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Re-Rise of Infective Endocarditis in Pediatrics? A Single Center Epidemiologic Study

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ABSTRACT

Background: Infective endocarditis (IE) is a rare disease yet with numerous health hazards. Currently no data is available about IE in Egyptian children. This work aimed to study the epidemiological pattern, mode of presentation, microbiology, and the outcome of IE at Cairo University Children's Hospitals.

Patients and methods: A cross-sectional study was conducted over a period of 6 months and included 100 patients diagnosed with IE. All patients were subjected to 1) Full medical history and examination to study their demographic date, detect risk factors, pattern of presentations, and type of treatment. 2) Laboratory investigations including blood cultures. 3) Complete echocardiography, and 4) Close follow up of the patients to determine the outcomes and fate of IE. **Results**: The age of included patients ranged from 1-168 months, with a mean 59.37 (SD 41.91). They were 63 (63%) males and 37 (37%) females. Most of patients (68%) were from rural areas, and 32% were from urban areas. Most important risk factors are type of congenital heart disease (CHD) (75%), central venous pressure (CVP) insertion (29%), and dental problems (24%). Vegetations were found in 77% of our patients, significantly in the neonatal intensive care units (NICU) (p=0.02). IE was caused mainly by gram positive organisms (85%).

Conclusion CHD, CVP, dental problems were the most frequent risk factors of IE in our patients. CHD was associated with significantly prolonged hospital stay and delayed response to treatment. Early and prompt management of CHD is highly recommended to reduce impact of IE in pediatric patients.

Keywords: Infective endocarditis; Epidemiology, Children, Congenital heart disease, Cairo University.

Abbreviations CHD: congenital heart disease; CVP: central venous pressure; NICU: neonatal intensive care units; IE: Infective endocarditis; VSD: ventricular septal defect; ASD atrial septal defect; DORV double outlet right ventricle; TGA: transposition of great arteries.

INTRODUCTION

Infective endocarditis (IE) is a fatal disease associated with high morbidity and mortality despite the achievements in its diagnosis and treatment [(1)]**.** Several factors including lack of randomized trials, rare nature of the disease, and the inadequate number of meta-analyses increase the need to multiple local studies in each country to outline its own characteristics and recommendations of the disease [(2)]**.** In the current work we aimed to assess the epidemiological pattern, risk factors, and outcome of IE in one of the largest tertiary centers for children in Egypt. To our knowledge, there is no similar study done before on Egyptian children.

PATIENTS AND METHODS

This is a cross-sectional study conducted over a period of 6 months at Cairo University Children's Hospital. The study enrolled 100 children admitted and diagnosed with IE according to modified Duke's criteria [(3)]**.** For all cases full medical history was taken with special emphasis on: Demographic data (age, sex, residence, and gender), fever history whether before or after admission, risk factors of IE (previous hospital admission with central venous line insertion, cardiac disease and its type, immunodeficiency, or any other chronic debilitating disease). Each patient was subjected to full clinical examination including vital signs, anthropometric measurements, and full cardiac examination. Blood cultures were done at admission and after 5 weeks of initiating treatment, including special culture medium used in cases of suspected fungal IE. Echo-Doppler examination by experienced pediatric cardiologists was performed for all cases according to the recommendations of American Society of Echocardiography [(4)] using GE Vivid 5 or 7 systems with probe 3 or 5MHz according to the age of the patient. The following criteria were considered for the diagnosis of endocarditis: (1) Presence of vegetations (**Figures 1& 2**), defined as mobile echo dense masses implanted in a valve or mural endocardium in the trajectory of a regurgitant jet or implanted in prosthetic material with no alternative anatomical explanation. (2) Presence of abscesses; or (3) Presence of new dehiscence of a valvar prosthesis. Abnormal echocardiographic findings not fulfilling those definitions were considered minor criteria. Since the definite diagnosis of endocarditis requires the presence of two major criteria, or one major and three minor criteria, echocardiography has assumed a crucial role in the diagnosis of the disease, particularly when blood cultures are negative.

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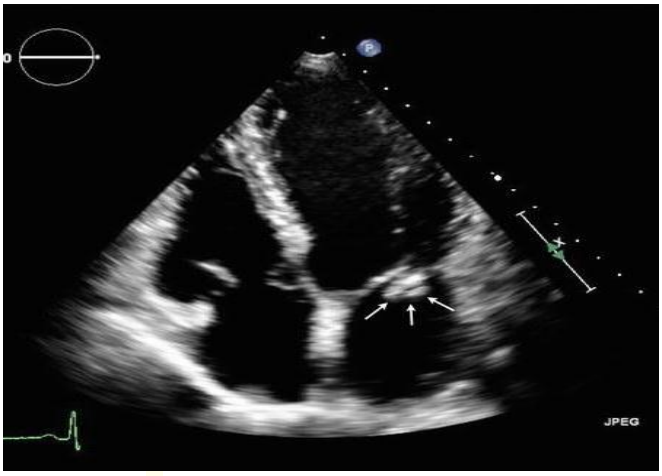

Figure (1): TTE mitral valve with large vegetation (arrows).

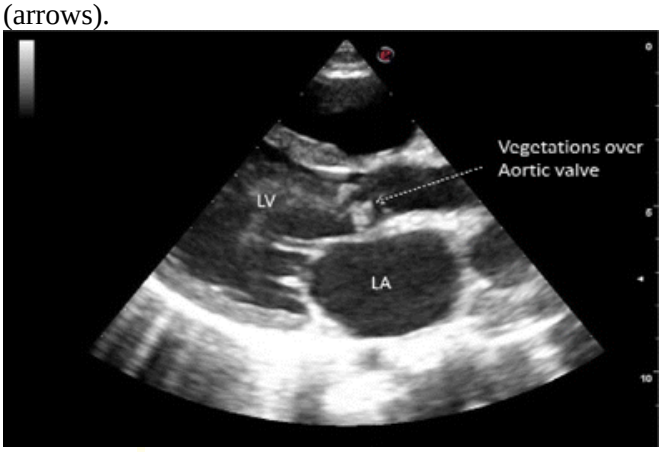

Figure (2): TTE showing aortic valve vegetations.

The following regimen was applied for treatment of all patients: After admission, the 1st line for IE treatment was IV double antibiotics for 2 weeks, in case of partial improvement, antibiotics continued for another 4-6 weeks until the case totally improved. If no response, or negative culture, empirical therapy was indicated. In case of prolonged hospital stay (>2 weeks) or suspected fungal infection, antifungal treatment was indicated. If the case deteriorated or complicated, surgery was indicated. In the current study, we considered: Partially improved means improved clinical signs and laboratory tests, but vegetation is still detected by echocardiography. Totally improved means no clinical signs of IE and normal laboratory tests and echocardiography findings. Deteriorated means deteriorated clinical signs and laboratory tests or developed complications e.g., embolism, heart failure. Patients were assessed at admission, then after 2 weeks and 4 weeks to detect patients' outcomes including mortality, need for surgery, extra-cardiac complications.

Ethics considerations: The study was approved by the Scientific Research and Ethical Committee, Faculty of Medicine, Cairo University. Guardians of every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Data management and statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The data were presented as numbers and percentages for the qualitative data, mean, standard deviations, and ranges for the quantitative data with parametric distribution and median with interquartile range (IQR) for the quantitative data with non-parametric distribution.

Chi-square test and Fisher's exact test were used in the comparison between two groups with qualitative data. Independent t-test and Mann-Whitney U test were used in the comparison between two groups with quantitative data. The comparison between more than two groups with quantitative data awas done by using One Way Analysis of Variance (ANOVA) test and Kruskall-Wallis test. Spearman correlation coefficients were used to assess the significant relation between two quantitative and non-parametric distributions in the same group, where the p-value was considered significant as the following: $p > 0.05$: Non-significant (NS), $p \leq 0.05$: Significant (S), $p \leq 0.01$: Highly significant (HS).

RESULTS

The age of our patients ranged from 1 to 168 months, with a mean 59.37 (SD 41.91) months. They were 63 (63%) males and 37 (37%) females. Most of patients (68%) were from rural areas, and 32% were from urban areas. Regarding weight percentile, 95 (95%) patients were between the 5th-95th percentile and 4 (4%) patients were below the 5th percentile, and one patient was above 95th percentile. Regarding height percentile, 99 (99%) patients were between the 5th-95th percentile, and one patient (1%) was below the 5th percentile.

Table (1): Distribution of all studied cases according to clinical presentation*.

Clinical presentation	No. (n=100)	(%)
General		
Fever	90	90%
Hematuria	2	2%
Dehydration	3	3%
Arthralgia	8	8%
Vomiting	16	16%
Wheezy chest and cough	1	1%
CNS		
Convulsion	7	7%
Stroke	3	3%
Coma	2	2%
Liver/spleen		
Splenomegaly	6	6%
Hepatomegaly	3	3%
Skin		
Skin rash	5	5%
Skin petechiae	2	2%

*: More than one symptom may be present in one patient.

The fever duration ranged from 2 to 90 days with a median of 7 days. The fever degree ranged from 37.5 to 40 with a mean of 39.02 (SD 0.73). The fever was continuous in 63 (63%) patients and intermittent in 37 (37%) patients. Ninety (90%) patients were feverish before hospital admission and 10 (10%) patients after hospital admission.

Table (2): Possible risk factors of IE in our patients

Possible risk factors		**No (%)**
Congenital heart diseases		75 (75%)
CVP insertion		29 (29%)
Dental problems	Poor oral hygiene	9 (9%)
	Dental caries	7 (7%)
	Dental procedures	8 (8%)
Recurrent Chest Infection		26 (26%)
CRF		8 (8%)
Cardiac surgery		5 (5%)
Recurrent Hospital Admission		3 (3%)
Abdominal surgery		2 (2%)
Surgical intervention		1 (1%)
Trauma		1 (1%)

As shown in **Table 2**, the most important risk factors for infective endocarditis in our patients were CHD (75%), and CVP insertion (29%). The most common congenital acyanotic heart diseases associated with infective endocarditis in our patients were ventricular septal defect (VSD), followed by atrial septal defect (ASD) 48%, 13.3% respectively, while the most common in congenital cyanotic heart diseases were double outlet right ventricle (DORV) (5.3%) followed by transposition of great arteries (TGA) (2.6%).

Blood cultures were done on admission and 5 weeks after the start of treatment. The number of cultures ranged from (3 - 6) cultures with a mean of 3.1 (SD 0.46). We identified gram-positive organisms in 85 (85%) patients, gram-negative organisms in 5 (5%) patients, fungal infections in 5 (5%) patients mixed organisms in 3 (3%) patients, while 2 patients (2%) showed no growth.

Echocardiography of our patients showed vegetations in 77 (77%) patients, the size of the vegetations ranged from 1 to 66 mm, with a mean of 19.99 (SD 18.38), the vegetations were detected on VSD in 28 (28%) patients, tricuspid valve (TV) in 14 patients (14%), right atrium (RA) in 7 (7%) patients, and ASD in 6 (6%) patients. Concerning the treatment of our patients, the most common given antibiotic was vancomycin (53%) in combination with other antibiotics to follow the double antibiotics regimen.

A total of 30 (30%) patients received antifungal treatment; fluconazole was the most used in 27 (90%) patients. The duration of hospital stay of our patients ranged from 14 to 98 days with a median of 42 days. Only 10 (10%) patients needed surgical interventions. The outcome of our patients was detailed in **Figure 3.**

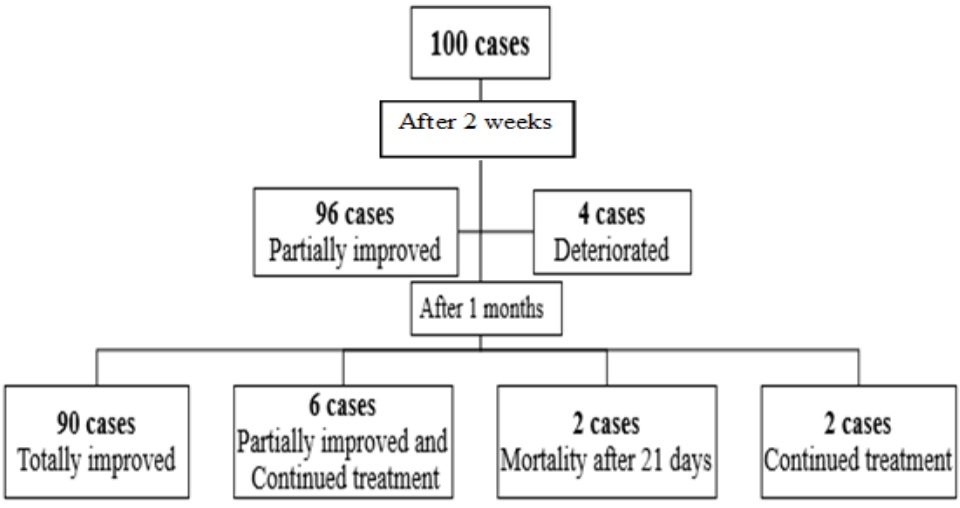

Figure (3). Flow chart of fate and outcome of our patients.

Table (3): Relation between risk factors and residence in all studied cases

Risk Factors:	Variable	Rural (n=68)	Urban (n=32)	Test of significance
Congenital heart disease:	No	13 (19.1%)	12 (37.5%)	**Fisher's test**
	Yes	55 (80.9%)	20 (62.5%)	0.08
Dental problems:	Poor oral hygiene	6 (8.8%)	3 (9.4%)	0.96
	Dental caries	5 (7.4%)	2 (6.25%)	
	Dental procedures	6 (8.8%)	2 (6.25%)	
Other Risk Factors:	Abdominal surgery	0 (0.0%)	2 (6.2%)	**Fisher's test**
	Cardiac surgery	4 (6.0%)	1 (3.1%)	0.56
	Chronic renal failure	5 (7.5%)	3 (9.4%)	
	CVP insertion	20 (29.9%)	9 (28.1%)	
	Rec. Chest Inf.	19 (27.9%)	7 (21.9%)	
	Rec. Hospital Admission	1 (1.5%)	2 (6.2%)	
	Surgical intervention	1 (1.5%)	0 (0.0%)	
	Trauma	1 (1.5%)	0 (0.0%)	
	No Risk factors	17 (25.4%)	8 (25.0%)	

As shown in **Table 3,** the residence of the patients whether in rural or urban areas didn't affect the risk factors for IE.

Table (4): Association between risk factors and presence of vegetation.

Risk factors	Course of treatment	Test of significance	P-value
Congenital heart disease	Vegetations	X^2= 2.75	0.1
	Size	W= 791	0.31
CVP insertion	Vegetations	X^2= 2.76	0.09
	Size	W= 823.5	0.11
NICU admission	Vegetations	F= 14.03	0.02*
	Size	K= 4.16	0.53

K: Kruskal Wallis test, W: Mann Whitney test, F: fisher test, $X^{2:}$ chi square test.

There was a statistically significant association between NICU admission, and the presence of vegetation (p=0.02) as detected in **Table 4**. Linking the presence of vegetations with the type of the organism, we found significant relation with gram positive organisms (p=0.05).

Table (5): Relation between risk factors and type and course of treatment.

Risk factors	Course of treatment	Test of significance	P-value
Congenital heart disease	Anti-biotics	F= 14.78	0.63
	Antifungal	F= 4.29	0.71
	Surgery needed	F= 2.2	0.14
	Duration of stay	W= 674	**0.03***
	Response after 2 weeks	F= 0.30	0.57
	Response after one month	F= 16.44	**0.02***
CVP insertion	Anti-biotics	F= 23.56	0.12
	Antifungal	F= 8.91	0.07
	Surgery needed	F= 0.19	0.47
	Duration of stay	W= 1193	0.16
	Response after 2 weeks	F= 0.15	0.58
	Response after one month	F= 7.83	0.73
NICU admission	Anti-biotics	X^2= 44.49	1
	Antifungal	F= 28.37	**0.04***
	Surgery needed	F= 1.22	0.80
	Duration of stay	K= 6.07	0.1
	Response after 2 weeks	F= 0.95	1
	Response after one month	X^2= 66.02	0.93

K: Kruskal Wallis test, W: Mann Whitney test, F: Fisher test, $X^{2:}$ chi square test.

As shown in **Table 5**, CHD as a risk factor of IE is associated with prolonged hospital stay and delayed response to treatment (after 1 month) (p values 0.03 and 0.02, respectively). Admission in NICU is significantly associated with increased use of antifungal treatment (p=0.04).

Table (6): Relation between demographic data and course of treatment.

Demographic data	Course of treatment	Test of significance	P-value
Age	Anti-biotics	K= 22.63	0.2
	Antifungal	K= 9.65	0.09
	Surgery needed	W= 444	0.95
	Duration of stay	r= 0.15	0.14
	Response after 2 weeks	W= 69	0.03*
	Response after one month	K= 13.1	0.07
Weight	Anti-biotics	K= 20.94	0.28
	Antifungal	K= 9.3	0.1
	Surgery needed	W= 438	0.89
	Duration of stay	r= 0.14	0.17
	Response after 2 weeks	W= 80.5	0.05*
	Response after one month	K= 13.3	0.06
Gender	Anti-biotics	F= 19.64	0.23
	Antifungal	F= 3.49	0.88
	Surgery needed	F= 0.31	0.49
	Duration of stay	W= 972	0.12
	Response after 2 weeks	F= <0.0001	1
	Response after one month	F= 6.19	0.55

K: Kruskal Wallis test, W: Mann Whitney test, r: spearman correlation, F: Fisher's test.

As demonstrated in **Table 6**, there was statistically significant relation between age, weight, and the response to treatment after 2 weeks (p values 0.03 and 0.05, respectively).

Univariate and multivariate logistic regression analysis were performed to determine predictors of mortality of IE in our patients but revealed no statistically significant predictors of mortality.

DISCUSSION

The occurrence of IE in children is perhaps increasing partly due to the increased incidence of IE inpatients with congenitally malformed hearts who are now surviving longer and partly due to increased use of central venous catheters in intensive care units [(5)]**.**

The incidence of neonatal IE is also increasing with high death rate in this vulnerable group due to increased use of indwelling intravenous lines and implantable devices, together with the fruition of neonatal intensive care [(6)]**.** Currently, there is no published data from Egypt regarding IE in children. The aim of the current study was to estimate the epidemiological pattern, mode of presentation, and the outcome of infective endocarditis at Cairo University Children's Hospitals. This study was carried out on 100 children admitted to Cairo University Children's hospital and diagnosed with IE. The age of studied cases ranged from (1 to 168) months, with a mean 59.37 (SD 41.91) months. The number of patients from rural areas outnumbered the patients from urban areas (68% and 32%, respectively) probably due to unavailability of adequate number of tertiary care centers in rural areas. The number of males with IE was higher than females (63% vs 37%, respectively). The same sex difference was found by other studies [(7,8)]; however, it was different from **Mahony *et al.*** study in which the males were less than females (47.1% and 52.9%, respectively**)** [(9)]**.** In comparison to a Tunisian multicentric registry, **Jomaa *et al.*** [(10)] reported among a total of 73 patients higher mean age of 12 (SD 4.8) years, besides, males and females were nearly equally affected [(11)]. In our study most of the children were between the 3rd-97th percentile of weight and height (95% and 97%, respectively) excluding failure to thrive and malnutrition as predisposing or presenting symptoms of IE in our patients as stated by other study.

In the current study, we found that the most common clinical presentations were fever in 90 (90%) patients, followed by vomiting in 16 (16%) patients, and arthralgia in 8 (8%) patients. In accordance with our results, other studies reported that the most frequent signs and symptoms of IE in CHD are fever (>80%), often of low grade, malaise, myalgia, arthralgia, and vomiting [(10,11)]**.**

Maintenance of good oral hygiene, prevention of gingival and dental disease, and access to routine dental

care for children at risk for IE are important factors to prevent relatively frequent, low-grade bacteremia predisposing to IE [6]. Accordingly, we studied the dental problems among the studied cases. Dental problems were present in 24 (24%) patients, including poor oral hygiene in 9 (9%) patients, dental procedures in 8 (8%\) patients, and dental caries in 7 (7%) patients. Consistent to **Jomaa *et al.*** [10] who found dental problems in 26% of their patients, yet inconsistent to previous studies which reported no impact from oral hygiene or disease on bacteremia as a risk of IE after dental procedures [12,13].

The most prevalent predisposing factor for IE in our patients was CHD (75%) which was agreed by other studies in high income countries, they reported 87% and 49% of their patients respectively had CHD [9]. We didn't record cases of RHD in our patients due to the effective prophylaxis against bacterial endocarditis in our rheumatic heart disease clinic, and later presentation of those patients to the adult life. In contrast to **Jomaa *et al***. [10] they reported that rheumatic heart disease (RHD) was the underlying heart disease in 17 (23.3%) cases, then **Mahony *et al.*** [9] study reported 3/51 patients with RHD possibly due to retrospective nature of these studies.

In the current study, the second most common risk factor for IE after CHD was CVP insertion in 29 patients (29%), similar to **Song *et al***. [14] who reported 10/15 cases with structurally normal heart had a history of indwelling venous catheters. The increased use of CVPs among hospitalized children, including premature infants has expanded the pediatric population at risk for IE [15,16].

Positive bacterial blood cultures are one of the key indicators for the diagnosis of IE. In the current work the most frequent organisms were gram-positive bacteria in 85 (85%) patients. It was equivalent to **Song *et al***. [14] who found gram positive cocci in 82.4% of his patients; the most common was Staphylococcus aureus, 24 (32.9%). Furthermore, in **Jomaa *et al.*** [10] study staphylococci were the most common organism (42.6%). The same was proved in Egypt but in adult study where staphylococci were the most common organism [17]. These former results confirmed that the changing prevalence of organisms from streptococci to staphylococci is observed in both high- and low-income countries.

Regarding vegetations detected by echocardiography among our patients, vegetations were present in 77 (77%) patients. A nearly equal percentage was detected in Egyptian adults 76.9% [17], yet higher ratios were reported by other studies in Africa 84.9% and 95.5%, respectively [5,10].

Antibiotics against staphylococci in different combinations were the most used in our work (53% of our patients) which contradict the Egyptian adult study where they used aminoglycoside in favor to the anti-staphylococcal (29.7% and 21.8%, respectively) [17].

In the current study, 2 (2%) patients of the deteriorated cases died after 21 days. Our lower mortality rate may be related to the short duration of follow up. Higher mortality rates were reported in multiple studies; in a Tunisian study, one-month mortality rate was 13.6% and increased after 6-months of follow-up to reach 19.2% [10]. In Egyptian adult registry, the in-hospital mortality rate was 19.9% [17].

In the current epidemiological study about Egyptian children with IE, we analyzed the most common risk factors in our patients and discussed its association with several factors. The risk factors (CHD, CVP insertion, recurrent admissions, abdominal or cardiac surgery) didn't change remarkably between rural and urban zones pointing to the improvement of the medical care in the rural areas recently. We discovered notable occurrence of vegetations in the NICU (p=0.02) possibly due to central lines insertion. Vegetations were significantly associated with the infection with gram positive organisms (p=0.05). Reluctance in the application of strict aseptic techniques is to blame.

CHD as a risk factor of IE was associated with prolonged hospital stay and delayed response to treatment (after 1 month) (p values 0.03 and 0.02, respectively). Admission in NICU was significantly associated with increased use of antifungal treatment (p=0.04).

Older age and heavier body weight were associated with good response to treatment after 2 weeks (p values 0.03 and 0.05 respectively). Highlighting the importance of adequate nutrition and primary care for the children especially those with CHD.

On performing univariate and multivariate analysis regression, we couldn't identify significant predictors of mortality in our patients perhaps due to low mortality rate (2%).

The limitations of this study included short duration of follow up, lack of recording of late complications, and failure to identify predictors of mortality due to low mortality rate in our patients.

CONCLUSION

To sum up, congenital heart disease, especially VSD, followed by central line insertions are increasingly significant risk factors for IE among Egyptian pediatric patients. Prolonged NICU admission in critically ill neonates is an important risk factor for IE. Antifungal treatment, and the presence of vegetations showed significant associations with NICU admission. Early and prompt management of CHD is highly recommended to reduce impact of IE in pediatric patients. Current data highlights the need for an Endocarditis Team, involving primary care physicians, cardiologists, surgeons, microbiologists, infectious disease (ID) specialists to allow for better care and outcome of our patients.

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