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Pancreatitis in Cystic Fibrosis and CFTR-Related Disorder

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1. Introduction

Named after the pathologic changes seen in the pancreas, cystic fibrosis (CF) is the most common lethal genetic disease in Caucasians, occuring in around 1 in 3000 live births. CF is uncommon among Asians (1 in 31,000 live births) and African Americans (1 in 15,000 live births) (Maitra & Kumar, 2005). It is caused by disease-causing mutations on both cystic fibrosis transmembrane conductance regulator (*CFTR*) alleles. Acute, recurrent-acute and chronic pancreatitis in association with *CFTR* mutations can develop in the setting of either CF disease or CFTR-related pancreatitis, which belong within the spectrum of disorders associated with CFTR dysfunction.

2. Cystic fibrosis (mucoviscidosis)

Cystic fibrosis was historically considered to be a multi-system disease which manifested clinically either at birth (with intestinal obstruction due to meconium ileus) or in infancy/early childhood (with failure to thrive due to pancreatic insufficiency and recurrent/chronic sino-pulmonary disease). Our understanding of this disease has changed in recent times, particularly after the discovery of the *CFTR* gene. Any one, or all of the manifestations of CF can occur at any point, from before birth through to childhood, adolescence and even in adulthood.

The *CFTR* gene responsible for CF is located on chromosome band 7q31.2, and encodes for a cyclic adenosine monophosphate (cAMP)-dependent chloride channel (Fig. 1). This particular chloride channel is located in the apical membrane of secretory and absorptive epithelium of the pancreas, intestine, liver, airway, vas deferens and sweat glands. The manifestations of CF generally arise from ductal and glandular obstruction due to an inability to hydrate macromolecules within the ductal lumen.

3. Pancreatic diseases associated with CF and CFTR-related diseases

Immunohistologic and pathologic studies have identified localisation of CFTR protein at the apical domain of the pancreatic ductal cells. Obstruction of proximal intralobular ducts by

inspissated protein plugs (obstructive tubulopathy) has been shown as early as during the in-utero period in CF (Oppenheimer & Esterly, 1976). The susceptibility of the pancreas to intraductal obstruction resulting from CFTR dysfunction is thought to be due to the high macromolecule concentration of the secretions and the dependence on the CFTR chloride (and bicarbonate) channel for maintaing fluid balance. Progressive ductal obstruction and fibrosis of acinar tissue presents as pancreatic insufficiency either at birth or in early childhood (Waters et al. 1990). Complete pancreatic exocrine deficiency is the seen in 85% to 90% of patients with CF (Durno et al., 2002; Ooi et al., 2011a).
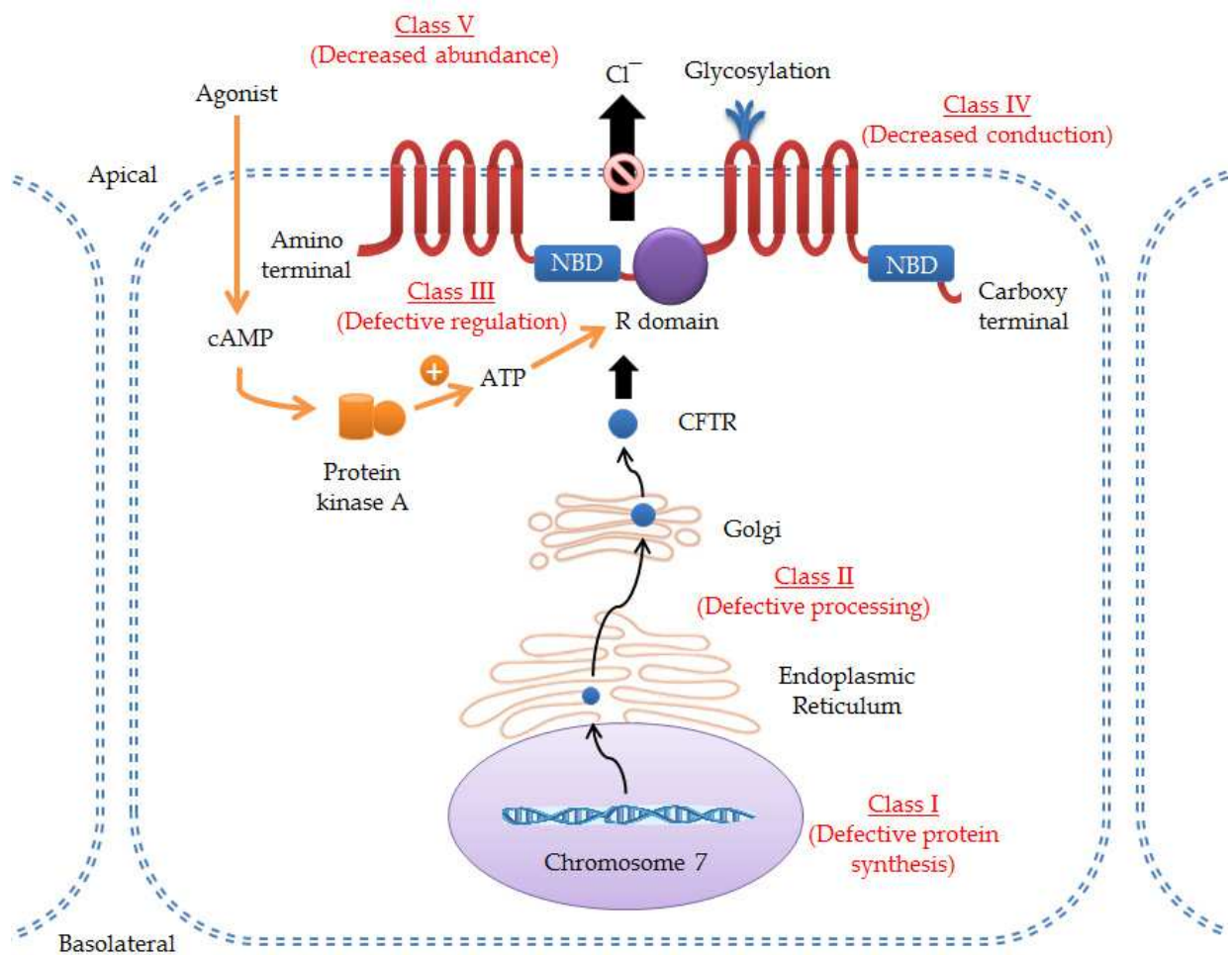

Fig. 1. Schema illustrating the processing, structure and function of the CFTR protein. The classes of genetic mutations (discussed later) and their effects on the CFTR processing/function are illustrated. The CFTR protein consists of two transmembrane domains, two nucleotide-binding domains (NBD), and a regulatory R domain. Normal functioning involves an agonist such as acetyl-chloine binding to epithleial cells, resulting in an increase in cAMP, which activates protein kinase A (PKA). PKA phosphorylates the CFTR protein at the R domain, thus resulting in opening of the chloride (Cl^-) channel. ATP, adenosine triphosphate; c-AMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator.

The majority of CF patients carrying functionally severe mutations on both alleles (Class I-III and VI) have a pancreatic insufficient (PI) phenotype (85% to 90%). A small proportion (2-3%) of patients carrying severe mutations on both alleles are pancreatic sufficient (PS) at diagnosis, but most experience gradual transition from PS to PI (Waters et al.,1990; Wilschanski & Durie, 2007). It is well established that PS-CF patients, who are often diagnosed at an older age, with more subtle disease manifestations, have mean sweat chloride values that are significantly lower than the current diagnostic reference criteria of 60 mmol/L (Farrell et al., 2008; Gilljam et al., 2004). Without sufficient enzyme activity (or enzyme replacement), PI patients suffer from malabsorption of proteins, fats and fat-soluble vitamins, and to a lesser extent, carbohydrates. Clinical manifestations of PI include: steatorrhoea, failure to thrive/poor weight gain, abdominal distension, a reduction in subcutaneous fat and muscle tissue, and fat-soluble vitamin deficiencies. In adolescents, absence of a pubertal growth spurt and delayed maturation may occur (Rosenstein, 2006).

With the increasing life expectancy of CF patients, it has become recognised that a significant proportion of PI-CF patients develop glucose intolerance, and up to 32% of patients over 25 years of age progress to insulin-requiring CF-related diabetes mellitus (Moran et al., 1999; Rosenstein, 2006). CF-related diabetes is characterised by an insidious onset and mild clinical course (e.g. gradual weight loss).

4. Pancreatitis in CF and CFTR-related disease: Pathogenesis

Pancreatitis is a well-known but uncommon manifestation in CF disease. This is not surprising as the majority of patients who carry functionally severe mutations on both alleles are PI. Since the presence of residual pancreatic acinar tissue is necessary for pancreatitis to occur, symptomatic pancreatitis does not (or rarely) occur in PI patients, but is not uncommon in PS-CF patients. Approximately 20% of PS-CF patients develop pancreatitis (Ooi et al., 2011a). Several studies have shown that individuals with idiopathic recurrent-acute or chronic pancreatitis have an increased incidence of mutations in the *CFTR* gene (Bishop et al., 2005; Cohn et al., 1998; Sharer et al.,1998). Bishop et al. (2005) showed that 43% and 11% of patients with idiopathic recurrent-acute or chronic pancreatitis carried at least one, and two *CFTR* mutations (and/or variants), respectively; the diagnostic criteria of CF could be fulfilled in 21% of these patients.

Whilst obstructive tubulopathy of the pancreas due to CFTR dysfunction is thought to be primary pathogenic factor, the exact mechanism of pancreatitis associated with *CFTR* mutations is still unknown. Based on murine models, CFTR dysfunction may also affect pancreatic acinar cells by impairing apical endocytosis through diminished ductal bicarbonate secretion and subsequently reduced alkalinization of the acinar lumen (Freedman et al., 2001). A recent study also suggests an important role of pH dysregulation in the development of pancreatitis. Co-release of protons (H^+) with proteins from secretory granules of acinar cells during pancreatic secretion was demonstrated (Behrendorff et al., 2010). Acidification of the pancreatic lumen led to a loss of tight junction integrity, which allowed the leakage of zymogens into the interstitial fluid. Abberant activation of calcium channels may also occur and result in the release and premature activation of zymogens, thus causing tissue damage and inflammation. The findings of this study fits with the development of pancreatitis in the setting of *CFTR* mutation(s) or CFTR dysfunction; reduced CFTR function impairs entry of bicarbonate into the ducts, and results in a more acidic and dehydrated pancreatic lumen. These studies support the complex interactions

that exist between the ductular and acinar components of the pancreas in the development of pancreatitis.

Parodoxically, *CFTR* genotypes associated with otherwise mild phenotypic effects have a greater risk of causing pancreatitis, when compared with genotypes associated with moderate to severe disease phenotypes. Patients with enough functional *CFTR* to confer a phenotypically functional pancreas have an increased risk of pancreatitis, as sufficient pancreatic acinar tissue is required for obstructive ductal lesions to cause disease (Fig. 2).
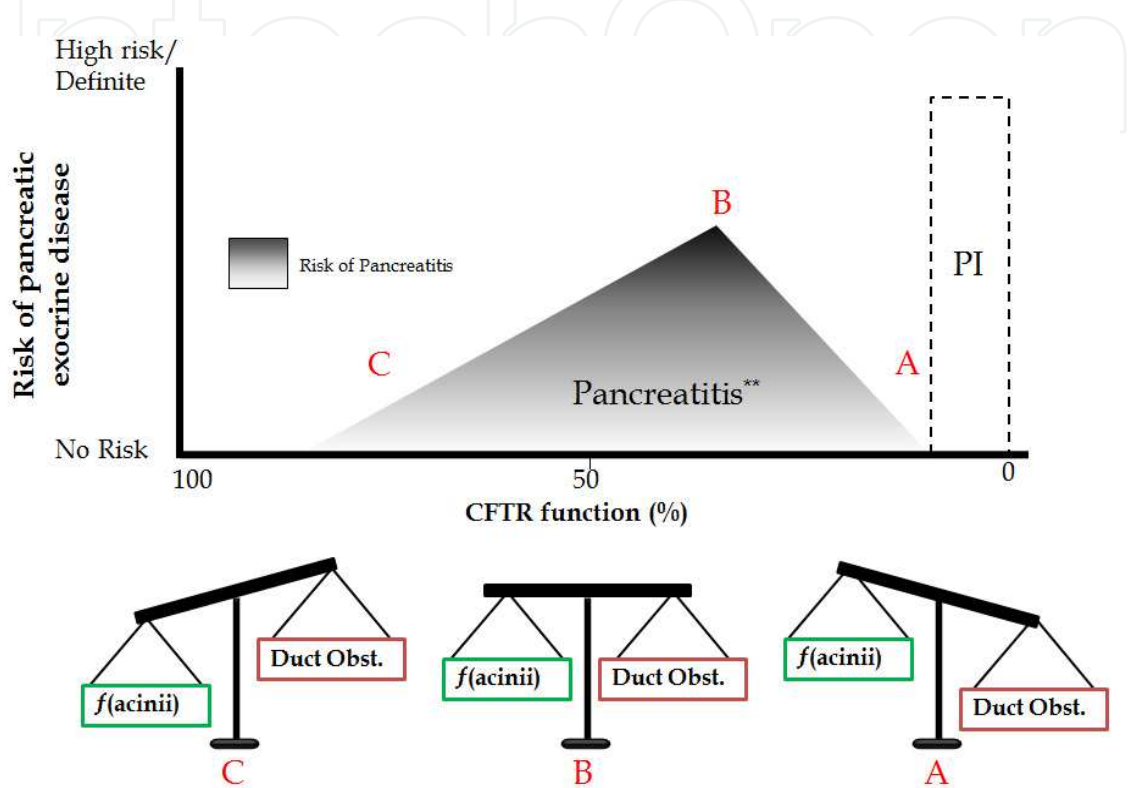
Fig. 2. Risk of pancreatitis in relation to severity of CFTR dysfunction. **The gradient within the pancreatitis curve reflects the relative risk of pancreatitis. A delicate balance between the degree of residual acinar tissue present and severity of ductal obstruction exists, and this balance correlates to the risk of pancreatitis. A. Patients with severe CFTR dysfunction have minimal/no risk of developing clinical pancreatitis despite severe ductal obstruction, as there is insufficient residual pancreatic acinar tissue. B. The risk of pancreatitis increases with decreasing CFTR dysfunction and is highest when there is adequately pathogenic ductal obstruction and sufficient residual acinar tissue present. C. With further increases in CFTR function, the degree of ductal obstruction is minimal, thus the risk of pancreatitis is low despite large amounts of pancreatic acinar tissue. The exception to this is when non-CFTR modifier factors play a role. CFTR, cystic fibrosis transmembrane conductance regulator; Duct Obst., degree of ductal obstruction; f(acinii), residual acinar function; PI, pancreatic insufficient.

5. *CFTR* mutations

Since the discovery of the *CFTR* gene in 1989, advances in molecular analysis techniques have identified > 1800 *CFTR* mutations (Dorfman, 2011). Mutation in this context simply

refers to a molecular alteration in the DNA sequence of a gene, with no inference made concerning the effect of this alteration on gene expression, protein function and, therefore, clinical phenotype. For many of the *CFTR* mutations which have been identified, the effect of the mutation on gene expression or function of the protein product is unknown. This is especially true for missense mutations (a base pair substitution in the DNA sequence) which represent approximately 40% of the identified mutations. To explain the use and interpretation of *CFTR* mutation analysis in clinical practice, the European Cystic Fibrosis Society (ECFS) published a consensus paper in 2008 which categorised mutations into four groups based on their predicted clinical consequences: (*i*) CF-causing mutations, (*ii*) mutations associated with *CFTR*-related disease, (*iii*) mutations with no known clinical consequence, and (*iv*) mutations with unknown clinical relevance (Castellani et al., 2008). Mutations which are associated with both PS and PI phenotypes are listed in Table 1. Note the more conservative list of mutations which are included on the recommended panel of CF-causing mutations for population screening developed by the American College of Medical Genetics (Farrell et al., 2008). This list is not entirely exhaustive, as other mutations can be predicted to be CF-causing if the molecular alteration results in a change in amino acid sequence that: severely affects CFTR synthesis and/or function; introduces a premature termination signal; or alters invariant nucleotides of intron splice sites. However, the vast majority of known mutations do not fulfill the accepted criteria for CF-causing mutations (Castellani et al., 2008; Farrell et al., 2008).

In CF, disease-causing mutations are often identified on newborn screening panels. In recent times, several diseases that resemble CF at an organ-specific level (e.g. pancreatitis, bronchiectasis and obstructive azoospermia) have also been found to be strongly associated with mutations in the *CFTR* gene (Ooi et al., 2010b). The functional consequence(s) of many *CFTR* gene alterations is unknown and unable to be determined. This is due to the interplay of mild and severe mutations, as well as the variation in genotype-phenoytpe expression, which is affected by non-*CFTR* modifiers (genetic and/or environmental).

The complex and heterogenous presentation of CF disease and CFTR-related disorders is associated with a continuous spectrum of CFTR dysfunction. A clear relationship between the number and functional severity of *CFTR* gene alterations, with the range of CFTR-mediated ion channel abnormalities has been established (Bishop et al., 2005; Wilschanski, 2006). This observation has helped develop our understanding of the threshold of CFTR-mediated ion channel function that is required for disease pathogenesis and diagnosis.

A 5-class classification system for *CFTR* mutations was originally developed to categorize the molecular characteristics of different mutations (Fig. 3) (Tsui, 1992). On the basis of its molecular defect, mutations in Classes I-III could be predicted to have severe functional and phenotypic consequences. Conversely, Classes IV-V may confer residual CFTR function and thus, be predicted to be associated with milder phenotypic consequences. Remarkably, genotype-phenotype studies demonstrated an excellent correlation between Classes I-III with a PI phenotype, and Classes IV-V with a PS phenotype (Ahmed et al., 2003; Kristidis et al.,1992). A 6th mutation class has subsequently been proposed which is also associated with severe functional and phenotypic consequences. In general, patients homozygous or compound heterozygous for severe mutations (class I-III, and VI) will be PI. Alternatively, patients with at least one mild mutation (class IV or V), will often be PS, as the milder of the two mutations confers a dominant phenotypic effect. In very young infants, *CFTR* genotype may not be closely associated with pancreatic phenotype; particularly those identified by

newborn screening. This is almost certainly due to the fact that some infants carrying severe mutations on both alleles have some residual exocrine pancreatic function at birth. However, almost all of the patients who are homozygous or compound heterozygous for severe mutations will develop PI within the first two years of life (Waters et al., 1990).

CFTR mutations and their associated clinical consequences			
Association	**Mutations**		**Phenotype**
CF-causing	F508del* R553X* R1162X* R1158X 2184delA* 2184insA 3120+1G>A* I507del* 1677delTA	6542X* G551D* W1282X* N1303K* 621+1G>T* 1717-1G>A* 1898+1G>T* R560T*	G85E* 711+1G>T* 1898+1G>A S549N E822X 1078delT 2789+5G>A* 3659delC*	**Usually PI**
	A455E* R334W* R347P*	711+3A>G 3849+10kbC>T* R117H-T5*	D1152H L206W TG13-T5	**Usually PS**
CFTR-related disease	R117H-T7* D1152H TG13-T5 D565G	TG12-T5 S997F R297Q L997F G576A	TG11-T5 R74W-D1270N R668C-G576A- D443Y M9521	**Usually PS**
No clinical consequences	I148T R75Q 875+40A/G M470V E528E	T854T P1290P 2752-15G/C I807M	1521F F508C I506V TG11-T5	-
Unknown or uncertain clinical consequence	Mainly missense mutations with subclinical molecular consequences (e.g. M470V), which may co-segregate on the same chromosome and exert a more potent, cumulative phenotypic effect.		-

Table 1. List of *CFTR* mutations with their associated clinical consequence(s) and pancreatic exocrine phenotype(s). Adapted from Castellani et al., 2008. Underlined are the mutations associated with both PS and PI phenotypes. * The CFTR mutations included on the recommended panel of CF-causing mutations for population screening (Farrell et al., 2008). CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; PI, pancreatic insufficient; PS, pancreatic sufficient.

Although this class system is useful as a conceptual framework, it does have several limitations which include (Ooi et al., 2010b): (*i*) molecular changes of different mutations within the same class (especially classes IV and V), may have varying functional consequences, (*ii*) mutations may have overlapping molecular defects which may be assigned to more than one class, (*iii*) the molecular consequences of the majority of rare

CFTR mutations, particularly missense alterations are unknown or cannot be predicted, and (*iv*) inferred properties of many mutations remain to be confirmed by functional studies.

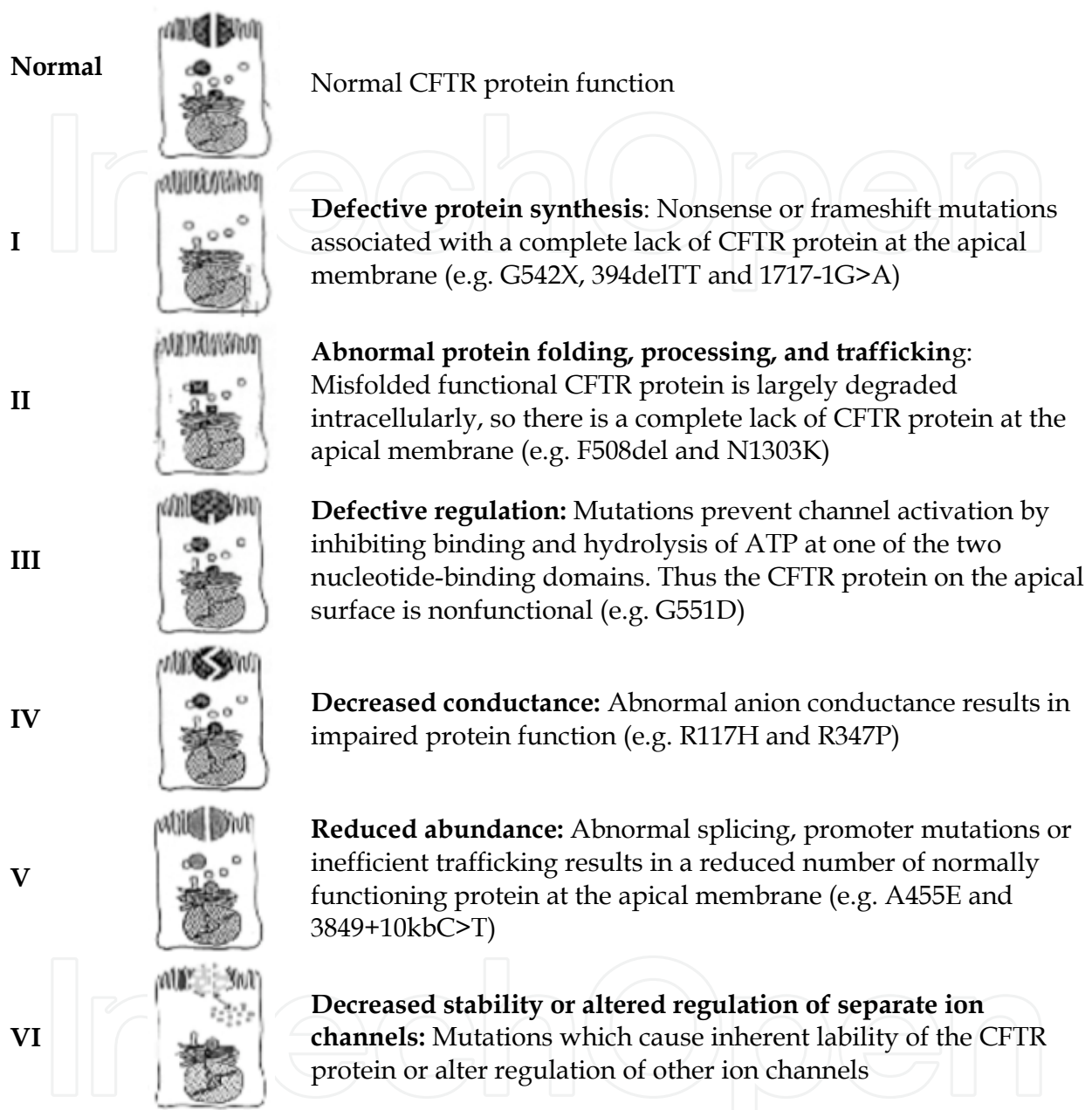|		
Normal		Normal CFTR protein function
I		**Defective protein synthesis**: Nonsense or frameshift mutations associated with a complete lack of CFTR protein at the apical membrane (e.g. G542X, 394delTT and 1717-1G>A)
II		**Abnormal protein folding, processing, and trafficking**: Misfolded functional CFTR protein is largely degraded intracellularly, so there is a complete lack of CFTR protein at the apical membrane (e.g. F508del and N1303K)
III		**Defective regulation:** Mutations prevent channel activation by inhibiting binding and hydrolysis of ATP at one of the two nucleotide-binding domains. Thus the CFTR protein on the apical surface is nonfunctional (e.g. G551D)
IV		**Decreased conductance:** Abnormal anion conductance results in impaired protein function (e.g. R117H and R347P)
V		**Reduced abundance:** Abnormal splicing, promoter mutations or inefficient trafficking results in a reduced number of normally functioning protein at the apical membrane (e.g. A455E and 3849+10kbC>T)
VI		**Decreased stability or altered regulation of separate ion channels:** Mutations which cause inherent lability of the CFTR protein or alter regulation of other ion channels

Fig. 3. Classes of *CFTR* mutations according to the functional consequences of the gene product with respect to chloride regulation. Severe mutations (classes I-III and VI) confer little or no functional CFTR at the apical membrane, whilst mild mutations (classes IV and V) confer some partial CFTR function. Adapted from Tsui, 1992; Wilschanski & Durie, 2007.CFTR, cystic fibrosis transmembrane conductance regulator.

A new surrogate measure for the severity of *CFTR* mutations, known as the Pancreatic Insufficiency Prevalence (PIP) score, was recently developed and validated (Dorfman et al., 2010; Ooi et al., 2011a). The PIP scoring system permitted a more refined classification of the functional severity of *CFTR* mutations, and in a far greater number of patients than previous

methods of classification. The PIP score is based upon a direct assessment of the effect of each genotype on exocrine pancreatic phenotype; which had been objectively determined in a large population-based CF database. This classification system is based on several premises: (*i*) the well-established correlation between severity of *CFTR* mutations and exocrine pancreatic function, (*ii*) the dominant phenotypic effect conferred by the milder of the 2 *CFTR* mutations, and (*iii*) the availability of a comprehensive database containing large numbers of CF patients, with stringent determination of clinical diagnosis and exocrine pancreatic status. Ooi et al. (2011a) described how mutations can be classified as either mild (≤0.25) or moderate-severe (>0.25) on the basis of the PIP score (Table 2).

Pancreatic Insufficiency Prevalence (PIP) Scores for Common, Well-Defined *CFTR* Mutations					
Mutation	**Class**	**Total PI**	**Total PI + PS**	**PIP Score**	**Phenotype**
R117H	IV-V	1	25	0.04	
3849+10kbC>T	IV-V	2	22	0.09	Mild
R334W	IV-V	1	10	0.10	
2789+5G>A	IV-V	6	16	0.38	
A455E	IV-V	18	37	0.49	
G85E	I-III,VI	16	22	0.73	
G551D	I-III,VI	59	67	0.88	
R1162X	I-III,VI	12	13	0.92	
N1303K	I-III,VI	45	48	0.94	
W1282X	I-III,VI	19	20	0.95	Moderate-severe
1717-1G>A	I-III,VI	20	21	0.95	
F508del	I-III,VI	1276	1324	0.96	
G542X	I-III,VI	74	75	0.99	
I507del	I-III,VI	11	11	1.00	
R553X	I-III,VI	24	24	1.00	
711+1G>T	I-III,VI	36	36	1.00	
621+1G>T	I-III,VI	96	96	1.00	

Table 2. PIP scores for common, well-defined *CFTR* mutations based on the prevalence of PI in a large and well-defined cohort of Canadian CF patients (n=2481) (Ooi et al., 2011a). The PIP score for a specific mutation is the ratio between the PI patients carrying the mutation (Total PI), and all PI and PS patients (Total PI + PS) carrying the same mutation when in a homozygous state or heterozygous combination with F508del, G551D or class I mutations (bona fide severe mutations). For example, a ratio of 1.00 indicates that all patients with 621+1G>T are PI. Similarly, a ratio of 0.1 demonstrates that 10% of subjects with R334W are PI. CFTR, cystic fibrosis transmembrane conductance regulator; PI, pancreatic insufficient; PIP, pancreatic insufficiency prevalence; PS, pancreatic sufficient.

Using the PIP score, a relationship between severity of *CFTR* genotypes with risk of pancreatitis was observed among PS-CF patients. Patients with genotypes associated with mild phenotypic (PIP score ≤ 0.25) effects have a greater risk of developing pancreatitis than patients with genotypes associated with moderate-severe phenotypes (PIP score > 0.25);

among the patients who developed pancreatitis, 70% had a mild genotype, while 30% carried a moderate-severe genotype (P = 0.004) (Ooi et al., 2011a). The genotype associated with mild PIP scores had a hazard ratio of 2.4 for pancreatitis (95% confidence interval, 1.3-4.5; P = 0.006). Furthermore, there was a gradation of risk of developing pancreatitis according to severity of each allele carried: highest risk seen in CF patients who carried 2 mild mutations (mild/mild) followed by those who carried 1 mild mutation (mild/moderate-severe), compared with those who carried functionally moderate-severe mutations on both alleles (Fig. 4). Thus, this is the first systematic study to date, demonstrating an association between higher risks of pancreatitis with different degrees of genotype mildness (based on the PIP score).

	0	10	20	30	40	50
Mild/Mild	9	7	3	2	1	0
Mild/Mod-Sev	138	115	84	58	34	10
Mod-Sev/Mod-Sev	130	111	82	54	28	7
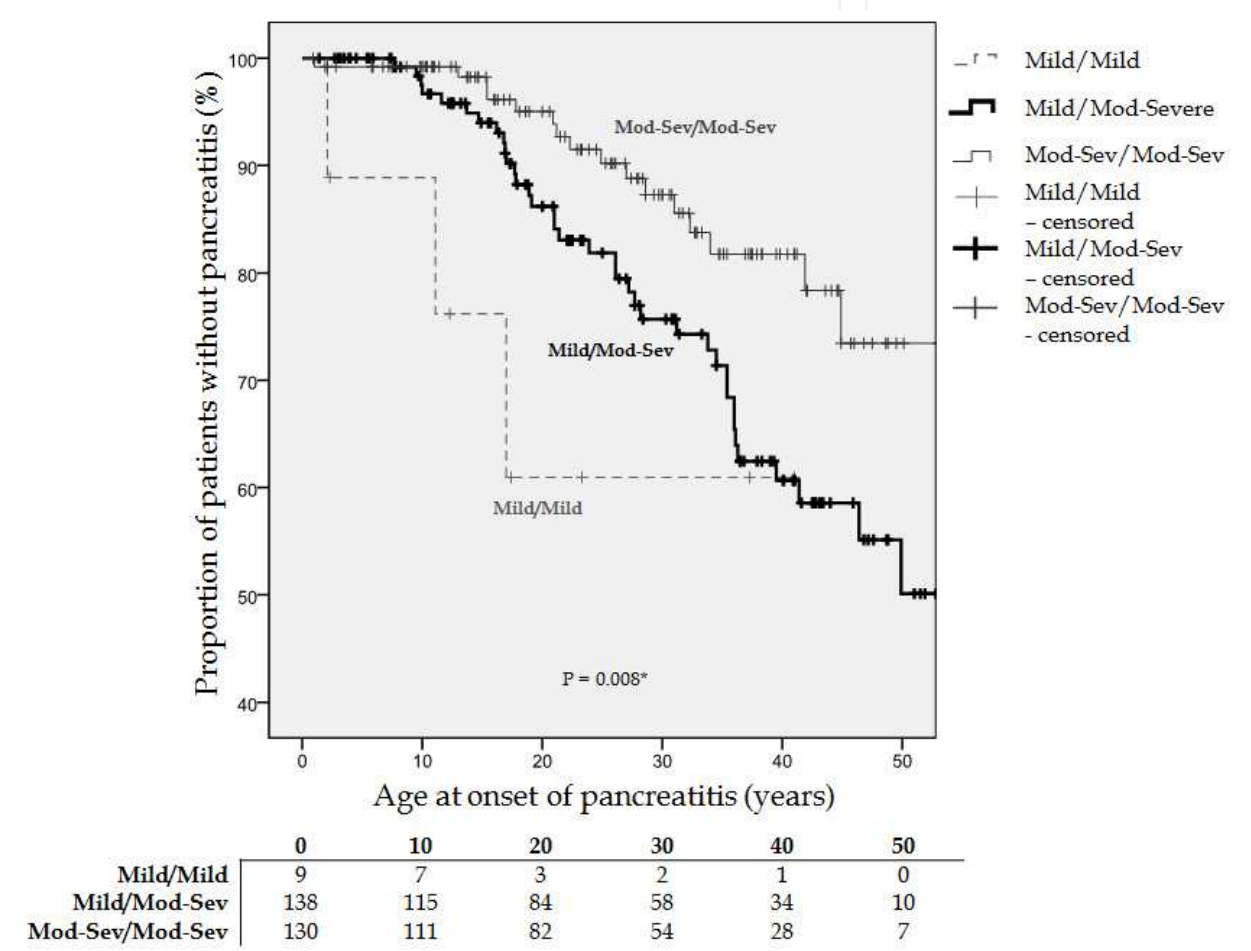
Fig. 4. Survival curves (Kaplan-Meier estimate) comparing time to pancreatitis in patients grouped according to severity of both *CFTR* alleles (mild/mild *vs.* mild/moderate-severe *vs.* moderate-severe/moderate-severe). The survival table (below the curve) indicates the number of patients/"survivors" at risk of pancreatitis at 0, 10, 20, 30, 40 and 50 years respectively. Adapted from Ooi et al., 2011a. * Log-rank test CFTR, cystic fibrosis transmembrane conductance regulator; Mod-Sev, moderate-severe.

All classification systems are limited by the fact that the heterogenous CF disease spectrum is not just explained by *CFTR* genotype, but is also influenced by environmental and other genetic modifying factors. Genes such as cationic trypsinogen (*PRSS1*), anionic trypsinogen (*PRSS2*), pancreatic secretory trypsin inhibitor (*SPINK1*), and chymotrpsinogen C (*CTRC*)

have been demonstrated to be involved in the regulation of trypsinogen autoactivation and also play a role in cases of idiopathic recurrent-acute and chronic pancreatitis (Ooi et al., 2010a). The interactions with environmental factors such as cigarette smoking, alcohol and diet are also highly complex, and are only beginning to unravel.

6. The spectrum of CFTR dysfunction

The notion of a spectrum of CFTR dysfunction is supported by the observation that CF may manifest at different ages, in different organs and with variable severity. Cystic fibrosis and CFTR-related disorders comprise of pancreatic exocrine insufficiency, pancreatitis, chronic sinopulmonary disease, intestinal diseases, hepatobiliary disease, and obstructive azoospermia in men.

Individuals who carry one or two *CFTR* gene mutation(s) show an overlapping clinical spectrum, ranging from no clinical disease at one extreme, through those with CFTR-related disorders, to those with CF disease (with/without sufficient pancreatic function) at the other extreme (Fig. 5).
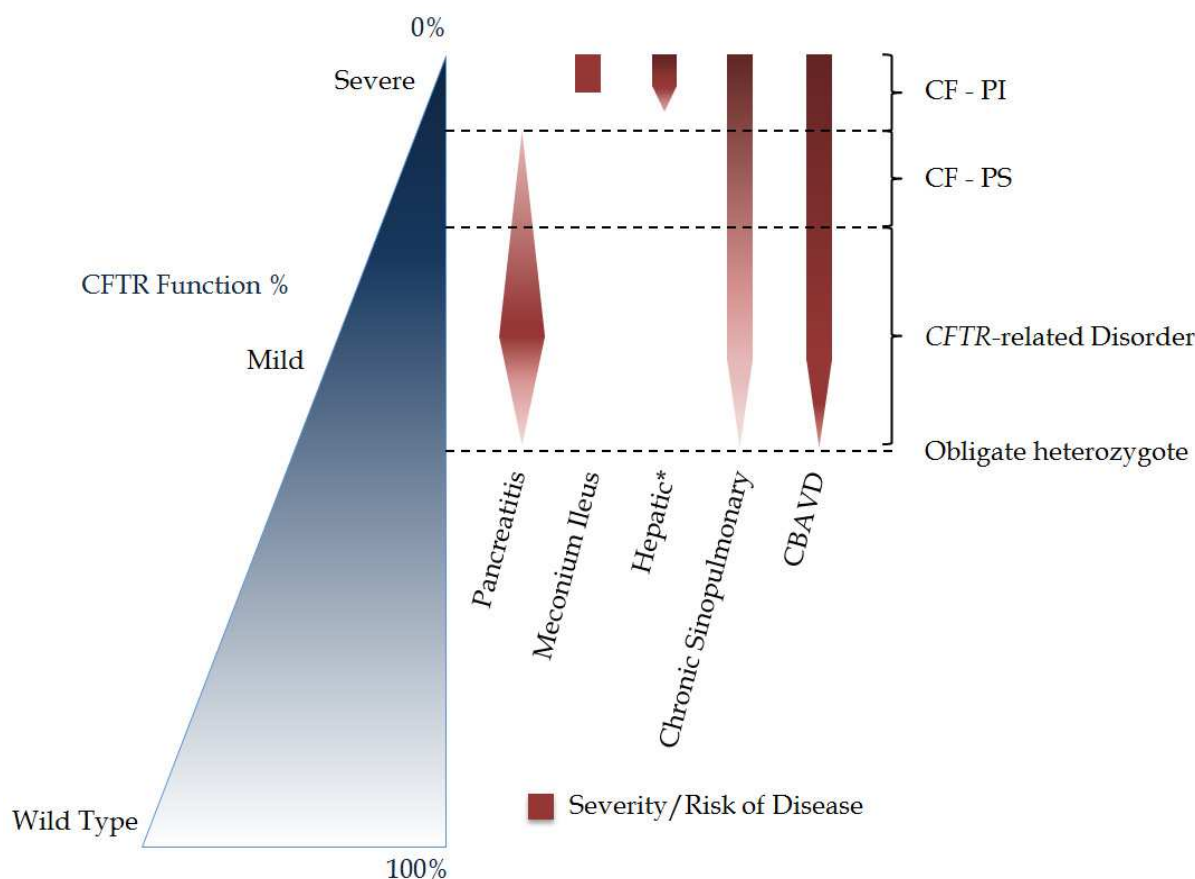
Fig. 5. Spectrum of disorders associated with the level of CFTR function and the respective severity/risk of disease. * Severe CF liver disease with cirrhosis ± portal hypertension. CBAVD, congenital absence of the vas deferens; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; PI, pancreatic insufficient; PS, pancreatic sufficient.

There is considerable debate and difficulty on where to draw the diagnostic line between CF disease and CFTR-related disorder. Although they can be divided into two entities, they form part of a continuous spectrum of diseases associated with CFTR dysfunction. Similarly, ion channel measurements in the sweat gland (sweat test) and nasal epithelium (nasal potential difference test) show a continuum of values with overlap, and no clear delineating point between individuals without CF (healthy controls and obligate heterozygotes) and patients with CF (pancreatic sufficient and insufficient). Consequently our ability to establish or exclude CF disease has become increasingly problematic.

The subset of clinically heterogeneous patients who are diagnosed with CF in adolescence and adulthood, who do not resemble the typical clinical presentation in infancy or early childhood are discussed later in this chapter.

7. Pancreatitis in CF and CFTR-related disorder: Clinical presentation and diagnosis

The initial clinical presentation of acute, recurrent-acute and chronic pancreatitis due to CFTR dysfunction can be indistinguishable from idiopathic pancreatitis. The clinical features and diagnostic criteria for pancreatitis are covered by companion chapter(s) in this textbook.

The most recent United States Cystic Fibrosis Foundation (USCFF) consensus report (Farrell et al., 2008), agreed that a diagnosis of CF can be made in individuals who present with a characteristic clinical phenotype or a history of CF in a sibling, *in the presence of* an abnormal sweat chloride value ≥ 60 mmol/L and/or two CF-causing mutations. It is important to note that a diagnosis of CF cannot be made based on the identification of *CFTR* mutations on both alleles alone, especially when one or both are not designated as disease-causing mutations.

Due to the vast array of phenotypes associated with *CFTR* mutations, the diagnosis of patients with CF disease has become increasingly difficult, and the demarcation line between those with CF and those not classified as having CF by current diagnostic criteria has blurred. To deal with the spectrum of disease, the USCFF consensus report stated that the classification of this disease should be limited to two terms (Farrell et al., 2008): (*i*) CF disease, to describe patients who fulfil the currently accepted diagnostic criteria, and (*ii*) "CFTR-related disorder," to describe individuals with a CF phenotype in at least one affected organ *plus* evidence of CFTR dysfunction, but insufficient to fulfil the diagnostic criteria for CF disease (e.g. borderline sweat test and/or 1 – 2 non-CF causing mutation(s)). Using this terminology, patients with recurrent-acute or chronic pancreatitis due to CFTR dysfunction , may receive a diagnosis of CF pancreatitis or CFTR-related pancreatitis.

Individuals with a CFTR-related disorder are recognised to be *at risk for developing CF disease* (Farrell et al., 2008)**.** Therefore, a diagnosis of CFTR-related pancreatitis may precede a diagnosis of CF, as it may be the initial manifestation of CFTR dysfunction, or it may be associated with other CFTR-related disorders at the time of presentation (e.g. infertile males with pancreatitis) or later on. Consequently, if repeat sweat chloride values remain in the intermediate range (40-59 mmol/L), further assessment has been recommended at a CF care center to clarify the diagnosis. Further assessment may include: clinical assessment, expanded genetic testing, exocrine pancreatic function testing, and respiratory tract culture for CF-associated pathogens. Depending on the clinical presentation, assessment may also include ancillary tests, such as pulmonary function testing and urogenital evaluation in males (genital examination, rectal ultrasound, and sperm analysis). It is important to

emphasise that treatment should be dependent on the disease presentation, and not on presence or absence of a diagnostic label.

7.1 Sweat chloride testing

The sweat chloride test has been in clinical use for over 50 years, and it still remains the principal test for the confirmation of the diagnosis of CF in the genomic era (Gibson & Cooke, 1959). Although the test is now commonly available in most diagnostic laboratories, appropriate performance of the sweat test in accordance to recommended standards is crucial for accurate diagnosis. The sweat test involves transdermal administration of pilocarpine by iontophoresis to stimulate sweat gland secretion, followed by collection and quantitation of sweat onto gauze or filter paper, or into a Macroduct coil. The reference ranges for sweat chloride concentration which we use today, were defined using studies of CF patients presenting with classical symptoms of CF at an early age (most were PI); there were no "truly healthy" controls, and the technical aspects of the sweat test methodologies would not meet currently accepted guidelines (Farrell et al., 2008; Shwachman & Mahmoodian, 1967). Furthermore, there has also been no study to accurately determine the reference ranges for sweat chloride values in infants and young children less than 5 years of age (Farrell et al., 2008). Several studies have also reported patients being diagnosed with CF (PS and PI), who have sweat chloride values < 60mmol/L (Desmarquest et al., 2000; Highsmith et al., 1994; Stewart et al., 1995). This is especially true among the well described CF disease-causing mutations associated with normal or intermediate sweat chloride values (e.g. 3849+10kbC>T).

Sweat chloride values are traditionally interpreted categorically. Due to the aforementioned limitations, it is not surprising that the reference values for the various sweat chloride categories are not universally agreed upon. According to the USCFF consensus guideline, sweat chloride values can be categorised as the following among individuals > 6 months old: normal ≤ 39 mmol/L, intermediate 40-59 mmol/L, or abnormal ≥ 60 mmol/L; the intermediate range is extended to 30-59 mmol/L in infants up to 6 months old (Farrell et al., 2008). This differs from the reference ranges recommended by the ECFS: normal ≤ 29 mmol/L, intermediate 30-60 mmol/L, and abnormal > 60 mmol/L, for all ages (De Boeck et al., 2006).

There is preliminary data to suggest that the individual sweat chloride value, taken into account with the clinical context, is of more value to the clinician than categorical interpretation (Ooi et al., 2011b). This study evaluated the diagnostic performance of sweat testing in the general population and in patients with idiopathic pancreatitis who were referred to a gastroenterology (GI)-CF clinic. This study raised an important point that sweat test parameters and results are dependent on the patient population and disease incidence in each population. When comparing the general population to symptomatic pancreatitis patients in a GI-CF clinic: the pre-test probability for CF is 1 in 3608 vs. 10%; the carrier rate is 4% vs. 50%; and the PI:PS CF ratio is 8:1 vs. all patients with pancreatitis being PS (Bishop et al., 2005; Castellani et al., 2010; Dupuis et al., 2005; Durno et al., 2002). It has also been reported that a diagnosis of CF can be made in 10% of idiopathic pancreatitis patients (referred to a GI-CF clinic), based on sweat testing and/or genotyping, however the diagnosis may be equivocal in up to 20% of patients (Bishop et al., 2005; Ooi et al., 2010a). As expected, there were vast differences in the diagnostic performance of sweat chloride testing in the two populations (Table 3).

An important observation from this study is the dramatic increase in the positive predictive value (PPV) of sweat chloride values ≥ 55 mmol/L in the general population, and the not

clinically insignificant high PPV in those who present with symptomatic pancreatitis and have sweat chloride values ≥ 40mmol/L (Fig. 6). These results demonstrate how the individual sweat chloride result (whilst also taking in to account the clinical context of the patient), may be more valuable to the clinician than using the traditional categorical interpretation.
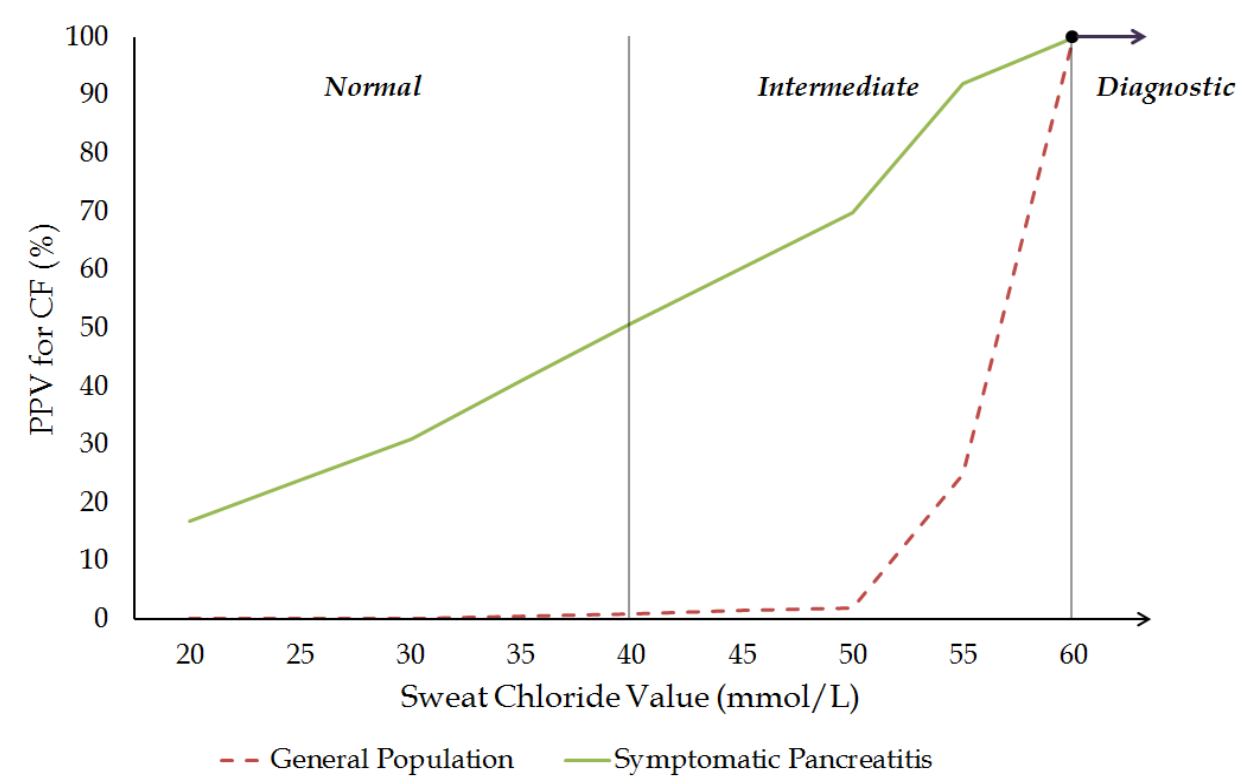
Fig. 6. PPV of sweat chloride testing in the general population and patients with idiopathic pancreatitis referred to a GI-CF clinic (Ooi et al., 2011b).CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; PPV, positive predictive value.

Sw Cl (mmol/L)	General Population				GI-CF Clinic			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
20	100	54	0.1	100	98	48	17	100
30	99	83	0.2	100	94	77	31	99
40	98	97	0.9	100	81	91	51	98
50	97	99	2	100	77	96	70	97
55	97	100	25	100	73	99	92	97
60	96	100	100	100	64	100	100	96

Table 3. Diagnostic performance parameters for various sweat chloride values in a general population and patients at a GI-CF clinic. (Ooi et al., 2011b). CF, cystic fibrosis; GI, gastroenterology; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity; Sw Cl, sweat chloride.

7.2 Genotyping

Despite the considerable optimism that genotyping would supersede the traditional sweat test, there remains considerable misunderstanding of the role of *CFTR* genotyping as a diagnostic aid in CF. In patients with a suspected, but unproven diagnosis of CF, mutation testing (including complete sequencing of the *CFTR* gene) appears to be the least helpful diagnostic tool and may be potentially misleading. In fact, carefully performed sweat chloride testing has been reported to be more sensitive and specific than complete sequencing in patients presenting with a single organ manifestation of CF including pancreatitis (Bishop et al., 2005; Gilljam et al., 2004; Wilschanski, 2006). In a cohort of 46 CF patients diagnosed in adulthood, only 15 (33%) fulfilled the diagnostic criteria of CF based on genotyping alone; all except one of the 15 (6.7%) had an abnormal sweat test > 60 mmol/L. Sweat testing alone diagnosed CF in 30 (65%) subjects and when sweat testing was combined with genotyping, the diagnostic sensitivity only improved slightly to 67% (n=31) (Gilljam et al., 2004).

If a clinician decides to assess a patient's genotype, it is important to consider that most patients presenting in adolescence and adulthood and/or those who present with single-organ disease, frequently carry one or more rare *CFTR* mutations which are often not included in screening panels. However, extensive genotyping or complete sequencing of the *CFTR* gene has major limitations also. The majority of mutations have unknown functional consequences, while some are considered to be benign polymorphisms with no pathogenic potential. Furthermore, some mutations are known to form complex alleles i.e. > 1 mutation occurs only on one allele and hence, may be mis-interpreted as the presence of mutations on both alleles. With all these variables, there is a potential risk of informing a patient with pancreatitis that they have *CFTR* mutations, and implying they have CF. Misinterpretation of genotyping results carries enormous psychosocial and medical implications, as well as affecting potential insurability. In a study reporting the outcomes from a commercially available extensive *CFTR* mutation test, 84% of patients identified with 2 *CFTR* mutations were incorrectly labeled as having CF (Keiles & Kammesheidt, 2006; Ooi et al., 2010a).

7.3 Transepithelial nasal potential difference testing

The transepithelial nasal potential difference (NPD) test is an electrophysiological test that assesses CFTR activity by measuring transepithelial potential difference of the nasal epithelium. This test is based on the characteristic bioelectric properties of amiloride-dependent sodium (Na^+) absorption (via ENaC) and CFTR-mediated Cl^- diffusion (Schuler et al., 2004). NPD has been used in CF research for decades but due to a lack of validated reference values and standardisation, it has only been cautiously applied in clinical practice as an adjunctive test to assist in clarifying the diagnosis of CF, especially for individuals with intermediate sweat chloride values (Farrell et al., 2008).

NPD is measured between a fluid-filled exploring bridge positioned on the nasal respiratory mucosa, and a reference bridge inserted into the subcutaneous space. Both bridges are linked by Ag/AgCl electrodes (or saturated calomel half-cells) to a high-impedence voltmeter. An otoscope is used to help place the tip of the exploring catheter on the respiratory mucosa inferior to the concha nasalis inferior. A basal potential difference is established once consistent baseline NPD measurements are obtained. Different solutions/drugs can be administered via the exploring catheter, and the changes in transepithelial potential difference as a response to superfusion can be measured. The

findings of a high potential difference during baseline measurements, followed by an absent or very low voltage response to zero-chloride plus isoproterenol perfusion, are indicative of CF (Knowles et al., 1995).

Patients who have equivocal sweat chloride results and/or CFTR mutation analysis may also have equivocal NPD measurements, and a consensus of what constitutes a borderline result is lacking (Ooi et al., 2010b). In addition, the procedure is complex to perform, labour intensive, and operator dependent. Although NPD testing has been reported in infants and young children, the accurate performance of this test requires undivided cooperation from the subject. False positives can occur with incorrect placement of the measuring catheter, minor perturbations of nasal epithelium, allergies, respiratory infections, and smoking (Cantin et al., 2006).

7.4 Intestinal ion channel measurement

Intestinal ion channel measurement (ICM) is an ex vivo test performed in an Ussing chamber using a freshly obtained rectal biopsy and measuring its electrical response to a series of secretagogues. Intestinal epithelia of CF subjects have been evaluated by two different laboratory methods (circulating vs. continuously perfused) (De Jonge et al., 2004; Mall et al., 2004). The common finding of both approaches demonstrates absent or diminished chloride secretion after stimulation with agonists that act via intracellular cAMP. Intestinal ICM has been reported to be useful in clarifying the diagnosis of CF in cases of uncertainty, but again the absence of standardisation and well-established reference values limits its use in clinical practice (Farrell et al., 2008).

7.5 Imaging in CF and CFTR-related pancreatitis

The typical changes of the pancreas on imaging in patients with CF are neither specific nor diagnostic for CF and CFTR-related pancreatitis. In CF, fatty replacement of the pancreatic parenchyma, with or without glandular atrophy (56-93%) is the most common finding at imaging in adult patients, and the mean age of fatty replacement is 17 years (Robertson et al., 2006; Shanbhogue et al., 2009). Other radiological findings include pancreatic calcifications (7%); cyst formation (pancreatic cystosis); and abnormalities of the pancreatic duct, including strictures, beading, dilatation, and obstruction (Shanbhogue et al., 2009). The pancreatic duct can be poorly demonstrated with ultrasonography (US) in CF patients with pancreatic atrophy and fatty replacement, and is best demonstrated with magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) (Robertson et al., 2006). Imaging has no role in monitoring of exocrine pancreatic function but has a yet to-be-defined role in surveillance for pancreatic adenocarcinoma.

8. Management of pancreatitis in CF and CFTR-related disorder

The management of pancreatitis associated with CF or *CFTR* mutations per se, is currently no different to other forms of pancreatitis (covered in companion chapters). Affected patients however should be referred to a CF clinic or gastroenterologist with interests/expertise in CF for a thorough evaluation. The main considerations in these patients are a progression from PS to PI, and the risk of developing CF disease and/or disease in other CF-affected organs (e.g. bronchiectasis) (Gilljam et al., 2004; Ooi et al.,

2011a). In addition, there are increasing concerns of an increased risk of pancreatic adenocarcinoma among those with CF and CFTR-related pancreatitis.

8.1 Pancreatic function testing

The exocrine pancreas has a large reserve capacity and requires between 90% and 99% of enzyme secretory capacity to be lost before a subject develops clinical manifestations of PI. It is recommended that patients with PS-CF and CFTR-related pancreatitis have their pancreatic exocrine function assessed. Individuals who have sufficient pancreatic function at presentation need to be assessed periodically, or when new symptoms suggestive of PI develop, as some may progress to PI (Gilljam et al., 2004; Ooi et al., 2011a). Progression of PI is dependent on the following factors: (1) the carriage of moderate-severe mutations on both alleles, and (2) the development of symptomatic pancreatitis. PS-CF patients with mild genotypes (i.e. those otherwise expected to remain PS) who develop pancreatitis are at an increased risk of progressing from PS to PI (odds ratio = 5.5) (Ooi et al., 2011a).

Exocrine pancreatic function can be measured through non-invasive and invasive methods. Currently, non-invasive pancreatic function tests are commonly utilised for defining the exocrine pancreatic phenotype. The 72-hour faecal fat balance test, expressed as the coefficient of fat absorption (CFA), is considered the gold standard as far as non-invasive tests are concerned (Ooi et al., 2010b). However, the test is inconvenient and not well tolerated by patients or laboratory staff. Faecal elastase-1 is an alternative indirect stool marker for pancreatic function, as elastase (an endogenous pancreatic secretion enzyme) is resistant to gastrointestinal degradation. Using a cut-off of 200 µg/g stool, the sensitivity for mild, moderate, severe and all patients with PI, was reported to be 63%, 100%, 100% and 93% respectively, whilst the specificity was 93% (Loser et al., 1996). Because of its ease of use, faecal elastase-1 is recommended for evaluating pancreatic function at diagnosis and for follow-up monitoring. Currently, a value of < 100 µg/g in individuals over the age of 2 to 3 years is considered indicative of PI. Values from 100 µg/g to 200 µg/g are associated with significant loss of pancreatic function, although not necessarily of sufficient severity to confer PI, and warrant the need for pancreatic enzyme supplementation (Farrell et al., 2008). In addition, there are differences in the diagnostic performance parameters (sensitivity and specificity) between monoclonal and polyclonal assays for faecal elastase; the monoclonal assay is superior due to less cross-reactivity and can be used whilst patients are on pancreatic enzyme therapy (Pezzilli et al., 2005). False positivity can occur due to malabsorption from an intestinal cause, particularly if there is stool dilution from severe diarrhoea (Beharry et al., 2002). Other indirect methods for assessing pancreatic function include the measurement of faecal concentrations of the pancreatic enzymes, trypsin and chymotrypsin. However, both faecal trypsin and chymotrypsin are prone to intestinal degradation and faecal chymotrypsin cross-reacts with exogenously administered enzyme therapy.

Serum trypsinogen has been used for newborn screening for more than two decades, and has been shown to help define pancreatic functional status in CF patients older than 7 years of age (Durie et al., 1986). This test has the added benefit of being able to predict the progression of pancreatic status from PS to PI (Couper et al., 1995). Serum trypsinogen is also capable of identifying the presence of pancreatic disease and dysfunction (loss of pancreatic reserve or pancreatitis) in individuals with a CFTR-related disorder (Ooi et al., 2010b).

Alternatively, the invasive direct pancreatic stimulation test allows assessment of both pancreatic acinar (enzyme) and ductular (electrolyte and fluid) status. There is currently no

standardized methodology for direct pancreatic stimulation testing and various techniques are used throughout the world. Measurements and diagnosis of exocrine pancreatic status based on pancreatic stimulation testing warrants careful interpretation and can be misleading if not performed accurately. The quantitative pancreatic stimulation test that uses perfusion markers with multiple sampling periods is sensitive, highly specific, and capable of evaluating the entire range of pancreatic function (Groman et al., 2004). This technique is regarded as the true gold standard in direct pancreatic stimulation testing. Nevertheless, this test is time consuming, technically complex to perform and not routinely available. Consequently, alternative and simpler direct pancreatic stimulation techniques (non-quantitative), are used at many clinical centers. These generally utilise a single-lumen duodenal tube or endoscope to aspirate duodenal pancreatic secretions, either as a spot sample and/or over a timed sampling period (Choi et al., 2001; Monaghan et al., 2004; Rohlfs et al., 2002; Suaud et al., 2007). Despite their popularity, non-quantitative techniques have a high false positive rate for misdiagnosing PI and have not been proven superior over non-invasive indirect pancreatic function tests. In fact, Schibli et al. (2006) demonstrated that these techniques carry the greatest risk of misclassifying a PS patient as PI, especially among PS patients with a secretory capacity between the threshold of PI and the lower limit of normal (Grody et al., 2001; Schibli et al., 2006).

8.2 Referral to a CF care centre

As mentioned previously, CF and CFTR-related disease may manifest with variable severity, in single or multiple organs, and at different ages. For the clinician at hand dealing with a patient with pancreatitis associated with borderline or abnormal sweat test results and/or *CFTR* mutations, a more detailed assessment of other affected organ systems may be necessary. The phenotypic features of CF which should be kept in mind are summarised in Table 4. Furthermore, other organs affected by CFTR dysfunction may not be clinically evident at the time of diagnosis, thus overall assessment and routine follow-up is crucial. Referral should be made to a multidisciplinary CF care centre that can provide comprehensive diagnostic testing, determination of involvement of all affected organs (e.g. pulmonary disease), timely intervention, disease-specific counseling (e.g. fertility and smoking cessation for pancreatitis and lung disease), genetic counseling, and monitoring. Beyond the well-established phenotypic features of CF, cystic-fibrosis-related diabetes (CFRD) should also be tested for and monitored, particularly among those confirmed as having CF and who progress to PI.

8.3 Prognosis

Data from the Canadian CF registry shows that the median survival age in patients with CF has risen from 29.1 years in 1988 to 46.6 years in 2008 (Canadian Cystic Fibrosis Foundation, 2008). Similar improvements have occurred in other countries, but differences in survival persist (Fogarty, 2000). End-stage lung disease is the primary cause of morbidity and mortality in CF, but discussions on the respiratory aspects of CF are beyond the scope of this chapter. For patients with CFTR-related pancreatitis, the long-term outcomes are unknown.

A recent study reported an association between *CFTR* mutations and a higher risk of pancreatic adenocarcinoma (OR 1.82; 95% CI, 1.14-2.94; P = 0.011) (McWilliams et al., 2010). Carriers of *CFTR* mutations were seen to be diagnosed at a younger age than non-carriers, with the effect exclusively seen in ever-smokers (median 60 years vs. 65 years; P = 0.028).

Phenotypic Features of CF		
Gastrointestinal Abnormalities	*i.*	Pancreatic: PI, recurrent-acute pancreatitis, chronic pancreatitis
	ii.	Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
	iii.	Hepatic: prolonged neonatal jaundice, chronic hepatic disease (focal biliary cirrhosis or multilobular cirrhosis)
	iv.	Nutritional: failure to thrive, hypoproteinemia and oedema, fat-soluble vitamin deficiency syndromes
Male Genital Tract Disease	*i.*	Obstructive azoospermia due to congenital absence of the vas deferens
Chronic Sinopulmonary Disease	*i.*	Persistent colonisation/infection with typical CF pathogens (Staphylococcus aureus, nontypeable Haemophilus influenza, mucoid and nonmucoid Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Burkholderia cepacia)
	ii.	Chronic cough and sputum production
	iii.	Persistent chest radiographic findings (e.g bronchiectasis, atelectasis, infiltrates, and hyperinflation)
	iv.	Airway obstruction, with wheezing and air-trapping
	v.	Nasal polyps
	vi.	Digital clubbing

Table 4. Phenotypic features of CF. (Adapted from Farrell et al., 2008). CF, cystic fibrosis; PI, pancreatic insufficiency.

9. Areas for future research

Greater understanding of the true prevalence of CFTR-related disorders, including CFTR-related pancreatitis is much needed, and long-term studies in these patients are lacking.

Despite CF being a monogenic disease, the development of pancreatitis in CF and CFTR-related disorder is dependent on complex interactions with non-CFTR genetic, environmental and anatomic factors. Future research is needed to investigate the complex interaction between *CFTR*, other known (e.g. *PRSS1* and *SPINK1* mutations) and unknown genetic factors, and their interplay with environmental factors. Future studies are needed to determine the risk and protective modifier factors (genetic and environmental) that lead to the different single organ phenotypes in CFTR-related disorders (i.e. "why do individuals with the same combinations of *CFTR* mutations present heterogeneously?"). This in turn may also lead to additional therapeutic potentials.

One such therapeutic potential in the pipeline are small molecule therapies, known as CFTR correctors and potentiators. These therapies may have a role in not only patients with CF, but also those with CFTR-related pancreatitis; in view of our recent increased understanding of the relationship between CFTR dysfunction and risk of pancreatitis (Ooi et al., 2011a). A recent study of a CFTR mutation-specific potentiator reported improvement in CFTR function (measured using NPD and sweat chloride testing) and lung function in affected CF patients with a G551D mutation (Accurso et al., 2010).

With increased longevity of patients with CF, the relatively infrequent condition of pancreatic adenocarcinoma is anticipated to become more clinically relevant. In view of its

associated high mortality rates, future studies into optimal screening regimens and modalities in patients with genetic causes of chronic pancreatitis are needed.

10. Conclusion

There has been a vast expansion in our understanding of the wide range of phenotypes associated with CFTR dysfunction since the discovery of the *CFTR* gene. Pancreatitis is one such phenotype, which is almost exclusively seen in patients who are PS. In addition, a relationship between the severity of *CFTR* genotypes and the risk of pancreatitis has been established. Paradoxically, genotypes associated with otherwise mild phenotypic effects have the greater risk for causing pancreatitis; compared with genotypes associated with moderate to severe disease phenotypes.

Idiopathic acute, recurrent-acute and chronic pancreatitis may be the initial manifestation of CF and CFTR-related disorder. However, diagnosing CF or CFTR-related disorder can be challenging. Sweat chloride testing is the principal diagnostic test and effectively diagnoses CF patients with the severe PI phenotype but it may have a limited ability to conclusively establish or exclude a diagnosis of CF disease. Careful interpretation of sweat chloride values and repeated testing may be necessary. *CFTR* genotyping for investigation of idiopathic pancreatitis has a limited diagnostic yield, may be misleading and may have uncertain "real life" consequence(s). Referral to a tertiary CF centre for further assessment is recommended, and periodical reassessment may be necessary to detect, monitor and intervene in treatable co-morbidities, even if the diagnostic criteria for CF cannot be fulfilled. Development of symptomatic pancreatitis is a strong risk factor for progressive decline in exocrine pancreatic function in patients with cystic fibrosis and possibly also in CFTR-related pancreatitis; thus, it is important to monitor for the development of exocrine pancreatic insufficiency over time.

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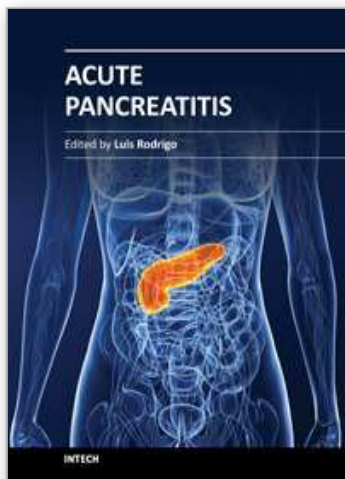
Acute Pancreatitis

Edited by Prof. Luis Rodrigo

Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

How to reference

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