REVIEW ARTICLE

The road for survival improvement of cystic fibrosis patients in Arab countries

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Abstract   Cystic fibrosis (CF) is a lethal, monogenic disorder that affects multiple organ systems of the body. The incidence has been described before in the Middle East to be 1 in 2000 to 1 in 5800 live births, and the median survival was estimated to be from 10 to 20 years of age.
    The present article attempts to revisit various facets of this disease and specifically highlights the most important lacunae that exist in treating CF. In addition, it also tries to emphasize the steps in improving the median survival of patients with CF, in these countries.
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1. Introduction

Cystic fibrosis (CF) is a lethal, monogenic disorder that affects multiple organ systems of the body [1]. As per a Cystic Fibrosis Foundation annual report, 60,000 to 70,000 people across the world suffer from CF [2]. However, this estimate is based on the data available from the existing registries in developed countries (primarily the United States, Europe, and Australia).

Symptoms in patients with CF include accumulation of thick mucus, recurrent lung infections, persistent cough at times associated with phlegm with or without hemoptysis, wheezing, poor growth/weight gain (in spite of a good appetite), frequent greasy, bulky stools or difficulty in bowel movements, and electrolyte imbalance particularly in countries with warm weather [3,4]. The estimated frequency of CF per live birth in Caucasians is believed to be 1 in 2000—2500 children. Determining the precise magnitude of prevalence of CF in South East Asian and Middle East countries remains elusive. Though the prevalence of CF has been estimated to fall in the range of 1 in 30,000 to 1 in 50,000, incidence of the disease has been reported in the range of 1 in 2000 to 1 in 5800 live births (4—13). Based

Table 1 Milestones of cystic fibrosis discovery in the Arab countries.

Year (reference)	Country	Comment
1958 [5]	Lebanon	First CF in Arabs
1977 [6]	Iraq	First report
1981 [7]	Kuwait	After death 2:1056, 1/3500 birth/year
1984 [8]	Jordan	A pilot study (post-mortem)
1985 [9]	Bahrain	19 incidence 1:5800, 80% consanguineous marriages
1986 [10]	Saudi Arabia	First case report
1991 [11]	UAE	First report
2001 [12]	Qatar	In a large Bedouin family

on this, research suggests that these regions may harbor a very large proportion of CF patients in the world [13]. As per a recent report on extrapolated CF prevalence rates, it is projected that 34,357 patients in India and 41,898 patients in China may have CF [13]. The high prevalence of CF in these countries may be accountable due to the large population (>1 billion) of these countries. These prevalence extrapolations for CF are only rough estimates derived by applying the prevalence rates from the United States (or a similar country) to the population of other countries, and therefore may not reflect the actual prevalence of CF [13].

Similarly, determining the precise magnitude of the prevalence of CF in the Middle East countries remains difficult. Though the prevalence of CF has been estimated to fall in the range of 1 in 2500—5000. Based on this, It is projected that with a population of 27 million in Saudi Arabia (14), and around 18 live birth/1000, at least 800—1000 cases may have CF (Table 1) [4—19]. These prevalence extrapolations for CF are only rough estimates and could be increased due to consanquinity (50% in the general population and 85% in CF families) [4—19], and therefore may magnify the actual prevalence of CF (Table 1) [5—19].

The median survival in some Arab countries was estimated to be from 10 to 20 years of age [4—19] for many reasons such as: Delayed diagnosis due to decreased awareness of the variable presentation of the disease. Unavailability of diagnostic tool such as quantitative sweat chloride test (e.g in the city of Jeddah, Saudi Arabia, with 5 million dwellers, only two centers with proper sweat chloride measurement's tool) [4—14]. Delayed institution of treatment due to delayed referral to a specialized CF center [4—19]. Early pseudomonas colonization at 3 years compared to 7 years in the western countries [4—16]. Poor compliance to treatment and chest physiotherapy, poor distribution of CF specialized centers, Delayed nutritional rehabilitation [4,16].

Even after more than 7 decades since CF is known, there are many aspects of the disease which still remain enigmatic [20]. The present review attempts to revisit various facets of this disease and specifically highlights the most important lacunae that exist in treating CF. Further, it aims to emphasize the precarious consequences, if this disease is ignored or left untreated. Therefore early diagnosis of the disease is the important first step towards improved care. In addition, this review also captures the steps toward improvement of median survival in Arab countries.

2. Pathophysiology of CF

Patients with CF inherit a defective gene in each chromosome (i.e. 2 defective copies) that encodes the protein "CF transmembrane conductance regulator" (CFTR). The CFTR gene, which is located on chromosome 7, spans ~250 kB in length, and translates into a protein of 1480 amino acids. The protein is a mucosal surface chloride channel present at the epithelial junctions and submucosal glands, and its dysregulation/failure in anion transport causes the disease manifestations [21—23].

Approximately 1800 known mutations have been identified for CF gene, which gives rise to disease phenotypes [2]. Increasing attempts have been made to classify the known mutations. Six different classes of mutations are described based on the fate of the CFTR protein (Table 2 and Fig. 1). These reported gene defects lead to altered protein synthesis such that there is insufficient, adequately active CFTR at the cell surface. This causes the body to secrete unusually thick and sticky mucus (Fig. 2).

The thick mucus clogs the lungs (pulmonary manifestation) leading to a vicious cycle of infection, inflammation, and lung tissue destruction, ultimately leading to life-threatening lung infections [21,22]. The secreted mucus also clogs the pancreatic ducts, thereby obstructing the flow of bile digestive enzymes (which help in digestion and absorption of the food, especially of fats) to the small intestine. This leads to multitudes of disease conditions such as pancreatic insufficiency, gall stones, cysts, and chronic digestive problems (maldigestion and malabsorption) [23—29]. In patients with CF, epithelial anion transport fails, causing functional disruption in a number of organs besides the airways, including the digestive system, exocrine pancreas, gall bladder, reproductive tracts, and the sweat ducts [21,23]. The types of complications in patients with CF largely depend on the degree and the type of CFTR mutation.

Diagnosis: CF is typically diagnosed based on typical clinical signs and symptoms and confirmed with high sweat chloride test >60 mmol/liter and or CFTR detection of 2 pathogenic mutations [1—3]. Reports from a retrospective study showed that diagnosis of CF in Saudi Arabia was done based on the typical clinical symptoms and high sweat chloride test [29]. In the past, newborn screening for meconium albumin using the BM test strip was used in Jordan to identify CF cases that were subsequently confirmed using the sweat chloride test [30].

The most common CFTR described in the United States and Europe is F508del, which constitutes 50%—85% of the CF population (Table 2), whereas those described in the Middle East were different due to consanguinity (Tables 3 and 4) [26—36].

F508del presents in small numbers 10—20% in the Gulf area, compared to 30—50 in North African countries [26—36]. Novel mutations characterized most Arab

Table 2 Spectrum of most common mutations or genotype reported in the cystic fibrosis patients [21].

Class	Effect	% of CF population	Mutations			
1	Defective CFTR protein and does not reach the cell surface	88.5%	G542X 1717-8G->A 1898+3A->G	711+1G->T W1282X CFTRdel19	1609delCA 1782delA 936delTA	R1162X Q890X
2	Total loss of protein because of incorrect processing of CFTR	2.4%	F508del	N1303K	1507del	R1066C
3	Deregulates the ion channel	4.4%	D1270N	G551D		
4	Reduced ion fluxes and altered selectivity		L206W D836Y	R334W P205S	R117H	R347H
5	Functional proteins with normal chloride channel activity but reduced rate of synthesis		2789+5G->A	1811 + 1,6	3849 + 10kbC->T	
6	Reduced expression of mutated CFTR protein because of rapid removal from the apical membrane		3272 + 26G->A	kbA->G		
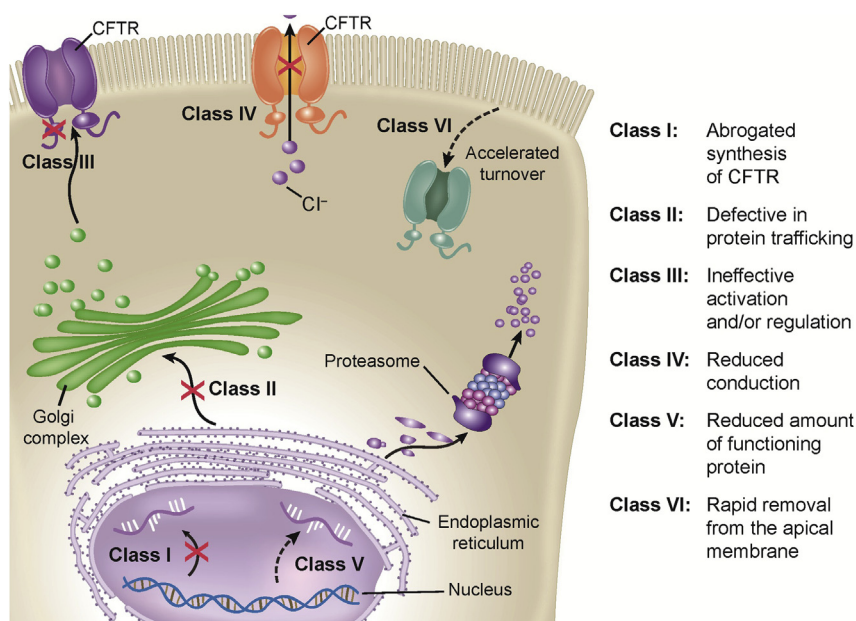
Figure 1 Overview of types of functional mutations in CFTR.

countries due to numerous communities (cosmopolitan) especially in Lebanon [27], and Jordan [33]. Consanguinous intermarriages in the Gulf area is high (80—96%) which was expected to play a major factor in perpetuating many rare mutations as in S549R in United Arab Emirates (UAE, 19%) [26], (3849 + 10KbC > T) in 26% in UAE [26], and (I1134V) 83% in Qatar [34].

In Saudi Arabia (Author's personal experience) (Table 4), reports in CFTR detection showed: 89% of CFTR alleles, have been identified [28—31]. F508del constitutes 12% of CFTR mutation. 1548 delG is the most common Saudi CFTR mutation identified (20%). 1548 delG, F508del, I1234V, 3120+1G > A, H139L, 711+1G > A, N1303K, S549R, 2043delG, 1507del 9 are the most common CFTR mutations of Saudi ethnic origin (80%). Screening for the previously mentioned 10 mutations would identify 80% of C.F. alleles (Table 4) [28—31].

3. Strategies for treating CF

3.1. Currently established conservative therapies for treating CF

The currently available therapies principally aim at maintaining efficient lung function, clearing airways of mucus, administering nutritional therapy (i.e. enzyme, multivitamin, and mineral supplements) to maintain adequate growth, and managing complications [37]. Although these therapies have been highly successful in managing the consequences of the gene defect, they are palliative in nature.

Treatment guidelines have been developed in the United States [38] and Europe [39], with the scope to enhance care of CF patients, by sharing best practice. To
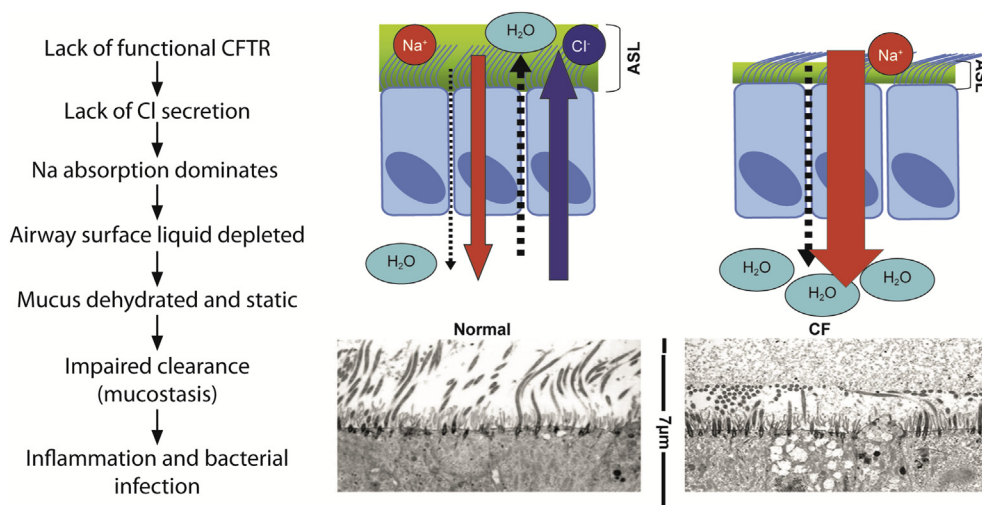
Figure 2   Comparison of normal vs defective epithelial fluid secretion in patients with cystic fibrosis.

Table 3   Important milestones in clinical and mutational findings in cystic fibrosis in the Middle East.

Country	Year	Authors (reference)	No. of patients	Major CFTR mutations
UAE	1994	Frossard et al. [26]	17	S549R F508del
Lebanon	1997	Desgeorges et al. [27]	20	F508del W1282X N1303K
Saudi Arabia	1997	El-Harith et al. [28]	15	$3120+1G \rightarrow A$ N1303K 1548delG
	1998	Banjar et al. [29]	70	F508del I1234V N1303K R553K $3120+1G \rightarrow A$
	2000	Kambouris et al. [31]	70	H139L S549R
Palestine	1999	Cahana et al. [32]	70	3120 + LKdel8.6kg
Jordan	2000	Rawashdeh [33]	202	F508del
Qatar	2001	Abdul Wahab [34]	29	I1234V
Bahrain	2002	Eskandarani [35]	19	2043delG
Tunisia	2005	Messadoud [36]	390	ΔF508, W1282, N1303K

Legend: NO- Number of patients, UAE- United Arab Emirates, CFTR- Cystic fibrosis transmembrane regulator.

the authors' knowledge, in the absence of regional or local guidelines, in other regions these recommendations serve as an example.

3.2. Gene therapy

The discovery of CFTR gene in 1989 spurred a great amount of interest among the researchers [24]. It was reckoned that replacement of CFTR gene during the neonatal period before the onset of airway damage might provide the much awaited cure to patients with CF [21]. However, effective gene delivery with aerosolized adenovirus vector could not be achieved due to the predominant presence of the adenoviral receptor at the entry on the basolateral surface of the epithelial cells [40].

3.3. Potentiators and correctors

Potentiators are compounds that enhance the channel gating characteristics of mutant CFTR via direct interaction [24]. Potentiators function by increasing the amount of time the CFTR channel is open, allowing for more Cl− to pass through the pores [24]. Despite the discovery of many potentiators by high-throughput method, the precise mechanism of action remains unclear [41]. Various clinical trials are currently underway which in due course may demonstrate the clinical benefits of these molecules in the treatment of CF. Ivacaftor, a CFTR potentiator, has shown efficacy and safety compared with placebo in CF patients with a G551D mutation [42,43]. Ivacaftor is approved in Europe, United States, and Canada for the treatment of CF

Table 4   Distribution of Common CFTR in KSA Total of 272 patients.

	Mutation	Type	Exon/intron	Pts	% of total	No. of homoz	Homoz % of +CFTR (230)	No. of heteroz	Heteroz % of +CFTR (230)
1	1548delG	Novel	Exon 10	47	20%	36	16%	11	5%
2	F508del	Caucasian	Exon 10	29	12%	28	12%	1	0.5%
3	I1234V	African	Exon 19	28	11%	28	12%		
4	3120+1G→A	African/ Greek	Intron 16	24	10%	24	10%		
5	H139L	Novel	Exon 4	21	9%	18	8%	3	1%
6	711+1G→A	Novel	Intron 5	20	8%	16	7%	4	2%
7	N1303K	European	Exon 21	7	3%	7	3%		
8	S549R	UAE (France)	Exon 12	7	3%	7	3%		
9	2043delG	Bahrain	Exon 13	6	2%	5	2%	1	0.5%
10	1507del 9	Novel	Exon 9	5	2%	5	2%		
11	Others			36	15%	36	16%		
12	Not Identified			11	5%				
	Total			241	100%	210	91%	20	9%

Legend: KSA- Kingdom of Saudi Arabia, Pts-number of Patients, No-number, Homoz- Homozgous, CFTR- Cystic fibrosis transmembrane regulator gene mutations, Heteroz- Heterozygous.

patients greater than or equal to 6 years of age who have a G551D mutation [42]. Ivacaftor treatment is not effective in CF patients with homozygous F508del-CFTR mutation, which is the most common mutation in Caucasian CF patients [44].

Similarly, compounds that correct the processing and facilitate the movement of mutant F508 CFTR (primarily class II mutations) out of the endoplasmic reticulum into the apical plasma membranes of epithelial cells are termed correctors. However, like the potentiators, the mechanism of action of correctors remains unknown. Lumacaftor (VX-809), an investigational corrector, has been shown to be effective in enhancing CFTR function in patients with F508del-CFTR [45]. A long-term phase III roll-over study of treatment with lumacaftor in combination with ivacaftor is ongoing; however, the study does not include CF patients from the Middle East region [46]. Molinski et al studied the molecular consequences of the c.3700 A > G (p.Ile1234Val) mutation in CF, which is characterized by defective folding and processing, similar to the F508del-CFTR [47]. Though rare in the west, this mutation is relatively common in the Middle East (12.3%) and is the second most common mutation in some Middle East countries [26–36,47]. Molinski et al hypothesized that the correction of the defective protein through lumacaftor may have a significant impact on medical treatment of CF in the Middle East.

3.4. Airways clearance

Congestion of the airways by viscous mucus is most common in patients with CF [48]. Clearance of the clogged airways is achieved by combination therapy that includes bronchodilators, postural drainage, and chest physical therapy [37]. Several mucoactive drugs that affect the physical characteristics or the quantity of mucus produced are known which fall under 2 broad categories of mucolytics and mucokinetics [49].

Dornase alfa, a recombinant human DNAse I, is a mucolytic drug which provides potential benefits by reducing the adhesiveness and viscoelasticity of CF sputum [50]. The results from clinical studies demonstrate that aerosolized dornase alfa significantly improves lung function achieving a 6%–7% increase from baseline in forced expiratory volume in 1 s (FEV_1) after 6 months therapy [51,52]. It has been reported that when the treatment is stopped, the respiratory function deteriorates below their previous values [53].

Hypertonic saline is a mucokinetic drug often been used for improving lung function by mucus clearance [54]. It is a highly concentrated salt solution (~7%) which increases the ion concentration of airway surface liquid and osmotically draws fluid into the airway lumen. This results in replenishment of fluid layer and accelerated mucus clearance [55]. Inhaled/nebulized hypertonic saline has demonstrated modest improvement in lung function and reduction in pulmonary exacerbations without substantial adverse events [56–58]. Few studies have demonstrated improvements in respiratory function, the effects were found to be transient, and therefore, predicted to be of limited therapeutic benefit [59]. Some reports also recommend the use of bronchodilators prior inhalation of hypertonic saline to avoid transient narrowing of the airways, coughing, and pharyngeal discomfort [60,61].

Mannitol dry powder (400 mg twice daily) is a recently developed product with mucolytic effect through osmotic mechanism. Mannitol is approved in Europe, for treatment of adult CF patients (above 18 years of age) as an add-on therapy to standard of care. In phase III trials it has been shown that 26 weeks treatment with mannitol dry powder improves lung function and reduces exacerbation rates [62].

In addition to the use of mucoactive drugs, physicians also recommend manual therapies/physiotherapy such as postural drainage, percussion and vibration or breathing through positive expiratory pressure device [60–63]. These methods enable mucus clearance by accelerated expiratory flow, reducing airway obstruction, and improving rheology of mucus [64,65]. Patients are also advised to do regular

physical exercises in addition to chest physiotherapy from an early age for efficient maintenance of respiratory function. Increased physical exercise strengthens the respiratory muscles and also helps to clear the tenacious mucus secretion that blocks the airways [66].

3.5. Bronchodilators

Bronchodilator treatment is the most commonly used therapy being prescribed in ∼80% of patients with CF [67–69]. Although bronchodilators are usually given to overcome airways obstruction and hyper-responsiveness in CF patients because of inhaled mucolytic and/or antibiotic therapy, the response to inhaled bronchodilators is variable both between and within patients [67–70]. However, long-term studies failed to demonstrate sustained clinical benefits [70]. Although their use in CF remains controversial, EU and US guidelines recommend regular use of inhaled β2-adrenergic bronchodilators to improve and maintain efficient lung function, and also can be used before inhaled antibiotics such as tobramycin and aztreonam [38,39,69].

3.6. Antibiotics in the treatment of CF

The significant improvement in the prognosis of CF can be largely attributed to the arsenal of newer antibiotics that combat with the pathogenic organisms [38,39]. Treatment with specific antibiotic remains the mainstay of CF treatment. It is highly recommended to be used in conjunction with other therapies such as physiotherapy and treatment with bronchodilators to promote clearance of the bronchial mucus [38,39]. Patients with CF often present with recurrent infections with *Haemophilus influenza* (*H. influenzae*), *Staphylococcus aureus* (*S. aureus*), and *Pseudomonas aeruginosa* (*P. aeruginosa*). *H. influenzae* and *S. aureus* are usually the first pathogens encountered in childhood which is later substituted by *P. aeruginosa*. An array of antibiotics is usually prescribed to treat these bacterial infections. However, the choice of antibiotics largely depends on the presence of specific pathogen in the respiratory tract. It is reported that overall 54.4% of the CF patients are infected with *P. aeruginosa* [2]. Chronic infections with *P. aeruginosa* result in rapid decline in lung function and increased need for antibiotic treatment and hospitalization [71]. Therefore, treatment with effective antibiotic regimen targeting this pathogen holds key in the successful management of CF. Aerosol antibiotics, such as colistin, tobramycin, and aztreonam are recommended to be used as regular maintenance therapy in the treatment of pseudomonas infection [38,39]. Although oral antibiotics (fluoroquinolones, amoxicillin, cephalexin, or trimethoprim) may be prescribed for patients with less severe exacerbations, *P. aeruginosa* related exacerbations are commonly treated with combinations of intravenous (IV) antibiotics for 1–3 weeks [25,38,39]. Despite frequent intravenous therapy, patients often continue to present with deteriorating respiratory function and eventually succumb to lung disease [72].

Inhaled antibiotics have been increasingly used to treat persistent airway infection in people with CF. Treatment with aerosolized antibiotics has been advocated for the management of the chronic *P. aeruginosa* infection. The CF pulmonary guidelines published recently recommend the use of aerosolized/inhaled tobramycin with or without dornase alfa in the treatment of *P. aeruginosa* infections in CF [38,39].

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*, and is indicated for the management of CF patients infected with *P. aeruginosa* [73]. It primarily disrupts protein synthesis by bacteria, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death [74]. Tobramycin has demonstrated in-vitro activity against a wide spectrum of gram-negative organisms including *P. aeruginosa*.

Tobramycin is also available as a specifically developed formulation for administration by nebulization. Evidence from clinical and pharmacological studies have demonstrated that tobramycin primarily concentrates in the airways following administration [75]. Inhaled tobramycin significantly improves lung function and reduces rate of exacerbations in patients with CF. Inhaled tobramycin is strongly recommended for chronic use in patients of ≥6 years of age with moderate-to-severe lung disease and with *P. aeruginosa* persistently present in cultures of the airways [38,39,76]. The quality of the evidence for the use of inhaled tobramycin in patients with mild disease is limited by the number of studies [38,39,58].

Macrolides antibiotics such as azithromycin are used at anti-inflammatory doses to treat CF patients. However, there is limited clinical evidence to support their use. A clinical trial has shown that long-term use of azithromycin in CF patients, ≥6 years of age, significantly reduced pulmonary exacerbations and the number of additional courses of oral antibiotics, irrespective of the infectious status [76]. Another randomized controlled trial demonstrated improvements in lung function after treatment with azithromycin compared with placebo [77].

Maintenance therapy with long-term macrolides has been proved to be beneficial in patients with CF [78]. However, long-term use of macrolides has shown evidences of emergence of bacterial resistance in CF patients [79,80]. Of particular recent concern is the potential of increased colonization of CF patients with nontuberculous mycobacteria [81].

3.7. Pancreatic enzyme therapy

Patients with CF and signs and symptoms of maldigestion due to pancreatic insufficiency are usually prescribed with pancreatic enzymes replacements to aid digestion [82]. It has been reported that ∼15% of patients with CF possess sufficient exocrine pancreatic function that enables normal nutrient absorption [83]. Although studies endorse normal pancreatic function in "pancreatic sufficient" CF patients, quantitative assessment studies in these patients have demonstrated impaired pancreatic ductal enzyme secretions [84,85]. Pancreatic enzyme preparations of porcine origin have been conventionally used to treat this type of maldigestion. Most marketed enzyme preparations come in special enteric-coated capsules that consist of desiccated porcine pancreatic extracts [25].

3.8. Nutritional support/high energy supplements

Besides the conservative treatment of CF, supplementation with appetite-rich food is essential for improved functional capacity and quality of life [86]. Nutritional supplementation particularly with fat-soluble vitamins A, E, K, and sometimes D and minerals constitute an integral part of treatment. The need for lipid-soluble vitamins can be assessed directly by the measurement of vitamin A, D, E levels [87].

4. Clinical implications of untreated CF

CF is a multi-manifestation disorder that affects respiratory, gastrointestinal, endocrine, sweat gland, and reproductive systems [74]. Improper or non-treatment of underlying disease may lead to several clinical implications.

4.1. Respiratory tract implications

Airways disease remains one of the worsening aspects in the course of CF. Most of the morbidity and mortality associated with CF result from progressive lung disease, upper airway infection, and chronic sinusitis [88]. CF patients acquire lung infection, which triggers the onset of inflammatory cascade. The hallmark of CF lung disease is bronchiectasis. This paves the way for the establishment of persistent infection by pathogens such as *S. aureus, H. influenzae,* and *P. aeruginosa* ultimately resulting in severely compromised airway defenses [53]. In few patients, diffuse bronchopulmonary disease is due to refractory *Burkholderia cepacia*, which further makes therapeutic management more cumbersome [88]. The progression of airways disease in patients with CF leads to eventual acute respiratory failure because of diffuse bronchopulmonary disease, pneumonia, or acute hemoptysis [86]. Supporting this, a US study reported that in ~80% of patients with CF, cardiorespiratory complications are the most common cause of death [89].

4.2. Pancreatic duct implications

The epithelial layers of the pancreatic ducts and the gastrointestinal tract have abundant ion exchange channels and CFTR levels similar to those found in the airway epithelium [20,90]. In patients with pancreatic manifestations of CF, the pancreas is compromised at birth [20]. Concretion of pancreatic ducts by thick, viscid mucus blocks digestive enzymes from entering the gut leads to poor digestion and malabsorption of food [91]. Pancreatic exocrine insufficiency contributes to growth retardation and delayed puberty in children and low body weight in adults [92]. It has been well documented that CF is the major cause of pancreatic exocrine failure in early childhood. In adults, it is commonly associated with chronic pancreatitis [92].

4.3. Gastrointestinal implications

Absence or abridged form of CFTR reduces fluid secretion in the gut [20]. The intestinal content in these patients contains minimal water content and becomes impacted. This may result in meconium ileus at birth and distal intestinal obstruction syndrome later in life [93]. Altered or malabsorption of the essential nutrients in the gut because of lack of digestive enzymes causes the nutrients to be excreted in the feces. This mainly leads to malnutrition and retarded growth and development [77]. In addition, people with CF experience other gastrointestinal symptoms such as severe gastroesophageal reflux disease, intestinal blockage by intussusception, and constipation [94]. Malnutrition is another common symptom in patients with untreated or poorly controlled CF that affects growth and reduces physical activity [95,96]. The prevalence of malnutrition/hyponutrition in CF has been reported to be high although it varies in different studies [97]. Negative energy balance is considered as central to the development of malnutrition [98].

4.4. Rectal prolapse in CF

Rectal prolapse is another clinical implication of CF (characterized by protrusion of the rectal mucous membrane through the anus) encountered in both pediatric and adult patients [99]. The incidence of rectal prolapse is high among male infants with CF than in adults with a peak incidence between 1 and 3 years [99—102]. In a study reported by Stern et al, rectal prolapse was found to occur in 18.5% of CF patients [97]. It further reported that though rectal prolapse preceded diagnosis of CF, physicians rarely appreciate its importance as a symptom of this disease [103].

4.5. CF-related diabetes

Diabetes, referred to as CF-related diabetes (CFRD), is a very common complication that develops over time in many patients with CF [104] CFRD is distinct as it usually combines the characteristics of both type 1 and type 2 diabetes [104]. Reported prevalence of diabetes in children with CF < 10 years of age is low. However, the prevalence increases significantly with age, with 50% of patients developing CFRD by the age of 30 years [105]. Few studies have demonstrated a plausible relationship between CFRD and poor nutritional and respiratory status [106,107]. In patients with severely impaired insulin secretion, a more rapid deterioration in the respiratory status is observed [108]. Similar to rectal prolapse, the worsening in respiratory status may also predate the diagnosis of CFRD [109].

4.6. Implications of CF on liver

Complications of liver disease represent the third most frequent cause of disease-related death in patients with CF [77,110]. CF-associated liver disease is presently classified among genetic cholangiopathies, which results because of lack or dysfunction of the CFTR at the apical membrane of bile duct cells [111]. Defective CFTR protein in a subset of CF patients leads to thickened bile secretions. This further chokes the bile ducts leading to liver and biliary complications [77,111]. Although the biliary tract manifestation is usually clinically evident, the involvement of liver may only

be apparent at the end stages [111]. Of the wide spectrum of hepatobiliary complications, progression of focal biliary cirrhosis to multilobular cirrhosis and potentially end-stage liver disease is the most clinically relevant problem in patients with CF [112].

4.7. Implications on the reproductive system

More than 95% of males with CF are infertile. This infertility is the result of obstructive azoospermia caused by maldevelopment of the mesonephric ducts, resulting in either agenesis or atresia of the epididymis, vas deferens, or seminal vesicles [113,114]. Other factors that may complement infertility in males with CF are the low serum levels of vitamins A and E or interference with the normal transport of the sperm [115]. Although not so frequent, impaired fertility is also seen in females with CF. Infertility characterized by thickened cervical mucus in females may be a consequence of the presence of thick mucus in the genital tract that barricades sperm penetration [114]. In severe cases, malnutrition disrupts ovulation and causes amenorrhea [116].

4.8. Socioeconomic implications of CF

CF poses significant financial burden on the patient and the society on the whole [117]. Socioeconomic status remains an important risk factor in CF management, as seen in many chronic diseases, [118,119]. The following factors profoundly impact the outcomes in CF patients: poor socioeconomic status, mental trauma in caregivers/patient, employment status, and education.

5. Barriers in treating CF

Following are the few barriers that affect the treatment in patients with CF.

5.1. Late diagnosis of CF

CF is detected with increasing frequency in older children, adolescents, and even young adults [120]. The clinical diagnosis of CF is often delayed because the early symptoms are minimal or nonspecific [120]. Considerable delays in diagnosis of children with CF occur as the disease is identified solely based on clinical presentation [120]. Another important reason responsible for protracted diagnosis of CF is lack of training among respiratory physicians [13].

5.2. Adherence

Treatment adherence is crucial in patients with CF. Reasons for poor adherence could be due to lack of access to care, insufficient patient education, and high treatment burden. Poor adherence is a notable problem, especially during adolescence [121]. Poor adherence leads to serious consequences, which includes increased morbidity and mortality, reduced quality of life, and greater health care costs. Although the rates of adherence to treatment for CF are generally low, they vary significantly between the different

types of treatment [122]. The rates of adherence are particularly poor in pediatric population than in adults with CF. For example, the adherence rates for children with CF are estimated to be 40%–47% for chest physical therapy [123,124], whereas adherence to dietary recommendations is even lower, ranging from 16% to 20% [125]. Briesacher et al have shown that high adherence to inhaled tobramycin solution is associated with a lower risk of hospitalization and also leads to a lower outpatient service cost, than patients with low adherence [126].

5.3. Limited number of CF testing centers in the Middle East countries

Decreased access to care is another impediment that adversely affects the health-related outcomes in many patients with CF [118,119]. Further, the limited number of dedicated CF diagnostic centers makes it one of the challenging diseases to treat [13]. The scenario can be well visualized by an example that in a city like Riyadh, the commercial capital of Saudi Arabia with 5 million dwellers, has only 2 CF diagnostic centers [4–13,26–36,127].

5.4. Lack of proper medical care and patient education

Therapeutic insufficiency is the main cause of precocious complications and poor prognosis in patients with CF [128]. It is now generally agreed that a team of trained experienced health professionals in a specialist CF center with more than 50 patients can best provide this type of care. CF is a complex disease with numerous medical, psychiatric, and social consequences. For patients and their families, it means a lifetime of adjustments. Lack of public awareness can make the family feel isolated in its attempts to cope. Patients with CF often need caregivers with the knowledge and sensitivity to provide appropriate palliative care when required.

5.5. Cost and availability of pharmaceutical drugs

Management of CF is very expensive, with best survival rates seen when patients are treated in specialized CF centers. Costs of care increase with the age of patients, mainly because of recurrent deteriorations in the lung function and colonization with the pathogens such as *P. aeruginosa* [129]. The majority of patients with CF are often required to be on continuous medication to control the unabated infections [117]. Apart from direct costs for medication, laboratory analyses and costs of health care visits further add to the economic burden [117].

5.6. Poverty

The links between poverty and CF are extensive, strong, and pervasive. In spite of availability of sustainable treatment options, people hardly utilize them because of their exorbitant cost. People with CF and very poor affordability are even unaware of the disease and are often deprived quality treatment. In a disorder such as CF, with an equal incidence in different social groups, a report suggested that survival is strongly influenced by social factors [130].

5.7. Improved therapies should be made available

The quality of life and longevity in patients with CF can be prolonged if diagnosis of CF is established in the early stages. This will enable initiation of appropriate therapeutic regimen to commence as soon as a diagnosis is made [131]. Recent advancements have transformed CF from a disease characterized by death in early childhood to a chronic illness, with most patients living to adulthood. Despite this progress, many patients with CF eventually succumb primarily because of infection of the airways and lung failure. There is still a lack of treatment modalities that can offer complete cure. Hence, future research is warranted to equip the biological arsenal so that CF-related complications including deaths because of CF may be significantly curtailed.

5.8. Recommendations

A holistic approach comprising of the following recommendations may be appropriate in the treatment of CF: Improve awareness of the disease, and its variable presentation, Early referral to CF specialized centers, make the diagnostic sweat chloride test measurement to be available in most major hospitals for most populated cities, Early diagnosis and early institution of treatment, Early nutritional rehabilitation, improve adherence to treatment and air way clearance techniques, and to make most of the CF drugs available to most CF centers.

Acknowledgments

Conflict of Interest

Dr. Hanaa Banjar has nothing to report. Dr. Gerhild Angyalosi is in employee of Novartis Pharma AG, Switzerland

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