J Hepatol. 2011;55(6):1377–1382.
114. Debray D, Narkewicz MR, Bodewes FAJA, et al. Cystic fibrosis–related liver disease: research challenges and future perspectives. J Pediatr Gastroenterol Nutr. 2017;65(4):443–448.
115. Lindblad A, Hultcrantz R, Strandvik B. Bile-duct destruction and collagen deposition: a prominent ultrastructural feature of the liver in cystic fibrosis. Hepatology. 1992;16(2):372–381.
116. Vawter GF, Shwachman H. Cystic fibrosis in adults: an autopsy study. Pathol Annu. 1979;14(Pt 2):357–382.
117. Rowland M, Gallagher CG, O'Laoide R, et al. Outcome in cystic fibrosis liver disease. Am J Gastroenterol. 2011;106(1):104–109.
118. Koh C, Sakiani S, Surana P, et al. Adult-onset cystic fibrosis liver disease: diagnosis and characterization of an underappreciated entity: Koh, Sakiani. Hepatology. 2017;66(2):591–601.
119. Stonebraker JR, Ooi CY, Pace RG, et al. Features of severe liver disease with portal hypertension in patients with cystic fibrosis. Clin Gastroenterol Hepatol. 2016;14(8):1207–1215, E1203.
120. Colombo C, Battezzati PM, Crosignani A, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. Hepatology. 2002;36(6):1374–1382.
121. Debray D, Kelly D, Houwen R, et al. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros. 2011;10:S29–S36.
122. Ayoub F, Trillo-Alvarez C, Morelli G, et al. Risk factors for hepatic steatosis in adults with cystic fibrosis: similarities to non-alcoholic fatty liver disease. World J Hepatol. 2018;10(1):34–40.
123. Bartlett JR, Friedman KJ, Ling SC, et al. Genetic modifiers of liver disease in cystic fibrosis. JAMA. 2009;302(10):1076–1083.
124. Cheng K, Ashby D, Smyth RL. Ursodeoxycholic acid for cystic fibrosis-related liver disease. Cochrane Database Syst Rev. 2014;12:CD000222.
125. Hayes D, McCoy KS, Sheikh SI. Improvement of sinus disease in cystic fibrosis with ivacaftor therapy. Am J Respir Crit Care Med. 2014;190(4):468.
126. Sabati AA, Kempainen RR, Milla CE, et al. Characteristics of gastroesophageal reflux in adults with cystic fibrosis. J Cyst Fibros. 2010;9(5):365–370.
127. Maqbool A, Pauwels A. Cystic fibrosis and gastroesophageal reflux disease. J Cyst Fibros. 2017;16:S2–S13.
128. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association medical position statement on the management of gastroesophageal reflux disease. Gastroenterology. 2008;135(4):1383–1391, 1391,E1381-E1385.
129. Jones GH, Walshaw MJ. Potential impact on fertility of new systemic therapies for cystic fibrosis. Paediatr Respir Rev. 2015;16:25–27.
130. Sueblinvong V, Whittaker LA. Fertility and pregnancy: common concerns of the aging cystic fibrosis population. Clin Chest Med. 2007;28(2):433–443.
131. Castellani C, Quinzii C, Altieri S, et al. A pilot survey of cystic fibrosis clinical manifestations in CFTR mutation heterozygotes. Genet Test. 2001;5(3):249–254.
132. Tipirneni KE, Woodworth BA. Medical and surgical advancements in the management of cystic fibrosis chronic rhinosinusitis. Curr Otorhinolaryngol Rep. 2017;5(1):24–34.
133. Feuillet-Fieux MN, Lenoir G, Sermet I, et al. Nasal polyposis and cystic fibrosis (CF): review of the literature. Rhinology. 2011;49(3):347–355.
134. Liang J, Higgins T, Ishman SL, et al. Medical management of chronic rhinosinusitis in cystic fibrosis: a systematic review: medical management of CRS in CF. Laryngoscope. 2014;124(6):1308–1313.
135. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(Suppl 1):S22–S209.
136. Mainz JG, Schaedlich K, Schien C, et al. Sinonasal inhalation of tobramycin vibrating aerosol in cystic fibrosis patients with upper airway Pseudomonas aeruginosa colonization: results of a randomized, double-blind, placebo-controlled pilot study. Drug Des Devel Ther. 2014
137. Mainz JG, Schien C, Schiller I, et al. Sinonasal inhalation of dornase alfa administered by vibrating aerosol to cystic fibrosis patients: a double-blind placebo-controlled cross-over trial. J Cyst Fibros. 2014;13(4):461–470.
138. Vreede CL, Berkhout MC, Sprij AJ, et al. Ivacaftor and sinonasal pathology in a cystic fibrosis patient with genotype deltaF508/S1215N. J Cyst Fibros. 2015;14(3):412–413.
139. Paccou J, Zeboulon N, Combescure C, et al. The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis. Calcif Tissue Int. 2010;86(1):1–7.
140. Marquette M, Haworth CS. Bone health and disease in cystic fibrosis. Paediatr Respir Rev. 2016;20:2–5.
141. Sermet-Gaudelus I, Bianchi ML, Garabédian M, et al. European cystic fibrosis bone mineralisation guidelines. J Cyst Fibros. 2011;10:S16–S23.
142. Sermet-Gaudelus I, Delion M, Durieu I, et al. Bone demineralization is improved by ivacaftor in patients with cystic fibrosis carrying the p.Gly551Asp mutation. J Cyst Fibros. 2016;15(6):E67–E69.
143. Botton E, Saraux A, Laselve H, et al. Musculoskeletal manifestations in cystic fibrosis. Joint Bone Spine. 2003;70(5):327–335.
144. Kaiser H, Brustad N, Pressler T, et al. Aquagenic wrinkling of the palms in patients with cystic fibrosis. Br J Dermatol. 2018.

145. Grasemann H, Ratjen F, Solomon M. Aquagenic wrinkling of the palms in a patient with cystic fibrosis. N Engl J Med. 2013;369(24):2362–2363.
146. Burgel PR, Paugam A, Hubert D, et al. Aspergillus fumigatus in the cystic fibrosis lung: pros and cons of azole therapy. Infect Drug Resist. 2016;9:229–238.
147. Gilchrist FJ, Cox KJ, Rowe R, et al. Itraconazole and inhaled fluticasone causing hypothalamic-pituitary-adrenal axis suppression in adults with cystic fibrosis. J Cyst Fibros. 2013;12(4):399–402.
148. Jones W, Chastain CA, Wright PW. Iatrogenic Cushing syndrome secondary to a probable interaction between voriconazole and budesonide. Pharmacotherapy. 2014;34(7):e116–e119.
149. Pilmis B, Coignard-Biehler H, Jullien V, et al. Iatrogenic Cushing's syndrome induced by posaconazole. Antimicrob Agents Chemother. 2013;57(11):5727–5728.
150. Préville-Ratelle S, Coriati A, Ménard A, et al. Adrenal insufficiency in cystic fibrosis: a rare phenomenon? Can Respir J. 2018;2018:1–7.
151. Handelsman JA, Nasr SZ, Pitts C, et al. Prevalence of hearing and vestibular loss in cystic fibrosis patients exposed to aminoglycosides. Pediatr Pulmonol. 2017;52(9):1157–1162.
152. Mulheran M, Degg C, Burr S, et al. Occurrence and risk of cochleotoxicity in cystic fibrosis patients receiving repeated high-dose aminoglycoside therapy. Antimicrob Agents Chemother. 2001;45(9):2502–2509.
153. Prayle A, Watson A, Fortnum H, et al. Side effects of aminoglycosides on the kidney, ear and balance in cystic fibrosis. Thorax. 2010;65(7):654–658.
154. Abdul-Karim FW, King TA, Dahms BB, et al. Carcinoma of extrahepatic biliary system in an adult with cystic fibrosis. Gastroenterology. 1982;82(4):758–762.
155. Davis TM, Sawicka EH. Adenocarcinoma in cystic fibrosis. Thorax. 1985;40(3):199–200.
156. Miller R, Bourke S, Immanuel A, et al. Subtotal esophagectomy for carcinoma in a patient with cystic fibrosis. A & A Case Rep. 2016;6(12):394–396.
157. Tedesco FJ, Brown R, Schuman BM. Pancreatic carcinoma in a patient with cystic fibrosis. Gastrointest Endosc. 1986;32(1):25–26.
158. Johannesson M, Askling J, Montgomery SM, et al. Cancer risk among patients with cystic fibrosis and their first-degree relatives. Int J Cancer. 2009;125(12):2953–2956.
159. Maisonneuve P, FitzSimmons SC, Neglia JP, et al. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. J Natl Cancer Inst. 2003;95(5):381–387.
160. Neglia JP, FitzSimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. N Engl J Med. 1995;332(8):494–499.
161. Sheldon CD, Hodson ME, Carpenter LM, et al. A cohort study of cystic fibrosis and malignancy. Br J Cancer. 1993;68(5):1025.
162. Qu X, Tang Y, Hua S. Immunological approaches towards cancer and inflammation: a cross talk. Front Immunol. 2018;9:563.
163. Yasunaga J-I, Matsuoka M. Oncogenic spiral by infectious pathogens: cooperation of multiple factors in cancer development. Cancer Sci. 2018;109(1):24–32.
164. Dorsey J, Gonska T. Bacterial overgrowth, dysbiosis, inflammation, and dysmotility in the cystic fibrosis intestine. J Cyst Fibros. 2017;16(Suppl 2):S14–S23.
165. Dai Z, Coker OO, Nakatsu G, et al. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. Microbiome. 2018;6(1):70.
166. Zhang J, Wang Y, Jiang X, et al. Cystic fibrosis transmembrane conductance regulator—emerging regulator of cancer. Cell Mol Life Sci. 2018;75(10):1737–1756.
167. Maisonneuve P, Marshall BC, Knapp EA, et al. Cancer Risk in cystic fibrosis: a 20-year nationwide study from the United States. Jnci. 2013;105(2):122–129.
•• **An important study describing increased risk of digestive cancers in CF adults.**
168. Gini A, Zauber AG, Cenin DR, et al. Cost-effectiveness of screening individuals with cystic fibrosis for colorectal cancer. Gastroenterology. 2018;154(3):556-567.
169. Niccum DE, Billings JL, Dunitz JM, et al. Colonoscopic screening shows increased early incidence and progression of adenomas in cystic fibrosis. J Cyst Fibros. 2016;15(4):548–553.
170. Hadjiliadis D, Khoruts A, Zauber AG, et al. Cystic fibrosis colorectal cancer screening consensus recommendations. Gastroenterology. 2018;154(3):736–745, E714.
• **Recent recommendation on screening for colon cancer.**
171. Berg KH, Ryom L, Faurholt-Jepsen D, et al. Prevalence and characteristics of chronic kidney disease among Danish adults with cystic fibrosis. J Cyst Fibros. 2018;17(4):478–483.
172. Quon BS, Mayer-Hamblett N, Aitken ML, et al. Risk factors for chronic kidney disease in adults with cystic fibrosis. Am J Respir Crit Care Med. 2011;184(10):1147–1152.
173. Yahiaoui Y, Jablonski M, Hubert D, et al. Renal involvement in cystic fibrosis: diseases spectrum and clinical relevance. Clin J Am Soc Nephrol. 2009;4(5):921–928.
174. Novel-Catin E, Pelletier S, Reynaud Q, et al. Aminoglycoside exposure and renal function before lung transplantation in adult cystic fibrosis patients. Nephrol Dialysis Transplantation. 2018. doi:10.1093/ndt/gfy084.
175. Santoro D, Postorino A, Lucanto C, et al. Cystic fibrosis: a risk condition for renal disease. J Ren Nutr. 2017;27(6):470–473.
176. Stirati G, Antonelli M, Fofi C, et al. IgA nephropathy in cystic fibrosis. J Nephrol. 1999;12(1):30–31.
177. Stankovic Stojanovic K, Hubert D, Leroy S, et al. Cystic fibrosis and AA amyloidosis: a survey in the French cystic fibrosis network. Amyloid. 2014;21(4):231–237.
178. Stephenson AL, Mannik LA, Walsh S, et al. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study. Am J Clin Nutr. 2013;97(4):872–877.
179. González Jiménez D, Muñoz-Codoceo R, Garriga-García M, et al. Excess weight in patients with cystic fibrosis: is it always beneficial? Nutrición Hospitalaria. 2017;34(3):578.
180. Alvarez JA, Ziegler TR, Millson EC, et al. Body composition and lung function in cystic fibrosis and their association with adiposity and normal-weight obesity. Nutrition. 2016;32(4):447–452.
181. Quittner AL, Goldbeck L, Abbott J, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of the International Depression Epidemiological Study across nine countries. Thorax. 2014;69(12):1090–1097.
182. Quittner AL, Abbott J, Georgiopoulos AM, et al. International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. Thorax. 2016;71(1):26–34.
•• **An important recent consensus on mental health in CF patients.**
183. Reichman G, De Boe V, Braeckman J, et al. Urinary incontinence in patients with cystic fibrosis. Scand J Urol. 2016;50(2):128–131.
184. Burge AT, Holland AE, Sherburn M, et al. Prevalence and impact of urinary incontinence in men with cystic fibrosis. Physiotherapy. 2015;101(2):166–170.
185. Elborn JS, Bell SC, Madge SL, et al. Report of the European Respiratory Society/European Cystic Fibrosis Society task force on the care of adults with cystic fibrosis. Eur Resp J. 2016;47(2):420–428.