Morbidity and mortality data of cystic fibrosis patients

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ABSTRACT

Objective: To identify factors that contributed to morbidity and mortality of cystic fibrosis (CF) population in the Kingdom of Saudi Arabia (KSA).

Method: This retrospective chart review was carried out in King Faisal Specialist Hospital and Research Centre, Riyadh, KSA, during a 9 year period, November 1993 to November 2002, on confirmed CF patients, for demographic, clinical and mortality data.

Results: A total of 190 CF patients were diagnosed during the 9 years. One hundred and sixty-four (86%) patients are alive, 26 (14%) died. Ninety-nine (52%) were males and 91 (48%) were females. Age at diagnosis 2.8 ± 3.5 years, and period of follow up 3 ± 3 years. In 80% of patients, symptoms started <1 year of age. Sixty-five percent of patients were in the mild to moderate malnutrition stage (<90th percentile), and 63% are in the mild to moderate stunted growth (<90th percentile). Factors that contributed to early mortality are: calculated weight/height (p-value 0.01), low albumin level at follow up (0.001), high hematocrit (HCT) (p-values=0.0002), low mean corpuscular volume (MCV) (p-0.0002), low mean corpuscular hemoglobin concentration (MCHC) (p-value 0.001), early development of antibiotic resistance (p-value=< 0.01).

Conclusion: High HCT, low MCV, low MCHC and low albumin are factors related to poor prognosis and early death in CF patients. Iron supplement should be given to these patients even in the presence of normal hemoglobin. Early nutritional rehabilitation is needed to improve survival of our CF patients. Cohort isolation should be encouraged in CF centres. Early treatment of chronic pseudo colonization should be adopted to improve survival.

Saudi Med J 2003; Vol. 24 (7): 730-735

The incidence of cystic fibrosis (CF) in the Kingdom of Saudi Arabia, (KSA) was reported to be 1 in 4243 children.[1] Epidemiological and genetic data have been described in detail in many Gulf countries,[2-5] but no morbidity or mortality data has been described before in the Arabian countries. In this report, we present the different factors that contributed to morbidity and mortality of the largest CF population in the Gulf area.

Methods. The charts of all CF patients referred to the CF clinic during a 9 year period from November 1993 through to November 2002 were reviewed in King Faisal Specialist Hospital and Research Centre in Riyadh, KSA which, is considered the main tertiary care center for referral of such patients in KSA and the only center for detection of cystic fibrosis transmembrane regulator gene mutations (CFTR) in the country. Cystic fibrosis was diagnosed on typical clinical picture and high sweat chloride test in 2 consecutive tests >60 mmol/L by the guantitative method (Wescor, United States of America).

Definitions. Calculated weight (CWT):[6] Express actual weight as a percentage of ideal body weight (IBW)=Actual weight (Wt) x100/IBW for height. Calculated height (CHT):[6] Actual height x100/50th percentile height for age. Nutritional failure: Wt for height index below 85% of ideal weight/standard height, loss of weight for >2 month and or plateau in Wt gain

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Received 8th February 2003. Accepted for publication in final form 27th April 2003.

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for 2-3 month.[6] Z score: It is the standard deviation of Wt and or height (Ht) from the mean of a reference population,[7] for example if a patient weight for height is at 97th percentile, the Z score will be (+1.9), but if another patient parameter at 17th percentile, his Z score will be (–1.0).

The data were analyzed on IBM, PL300 computer using JMP program version 3.2 from statistical analysis software institute. All variables with normal distribution, mean, standard deviation (SD) and median were calculated using student t-test, other wise a non-parametric test is used Wilcoxon test. For categorical variables, Chi-square of first exact test was used. Uni-variant analysis was performed in all variables. Results were presented at a level of significance of p=<0.05. All values were expressed in mean ± SD. Epi Info version 6 (Center for Disease Control, Bethesda, Maryland, United States of America, 1994) was used to calculate Z-score, namely, Wt for Ht Z-score, Ht for age Z-score, Wt for Ht percentile and Ht for age percentile. The mean and standard deviation was calculated for all scores. Initial 77 patients were studied, but only individuals (30 patients) with data at all time points were presented.

Patient management. All confirmed CF patients had their Wt and Ht measured during their first visit and each follow up visits thereafter, which are usually every 2-4 months. Respiratory culture, which includes sputum in children who were able to give such a sample or nasopharyngeal aspirate in smaller children, is taken routinely on initial diagnosis and every clinic visits there after. All patients who have respiratory symptoms that include: tachypnea, increase in sputum production and wheezing will be started on prophylactic broad-spectrum antibiotic for the first 1-2 years as recommended by other studies.[8-10] These antibiotics include either one of the following: Amoxil, first generation Cephalosporin and Bacterim.[8-10] Anti-microbial prophylaxis are then reevaluated according to persistence of bacteria, and given only during acute attacks. Patients who do not respond to oral antibiotics during acute attacks and inhaled amino glycosides[8,11,12] are admitted for intravenous antibiotics third generation Cephalosporin and amino glycoside according to culture results.[8,11,12] All patient with signs and symptoms of pancreatic insufficiency as diarrhea or positive fat in the stool are started on pancreatic enzymes according to CF foundation recommendation[6] and fat-soluble vitamins (A, D, E and K).

Results. A total of 190 CF patients were diagnosed on typical clinical picture and sweat chloride test >60 mmol/L during a 9 year period. One hundred and sixty-four (86%) patients are alive, 26 (14%) died. Ninety-nine (52%) were males and 91 (48%) were females. Age at diagnosis 2.8 ± 3.5 years, and period of follow up 3 ± 3 years. Eighty-eight percent of the families were of consaquinous marriage (Consanguinity is 50% in the general population).[3] More than 90% of patients presented with cough, wheezing, failure to thrive, diarrhea and repeated chest infection. There was a delay of 27 months from the age when symptoms started to time of referral to our centre. Median survival of 11 years. Most of the patients are referred in an advanced stage.[3] The most common cystic fibrosis transmembrane regulator gene mutations (CFTR) that constituted 75% of our CF population were: 1548delG, I1234V, 3120G to A, H139L, and DF-508.[2] Mean Wt at diagnosis 9.5 ± 7 kilogram (kg), a range of 2.4-36 kg. Calculated Wt/Ht 82 ± 19%, a range of 40 ± 162%. Sixty-five percent of patients were in the mild to moderate malnutrition stage (<90th percentile) (Table 1), and 35% in the normal level for Wt/Ht. Calculated Ht/age a mean of 91 ± 12 centimeter (cm), 63% are in the mild to moderate stunted growth **(Table 1)**. Weight/Ht Z score has shown improvement in the first 6 month from (-1.7 ± 0.16) to (-0.77 ± 2) (p-value= 0.0001), but developed a pleatu level thereafter at 12,18 and 24 months (p-value >0.05) **(Table 2) (Figure 1)**. Height/age Z score has shown no significant improvement in the first 12 months, but better response at 18 and 24 month. Vitamin D (1,25 di-hydroxy cholecalciferol levels a mean of 48 ± 27 (N=52-312 nmol/L). Albumin levels a mean of 40 ± 0.5 (N= 35-50g/L). Initial hemoglobin level was 116 ±15 (normal 132-17 g/L), hematocrit (HCT) 0.244 ± 123 (N=0.38-0.52 ratio), mean corpuscular volume (MCV) 192 ± 13 (N=80-94 fl), mean corpuscular hemoglobin concentration (MCHC) 333 ± 9 (N=290-370 g/L), mean corpuscular hemoglobin (MCH) 26 ± 3 (N=27-32 pg), platelets (Plat) 412 ± 137 (10 ^ 9/L), Reticulocyte count (Retic) 79 ± 30 (N 25-85 10 ^ 9/L), Iron level 11 ± 6 (N 6-24 umol/L), total iron binding capacity 64 ± 20 (N 19.7-60.2 umol/L), Transferrin 0.143 ± 0.09 (N=2.1-3.0 g/L), Vitamin E (Alpha Tocopherol)19 ± 12 (N=14-44 umol/L), total protein level 67 ± 12 (N=65-81g/L) and albumin 40 ± 0.5 (N=35-50 g/L). The most common bacteria that were grown from the first culture samples in 190 patients were: *Pseudomonas aeruginosa* in 83 (44%) of patients, *Hemophilus influenza* in 32 (17%), *Staphylococcus aureus (S. aureus)* in 29 (15%), *Streptococcus pneumonia* in 11 (6%), Methicillin resistant *staph aureus* (*MRSA*) in 4 (2%), *Branhamella Cattarrhales* in 11 (6%), and respiratory syncytial viruses (RSV) in 2 (1%) **(Table 3)**. Follow up culture within 1-6 months of treatment in 160 patients that were able to do the study showed doubling the number of Branhamella culture to 21 (13%), and increase in the number of *MRSA* cultures to 6 (4%) from the same patient population which may point to cross contaminations between patients that were seen in the same clinic **Table 3**. Development of resistant Pseud. aeruginosa to Gentamycin had the shortest duration of 2 ± 3 years after diagnosis, Amikacin (Amika) in 3.4 ± 0.1 years, Ceftazidime 3 ± 0.1 years, Ciprofloxacin in 3.4 ± 2 years, Piperacillin 4 ± 2 years **(Figure 2)**, Imipenum 4 ± 2 years and development of resistance of *MRSA* to

Table 1 - Cystic fibrosis growth parameters in Saudi population.

Variable	n	(%)	Percentile	Status
CWT	65	(34)	<75%	Severe malnutrition
	13	(7)	75-79%	Moderate malnutrition
	21	(11)	80-84%	Mid malnutrition
	21	(11)	85-89%	Under weight
	59	(31)	90-110%	Normal weight
	8	(4)	>110%	
CHT	38	(20)	<85%	Severe stunted
	15	(8)	85-89%	Moderately stunted
	48	(25)	90-94%	Mildly stunted
	68	(37)	95-100%	Normal

CWT - calculated weight for age
CHT - calculated height for age

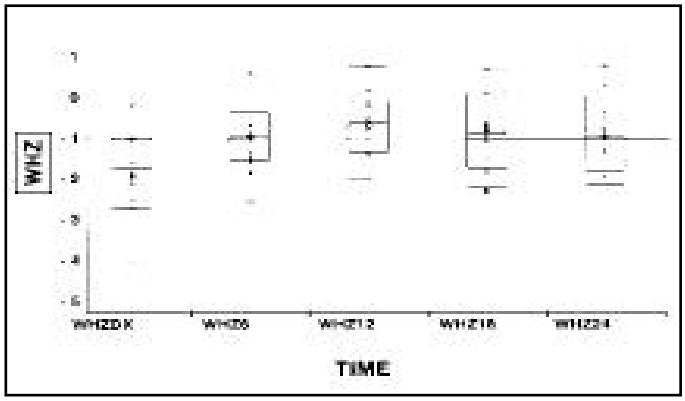

Figure 1 - WHZDX - weight for height Z-score at diagnosis, WHZ6 - weight for height Z-score at 6 months follow up, WHZ12 - weight for height Z-score at 12 months follow up, WHZ18 - weight for height Z-score at 18 months follow up, WHZ24 - weight for height Z-score at 24 months follow up. Zero line=determine the mean weight Z-score of the standard population, -1 line=determine the mean weight Z-score of the study population.

Table 2 - Weight for height Z-score during 2 years follow up.

Period	Mean score	n	p-value
WHZ at diagnosis	-1.7 ± 0.16	74	
WHZ at 6 months	-0.77 ± 2	74	0.0001
WHZ 12 months	-0.86 ± 1.01	58	
Z score 12 and 6 months			0.918
WHZ 18 months	-0.89 ± 1.01	48	
Z score 18 and 12 months			0.588
WHZ 24 months	-0.93 ± 1.01	46	
Z score 24 and 18 months			0.703

WHZ - weight for height Z score

Table 3 - Culture results of cystic fibrosis patients. (N=190)

Organism	(a) First culture (190) n	(%)	(b) Follow up (160) n	(%)
Staphylococcus aureus	29	(15)	26	(16)
Hemophilus influenzae	32	(17)	20	(13)
Pseudomonas aeruginosa	83	(44)	11	(7)
Streptococcus pneumonia	11	(6)	26	(16)
Methicillin resistant	4	(2)	6	(4)
Branhamella catarrhales	11	(6)	21	(13)
Gram negative rods	6	(3)	8	(5)
Gram positive cocci	6	(3)	3	(2)
Virus	2	(1)	3	(2)
Other	2	(1)	19	(12)

a=first culture after diagnosis
b=follow up culture, which is taken 1-6 month after diagnosis

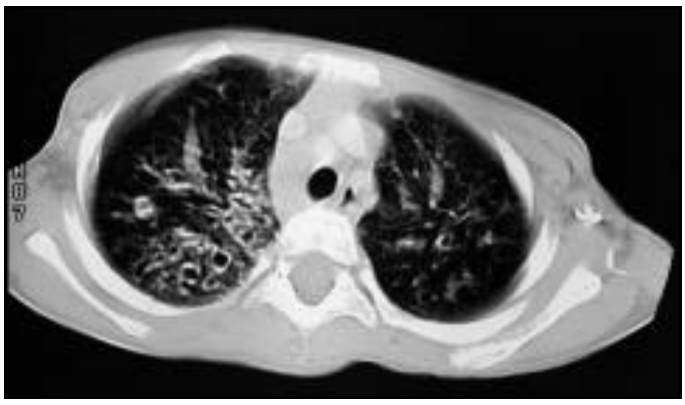

Figure 2 - Computerized tomography scan of the chest of a cystic fibrosis patient and methicillin resistant staphylococcal aureus colonization, hilar lymphadenopathy and the paracarinal region. Bronchiectatic changes within the middle lobe, the left upper lobe and the left lower lobe. Peribronchial wall thickening and consolidation in these areas.

Table 4 - Nutritional factors and their relation to mortality. (N=190)

Variables	Alive	Died	p-value
Sex			
Females	78	13	0.9
Males	86	13	
Age at diagnosis	2.88 ± 3.5	3.2 ± 3.5	0.7
Period of follow up in years	3 ± 3	4 ± 3	0.1
Age at follow up	6 ± 4	8 ± 6	0.2
Calculated weight for height	84 ± 18	71 ± 17	0.01
Calculated height for age	92 ± 12	91 ± 10	0.8
Vitamin E, Alpha tocopherol at diagnosis	19 ± 12	19 ± 18	0.9
Vitamin E, Alpha tocopherol at follow up	23 ± 2	16 ± 7	0.34
Protein	65 ± 11	70 ± 11	0.1
Albumin at diagnosis	37 ± 7	35 ± 5	0.3
Albumin at follow up	40 ± 0.5	35 ± 1	0.001
Date of first culture (+)	0.7 ± 2	1.5 ± 3	0.1
Date of first pseudomonas (+)	1.2 ± 2	1.9 ± 3	0.4
Date of first mucoid pseudomonas (+)	1.8 ± 3	2.8 ± 2	0.3
Date of R-Gentamycin (+)	1.1 ± 0.7	3.4 ± 2	0.04
N of Pseud resistance to Ampicillin**	29	15	0.07
N of positive pseudomonas**	47	14	0.01
N of positive mucoid pseudomonas**	30	8	0.06
N of positive *MRSA***	3	3	0.02
N of resistance to Gentamycin**	25	15	<0.0001
N of resistance to Amikacin**	6	12	0.0002
N of resistance to Ceftazidime**	6	10	<0.0001
N of resistance to Ciprofloxacin**	2	8	<0.0001
N of resistance to Piperacillin**	8	8	0.0005
N of resistance to Imipenum**	2	3	0.01
Hemoglobin	115 ± 18	121 ± 17	0.2
Hematocrit*	0.224 ± 0.12	0.350 ± 0.07	0.0002
Mean corpuscular volume*	214 ± 138	76 ± 7	0.0002
Mean corpuscular hemoglobin concentration*	334 ± 8	328 ± 9	0.01
Mean corpuscular hemoglobin*	26 ± 3	25 ± 3	0.11
Platelets*	402 ± 126	463 ± 182	0.1
Reticulocyte count*	82 ± 31	68 ± 32	0.5
Iron*	12 ± 5	6 ± 4	0.12
Total iron binding capacity*	64 ± 22	63 ± 9	0.9
Transferrin*	0.16 ± 0.1	0.10 ± 0.04	0.3

(+)=All dates in years - date of first positive culture from the diagnosis
(**)=Number of patients, abbreviations are the same as in the text
(*)=All blood indices abbreviations as in the text

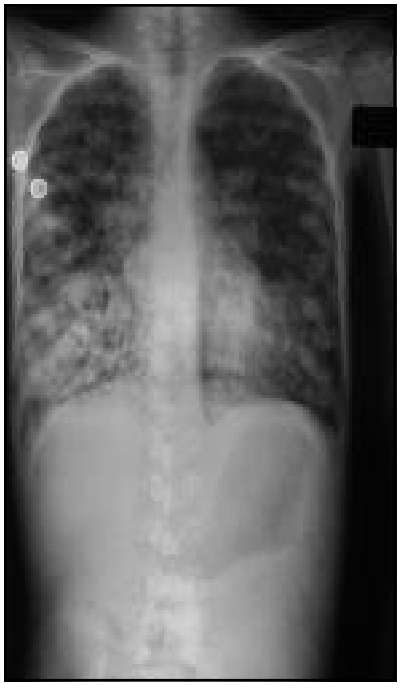

Figure 3 - Chest x-ray antero-posterior and lateral of a cystic fibrosis patient and pseudomonas colonization of the respiratory system that is resistant to Ciprofloxacin, showing multiple pulmonary infiltrates at both lungs with thickening and dilation of the multiple bronchi and dilated cystic areas with air fluid level and bilateral hilar lymphadenopathy. Hepatomegaly with normal bowel gas pattern are also apparent on the film.

antibiotics except Vancomycin was 2 ± 3 years. Factors that were significantly related to progressive lung disease and early mortality of CF patients were the following **(Table 4)**: calculated Wt/Ht (p-value=0.01) and albumin level at follow up (p-value=0.001), high HCT (p-values=0.0002), low MCHC (p-values=0.01), low MCV (p-value=0.0002), date of development of *P. aeruginosa* resistance to Gentamycin (p-value=0.04), date of resistance to Ampicillin (p=0.07), positive culture of *P.aeruginosa* (p-value=0.01), +ve *MRSA* (p-value=0.02) **(Figure 2)**, Development of resistance to the following antibiotics: Gentamycin (p-value=<0.0001), Amikacin (P= 0.0002), Ceftazidime (p-value=<0.0001), Ciprofloxacin (p-value=<0.0001) **(Figure 3)**, Pipera (p= 0.0005) and Imipenum (p-value=0.01) **(Table 4)**.

Discussion. Many studies have shown that development of specialized CF centres and development of guidelines in the treatment of such patients have shown marked improvement in median survival and decrease the mortality.[13] Early nutritional intervention has improved survival.[14-16] Other studies have shown that early nutritional rehabilitation has improved lung function and improvement to participate in the activity of daily living.[14-16]

Our study has shown that early mortality from CF is multifactorial, but mainly includes factors that are related to early diagnosis and proper management with emphasis on early nutritional rehabilitation. It also showed that early development of multi-resistant Pseud. aeruginosa to different antibiotics has significant relation to mortality. One hypothesis that explains the development of multi resistant bacteria is the use of long-term continuous Gentamycin nebulization treatment to prevent frequent hospitalization due to bed limitation. Intermittent Gentamycin nebulization treatment instead of continuous regimen may need to be adopted.[11] *Methicillin resistant staphylococcus aureus* colonization has been reported before in CF patients,[17] but its contribution to mortality was not discussed before in CF patients. Our study has shown significant relationship to mortality (p=0.02) **(Table 4)**. Reduction of Pseud. aeruginosa cultures in follow up samples may not mean eradication of such bacteria, but factors such as poor sampling techniques may have some contribution.

In our study, the initial presentation of most of our patients have shown normal hemoglobin with hypodermic normocytic picture. But, further follow up of these patients have shown poor prognosis of those patients who develop high hematocrit, low MCV, low MCHC and low albumin **(Table 4)** in the presence of normal hemoglobin due to increase in erythroprotein activity which gives a false high hemoglobin level in the presence of anemia due to chronic infection and malnutrition. To our knowledge, this is the first study that shows the relationship of hematological indices to mortality.[17-19] Other factors that may have contributed to mortality but not mentioned in our study are: The role of advanced lung disease, the different types of CFTR mutations, and poor compliance to treatment and adherence to chest physiotherapy. Further studies need to be carried out to evaluate such factors to mortality.

Acknowledgment. The author would like to thank all Physicians and Medical staff that shared in the care of CF patients including Dr. Mogarri, Pediatric Pulmonologist, Dr. Al-Mehaidib, Pediatric Gastroenterology, Ms. Lena Al-Ohaly, Nutrition Department, and Mr. Hasan Al-Orainy, Respiratory Therapy Department). Special extended thanks to both Dr. William Greer and Dr. Jamal from the BioStatistics Department.

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Related Abstract
Source: Saudi MedBase

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Title: Cystic Fibrosis in Saudi Arabia

Source: Saudi Med J 1986; 2: 189-191

Abstract

Cystic fibrosis in a 7-month-old female saudi child is reported. The main symptoms were failure to thrive, recurrent respiratory tract infections, diarrhea and rectal prolapse. The diagnosis was confirmed by performing a repeated sweat test using 3 different methods of sweat collection. A noniontophoresis method for collection of sweat is described. The problems of diagnosis and management of these cases in developing countries are highlighted.