EDITORIAL
Swine-origin Influenza A (H1N1) Virus Pandemic: Is it a Sprint or a Marathon?
Nasser Behbehani

185

REVIEW ARTICLE
Population Health Genomics in Member Countries of the Cooperation Council for the Arab States of the Gulf
Badr Aljasir, Julian Little, Najlaa A Mandoura, Mohammed H AlThani

187

ORIGINAL ARTICLES
Evaluation of Dermatology Residents Using the Multisource (360-Degree) Assessment Method
Yesim Senol, Ozlem Dicle, Halil Ibrahim Durak

205

Mode of Detection of Transvenous Defibrillation Lead Malfunction in Implantable Defibrillators
Fawzia Y Al Kandari, Abdul Mohammed Shukkur, Saad A Al Kandari

210

External Non-Invasive Cardiac Pacemaker: Evaluation of Usefulness, Function and Capture Failure Rate
Ali Mohmad Hegazy, Ahmad Ali Al-Dousary, Mousa Aj Akbar, Saleh El-Enezy

215

Clinical Characteristics and Outcome of Acute Decompensated Heart Failure Patients (ADHF) in Adan Hospital, Kuwait
Mustafa Ridha, Ihab Hamdy, Amin AlSayed, Boby Cherian, Sathyan H Cherian

222

Blunt and Penetrating Thoracic Trauma: Management Strategy and Short Term Outcome
Adel K Ayed, Hassan Jamal-Eddine, Chazian Chandrasekran, Murugan Sukumar, Nael Al-Sarraf

226

Small Bowel Tumors: Insidious and Important Abdominal Problems for Surgeons
Mehmet Yildirim, Savas Yakan, Ozgur Oztekin, Emrah Bayam, Hakan Postaci, Mehmet Haciyanli

230

Clinical and Radiological Aspects of Closed Reduction in Developmental Dysplasia of the Hip Treated in the First Six Months
Mohamed Z Hatata, Nariman Aboloyoun, Eva M Bilke, Ralf Stuecker

236

CASE REPORTS
Severe Diabetic Ketoacidosis Precipitated by an Atypical Antipsychotic Drug
Mohammad Naeem Niazy, Thomas Isaac Neyyarapally, Ghassan Baidas

240

Acquired Hemophilia in a Child: Response to Rituximab
Najwa Ali Akar, Adekunle Adekile

243

Short QT Syndrome : A Case Report and Review of Literature
Jamal Hilal, Manal Al Suraikh, Rashid J Al Hamdan

246

Hair - Thread Tourniquet Syndrome
Hussah AlBuainain, Yasser Al-Jehani, Zeed Al-Ghamdi

248

Neurosarcoidosis as a First Presentation of Systemic Sarcoidosis: Case Report
Sana Sawan, Majeda Al-Saleh, Ibraheem Lasheen

250

Urosepsis Simulating Congenital Adrenal Hyperplasia in an Infant
Fahad Al-Mukhaizeem, Abdullah Shamsah, Homoud Taher

254

Rituximab in Severe Refractory Autoimmune Hemolytic Anemia in Children
Ravishankar Nagaraj, Sundus Alsherida, Adekunle Adekile

257
CONTENTS

SELECTED ABSTRACTS OF ARTICLES PUBLISHED ELSEWHERE BY AUTHORS IN KUWAIT

FORTHCOMING CONFERENCES AND MEETINGS

WHO-FACTS SHEET

1. Global use of Rotavirus Vaccines Recommended
2. Food Standards Commission Targets Dangerous Bacteria, Chemicals
3. Infection Prevention and Control in Health Care for Confirmed or Suspected A(H1N1) Swine Influenza Patients

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Congratulations and best wishes to all our contributors and collaborators.

Professor Adel Khader Ayed

Editor
The new influenza virus pandemic, Swine-origin Influenza A(H1N1), is a major threat to public health and several authorities have been warning us about this risk. History tells us that such pandemics usually cause tremendous morbidity and mortality. The most prominent Influenza A virus pandemics occurred from 1918 through 1919 (H1N1), from 1957 through 1963 (H2N2), and from 1968 through 1970 (H3N2)[1]. The current H1N1 pandemic started in late March 2009 in Mexico and by July 6, 2009 there were 94,512 (429 deaths) laboratory confirmed cases in 135 countries including 35 cases in Kuwait. Out of the 35 cases, 18 were among American soldiers in Kuwait while the rest were sporadic cases[2].

The virus which is causing the current pandemic is triple-reassortant swine influenza A virus. This means that the H1N1 virus genome includes combinations of avian, human and swine influenza virus gene segments. It has been hypothesized for some time that pigs may act as a mixing vessel for the reassortment of avian, swine and human influenza viruses and might play an important role in the emergence of a potential pandemic caused by a novel influenza virus. Even prior to the emergence of this pandemic, the Centre for Disease Control (CDC) in the United states received notification of 11 sporadic human cases of infection with this virus which occurred between 2005 and 2009[3]. There was confirmed history of exposure to pigs in nine out of the 11 cases prior to the development of influenza like symptoms. All of the 11 cases had recovered. However, four patients were hospitalized and two required mechanical ventilation.

The pandemic started on a large scale in late March 2009 when this novel virus was able to cause sustained human to human transmission. The pace of spread of this virus has been very extraordinary. During the month of April 2009, there were 367 (nine deaths) new confirmed cases of H1N1 in 11 countries, followed by 17,043 (108 deaths) new cases in 62 countries in May, and 59,791 (217 deaths) in 135 countries in June[4]. The clinical presentation of the initial 642 confirmed cases that were reported to CDC between April 15 and May 5, 2009 showed that the age range of patients with H1N1 was from three months to 81 years and 60% were 18 years or younger[5]. Only 9% of patients required hospitalization and two died. The most common presenting symptoms were fever (94%), cough (92%) and sore throat (66%); 25% of patients had diarrhea and 25% had vomiting. Despite the fact that most countries reported that most of the cases were mild, Mexico reported a greater number of severe cases and deaths related to this novel virus initially. The first 18 cases of severe pneumonia related to H1N1 reported from Mexico showed that the age range was from eight months to 61 years and only eight cases had pre-existing medical conditions[6]. Out of the 18 cases with severe pneumonia, 12 cases required mechanical ventilation and seven died. The clinical features of the severe cases included bilateral patchy pneumonia, increased serum lactate dehydrogenase level and increased creatinine kinase level (62%) and lymphopenia (61% patients). Also, out of those 18 patients, 14 received oseltamivir after admission (a mean eight days after onset of symptoms). However, it is worth noting that all the four patients who did not receive oseltamivir survived. From this initial hospital-based epidemic, 22 health care workers (HCW) developed mild to moderate flu like illness within seven days of contact with the cases and all HCW’s treated with oseltamivir recovered completely. It is interesting to note that in seasonal influenzae epidemics, severe cases and deaths usually occur among the very young (< 5 years of age) or the elderly. However, the current pandemic seems to have a different pattern that the majority of severe cases occur in middle aged individuals. In a study from Mexico reporting on the first 2,155 cases of pneumonia related to H1N1 involving 821 hospitalizations and 100 deaths, 87% of deaths and 71% of cases of severe pneumonia
occurred in patients between age five and 59 years as compared to the average rates of 17 and 32% in the seasonal influenza epidemics\[7\].

Several countries have published national guidelines on the treatment and testing of confirmed, probable and suspected cases of H1N1. There is a detailed review in the Up-to-date database which outlines the current recommendation regarding treatment and prevention of H1N1 influenza\[8\]. There are two classes of antiviral drugs for influenza: inhibitors of neuraminidase such as oseltamivir and zanamivir; and adamantanes, such as amantadine and rimantadine. Tests on viruses obtained from patients in Mexico and the United States have indicated that current new H1N1 viruses are sensitive to neuraminidase inhibitors, but that the viruses are resistant to the other class, the adamantanes. The CDC in the United States currently recommends antiviral medication for all hospitalized patients with confirmed, probable or suspected H1N1 influenza A virus infection. However, the case definitions should be adhered to and with the availability of testing for H1N1, early diagnosis and appropriate management are essential as the wide use of antiviral therapy will probably create a problem of increasing resistance. The other group for whom antiviral therapy is recommended are patients at increased risk for complications including children less than five years, elderly (> 65 years), pregnant women, people with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), neurologic, neuromuscular, or metabolic disorders (including diabetes mellitus) and people taking immunosuppressants\[9\]. The Ministry of Health in Kuwait has issued a circular to physicians on how to deal with suspected cases of H1N1. The current policy emphasizes the need for referral to the Infectious Disease Hospital for investigations and management of suspected cases. All confirmed cases are admitted in the hospital for treatment. This policy may need to be revised as the number of suspected cases is likely to rise with the new epidemic of seasonal influenza.

The international response especially from the World Health Organization has been swift. Between April 25 and April 29, WHO raised the global pandemic alert from phase 3 to phase 5 which indicates human to human transmission of the virus in at least two countries in one WHO region. Raising the alert level to its highest degree, i.e., phase 6 did not occur until June 11 despite the fact that the criterion for phase 6 (which is sustained human to human transmission in two WHO regions) was met long before this date. The delay in raising the alert level to phase 6 was due to the mild nature of the pandemic despite the high number of people affected. However, virology experts say that it is very difficult to predict the behavior and the virulence of a new influenza virus. There is already a report which indicates the emergence of H1N1 strain resistant to oseltamivir\[10\]. Dr. Keiji Fakuda, WHO top influenza expert commented on raising the alert level to phase 6 by saying that “When you’re talking about pandemic influenza, you are talking about a marathon, and not about a sprint”

REFERENCES

Population Health Genomics in Member Countries of the Cooperation Council for the Arab States of the Gulf

Badr Aljasir\textsuperscript{1,2}, Julian Little\textsuperscript{1,3}, Najlaa A Mandoura\textsuperscript{1}, Mohammed H AlThani\textsuperscript{5}

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ABSTRACT

The member countries of the Cooperation Council for the Arab States of the Gulf, also known as the Gulf Cooperation Council (GCC), have a diverse population of 35.1 million people and an overall population growth rate of over half a million people a year. The GCC countries have fast-growing economies based mainly on revenues from petroleum and related industrial products. Health services are provided by the government and the private sector, and GCC citizens have no mandatory health insurance plan. Patients incur no cost for government-provided health services at the point of care. Among the distinctive socio-cultural characteristics of GCC countries are marriage at a young age (sometimes at less than 15 years of age), child-bearing until menopause, a high birth rate (16 - 43 births/1000 population), large family size resulting from a high fertility rate (2 - 7 children per woman), and a high rate of inbreeding or consanguineous marriage (up to 58% of marriages in some areas).

The prevalence of genetic diseases in the GCC countries is high in comparison with rates in Europe and North America. Hemoglobinopathies, G6PD deficiency, inborn errors of metabolism, congenital hypothyroidism, deafness, and Down’s syndrome represent the most prevalent genetic diseases in the GCC countries and have been discussed frequently in the literature. Public health activities are resourced by government. Premarital medical counselling is obligatory in Bahrain and Saudi Arabia, while it is encouraged in the rest of the GCC countries. Prenatal screening is offered as part of routine clinical prenatal services. Newborn screening programs vary between GCC countries with respect to organization and the conditions screened for. The many gaps that remain in current screening programs reflect gaps in effective surveillance and a resulting lack of national incidence and prevalence data for certain genetic diseases. The GCC countries as a whole would benefit from the adoption of a comprehensive screening and surveillance framework for genetic diseases. Adequate stakeholder engagement and good communication between medical and public health disciplines is needed for such a framework to be effective. Regular evaluation, dissemination of information, and the application of evidence-based knowledge to the specific needs of the region will be essential to improvements in genetic services.

KEY WORDS: GCC countries, genetic counselling, newborn screening, premarital counselling, prenatal diagnosis

BACKGROUND

The Cooperation Council for the Arab States of the Gulf, also known as the Gulf Cooperation Council (GCC), includes the Kingdom of Bahrain, the United Arab Emirates, the State of Kuwait, the Sultanate of Oman, the State of Qatar, and the Kingdom of Saudi Arabia. The populations of these countries have common ethnic, social, cultural, and religious backgrounds. These countries encompass a total land area of 2,673,000 km\textsuperscript{2} and have a total population of 35.1 million people (Table 1). The annual number of live births is 680,000 and exceeds the annual number of deaths (102,000), resulting in a population growth of over half a million per year. The majority of the GCC populations are ethnic Arabs; minority subgroups reflect immigration from East and south Asia, Europe, and Africa (up to 50% in some of the GCC countries). During the last few centuries, the GCC countries have been the main destination for migrant workers in the Arab world. These immigrants tend to live and work in the GCC countries for long periods. Historically, one factor...
that facilitated immigration was trade between the GCC countries and India and other Asian countries in pearls, fish, coffee, and foodstuffs such as spices. The original people of the GCC countries were organized into tribes that tended to have similar cultural and social characteristics and hence a high degree of social cohesion and tribal loyalty.

During the last century the discovery of oil accelerated economic development spectacularly, and the GCC countries have become one of the main producers of oil and oil products worldwide. According to the World Health Organization, the gross national product per capita of GCC countries ranges from 19,740 to 48,310 international dollars (Table 1), and total per capita expenditures on health care range from 390 to 1283 international dollars. Health services are provided by the government and by the private sector. Health services provided by the government entail no cost to the patient at the point of care. There is no mandatory health insurance plan for GCC citizens. According to 2004 statistics, there are currently 372 government and 165 private hospitals in the GCC countries, with a total of 75,000 beds. There are 2221 government primary health care centers providing curative and preventive services to the general community.

The Arab population in general and the GCC countries in particular have distinct socio-cultural characteristics, which include marriage at a young age (sometimes even at less than 15 years of age), child-bearing until menopause, a high birth rate (16 - 43 births/1000 population), large family size as a result of the high fertility rate (2 - 7 children per woman) and a high rate of inbreeding or consanguineous marriage (up to 58% of marriages in some areas). In addition, few public health measures are directed toward the control of congenital and genetically determined disorders.

Consortium marriages

Although there is no consistent definition of consanguineous marriage in the literature, from the Islamic and Arab perspective consanguineous marriage is considered marriage between individuals with a recent common ancestor, as between first and second cousins; marriage to a closer relative is prohibited by Islamic regulation. Consanguineous marriage is a traditional custom practiced within the same tribe, village, or social unit. It is frequent in all of the GCC countries; various surveys, including national and hospital-based studies, report a frequency ranging from 20 to 58% of marriages, and even up to 80% in some isolated areas among selected tribes. The most common form is first-cousin marriage, followed by marriage between second cousins (Table 2). Consanguineous marriage is encouraged in these societies, as it is considered to increase family cohesion, minimize marital burdens (in particular, the financial burden on the husband), assure cultural and social compatibility, and safeguard inheritance within wealthy families.

However, consanguinity has deleterious effects on the health of the children that result from these marriages, among whom there is an increased frequency of homozygosity for autosomal recessive traits such as cystic fibrosis, sickle cell anemia, and Tay-Sachs disease (Table 3). The risk of genetic disorders is increased by 2.5 times for children of first-cousin marriages in comparison to children of non-consanguineous marriage. Consanguineous marriage is also associated with a higher prevalence of mental retardation and disability and increased risk of miscarriage.

### Table 1: Demographic indicators of member countries of the GCC

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (persons)</th>
<th>Population density (persons/km²)</th>
<th>Annual live births (1000s)</th>
<th>Gross national product per capita (international $)</th>
<th>Total health expenditure per capita (international $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>742,562</td>
<td>1010</td>
<td>14</td>
<td>34,310</td>
<td>933</td>
</tr>
<tr>
<td>Kuwait</td>
<td>3,051,845</td>
<td>171</td>
<td>48</td>
<td>48,310</td>
<td>490</td>
</tr>
<tr>
<td>Oman</td>
<td>2,577,062</td>
<td>8</td>
<td>40</td>
<td>19,740</td>
<td>390</td>
</tr>
<tr>
<td>Qatar</td>
<td>838,065</td>
<td>72</td>
<td>13</td>
<td>24,890</td>
<td>1283</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>23,678,849</td>
<td>11</td>
<td>500</td>
<td>22,300</td>
<td>570</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>4,229,000</td>
<td>51</td>
<td>65</td>
<td>31,190</td>
<td>625</td>
</tr>
<tr>
<td>Total</td>
<td>35,117,383</td>
<td>–</td>
<td>680</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

### Table 2: Consanguineous marriages in the GCC countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Overall consanguinity (%)</th>
<th>First-cousin consanguinity (%)</th>
<th>Inbreeding coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>20–25</td>
<td>12.5</td>
<td>0.0165</td>
</tr>
<tr>
<td>Kuwait</td>
<td>54.3</td>
<td>30</td>
<td>0.0210</td>
</tr>
<tr>
<td>Oman</td>
<td>36–50</td>
<td>23.5</td>
<td>0.0169</td>
</tr>
<tr>
<td>Qatar</td>
<td>51–54</td>
<td>33.5</td>
<td>0.0237</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>57.7</td>
<td>31</td>
<td>0.0226</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>50</td>
<td>30</td>
<td>0.0223</td>
</tr>
</tbody>
</table>
stilbirth, congenital anomaly, and early childhood death.[17] Furthermore, increases in the incidence of common adult-onset diseases such as cancer, mental disorders, heart diseases, gastrointestinal disorders, and hypertension have been reported.[12]

Even though the prevalence of genetic diseases in the GCC countries is high in comparison with rates in Europe and North America,[23–28] these diseases are acknowledged in Europe and North America as a major cause of morbidity and mortality,[28,29] whereas their importance has been underestimated for a long time in GCC countries. This might be a result of the attention that has been given to other public health problems in the region, such as road traffic accidents, infections, and chronic diseases.[12,27,28,30–32] An investigation of cause-specific death rates for children 0 - 4 years of age found a notable reduction in the number of reported causes for the period 1999 - 2000, except for perinatal causes in the Middle East and North African area; perinatal diseases are the leading determinant of disability-adjusted life years (DALYs).[33] Other factors, such as cultural and social customs and religious beliefs have made this topic a sensitive one to investigate.[11,27,28,34–36]

### Table 3: Prevalence of commonly investigated genetic diseases in the GCC countries (% unless otherwise specified)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Bahrain</th>
<th>United Arab Emirates</th>
<th>Kuwait</th>
<th>Oman</th>
<th>Qatar</th>
<th>Saudi Arabia</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-thalassemia</td>
<td>20.0[46]</td>
<td>49.0[50]</td>
<td>17.0[54]</td>
<td>14.0–20.0[57]</td>
<td>12.28[58]</td>
<td>16.3–28.0[59]</td>
</tr>
<tr>
<td>Data source</td>
<td>PB</td>
<td>HB</td>
<td>HB</td>
<td>HB</td>
<td>HB</td>
<td>PB</td>
</tr>
<tr>
<td>β-thalassemia trait (minor)</td>
<td>5.7[44]</td>
<td>8.7[51]</td>
<td>14.0[54]</td>
<td>2.0[61]</td>
<td>30.43[59]</td>
<td>3.22[63]</td>
</tr>
<tr>
<td>Data source</td>
<td>PB</td>
<td>PB</td>
<td>HB</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>1.29 CM[44]</td>
<td>2.0 HN[48]</td>
<td>0.12[64]</td>
<td>5.2 [47]</td>
<td>0.18[64]</td>
<td></td>
</tr>
<tr>
<td>Data source</td>
<td>HB</td>
<td>HB</td>
<td>PB</td>
<td>HB</td>
<td>PB</td>
<td>PB</td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>0.9/100[51]</td>
<td>2.63/100[51]</td>
<td>2.9/100[51]</td>
<td>0.5/100[72]</td>
<td>1.95/100[51]</td>
<td>1.8/1000[44]</td>
</tr>
<tr>
<td>Data source</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
</tr>
<tr>
<td>Data source</td>
<td>HB</td>
<td>HB</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>0.7/10,00[9]</td>
<td>3.8/10,000[54]</td>
<td>0.4/10,000[54]</td>
<td>1.23/10,000[52]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data source</td>
<td>PB</td>
<td>PB</td>
<td>HB</td>
<td>HB</td>
<td>HB</td>
<td>HB</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>0.26[52]</td>
<td>0.2[54]</td>
<td>0.2[54]</td>
<td>0.26[50]</td>
<td>PB</td>
<td>PB</td>
</tr>
<tr>
<td>Data source</td>
<td>PB</td>
<td>PB</td>
<td>HB</td>
<td>PB</td>
<td>PB</td>
<td>PB</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>0.9[54]</td>
<td>0.9[54]</td>
<td>6.0[57]</td>
<td>6.0[42]</td>
<td>14.63[58]</td>
<td>4.2[53]</td>
</tr>
<tr>
<td>Data source</td>
<td>HB</td>
<td>PB</td>
<td>HB</td>
<td>PB</td>
<td>HB</td>
<td>HB</td>
</tr>
</tbody>
</table>

HB = hospital based; PB = population based; M = male; F = female; HN = healthy newborn; HR = high risk; CM = consanguineous marriages; NCM = non-consanguineous marriages

*For all types of β-thalassemia (minor, intermediate and major). † For congenital heart diseases. †† Might contain false positive results ††† For hydrocephalus and meningomyelocele

### THE ISLAMIC PERSPECTIVE

The implementation of preventive and management services for genetic diseases is impeded by several challenges.[36] A crucially important issue for the GCC population is the Islamic view of genetic disease. The question of how to extend the adoption of new and emerging technologies related to the prevention of genetic diseases in the context of Islamic regulations has been discussed extensively in the last 10 to 15 years in the Arab world, and especially in the GCC countries, through scientific meetings, conferences, and workshops.[30,34–39] Despite these efforts, many Arab people and even a number of researchers are still unaware of Islamic views and regulations with regard to genetic services.[28,35]

Islamic bioethics emphasize the importance of respect for dignity and the rights of human beings. At the same time, Islam has the flexibility to enable the adoption of new and emerging technologies intended to improve human health.[34] Islam aims to encourage prevention of disease rather than cure.[40] Islamic teaching discourages first-cousin marriages.[40] Genetic counseling and premartial counseling are encouraged in contemporary Islam, provided that this is conducted by well-qualified and experienced individuals who are knowledgeable...
about Islamic regulation pertaining to marriage and genetic diseases, and on condition of absolute respect for client confidentiality\textsuperscript{34,40,41}.

Neonatal screening also is encouraged by Islam, since it is aimed at minimizing the adverse effects of genetic diseases that are highly prevalent in Islamic countries, especially those related to hemoglobinopathies, which have a high reported prevalence in several countries, such as Saudi Arabia\textsuperscript{40,41}.

Abortion is allowed in Islam if the fetus is grossly malformed with an untreatable, severe condition as demonstrated by medical investigation and agreed upon by a committee formed by competent, trustworthy physicians, and provided that abortion is requested by the parents and the fetus is less than 120 days old (as calculated from conception, which is reckoned as having occurred 14 days after the last menstrual period, i.e., a total of 134 days from the last menstrual period\textsuperscript{39–41}).

PUBLIC UNDERSTANDING OF ISLAM IN RELATION TO POPULATION HEALTH GENOMICS
A substantial proportion of parents of children with hemoglobinopathies who responded to a survey reported that they were unaware of the Islamic fatwa \textemdash \textit{i.e.}, an Islamic religious ruling based in scholarly opinion on a matter of Islamic law\textsuperscript{42} \textemdash regarding genetic diseases and, particularly, abortion regulations. The acceptance of abortion was significantly increased after clarification of the Islamic perspective and fatwa education (p-value < 0.001)\textsuperscript{39}.

In addition, a large proportion of parents surveyed were against premarital medical counseling and prenatal diagnosis because of a lack of awareness of the religious fatwa\textsuperscript{38}. Such misunderstanding can reinforce the fear that attending a premarital or genetic clinic may result in the cancellation of a planned marriage or the termination of an existing marriage. Also, concerns about the confidentiality of family medical history can make such consultation difficult to pursue, especially when genetic disease is known to have occurred in the family\textsuperscript{20,43,44}.

These findings indicate the need for a comprehensive health promotion campaign to clarify the options permissible within Islamic bioethics that may help people to prevent genetic diseases. The purpose and content of premarital and genetic counseling should be explained in detail. We believe that such a campaign would help to improve the uptake of these services and to make couples more comfortable with their decisions.

POLICY PERSPECTIVE
The perceived importance and impact of genetic diseases have been demonstrated by the establishment of government and non-government non-profit organizations and centers throughout the GCC countries (e.g., Saudi Arabia,\textsuperscript{26} Bahrain,\textsuperscript{45} and the United Arab Emirates\textsuperscript{37}.) Bahrain and Saudi Arabia have made premarital genetic consultation obligatory for each couple before marriage; the other GCC countries support this measure but have not made it mandatory\textsuperscript{18,27,45}.

Newborn screening is conducted in all of the GCC countries, but with some variation in the number of conditions included in the screening program. Some of the GCC countries have national screening programs for 16 or more diseases, while others include only two or three diseases, such as congenital hypothyroidism and phenylketonuria\textsuperscript{8,9,15,16,18,19,26,46,47–51}.

Prenatal services for pregnant women are available in all GCC countries. As a part of these services, ultrasound diagnosis of fetal health status is provided. Women with high-risk pregnancies are referred to more specialized maternal-fetal services. With regard to the Islamic perspective and regulations regarding termination of a pregnancy on grounds of fetal abnormality, such intervention would be legally permissible only in Bahrain, Kuwait, and Qatar. However, if the fetal condition would affect the life or the physical or mental health of the mother, then abortion is permitted in all of the GCC countries, except Oman and the United Arab Emirates, which allow abortion only to save the life of the mother\textsuperscript{42}.

The World Health Organization (WHO) has acknowledged that the primary implementation of some public health genetic health services may be costly but will help narrow the inequities between developed and developing countries with respect to health\textsuperscript{43}. Collaborative work involving the private sectors of developed countries may be of benefit\textsuperscript{43,53}. On the other hand, several genetic services available to the public are inexpensive and can be integrated with general health care services at different levels\textsuperscript{28}.

POPULATION HEALTH GENOMICS IN THE GCC COUNTRIES
To provide an overview of the epidemiology and burden of genetic diseases and to take stock of genetic health services devoted to reducing the burden of genetic diseases in the GCC countries, we conducted a review of all published literature available through MEDLINE, Internet sites for government and private sectors of the GCC countries, and reports from other national and international organizations such as the WHO, the United Nations and the US Centers for Disease Control and Prevention. In this review we made an effort to include the most recent...
published research on genetic diseases and on the factors that have contributed to high rates of these diseases in the region. Challenges and activities were discussed for each country in our effort to provide a comprehensive assessment and to identify current gaps in knowledge and services that, if remedied, would improve population health genomics in the GCC countries. Most of the available research originating from the GCC countries has investigated rates of genetic diseases in different settings (e.g., population based and hospital based). Some of this research has addressed the role of a predisposing factor, mainly consanguineous marriage. Diseases such as the hemoglobinopathies were the most commonly investigated, and in some of the GCC countries we found no reports investigating other genetic diseases such as neurological, muscular, and metabolic disorders. Table 3 presents the most recently published rates of genetic diseases in the GCC countries. We sought to retrieve data that represented the entire population of the country or a large proportion of the population wherever possible. In cases where we could not find such sources of data, hospital-based research or data on other specific subgroups were presented. Despite these differences, Table 3 shows that the rates of genetic diseases in the different GCC countries were generally similar. Usually, however, rates derived from sources of data such as national screening programs and national surveys were lower than those estimated from hospital-based studies.

**KINGDOM OF BAHRAIN**
Metabolic diseases in Bahrain were reported in 1995 to have a prevalence of 1/1000 live births[49]. Alpha and beta thalassemia trait were reported among 20.0%[54] and 5.7%[60] respectively of the studied group. G6PD deficiency was found in 18% of males and 10% of females[45]. In addition to congenital hypothyroidism, genetic blindness and deafness have been reported by several researchers and ministry of health correspondents[15,19] as important genetic diseases in Bahrain. Sickle cell disease showed a drop in prevalence over the last 18 years, from 2.1% in 1984 to 0.9% in 2002, and the prevalence of sickle cell trait declined from 26.4% to 16.3%[15]. These declines, reaching 60% in some cases, were attributed to the implementation of genetic services in the early 1980s. The first genetic clinic was established in 1984 for families at risk of genetic diseases; this was accompanied by community and public health awareness programs. In 1992, the National Committee for the Prevention of Genetic Diseases in Bahrain was formed with the aim of reducing the prevalence of genetic diseases in general and hemoglobinopathies in particular[45].

**Consanguineous marriage**
As was observed with respect to the outcomes of the genetic preventive campaign implemented in Bahrain in the early 1980s, a significant reduction in the rate of consanguineous marriage – from 39% to 20% over 18 years – was observed in the country[15]. This reduction in consanguinity was accompanied by a reduction in the prevalence of genetic diseases[15,19].

**Premarital medical counseling**
Premarital medical counseling is mandatory in Bahrain for all couples planning to get married[45]. Blood diseases such thalassemia and sickle cell anemia are a focal point in the counseling program.

**Newborn screening**
Newborn screening is currently carried out for blindness and deafness. The Ministry of Health plans to introduce a national screening program for hemoglobinopathies and hypothyroidism. This program will be centralized, with central data supported by government funding[15,19].

**UNITED ARAB EMIRATES**
An evaluation of the burden of hemoglobinopathies among preschool children showed a prevalence of 9.1% for G6PD deficiency and of 8.7% for beta thalassemia. These figures were considered higher than those for western countries, but were comparable to rates in surrounding GCC countries[81].

**Consanguineous marriage**
The proportion of marriages that are consanguineous has been reported to be 54%, of which a high proportion are first-cousin marriages[80]. The finding that consanguineous marriage is an important predisposing factor for hemoglobinopathies[83] and neonatal deaths associated with autosomal recessive disorders has resulted in a recommendation to implement premarital counseling and newborn screening[86]. In a survey of public attitudes toward consanguineous marriage, parents who have children affected by genetic diseases reported that they did not want their children to find spouses from within the same family[11].

**Premarital medical counseling**
Premarital and genetic counseling clinics are currently available in Abu-Dhabi, Dubai, and Al-Ain, the first having been established in 1989. These
centers provide services that focus on blood diseases, with particular emphasis on thalassemia. Premarital counseling services are also provided by a few private clinics, mainly in the State of Dubai. Premarital and genetic counseling is encouraged by the government of the United Arab Emirates but is not obligatory[65]. There is a need to expand the services available in the United Arab Emirates to provide premarital and genetic counseling on a national basis.

Newborn screening

Newborn screening programs started in the United Arab Emirates in 1985. Screening programs for phenylketonuria and congenital hypothyroidism were among the earliest to be implemented[65].

Evaluation of the newborn screening program was done for the period from 1998 to 2000. The results showed improvement in screening coverage for newborns within the different states, with varying rates of progress. With regard to process measures, over time these have approached international norms, except for the time needed to deliver specimens to laboratory facilities for analysis[7].

The current national newborn screening program provides coverage for 94% of the population and includes screening for phenylketonuria (PKU), congenital hypothyroidism, sickle cell disease, and congenital adrenal hyperplasia[65]. The program aims to provide 99% coverage by the year 2010. The reported incidence of confirmed congenital hypothyroidism was 1/1963 live births, while it was 1/10,000 and 4/10,000 live births for PKU and congenital adrenal hyperplasia, respectively[65]. The rate of sickle cell trait has dropped from 4.6% to 0.9% since the beginning of the program in 1985[6,13,51].

STATE OF KUWAIT

In Kuwait the incidence of inherited diseases varies from 1/2500 to 1/20,000 live births[6]. With regard to hemoglobinopathies, analysis of samples from a tertiary hospital blood bank in 2002 revealed that β-thalassemia trait had a prevalence of 14%, sickle cell trait 6%, and sickle cell disease 0.9%. These rates are similar to those reported in the remaining GCC countries.

Cystic fibrosis, G6PD deficiency, PKU and spinal muscular dystrophy were reported to be common genetic disorders[7,8].

Consanguineous marriage

The frequency of consanguineous marriage in Kuwait has been reported to be 54.3% in the general population[6], 88% among parents of children with cystic fibrosis, and 77% among parents of children with PKU[89]. Consanguineous marriage has been reported in 46% of cases of congenital hypothyroidism detected by newborn screening[10]. Other studies have observed that consanguinity predisposes not only to PKU[80] but also to glaucoma[91]. In an investigation of rates of major congenital malformation in the Al-Jahra region, a rural area in which the majority of the population is Bedouin, a prevalence at birth of 12.5/1000 was reported[108]. A high proportion had autosomal recessive disorders, and this was attributed to the high rate of parental consanguinity among the study population[58].

Premarital medical counseling

Currently, a premarital and genetic counseling program is being conducted in the Kuwait Medical Genetic Center, established in 1979. Among the services provided, the center provides particular attention to congenital malformations, chromosomal disorders, mental retardation, and genetic blood disorders[92]. This program has been shown to have reduced the burden of specific genetic diseases over the last 20 years. In particular, the prevalence at birth of anencephaly has decreased from 1.3/1000 to 0.3/1000, keeping into consideration the role of other preventive campaigns[18,93].

Newborn screening

The screening program is currently implemented in four government hospitals, but does not cover all newborns in the country. It includes screening for congenital hypothyroidism, PKU, very long chain Acyl-CoA dehydrogenase (VLCHAD) deficiency, hyperphenylalaninemia, pyruvate carboxylase deficiency, tyrosinemia, non-ketotic hyperglycinemia, long-chain 3 hydroxyacyl CoA dehydrogenase (LCHAD) deficiency, and methylmalonic acidemia[90]. In the pilot stages of this expanded newborn screening program, the prevalence of some of these conditions exceeded that reported by previous research on symptomatic diseases. This could be attributable in part to the detection of minor manifestations of inborn errors of metabolism that are not of clinical significance[6].

In an evaluation of the need for a newborn hearing screening program in the hospital setting the prevalence of profound and severe sensorineural hearing loss was 2% among newborns in the general nursery ward, while the prevalence of sensorineural hearing loss was 46.67% among high-risk newborns in the intensive wards. According to the investigators, these figures demand the presence of a screening program in the State of Kuwait for the purpose of early intervention and management[65].

SULTANATE OF OMAN

The prevalence at birth of inborn errors of metabolism was reported to be 1/1555 live births in
the period from 1998 to 2000, a rate higher than that reported in British Columbia, Canada (1/2500)\(^{78,94}\). Among 1800 children with clinical findings suggestive of genetic disease, the proportion found to have chromosomal abnormalities was 28.3% in the period 1999 - 2004\(^{69}\).

Consanguineous marriage

Consanguinity was reported to be present in 36% of marriages in the Sultanate of Oman\(^{66}\) and in up to 50% in some isolated areas. In these areas, consanguinity is encouraged in many families to promote homogeneity of the family\(^{21}\). Consanguineous marriage is considered an important predisposing factor to genetic diseases in the Omani population\(^{69}\).

The prevalence of consanguinity was reported to be twice as high among parents of children with inborn errors of metabolism than among the general population\(^{78}\). Consanguinity was reported to be a predisposing factor for a higher rate of hearing impairment among newborns in comparison with rates in other countries in which newborn hearing screening has been implemented\(^{66}\).

With the exception of hemoglobinopathies, the frequency of autosomal recessive genetic diseases in Oman is high in comparison with rates in Western countries; this difference is thought to reflect the frequency of consanguineous marriage in Oman\(^{69}\). These findings have led to the implementation of a national surveillance system and a preventive genetic program\(^{97}\).

Premarital medical counseling

To our knowledge, no premarital medical counseling is offered to the general population of Oman, although genetic counseling clinics at the Sultan Qaboos University and the Ministry of Health serve subsets of the population\(^{98}\). The implementation of premarital and genetic counseling clinics has been recommended to reduce the burden of genetic diseases, with the proposal that these services be integrated into primary health care clinics for the purpose of improving accessibility to the general population\(^{98,99}\).

Newborn screening

A national screening program for hypothyroidism was implemented in Oman in 2006; the prevalence at birth of detected cases is 1/2750 live births per year\(^{49}\). In addition, a special screening program for hemoglobinopathies and inborn errors of metabolism has been run by the Sultan Qaboos University Hospital for the last 10 years\(^{49}\). Attempts are currently in place to generalize this program to the national level to include all Omani newborns, especially those at high risk\(^{49}\).

In a review of the national newborn hearing screening initiative, the reported rate of hearing impairment was 1.2/1000 live births; the cost of screening was US$ 7.10 per newborn\(^{66}\).

STATE OF QATAR

Hemoglobinopathies occur with a high frequency in the population of Qatar\(^{58}\). Beta-thalassemia is reported to have a wide variation in its underlying molecular sequences as a result of immigration and intermarriage between the Qatari population and surrounding countries\(^{100}\). The high prevalence of hemoglobinopathies in Qatar stimulated the public health authorities to include these disorders in the national newborn screening program\(^{8}\).

Consanguineous marriage

In two survey studies in Qatar, about half of the respondents reported consanguineous marriage, of which first-cousin marriage was the most prevalent type. Such marriages were associated with high rates of genetic and chronic diseases in comparison with the general population\(^{22,101}\). Moreover, this was reported to predispose the Qatari population to higher rates of rare genetic diseases such as Ehlers - Danlos syndrome, homocystinuria, and cystic fibrosis in comparison with Western populations\(^{102}\). The last two disorders were reported as major population health problems in Qatar\(^{30,103}\) with a prevalence at birth for homocystinuria of at least 1/3000 live births, the highest in the world\(^{104}\). Consanguineous marriage was also reported to be an important predisposing factor for hearing loss in newborn infants\(^{67}\).

Premarital medical counseling

In an assessment of women’s knowledge regarding preconceptional health, 20.4% of Qatari women reported taking a folic acid supplement in the preconception period as a preventive measure, and 14% knew that such supplements can prevent birth defects (neural tube defects)\(^{50}\).

Despite important progress in the implementation of genetic services in the State of Qatar, currently there are no national premarital or genetic counseling clinics that cover the entire population. Participants at the first Qatar International Conference on Newborn Screening, held in November 2007, concluded that further development of premarital and genetic counseling would be crucial to decreasing the burden of genetic diseases, especially in the view of the high frequency of consanguineous marriage and of several genetic diseases\(^{22,30,98,102,104}\).
Newborn screening

An extended national newborn screening program for more than 20 genetic disorders using tandem mass spectrometry (MS/MS) was implemented in Qatar in 2003 in collaboration with the University Children's Hospital of Heidelberg, Germany[8,24]. The reported prevalence of the screened disorders combined was 1/1327 live births, a high rate relative to Western countries[24]. In 2007, the program was evaluated as having a high cost-benefit ratio: each Euro spent on the program resulted in a savings of 25 Euros that would otherwise be spent on medical management and social support[24]. It has been recommended that the program continue with minimal modifications, such as the inclusion of screening for blood hemoglobinopathies. The program currently screens for the disorders listed in Table 4[24]. The extended national screening program identified other genetic disorders, such as medium-chain Acyl-CoA dehydrogenase deficiency, that had not previously been known to exist in the Qatari population[8].

KINGDOM OF SAUDI ARABIA

The Saudi Ministry of Health reported a prevalence at birth of metabolic disorders of 1/1000 as compared to 1/4000 in the United States and 1/7000 in Japan[79]. The prevalence at birth of G6PD deficiency ranged from 2 to 4% in the different regions of the kingdom in which newborn screening had been implemented. A particularly high rate has been reported in the eastern region of the kingdom: Al-Hasa and Al-Qatif have a prevalence of 14.7 and 30.0%, respectively[59,76,77,105].

Consanguineous marriages

An overall rate of consanguineous marriage of 57.7% has been reported, the highest rate, 80.6%, occurring in Samtah; a rural village in the Southern part of the kingdom[17]. The regional background of the family was associated with an increased prevalence of consanguineous marriage (p < 0.001), whereas level of education was inversely associated with consanguineous marriage (p < 0.001)[13].

Consanguineous marriage was also reported to be an important predisposing factor for childhood hearing impairment[106]. The prevalence of hereditary sensorineural hearing loss was found to be 66% when parents were first cousins and 37% when they were second cousins[107].

Autosomal recessive diseases such as congenital primary glaucoma are considered the most common cause of childhood blindness in Saudi Arabia,[108] and this is likely to be the case in other GCC countries because of similar patterns of consanguinity[91].

In Riyadh, capital city of Saudi Arabia, the 56.0% prevalence of consanguineous marriage was found to have a statistically significant association with congenital heart diseases (p = 0.01); a borderline statistically significant association with major congenital malformations was also found (p = 0.05)[108]. The rate of consanguineous marriage was 52.0% in the industrial city of Dammam; of these, first-cousin marriages were the most common (39.3%). Although consanguineous couples had a significantly higher number of pregnancies than non-consanguineous couples, no significant differences were noted for rates of reproductive wastage or inherited diseases[110].

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Specific disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoacidopathy and urea cycle disorder</td>
<td>Argininosuccinic aciduria, Benign hyperphenylalaninaemia (HPA), Citrullinaemia, Defects of biopterin cofactor biosynthesis (BS), Homocystinuria (HCY); cystathionine beta-synthase deficiency, Maple syrup urine disease (MSUD), Phenylketonuria (PKU), Tyrosinaemia type I, Endocrinopathy</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>Congenital hypothyroidism, Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Fatty acid oxidation disorder</td>
<td>Carnitine palmitoyltransferase (CPT) I, Carnitine palmitoyltransferase (CPT) II, Carnitine transporter deficiency, Long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) / mitochondrial trifunctional protein (mTTP) deficiency, Lyase 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) deficiency, ketothiolase deficiencies, Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, Short-chain acyl-CoA dehydrogenase (SCAD) deficiency, Very long-chain acyl-CoA dehydrogenase (VLCD) deficiency</td>
</tr>
<tr>
<td>Organic aciduria</td>
<td>Cbl disorders, Glutaric aciduria type I, Isobutyryl-CoA dehydrogenase (IBDHD) deficiency, Isovaleric aciduria, Methylmalonic aciduria, 3-Methylcrotonylglycinuria, Multiple acyl-CoA dehydrogenase (MAD) deficiency, Propionic aciduria</td>
</tr>
<tr>
<td>Other classical disorders</td>
<td>Biotinidase deficiency, Galactosaemia</td>
</tr>
</tbody>
</table>
In the rural area of Al-Thugbah in the Eastern province, the prevalence of consanguineous marriage was 54.6%; most of these marriages were between first cousins. Mental retardation, cerebral palsy, and microcephaly were considered common pediatric problems, with a prevalence of 6.27, 5.30, and 1.99 per 1000 population respectively in the surveyed area[34]. In an investigation of the incidence of rare genetic diseases in the Eastern province of Saudi Arabia, the prevalence at birth of severe combined immunodeficiency was reported to be 19/100,000 live births, the highest reported in the world. Most of the infants affected were from consanguineous marriages[111].

Premarital medical counseling
In 2003, Saudi Arabia passed legislation that made premarital medical counseling for all couples planning to get married obligatory, but without directive counseling obligations[27].

An evaluation of the implementation of an obligatory premarital medical consultation in Saudi Arabia showed that this service had good accessibility. Two percent of couples identified as being at high risk of having children affected by genetic disease got married. Because the result of this consultation does not prevent the marriage of high-risk couples, only 10.4% of couples identified as being at high risk did not proceed with their marriages[63]. These results indicate the need to improve public awareness of the risk of genetic diseases and the role of premarital medical consultation in decreasing the burden of genetic disease in the population. An evaluation of attitudes toward premarital counseling of Saudi parents whose children were affected by hemoglobinopathies found a high rate of marital consanguinity (72%) in comparison with the general population. A large proportion of parents stated that they would discourage consanguineous marriage, while a great proportion of the rest believed that couples contemplating such a marriage should receive obligatory premarital medical counseling[35]. Over 80% reported that they would accept prenatal diagnosis. The survey indicated that some of the premarital counseling currently taking place in Saudi Arabia needs improvement in areas such as the explanation of possible medical interventions (e.g., prenatal or pre-implantation diagnosis) that would reduce the probability of genetic disease in the children of high-risk couples[35].

Newborn screening
The Saudi National Newborn Screening Program (SNBS) operates in 24 birth centers and covers about 120,000 newborns per year; this number represents 24% of the total annual births in the kingdom. Currently, the program tests for 16 disorders (Table 5)[26,46–48]. An evaluation of the results of the program reported an overall annual incidence for the screened genetic diseases of 1/758 live births[46].

<table>
<thead>
<tr>
<th>Laboratory technology</th>
<th>Disorders</th>
</tr>
</thead>
</table>
| Tandem mass spectrometry (MS/MS) | • Argininosuccinase deficiency (ASL)  
• Beta-keto thiolase deficiency (BKT)  
• Citrullinemia (ASD)  
• Glutaric acidemia type-I (GA-I)  
• HMG-CoA Lyase Deficiency (HMG)  
• Isovaleric acidemia (IVA)  
• Maple syrup urine disease (MSUD)  
• Medium-chain Acyl-CoA dehydrogenase deficiency (MCAD)  
• Methylmalonic acidemia (MMA)  
• 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)  
• Phenylketonuria (PKU)  
• Propionic acidemia (PA) |
| Kit-based assays | • Biotinidase deficiency (BD)  
• Congenital hypothyroidism (CH)  
• Congenital adrenal hyperplasia (CAH)  
• Galactosaemia |

The SNBS is supported by non-profit organizations, with whom the Ministry of Health is currently working to extend the program to cover more than 400,000 newborns per year (that is, two-thirds of the total annual births) and to involve more centers across the country[26,47].

DISCUSSION
GCC countries have made diverse efforts to implement policies to improve population health through the responsible and effective translation of genome-based knowledge and technologies[112]. Research activities related to gene-disease associations have accelerated recently. Although 15 or 30 years ago the main focus of this research was the hemoglobinopathies[59,77,105,113,114], research is now ongoing on all types of diseases related to genetic predisposition[21,30,31,65,78,88]. Despite the tremendous activities and research conducted by individual researchers and GCC governments, the unfortunate lack of regularly published data from national surveillance systems has led to an underestimation of the health, social, and economic consequences of genetic diseases.

The development of databases and of the necessary infrastructure for bioinformatics will be of crucial importance in improving population health genomics[43,115,116]. A database of published...
research of genetic diseases in the Arab world was established six years ago in the United Arab Emirates with the aim of improving research and the exchange of information among researchers. Recently, Saudi Arabia launched a genetic research project that includes a biological bank with the capacity to accommodate a large number of biological samples and thus to encourage genetic research in the kingdom, especially the investigation of gene-disease associations and gene-environment interactions.

Although there is great variation in the types and rates of genetic diseases in the Arab world, the GCC population tends to have similarities in this regard as a result of common demographic, cultural, social and health characteristics.

Differences among screening programs for newborns in the GCC countries are similar to those observed in Europe. Several countries, e.g., Austria and Germany, have included a large number of genetic diseases in their screening programs, whereas others, e.g., Great Britain and Switzerland, include very few diseases for reasons such as cost-effectiveness. Some European countries have not introduced any newborn screening programs for a variety of reasons such as the economic impact of such programs on health care resources.

The detection of diseases through newborn screening programs at present will increase awareness and knowledge and this would be expected to lead to improvements in health care management protocols, especially if there is collaboration across jurisdictions. Genetic disorders that are untreatable today may be manageable and even preventable in the future, and this argues for the importance of implementing screening programs in any country, establishing infrastructure first for conditions for which there is evidence that benefits are greater than harm and which can then be extended as evidence for other conditions as resources become available.

In the GCC countries, reported obstacles to the implementation of newborn screening programs include underdeveloped health systems and problems with the referral process, particularly in remote and rural areas. Other challenges include the provision of adequate education and training for medical staff to diagnose and manage genetic diseases, economic burden, public awareness, processes for collection and transportation of samples and reporting of results and the development of an efficient information system. Finally, the inclusion of appropriate screening tests for a specific population requires detailed research and investigation to evaluate cost-effectiveness and increase the public’s acceptance of screening programs.

The number and nature of genetic diseases included in screening programs should be based on local community experiences, reported surveillance data, and the results of previous research on the balance of benefits and harm. In circumstances where evidence to support a broadly based screening program is lacking or insufficient, the implementation of a pilot program targeted toward a subcategory of the population is recommended to investigate its impact and cost-effectiveness and potentially to encourage health policy-makers to implement the program at a national level.

In our review of the available data we found similarities between the GCC countries with respect to genetic disease prevalence (with rates that were high in comparison with those reported in Europe and North America) and with respect to the contribution of consanguineous marriage to those high rates. These similarities may be considered an advantage insofar as they provide a rationale for the GCC countries to collaborate with each other in disease surveillance and research and to adopt similar screening programs. A common screening program involving the total GCC population would also have a particular benefit for individual countries in that some of the monitored diseases are considered to be rare; thus, the pooling of data from different countries will enable faster progress in research. Effective population health genomics requires a multidisciplinary approach in which knowledge and experiences related to population health genomics are exchanged between the different sectors in each country.

Public understanding of genetic diseases has been shown to be correlated with educational level in the GCC countries. Although parents of affected children may react with either denial or resignation to their situation, providing a scientific explanation can reduce feelings of guilt. Health promotion activities regarding genetic diseases should be encouraged among the public at all levels, especially for younger people.

There has been an emphasis on the use of non-invasive methods such as ultrasound to detect congenital abnormalities in the prenatal period, since they do not cause discomfort when administered and are more readily accepted than invasive techniques. However, pre-implantation genetic diagnosis (PGD) has the advantage of enabling therapeutic abortion to be avoided, since it is performed very early after fertilization in vitro. This procedure seems to be acceptable among the GCC countries despite its high cost, but it is not widely available due to technology and economic barriers. Because the diagnosis is made before implantation, the technique presents fewer ethical and religious concerns and can reduce pregnancy terminations for high-risk couples. Despite these advantages it requires
a cost-effectiveness evaluation to determine its feasibility for wider use among target groups\textsuperscript{[26,29]}.

Pre-implantation diagnosis could help couples who do not take the recommendation of premarital counseling and proceed with marriage despite a high risk for single-gene and chromosomal disorders \textsuperscript{[30,122,123]}.

Medical education and training for health staff is a very important means of improving genetic health services in any country\textsuperscript{[25,43]}. The

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\textbf{Fig. 1:} Framework for improving population health genomics in the GCC countries
dissemination of information through health staff to the public is also crucial. Hence, the training of primary health care staff in the area of genetic health education is vital, since these workers represent the first line of contact with genetic services for the general public[25,27,30,43,44,112,115,124-126].

There is no single perfect framework for providing genetic services, and differences in research results and in the methodological quality of studies make the development of such a framework even harder. Religious, ethical, cultural and social differences can mean that a solution that is suitable for one country cannot be implemented in another[127]. For the purpose of improving population health, an integrative genomic program should be adopted that involves all community levels. This program should be in close communication with policy-makers and decision-makers in all of the GCC countries, and should undergo regular evaluation, with the sharing of knowledge between the different participating sectors. Fig. 1 represents a proposed framework for improving population health genomics across all levels of a community. As discussed earlier, GCC countries have implemented some of the proposed components and have achieved various degrees of success. Integrated into a national comprehensive program, these advances could be even more effective in improving population health.

FRAMEWORK COMPONENTS

To support the translation of currently available knowledge into action and thus reduce the gap between the current level of available services and actual need, the proposed framework was created after a review of the pertinent literature and discussion with experts in the field of population health genomics and public health. It is important to bear in mind that the implementation of each component of this framework is intended to be adjusted to the specific needs and expectations of the populations of the GCC countries. At the same time, it is hoped that in moving forward in population health genomics and facilitating the implementation of current knowledge, the experience gained in one country might be generalized to others. Although it is acknowledged that GCC countries have tried to improve services related to population health genomics, a more comprehensive and integrated approach is needed to optimize the effectiveness of these services. The guidelines proposed here are not intended to be adapted in a rigid manner; rather, they are meant to accommodate further suggestions and the integration of new services and to provide the necessary flexibility to implement each component according to the needs and expectations of each country. These guidelines are thus open to the kind of innovation and adaptation necessary for any health care system to continue to improve and to provide effective health care services[128-130].

- **Stakeholder engagement and communication:** Provision of support by the higher authorities is an important component of any successful program. Supportive policies, strategic planning, and legislation will improve the genomic health of the population. Another important role of stakeholders is to ensure accessibility and equity in the provision of services to all population subgroups. Religious, ethical, social, and cultural issues related to the implementation of genetic services should be taken into consideration in the appropriate application of genetic services. Communication between the different disciplines involved in implementing the framework is also important for programs to be run effectively and should be encouraged and reinforced by stakeholders in all of the GCC countries. The process of communication involves sharing evidence-based knowledge, addressing challenges, and applying possible solutions in different disciplines to enhance outcomes, while bearing in mind that each discipline has its own characteristics, such as target population and methods of operation and of communication[112,131].

- **Community level:** The promotion of genetic health in the general population is required to support all disciplines that provide genetic services. Such promotion can be divided into a general approach that focuses on improving the engagement of the public in regard to genetic health, diseases, associated burden and predisposing factors. For specific groups, a more detailed approach can be used to provide information about particular programs that are available, clarifying their purpose and encouraging the targeted group to participate[131]. It is important to frame the message carefully and to use channels of communication that are appropriate for the target group. Community-level interventions can also involve campaigns to promote the adequate intake of folic acid by women of child-bearing age, campaigns to provide immunization against rubella for girls before they reach puberty, and campaigns that involve the private sector, as for example in the fortification of salt to prevent iodine...
deficiency in pregnant women[^132]. Pregnant women and health professionals responsible for their care should also be educated to avoid carcinogenic and teratogenic exposures such as ionizing radiation (through X-rays) and medications. These educational campaigns need to be integrated across different health care disciplines to achieve a maximum benefit. It is important to bear in mind that because, in addition to consanguineous marriage and advanced maternal age, dietary deficiencies and teratogenic exposures are considered the major predisposing factors for genetic diseases in the region, it is important to provide adequate public health education about risk factors during pregnancy[^131,132].

- **School health:** Schools provide an important venue for genetic health education, given that 34.58% of the general population of the GCC countries is below the age of 19 years. Effective school-based programs devoted to explaining the burden of genetic disease at the level of the family and the community, the role of consanguineous marriage and predisposing factors, the importance of prematual and genetic counseling, and the Islamic perspective on these issues are needed. Such knowledge can be incorporated into the regular curriculum as well as being presented as special events and as part of extra-curricular learning. Other important health promotion activities include the immunization of girls against rubella before puberty, addressing the importance of nutrition, especially the prevention of iodine deficiency, and avoidance of carcinogenic and teratogenic exposures[^132].

- **Premarital and genetic counseling:** GCC countries should encourage premarital and genetic counseling for the benefit of their population and, if feasible, should consider making such counseling obligatory, as it is currently in Bahrain and Saudi Arabia. Although counseling will not prevent all consanguineous marriages, it can address the consequences and provide evidence-based solutions for high-risk couples who want to proceed with marriage. Assessing and addressing the factors that contribute to the risk of genetic diseases should take place. Women in their child-bearing years should take 400 micrograms of folic acid per day in countries where food fortification is not possible. Accordingly, high-risk couples who want to proceed with marriage and having children (such as those with a proved laboratory diagnosis of high genetic risk and women above age 35 who wish to get pregnant) can be referred to specialized health services that can advise them on reducing the risk of genetic diseases in the next generation. And, as discussed earlier, pre-implantation genetic diagnosis, although new to the region, can be of value to high-risk couples with a family history of genetic disease. Education campaigns to clarify the purpose of these counseling clinics and the expected outcomes of counseling should be addressed to the general community. Other issues such as provision of proper training in the field of premarital and genetic counseling and the assurance of confidentiality should be taken into consideration[^112].

- **Prenatal screening:** Prenatal and pregnancy care is already well established in all GCC countries and is conducted by primary care physicians and obstetricians in the government and private sectors. Addressing the importance of genetic diseases and related congenital anomalies early in pregnancy can reduce the burden of these diseases for women and their offspring. Early identification allows for timely referral and early management by specialized health staff. In cases of a congenitally impaired fetus, early detection allows for the early termination of pregnancy through abortion when it is requested by the parents in accordance with Islamic law and the legislation of the country. Families with a history of genetic disease, as well as women with high-risk pregnancies, should undergo more advanced prenatal investigations. As presented in Table 3, the rates of Down’s syndrome in the GCC countries, are considered high in comparison with rates in Western countries[^6,70,71,73,74,131,133,134]. Women above 35 years of age should receive testing for Down’s syndrome and trisomy 18; in fact, Canadian national practice guidelines now advise such investigation for all pregnant women regardless of their age using maternal serum screening, which has a detection rate of 75%[^135]. Amniocentesis or chorionic villus sampling (invasive techniques) should be used for women below 40 years of age only when non-invasive techniques have obtained a positive test result[^133].

- **Newborn screening:** Early detection of genetic diseases can improve outcomes for newborns. For example, early diagnosis of PKU enables interventions that prevent mental retardation and have an excellent prognosis[^127]. GCC countries are encouraged to adopt an extended population-
based newborn screening program. Such programs have been implemented to different degrees in the GCC countries. Collaboration between the GCC countries can help to facilitate implementation, and the adoption of a common screening program will facilitate the future evaluation and implementation of preventive and curative services[132,135]. High-risk newborns such as those born into families in which genetic diseases have been identified or to mothers aged 35 years and above should receive further investigation to ascertain their health status and enable early management, thus improving outcomes for the newborn and for the family as a whole[132,136].

• National genetic disease surveillance system: To be effective, a newborn screening program must be supported by a surveillance system for the collection of data, verification of results, reporting of information to a centralized database, data analysis, and dissemination of results through national reports. At the same time, the confidentiality of individual information must be assured. Ongoing surveillance would assist the assessment of the overall burden of genetic diseases and the adequacy and cost-effectiveness of existing health services. A surveillance system can also improve the research process by supporting the generation and testing of hypotheses related to genetic diseases and related services.

• Health care system and staff training: Integrated primary, secondary, and tertiary care centers working in tandem with diagnostic services can decrease the burden of genetic diseases in any country. Such facilities and services also require specialized staff education and training. Health care staff qualified in the investigation, diagnosis, and management of genetic diseases is essential in any health care system. On-the-job training and continuing medical education to develop specific expertise in the field of genetic diseases can be provided through conferences, seminars, workshops, and courses [112,131,133].

• Genomic health research: In spite of gaps in our current knowledge, research to date on genetic diseases and genetic health services in the GCC countries does allow us to construct a general profile of the needs of the region. Because genomic research plays a central role in any population health genomics program, the process of collecting data from different sources to assess the burden of genetic disease, predisposing factors for genetic disease and the best means of translating this knowledge into evidence-based practice should be incorporated into all components of a population health genomics framework. Although researchers have investigated rates of genetic disease during the last 30 years, participation in areas of inquiry that have developed more recently is to be encouraged[56,57,62,64,69,80,83,137-139]. The provision of supportive infrastructure to sustain and improve research efforts is also strongly recommended. This infrastructure could include an electronic storage and reporting surveillance system for genetic diseases, the establishment of research institutes for genetic research, including access to international databases of medical literature, biological banks for genetic samples, and funding and incentives for research activities. The provision of advanced education and training in health genomics, together with collaborative work with international centers and experts in genetic research can significantly improve the quality of research in this field[110,126].

• GCC collaboration: The similar cultural, social and economic background of the GCC countries heightens the importance of collaboration in the field of population health genomics. Published research on the national populations of the region has shown generally similar rates of and shared predisposing factors for genetic disease. The exchange of information among the GCC countries will foster the development of evidence-based, effective interventions and will help to overcome gaps in our current understanding.

• Evaluation and dissemination of knowledge: Continuous evaluation of existing services and activities related to the improvement of population health genomics will help to determine effectiveness and monitor improvements in population health genomics. Evaluation should be carried out on a regular basis and should involve all the disciplines to identify gaps in programs and services and support suggestions for improvement. The results of evaluation should be reported not only internally within a particular discipline, but also across disciplines and to the general public. Modifications to existing programs should be made only after the comprehensive evaluation of results and should be based on the best available evidence on best practices.
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INTRODUCTION

The American Accreditation Council for Graduate Medical Education (ACGME) endorsed six general competencies that the residents should be expected to meet in 1999. These competencies were in the areas of patient care, medical knowledge, practice-based learning, interpersonal and communication skills, professionalism and system-based practice. Consequently, many medical schools and institutions have been conducting studies that aim to develop proper, valid and reliable assessment tools to assess these competencies. Various assessment tools were developed, tested and used for both formative and summative purposes. One of the most promising among those newly developed methods is the 360-degree assessment.

360-degree assessment, which is also referred to as “360-degree performance assessment”, “360-degree feedback” or “multi-source performance appraisal”, aims to collect the information on the performance of the employee by using different evaluation perspectives. It originates from quality work in business and its use in medical education has been reviewed by Lockyer. This method aims to evaluate the employees in a versatile and continuous manner and collect information about the performance of their employees from different sources that have different type of relations with them.

In recent years, the 360-degree assessment has been tested for both undergraduate and postgraduate medical education. Studies have stated that the 360-degree assessment is one of the best methods in the evaluation of professionalism and communication skills while at the same time it is valid, reliable and applicable. However, the great majority of these studies have been conducted in North American countries and validity, reliability

ABSTRACT

Objective: To test the applicability of the 360-degree assessment method of postgraduate medical education (dermatology) in a Turkish setting and discover the possible areas of improvement

Design: Cross-sectional research

Setting: Akdeniz University Faculty of Medicine, Antalya, Turkey

Subjects and Methods: Using the competencies framework of the The American Accreditation Council for Graduate Medical Education (ACGME), a 71 item containing pool was formed. Based on evaluation aspects of possible evaluator groups, the pool was converted into seven different evaluation forms for the following groups: teachers (faculty), nurses, peers, secretaries, auxiliary staff, patients and self. All seven residents and members from each department voluntarily participated in the study. Data was collected over a period of three months.

Main Outcome Measures: In the data analysis process, mean scores, and internal consistency scores were measured and evaluator groups’ scores and resident’s ranks in competency areas were compared to find out differences.

Results: A total of 259 forms were filled out by seven groups to evaluate seven residents. All the staff in the dermatology clinic participated in the process. The reliability coefficient for the faculty members was 0.99 while it was 0.60 for the auxiliary staff. Low scores were clustered.

Conclusions: Our results show that the 360-degree assessment is very well received by the evaluator group and residents and the method is acceptable in the Turkish setting of postgraduate dermatology specialist training. There is a need for larger sample study for other settings.

KEY WORDS: 360-degree assessment, medical education, resident
and applicability of the method in postgraduate dermatology education was not particularly investigated. Also its use in Turkey needs to be evaluated. Studies conducted in non-medical fields have shown that 360-degree assessment method may produce different results among cultures. However, there is no similar study conducted in the field of medicine. Turkish culture is considerably different from the cultures of countries in which the previous studies were performed. Therefore, the present study may address whether the method may differ in different cultures.

The main purpose of this study was to test the applicability of the 360-degree assessment method in the Turkish setting of postgraduate medical education. An additional aim was to evaluate the 360-degree assessment of residents in the Department of Dermatology of Akdeniz University School of Medicine. These students were on a five-year education program and were keeping records of their studies in “log books”. Out of these residents, four were in their 2.5 years of training, two were in their 1.5 year and one was in the first year. In order to ensure reliable collection of the data, researchers focused on this step with high priority. Code numbers were assigned to the residents who would assess the performances. The 360-degree questionnaires were submitted to the evaluators during March 2007 and all were received during next June. The respondents were informed in detail about how to complete the questionnaire. The evaluators consisted of seven residents, four faculty members, nine nurses, three auxiliary staffs, three secretaries and ten patients for each assistant. After scoring the assessment forms, they were all collected in the closed boxes of each department. The residents’ identities were blinded to avoid bias from those who carried out data analyzing.

The second step was the data collection. When the study was conducted, there were seven residents in the Department of Dermatology of Akdeniz University School of Medicine. These students were on a five-year education program and were keeping records of their studies in “log books”. Out of these residents, four were in their 2.5 years of training, two were in their 1.5 year and one was in the first year. In order to ensure reliable collection of the data, researchers focused on this step with high priority. Code numbers were assigned to the residents who would assess the performances. The 360-degree questionnaires were submitted to the evaluators during March 2007 and all were received during next June. The respondents were informed in detail about how to complete the questionnaire. The evaluators consisted of seven residents, four faculty members, nine nurses, three auxiliary staffs, three secretaries and ten patients for each assistant. After scoring the assessment forms, they were all collected in the closed boxes of each department. The residents’ identities were blinded to avoid bias from those who carried out data analyzing.

In the third step, the data were analyzed with SPSS 13.0 computer program and mean scores were calculated for each resident. Internal consistency of the scores was measured by Cronbach’s alpha. Faculty members’, nurses’ and colleagues’ evaluation scores were compared using Spearman’s correlation and ANOVA statistics. A significance level of 0.05 was determined for all statistical procedures.

In the last step, feedback on the assessment was provided both to each of the residents and the head of the department in order to enhance the quality of learning environment.

RESULTS

In the present study, a total of 259 forms were filled out to evaluate seven residents. All the staff in the dermatology clinic participated throughout the process. Internal consistency of scores is given in the Table 1. The consistent scores were very high for all
Table 1: Internal consistency of the evaluation scores (Cronbach’s alpha)

<table>
<thead>
<tr>
<th></th>
<th>Faculty</th>
<th>Nurses</th>
<th>Colleagues</th>
<th>Secretaries</th>
<th>Auxiliary Staff</th>
<th>Patient</th>
<th>Self Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient care</td>
<td>0.96</td>
<td>0.91</td>
<td>0.93</td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Medical knowledge</td>
<td>0.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>Practice-based learning</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Professionalism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication skills</td>
<td>0.96</td>
<td>0.91</td>
<td>0.92</td>
<td>0.77</td>
<td>0.60</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>System based practice</td>
<td>0.93</td>
<td>0.90</td>
<td>0.93</td>
<td></td>
<td>0.77</td>
<td>0.60</td>
<td>0.78</td>
</tr>
<tr>
<td>Reliability</td>
<td>0.99</td>
<td>0.96</td>
<td>0.95</td>
<td></td>
<td>0.77</td>
<td>0.60</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Table 2: Mean scores given to residents through the 360-degree assessment form

<table>
<thead>
<tr>
<th>Resident Code Number</th>
<th>Faculty Mean ± SD</th>
<th>Nurses Mean ± SD</th>
<th>Colleagues Mean ± SD</th>
<th>p*-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.9 - 0.5</td>
<td>3.9 - 0.6</td>
<td>3.6 - 0.6</td>
<td>0.547</td>
</tr>
<tr>
<td>2</td>
<td>4.1 - 0.5*</td>
<td>3.7 - 0.4</td>
<td>3.2 - 0.7*</td>
<td>0.041</td>
</tr>
<tr>
<td>3</td>
<td>2.3 - 0.5*</td>
<td>3.5 - 0.4*</td>
<td>2.6 - 0.4*</td>
<td>0.001</td>
</tr>
<tr>
<td>4</td>
<td>2.7 - 0.8</td>
<td>3.6 - 0.8</td>
<td>3.1 - 0.8</td>
<td>0.268</td>
</tr>
<tr>
<td>5</td>
<td>3.5 - 0.4</td>
<td>4.2 - 0.3*</td>
<td>3.2 - 0.6*</td>
<td>0.009</td>
</tr>
<tr>
<td>6</td>
<td>3.7 - 0.2</td>
<td>4.1 - 0.5</td>
<td>3.7 - 0.4</td>
<td>0.193</td>
</tr>
<tr>
<td>7</td>
<td>3.6 - 0.3</td>
<td>4.0 - 0.5</td>
<td>3.6 - 0.5</td>
<td>0.300</td>
</tr>
</tbody>
</table>

* ANOVA statistics, post test’s results

evaluator groups, except the auxiliary staff.

Table 2 presents the mean scores of the residents given by faculty members, nurses and colleagues. Differences were observed among evaluating groups. However, all three evaluator groups gave the lowest score for the third and fourth residents. There was a moderate correlation among faculty members’, nurses’ and colleagues’ results. Correlation between faculty members and nurses, nurses and colleagues, and faculty members and colleagues were calculated as 0.40 (< 0.03), 0.37 (< 0.02) and 0.45 (< 0.02), respectively.

In Table 3, the results regarding the two competency areas, which the 360-degree method measures most precisely, are presented. Resident number 7 received the highest scores from four of the five groups of evaluators.

Fig. 1 shows the residents’ rank order derived from communication skills and professionalism competence domains’ scores of the five evaluator groups. Due to the minimal information gathered from peers and self-evaluation form we did not include these evaluation scores for ranking. As depicted in Fig. 1, the residents were mostly graded as top, moderate or low by the groups. Only the rank order of the faculty for second resident and the rank order of the patients for the fourth resident were different from other groups.

The most commonly stressed points in the answers provided to the open-ended questions in the evaluation forms were as follows: resident number seven needs to increase his knowledge level and residents number three and four need to improve their communication skills while auxiliary staff demanded more attention to their voice level / speak.

In the feedbacks from their evaluators, especially nurses and faculty members stated that the questionnaire was too long and needed to be shortened.

DISCUSSION

There are many assessment tools to assess the knowledge level, skill, professional attitude and behavior of residents. The 360-degree assessment scale is presented as an important method that enables the evaluation of the resident by multiple sources. We found that the questionnaire form, which we used as an initial test had high reliability and reliability coefficients and provided relatively consistent opinions that are similar to published studies[6-10,13]. We had a great participation in the study by all stakeholders. Therefore, we may conclude that the 360 degree assessment of residents is applicable in a Turkish setting of postgraduate...
specialist training. However, the application of the form to wider groups may yield more precise results regarding its validity and reliability.

Disparities were observed in the scores given by different evaluators. We think that the presence of such disparities is important in the interpretation of the results. A crucial point that we determined during the interpretation of the results was that the low scores showed some pattern of clustering. This clustering is effective in the determination of the weak areas of the residents and may serve as a guide for compensation of deficiencies. Also to some degree, disparities can be observed between the scores given by the health care personnel and secretaries and those given by the remaining evaluator groups. One possible factor for this outcome may be the closer interpersonal relations of the auxiliary staff and the secretaries with the residents. However, during the interpretation of the results, it must be taken into consideration that the Cronbach reliability coefficients of the auxiliary staff and secretaries are relatively low. In a similar study, the authors concluded that secretaries should not take part in 360 degree assessment since the intra-assessor reliability was low[7].

It can be seen that the self-evaluation scores were not included in the published studies in literature[9]. However, we think that self-evaluation is beneficial in order to determine at which level the residents view themselves. Through this evaluation, it is possible to evaluate how the residents perceive their knowledge, skills, attitudes, beliefs and behavior.

The most important feature of this study is that it is the first to be conducted in the field of medical education in Turkey and as a preliminary data it will be helpful for future studies. It also serves as a guide for the determination and evaluation of competent areas. Another advantage is to offer certain improvements in the department where the evaluation is made. Additionally, it will serve as a guide in the arrangement of the education program, determination of deficiencies and their compensation and the removal of prejudices on the residents.

Although it seems to be a limitation that the study was conducted in a single department and the sample size was relatively small, the inclusion of all residents and all employees in the department offered reliable results for performance measurement. The low number of patients may be another limitation. It has been suggested that as many as 50 patient surveys may be necessary to achieve sufficient reliability[14]. In addition, faculty members and nurses mentioned in their feedbacks received after the application of the questionnaire that the number of questions is very high. Taking the feedbacks into consideration, modification of the questionnaire will be needed for the further studies. We also suggest shortening the questionnaire to apply in large sized groups in different fields.

CONCLUSION

In the present study, 360-degree evaluation was used for the first time in our country. Our data show that the evaluation made by multiple sources contributes to a more objective evaluation of the residents’ professional competencies and yields beneficial results for the determination of their weak and strong sides. We conclude that the preliminary data obtained from this method may be used to enhance educational quality of the residency program and follow-up. It is obvious that similar
studies conducted with larger samples in the future will lead to even more informative outcomes.

ACKNOWLEDGEMENTS
This study was supported by Akdeniz University Research Foundation.

REFERENCES
INTRODUCTION

The implantable cardioverter-defibrillator (ICD) has become the treatment of choice for patients with life threatening ventricular arrhythmias. With increasing number of both ICD implantations and patients with longer follow-up after implantation, complications of both the defibrillator and its leads have been recognized more frequently than before\(^1,2\). Defibrillation lead failure is a typical long-term complication and constitutes a major risk for patients with ICD. ICD lead failure may result in inappropriate shocks with its psychological distress and need for new lead implantation. It can also cause failure of ICD to deliver therapy for ventricular arrhythmias which may result in sudden death\(^3,4\). Despite recent advances in ICD technology, the long-term reliability of ICD leads remains a significant problem. Therefore the purpose of the present analysis was to evaluate the clinical presentation, and a novel mode of detecting lead failure.

ABSTRACT

Objectives: To assess the clinical presentation and mode of detection of transvenous defibrillation lead failure and therefore enhance earlier diagnosis and prevent subsequent complications  
Design: Retrospective study  
Setting: Electrophysiology outpatient clinic, Cardiology Division, Kuwait Heart Center  
Subjects: Four hundred and ninety-three patients who underwent first implantation of an implantable cardioverter-defibrillator (ICD) were enrolled and followed-up in the clinic.  
Intervention: Implantation of ICD  
Main Outcome Measures: ICD lead malfunction could be readily diagnosed by clinical presentation and device evaluation on an outpatient basis  
Results: Eight patients demonstrated clinical defibrillation lead failure on follow-up. It was diagnosed at a mean follow-up of 47.1 ± 29.1 months after device implantation. Four patients presented with inappropriate shocks due to noise oversensing with an average of 4 ± 6 shocks per patient. Lead malfunction was discovered during routine device follow-up in the remaining patients who were asymptomatic and ICD interrogation showed lead impedance out of normal range, increased chronic pacing threshold and / or sensing failure evidenced by drop in ventricular signal to less than two millivolts. All patients who sustained ICD lead failure had a new lead implanted.  
Conclusion: ICD lead malfunction requiring new lead implantation is not uncommon during long term follow-up and urge for continued close routine follow-up. Both old and new leads of different models are liable for malfunction. In asymptomatic patients lead failure can be readily diagnosed in most cases on an outpatient basis by finding abnormal measures of sensing / pacing parameters, lead impedance, stored electrograms and possibly radiographic data.

KEY WORDS: earlier diagnosis, high voltage lead impedance, implantable cardioverter-defibrillator, inappropriate shocks

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) has become the treatment of choice for patients with life threatening ventricular arrhythmias. With increasing number of both ICD implantations and patients with longer follow-up after implantation, complications of both the defibrillator and its leads have been recognized more frequently than before\(^1,2\). Defibrillation lead failure is a typical long-term complication and constitutes a major risk for patients with ICD. ICD lead failure may result in inappropriate shocks with its psychological distress and need for new lead implantation. It can also cause failure of ICD to deliver therapy for ventricular arrhythmias which may result in sudden death\(^3,4\). Despite recent advances in ICD technology, the long-term reliability of ICD leads remains a significant problem. Therefore the purpose of the present analysis was to evaluate the clinical presentation, and a novel mode of detecting lead failure.

PATIENTS AND METHODS

A total of 493 patients who underwent first implantation of an ICD or biventricular cardioverter defibrillator (bivent-ICD) with transvenous defibrillation lead and were followed-up by a single electrophysiologist at the Kuwait Cardiac Center from the year 2000 to September 2008 were analyzed. Evaluation of devices in the clinic is routinely done every three to six months. This includes retrieval of all stored events and intracardiac electrograms, measurement of sensing and pacing thresholds, measurement of lead impedance, checking sensing integrity and recording of real time electrograms for evaluation of any noise. Sensing integrity counter is a feature that uniquely enables physicians to view the number of short intervals sensed by the device, a possible early indicator of lead sensing issues (fracture, non-physiologic signals). If the number of short intervals that are displayed exceeds 300 sensing issues should be checked; the programmer at that time displays a Quick look observation to
warn physicians. Lead malfunction is defined as lead failure that requires lead replacement. Lead failure is diagnosed if noise oversensing is present that is not related to cardiac cycle, lead impedance is out of normal range and/or sensing failure evidenced a drop in ventricular sensing signal less than two millivolt or lead fracture is seen on X-ray.

Eight patients were included after having signed an informed consent form. This study was approved by the local ethical committee.

RESULTS

A total of eight defibrillator leads failed during follow-up. Lead failure was diagnosed at a mean time of 47.1 ± 29.1 months (range: 16 - 60.1 months) after ICD implantation. Six patients had a defibrillator device and two patients had bivent-ICD. Baseline clinical characteristics of patients with lead failure are listed in Table 1. There were five male and three female patients with a mean age of 48.3 ± 18.9 years (range: 14 - 66 years) at the time of diagnosis of lead failure. Four patients had the device implanted as primary prevention of sudden cardiac death due to ischemic cardiomyopathy and one for long QT syndrome. One patient had the device implanted for syncope and inducible ventricular tachycardia on electrophysiological study. The other two patients had the device implanted after resuscitation from spontaneous ventricular tachycardia / ventricular fibrillation. The affected lead models are listed in Table 2. All patients except one had the leads implanted through left subclavian venous access. Diagnosis of lead failure was made by clinical presentation as inappropriate shocks in four patients due to noise oversensing on a ventricular electrogram during sinus rhythm (Fig. 1A and 1B) and was discovered during routine follow-up in the remaining four patients who were asymptomatic. Routine device testing revealed high lead impedance out of normal range (Fig. 2A), noise registration on stored electrogram and drop in ventricular sensing signals in two patients (Fig. 2B). In other two patients routine testing revealed increased lead pacing threshold and sudden increase in lead impedance out of normal range without noise oversensing (Fig. 2C). None of the patients had radiographic signs of lead fracture except patient no. 8 in whom the lead failure was due to Twiddler’s syndrome. All patients underwent new lead implantation without complications.

DISCUSSION

The annual rate of ICD lead failure requiring intervention increases with time and reaches

Table 1: Baseline clinical characteristics of patients with ICD lead failure

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>LVEF %</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>M</td>
<td>Idiopathic VT/VF, SCD</td>
<td>65</td>
<td>Idiopathic VT/VF Survivor of SCD</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>F</td>
<td>DCM, HF</td>
<td>25</td>
<td>Primary prevention</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>Ischemic CMP, S/P CABG</td>
<td>30</td>
<td>Syncope and inducible VT</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>M</td>
<td>Ischemic CMP, S/P CABG</td>
<td>25</td>
<td>Primary prevention</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>F</td>
<td>Long QT</td>
<td>65</td>
<td>Primary prevention</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>Ischemic CMP</td>
<td>35</td>
<td>Spontaneous VT</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>F</td>
<td>DCM</td>
<td>23</td>
<td>Primary prevention</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>M</td>
<td>Ischemic CMP</td>
<td>20</td>
<td>Primary prevention</td>
</tr>
</tbody>
</table>

M = Male, F = Female, VT= Ventricular tachycardia, VF= Ventricular fibrillation, Pt. = Patient, SCD- Sudden Cardiac Death, DCM = Dilated cardiomyopathy, HF = Heart Failure, CABG = Coronary Artery Bypass Graft, LVEF = Left Ventricular Ejection Fraction, CMP = Cardiomyopathy

Table 2: Clinical presentation and follow-up of patients with ICD lead failure

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Venous Site</th>
<th>Lead Model</th>
<th>ICD Implant</th>
<th>Implant to fracture (Months)</th>
<th>Clinical presentation at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left subclavian</td>
<td>Medtronic 6947</td>
<td>Single Chamber Device</td>
<td>89</td>
<td>High impedance sensing failure, noise over sensing</td>
</tr>
<tr>
<td>2</td>
<td>Left subclavian</td>
<td>Medtronic 6949</td>
<td>Biventricular device</td>
<td>16</td>
<td>Inappropriate shocks</td>
</tr>
<tr>
<td>3</td>
<td>Left subclavian</td>
<td>Medtronic 6945</td>
<td>Single Chamber Device</td>
<td>85</td>
<td>Inappropriate shocks</td>
</tr>
<tr>
<td>4</td>
<td>Left subclavian</td>
<td>Medtronic 6949</td>
<td>Dual chamber device</td>
<td>20</td>
<td>High impedance</td>
</tr>
<tr>
<td>5</td>
<td>Left subclavian</td>
<td>Medtronic 6943</td>
<td>Single Chamber Device</td>
<td>49</td>
<td>Inappropriate shocks</td>
</tr>
<tr>
<td>6</td>
<td>Left subclavian</td>
<td>Medtronic 6944</td>
<td>Dual chamber device</td>
<td>54</td>
<td>High impedance</td>
</tr>
<tr>
<td>7</td>
<td>Right subclavian</td>
<td>Medtronic 6948</td>
<td>Biventricular Device</td>
<td>48</td>
<td>Inappropriate shocks</td>
</tr>
<tr>
<td>8</td>
<td>Left subclavian</td>
<td>Guidant 0185</td>
<td>Single Chamber Device</td>
<td>16</td>
<td>High impedance and loss of capture (Twiddler’s Syndrome)</td>
</tr>
</tbody>
</table>

Pt. = Patient, ICD = Implantable cardioverter-defibrillator
20% in ten year old leads. It is encountered in all types of lead models. In addition, a growing number of insulation defects have to be expected with increasing time after implantation. The mechanism leading to lead failure could be related to multiple leads implanted, specific lead designs and chronic pressure on the lead from ligature used to fix the lead. Higher activity as in young patients could also result in chronic mechanical stress on the lead leading to higher lead failure as in two of our patients (patient no. 1 and 5). In addition subclavian crush syndrome could also be a cause of lead failure. There are many reports on higher lead complication rate with subclavian venous puncture. All patients with lead failure were implanted with subclavian technique. Lead failure was diagnosed by inappropriate shocks as in four patients. All were due to artifact sensing and detection consistent with other reports. In the present study the number of inappropriate shocks ranged from four to ten. Routine ICD follow-up lead to diagnosis of lead failures in the other four patients emphasizing the need for continuous follow-up of old leads including sense / pace parameters, lead impedance, far field sensing and possibly high voltage coil impedance. Novel and innovative ways to better help improve cardiac patient care by providing timely diagnosis of patient conditions without the need of a face-to-face visit mainly by Telemedicine, the provision of healthcare

![Fig. 1A: Shows inappropriate shock during sinus rhythm from noise artifact causing far field sensing and short V-V intervals on ventricular electrogram](image1.png)

![Fig. 1B: Noise on the ventricular electrogram from patient with far field sensing during sinus rhythm from one of the episodes stored by the device](image2.png)

![Fig. 2A: Device interrogation indicating defibrillator lead impedance out of normal range](image3.png)
services at a distance, and the availability of a RV Lead Integrity Alert feature designed to extend the advance warning time of a lead related issue may be used to identify ICD lead failures and thus reduce inappropriate shocks.

The Medtronic CareLink Network is one of the largest and most comprehensive remote patient management tool; the introduction of remote ICD monitoring with the Medtronic CareLink Monitor and the Medtronic CareLink Network permits transmission of complete ICD interrogation via the internet enabling healthcare professionals (HCPs) to provide a ‘continuum of care’ for patients, including ongoing diagnosis, monitoring and management. This may enhance non-invasive identification of subclinical lead failure. CareLink transmits a comprehensive set of data based on the same data set examined during an in-office follow up visit as it provide Care Alert Notification allowing continuous care of patients.

Additionally, a new proactive protection for less shocks, improved monitoring and Advanced Warning Alert (lead integrity alert) have been verified and released recently. The algorithm uses two measures of oversensing and one measure of abnormal impedance to detect a lead failure. The oversensing measures consisted of a counter for RR intervals < 140 ms and non-sustained ventricular tachycardia episodes with mean RR interval < 200 ms. The impedance measure tracked lead impedances every day and each week.

The Lead Integrity Alert continuously monitor lead integrity and provide advanced warning (76% of patients will receive a minimum of three days notice to seek medical attention increasing sensitivity of detecting lead fractures compared with fixed impedance.

**CONCLUSION**

Transvenous ICD lead failures requiring lead replacement is not uncommon and increases with time. In nearly 50% of patients it can be detected during routine device evaluation whereas in others lead defect is recognized only after occurrence of inappropriate shocks. Inappropriate shock detected in 20% of cases could reflect lead fracture, SVT, or sensing physiological signals as T-wave oversensing or rarely electro magnetic interference. Therefore patients with longer follow-up after lead implantation need close lead monitoring together with careful lead evaluation at the time of pulse generator replacement for early detection of lead failure in order to minimize inappropriate shocks, prevent failure of device to deliver the appropriate therapy when needed and minimize number of lead revisions.

**REFERENCES**


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**Fig. 2B:** Device interrogation on routine follow-up in patient indicates defibrillator lead failure as shown by sensing integrity counter, lead impedance out of normal range and drop in ventricular sensing signal

**Fig. 2C:** Testing pacing threshold in patient showing increased threshold at 3 V at 0.4 millisecond


External Non-Invasive Cardiac Pacemaker: Evaluation of Usefulness, Function and Capture Failure Rate

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¹Department of Medicine, Farwania Hospital, Kuwait
²Department of Medicine, Sabah Hospital, Kuwait

ABSTRACT

Objectives: To evaluate the clinical usefulness, safety and efficacy of the non-invasive temporary pacemaker (NTP) Design: Cohort observational study
Settings: Department of Medicine, Farwania and Sabah Hospitals, Kuwait
Subjects: One hundred and forty patients who presented with asystolic cardiac arrest and symptomatic bradyarrhythmias
Interventions: Application of a NTP that functions as VVI demand pacemaker with separate external pacing and sensing electrodes.
Main Outcome Measures: Evaluation of pacemaker capture done by palpating carotid artery pulse, non-invasive blood pressure recording and transthoracic echocardiography
Results: Out of 140 patients, only 76 patients responded well to NTP. Predictive indices revealed that dilated cardiomyopathy is considered as negative predictor for the failure of NTP to capture the ventricle. Sensitivity was 73%, specificity = 90%, accuracy = 78%, positive predictive value = 95% and negative predictive value = 59% respectively. Multivariate analysis revealed that chronic obstructive pulmonary disease (COPD) status, left ventricular ejection fraction (LVEF), serum potassium, chest size and left ventricular end diastolic dimension (LVEDD) as independent variables were negative predictors for failure of NTP to capture the ventricle (p < 0.05). Receiver operating characteristic (ROC) curve data revealed that the best cut-off value for serum potassium was 3.0 mmol/l with a sensitivity = 77% and false positive = 24%, LVEF = 15% with sensitivity = 84% and false positive = 19% and LVEDD = 7.6 cm with sensitivity = 74% and false positive = 28% to predict the failure of NTP to capture the ventricle.
Conclusion: Transcutaneous pacemaker appears to offer benefit and may become an important tool in the management of patients with symptomatic bradycardia and asystolic cardiac arrest.

KEYWORDS: bradyarrhythmias, cardiac arrest, cardiac pacemaker

INTRODUCTION

External non-invasive electric cardiac stimulation was introduced in 1952 as a clinically useful means of providing effective ventricular beats in emergency situations of ventricular standstill or symptomatic bradyarrhythmias. A technique for this purpose had to be simple, reliable, and quickly and easily applied. Since arrest often recurs, the technique also had to be free of invasive procedures or other significant risks. External electric stimulation did meet these requirements and was widely used for many years for ventricular standstill or bradycardia of any cause and for prevention by overdrive suppression of multifocal and repetitive ventricular beats, tachycardia and fibrillation. Non-invasive temporary pacemakers (NTPs) were often prepared for emergency use by preliminary determination of the threshold for stimulation and were kept in standby readiness during periods of increased risk of arrest. Cardiac stimulation by any technique was found to be ineffective in patients in cardiac arrest due to ventricular tachycardia or fibrillation or to severely depressed myocardial excitability: it rarely aroused electrical and mechanical response after prolonged anoxic arrest.

A modified external NTP-monitor was introduced in 1983. This instrument achieves temporary stimulation in the conscious patient that is usually comfortable and also allows clear recognition of cardiac responses to stimulation. The aim of this study was to evaluate clinical usefulness, safety and efficacy of external NTP in patients with symptomatic bradyarrhythmias, as well as evaluate independent negative predictors for the failure of NTP to capture the ventricle.
PATIENTS AND METHODS
Study patients:
Initially we enrolled 162 patients with symptomatic bradycardia or asystolic cardiac arrest but only 140 patients (124 male and 16 female) with a mean age of 55.3 ± 6.4 years were included in the study. Twenty-two patients were excluded due to incomplete data. All patients were admitted in the coronary care unit (CCU) of the department of medicine with hemodynamically significant bradyarrhythmias between January 1997 and September 2004. All patients were evaluated clinically by looking at history, physical examination, 12-leads ECG, chest X-ray, routine laboratory investigations and echocardiography and Doppler study. Thirty-eight patients had type 2 diabetes mellitus but no patient had ketoacidosis. Twenty-three patients had history of chronic obstructive pulmonary disease (COPD). Twenty-six patients had history of coronary artery bypass graft (CABG) surgery with post-sternotomy scar. The study was approved by the hospital ethical committee.

Methods:
We trained all CCU nursing staff to perform transcutaneous pacing in one to two-hour classes. Informed consent was obtained from patients for insertion of intravenous temporary pacemaker (ITP) if necessary.

Pacing devices:
Three different new pacemaker devices were used in the study and all were devices of the modified version which was introduced in 1983[8].
1. CardioMaster device in 48 patients
2. CardioLife device in 40 patients
3. CardioServe device in 52 patients

The NTP consists of an electric cardiac pacemaker combined with a cardiac monitor and a paper recorder. The pacemaker monitor senses voltage changes of appropriate amplitude and slew rate from cardiac depolarizations or pacemaker stimuli. It provides audible and visual signals of such events with oscilloscopic and paper recordings, displays their rate and rings an alarm if selected limits are exceeded. The pacemaker functions in the demand mode (VVI), emitting stimuli that are synchronized to the sensed electrical signals at escape rates up to 180 beats/minute and an amplitude upto 140 mA.

Large stimulating electrodes of high impedance are placed on the apex and at right upper border of the sternum and monitor leads are attached. The pacemaker output is lowered to zero and the power is turned on. The pacemaker amplitude is then increased until a stimulated QRS-T response follows the artifact immediately and suppresses any intrinsic complex that might fall in its refractory period (Fig. 1). The stimulus amplitude is kept just above this stimulation threshold. In emergency situations, stimulation may be started within seconds.

Treatment protocol:
Asystolic cardiac arrest patients: Asystole is defined as the absence of electrical activity greater than 1 mm (calibrated to 10 mm per millivolt) for at least 15 seconds[10]. Cardiopulmonary resuscitation was started immediately with endotracheal intubation by an anesthetist followed by placing of transcutaneous NTP leads and adjusting the current for capturing the heart myocardium.
Symptomatic bradycardia patients: Patients with hemodynamically significant sinus bradycardia, complete heart block with idioventricular rhythm and escape junctional rhythm were indicated for NTP.

Evaluation of pacemaker capture:
1. Carotid pulse rate and volume: by palpating right or left common carotid artery in the neck between medial border of the sternomastoid muscle and the trachea
2. Blood pressure response: non-invasive measurement of BP by an electronic device
3. Monitor rhythm: as detected on cardiac monitor screen display
4. Echocardiogram: transthoracic parasternal long and short axis views were obtained to detect presence or absence of myocardial wall motion as an indication of proper electrical capture of the NTP stimulation

Collection of data and clinical outcomes:
1. Variables related to the emergency device such as type of external pacemaker, current (mA), pulse duration (msec) and pacing electric capture
2. Variables related to the hemodynamically significant bradycardia patients such as etiology, diagnosis
and indication for temporary pacemaker, time of admission, pulse rate, blood pressure, urine flow, conscious level, central venous pressure (CVP) and arterial oxygen saturation

3. Survival and transfer to chest hospital for insertion of a permanent internal pacemaker (PIP) if it was indicated

**Statistical analysis:**

Continuous variables were summarized as a mean ± standard deviation (SD). Comparison between two groups was performed with t-test for continuous variables and chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant and a p-value < 0.01 was considered statistically highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with decreased utility of NTP to capture the ventricle. The strength of the association with failure of NTP to capture the heart was presented as 95% confidence intervals. Potential confounding of clinical variables was entered as independent variables.

The validity of independent variables to predict the likelihood of decreased NTP capture of the heart was assessed by estimating the Kappa coefficient to determine the overall agreement with the data obtained after insertion of ITP and estimating the predictive indices. Kappa coefficient value (k) = (Observed frequency of agreement – Expected frequency of agreement) / (Total observed – Expected frequency of agreement). Predictive indices: true positive (TP), true negative (TN), false positive (FP), false negative (FN), sensitivity (TP / TP + FN), specificity (TN / TN + FP), accuracy (TP + TN / TP + TN + FN + FP), positive predictive value (TP / TP + FP) and negative predictive value (TN / TN + FN) were calculated.

Receiver operating characteristic (ROC) curve (grade of sensitivity versus false positive) was used to identify the sensitivity and false positive of certain value of the variable with area under curve and probability of error with a sensitivity of 100% to detect usefulness of echocardiography-derived variables of left ventricular function and serum potassium for prediction of the likelihood of non-responders to transcutaneous NTP. ROC was calculated using likelihood ratio method. Likelihood ratio + ve = sensitivity / 1 - specificity and likelihood ratio -ve = 1 - sensitivity / specificity. The best cut off point should be close to the top left hand corner of the graph. This gives a high detection rate with low false positive rate.

**RESULTS**

Table 1 shows the disease-wise distribution of patients in the study group.

Out of 140 patients of the study cohort, only 76 responded well to NTP and 64 patients were non-responders. Out of the responders to NTP, only 74 patients responded well to ITP and only 15 patients had an indication for PIP. Out of non-responders to NTP, only 49 patients responded well to ITP and only eight patients had an indication for PIP (Fig. 2).

**Clinical predictors of the utility of NTP to capture the ventricle:**

There was a significantly increased number of patients with COPD, (p < 0.01), increased size of the chest wall (p < 0.05), increased LVEDD (p < 0.05), decreased serum potassium (p < 0.05) and Echo-derived LVEF (p < 0.01) in non-responders than responders to NTP (Table 2).

**Validity and reliability of NTP to capture the heart:**

There was an agreement between the NTP and ITP as regards cardiac ventricular capture in all patients in the study (Table 3). The patients with AMI, had more increased Kappa value than the patients with dilated cardiomyopathy (0.726 and 0.605, respectively), as there was an increased number of true negative in patients with dilated cardiomyopathy (Table 4, 5). The predictive indices showed that dilated cardiomyopathy is a negative predictor of NTP to capture the ventricle.

**Table 1: Number of patients studied with bradycardia or asystolic cardiac arrest as regards different cardiac diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>SSB</th>
<th>CHB</th>
<th>EJR</th>
<th>Asystole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute anterior infarction</td>
<td>17</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Acute inferior infarction</td>
<td>40</td>
<td>8</td>
<td>7</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>37</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>BB-induced bradycardia</td>
<td>23</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>12</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Aortic sclerosis &amp; LVF</td>
<td>11</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>140</td>
<td>32</td>
<td>29</td>
<td>21</td>
<td>58</td>
</tr>
</tbody>
</table>

CHB = complete heart block, BB = beta blockers, EJR = escape junctional rhythm, SSB = symptomatic sinus bradycardia, LVF = left ventricular failure.

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Fig. 2: Schematic panel of the consequent events for responders and non-responders to non-invasive pacing. ITP = intravenous temporary pacing, NTP = non invasive temporary pacing.
as the predictive indices were higher in patients with dilated cardiomyopathy than in patients with acute myocardial infarction (Table 6).

Receiver operating characteristic (ROC) curve:

The best cut-off value of serum potassium to predict the likelihood of decreased utility of NTP to capture the ventricle was 3.0 mmol/l at 77% sensitivity and 76% specificity (the maximum sensitivity and maximum specificity near to the left diagonal), with 55% probability of error at 100% sensitivity and the area under curve was 0.759 (Fig. 3). The ideal cut-off value of chest size to predict the failure of NTP 1.16 meter at 84% sensitivity and 81% specificity with 44% probability of error at 100% sensitivity and the area under curve was 0.697 (Fig. 3). The ideal cut-off value of LVEF and LVEDD to predict the failure of NTP was 15% at 74% sensitivity and 72% specificity, and 7.6 cm at 80% sensitivity and 73% specificity with 40 and 46% probability of error at 100% sensitivity and the area under curve was 0.824 and 0.665 respectively (Table 7).

Modulators and confounders:

Stepwise logistic multivariate analysis revealed that COPD status, chest size, serum potassium, LVEF and LVEDD were negative predictors for the failure of NTP to capture the ventricle (p < 0.05, Table 8). There was no significant relationship between the age of the patient, gender, pericardial effusion, precordial scar, the version of pacemaker devices and the response of the study cohort group to NTP (p = NS).

Hemodynamic response to NTP

There was a significant increase in heart rate and systolic blood pressure in the responders to NTP after electrical capture (p < 0.05) but there was non-significant change in cardiac output, central venous pressure and arterial oxygen saturation as the predictive indices were higher in patients with dilated cardiomyopathy than in patients with acute myocardial infarction (Table 6).

<table>
<thead>
<tr>
<th>Variables</th>
<th>NTP +ve n = 74</th>
<th>NTP -ve n = 49</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD n (%)</td>
<td>6 (8.1)</td>
<td>17 (34.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Chest size (meter)</td>
<td>0.93 ± 11</td>
<td>1.42 ± 18</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.3 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>30.5 ± 3.1</td>
<td>15.7 ± 2.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>62.8 ± 2.3</td>
<td>74.6 ± 3.4</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease, NTP +ve = responders to non-invasive temporary pacing, NTP –ve = non-responders to non invasive temporary pacing.

Table 2: Comparison between responders and non-responders to transcutaneous NTP as regards chest size, serum potassium and echocardiography-derived left ventricular function

Table 3: Agreement of NTP and ITP as regards cardiac ventricular capture in all patients of the study

<table>
<thead>
<tr>
<th>ITP +ve</th>
<th>ITP -ve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTP +ve</td>
<td>74</td>
<td>1</td>
</tr>
<tr>
<td>NTP -ve</td>
<td>49</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td>17</td>
</tr>
</tbody>
</table>

Kappa coefficient value (k) = 0.681

ITP +ve = responders to invasive temporary pacing, ITP -ve = non-responders to invasive temporary pacing, NTP +ve = responders to non-invasive temporary pacing, NTP –ve = non-responders to non invasive temporary pacing.

Table 4: Agreement of the NTP and ITP as regards cardiac ventricular capture in patients with acute myocardial infarction

<table>
<thead>
<tr>
<th>ITP +ve</th>
<th>ITP -ve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTP +ve</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>NTP -ve</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>6</td>
</tr>
</tbody>
</table>

Kappa coefficient value (k) = 0.726

ITP +ve = responders to invasive temporary pacing, ITP -ve = non-responders to non-invasive temporary pacing, NTP +ve = responders to non-invasive temporary pacing, NTP –ve = non-responders to non invasive temporary pacing.

Table 5: Agreement of NTP and ITP as regards cardiac ventricular capture in patients with dilated cardiomyopathy

<table>
<thead>
<tr>
<th>ITP +ve</th>
<th>ITP -ve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTP +ve</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>NTP -ve</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>11</td>
</tr>
</tbody>
</table>

Kappa coefficient value (k) = 0.605

ITP +ve = responders to invasive temporary pacing, ITP -ve = non-responders to non-invasive temporary pacing, NTP +ve = responders to non-invasive temporary pacing, NTP –ve = non-responders to non invasive temporary pacing.

Table 6: Aetiology of bradycardia or asystole as variables for prediction of likelihood of the decreased utility of NTP to capture the ventricle

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sen (%)</th>
<th>Spec (%)</th>
<th>Acc (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study cohort (n = 140)</td>
<td>74</td>
<td>15</td>
<td>2</td>
<td>49</td>
<td>60</td>
<td>88</td>
<td>64</td>
<td>97</td>
<td>23</td>
</tr>
<tr>
<td>Acute myocardial infarction (n = 57)</td>
<td>29</td>
<td>5</td>
<td>1</td>
<td>22</td>
<td>58</td>
<td>83</td>
<td>54</td>
<td>96</td>
<td>19</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (n = 37)</td>
<td>19</td>
<td>10</td>
<td>1</td>
<td>7</td>
<td>73</td>
<td>90</td>
<td>78</td>
<td>95</td>
<td>59</td>
</tr>
</tbody>
</table>

TP = true positive, TN = true negative, FN = false negative, FP = false positive, Sen = sensitivity, Spec = specificity, Acc = accuracy, PPV = positive predictive value, NPV = negative predictive value.
There was a significant increase in systolic blood pressure after insertion of ITP versus transcutaneous pacing (p < 0.05).

Complications and Side effects
The transcutaneous pacing did not induce ventricular arrhythmias in any patient in the study. Discomfort was felt in most patients, but to a very variable degree. At a current threshold of 20 mA, 14 patients complained of a prickly sensation. With the current increased to 40 mA, 10 patients complained of a painful sensation and at current threshold of 60 mA, 22 patients complained of contractions of pectoral muscles and four patients complained of skin burns (Table 10).

DISCUSSION
In our study, 52% of the study cohort had clinical benefit from NTP. 59% of patients who presented with bradycardia had clinical benefit from NTP. Patients with asystolic cardiac arrest may confound the result as only two patients with asystolic cardiac arrest survived. Our results revealed that only 77% of non-responders responded to internal pacemaker. Other non-responders (23%) who did not respond to internal pacemaker could affect the result of agreement which may be due to technical failure, contraindications, delayed insertion of electrode, underlying heart disease and complications. White et al[11] reported that the NTP has been of clinical benefit, resulting in resuscitation from arrest in 43 cases. Even under the most difficult circumstances of prolonged emergency arrest eight patients were resuscitated and four survived. NTP can be applied more quickly and easily and for as long and as often as needed. In patients with contraindications to, or delays, failures or complications associated with temporary endocardial pacing, the NTP may be the only effective modality available. Under the urgent and often hectic circumstances of cardiac arrest, endocardial electrode placement is much too slow and too difficult, often interfering with other resuscitative procedures[12].

Table 7: Receiver operating characteristic curve data to define the ideal cut off values of the LV dimension and function, chest size and serum potassium for prediction of likelihood of the decreased utility of NTP to capture the ventricle

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ideal cut-off values</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>False positive (%)</th>
<th>Likelihood ratio +ve</th>
<th>Likelihood ratio -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K+</td>
<td>3.0 mmol/l</td>
<td>77</td>
<td>76</td>
<td>24</td>
<td>4.13</td>
<td>0.188</td>
</tr>
<tr>
<td>LV EF</td>
<td>15 %</td>
<td>84</td>
<td>81</td>
<td>19</td>
<td>4.42</td>
<td>0.167</td>
</tr>
<tr>
<td>LVEDD</td>
<td>7.6 cm</td>
<td>74</td>
<td>72</td>
<td>28</td>
<td>2.64</td>
<td>0.361</td>
</tr>
<tr>
<td>Chest size</td>
<td>1.16 m</td>
<td>80</td>
<td>73</td>
<td>27</td>
<td>3.81</td>
<td>0.253</td>
</tr>
</tbody>
</table>

The ideal cut off value = high detection rate (sensitivity) with low false positive, false positive = 1-specificity, Serum K+ = serum potassium, LVEDD = left ventricular end diastolic dimension, LVEF = left ventricular ejection fraction

Table 8: Stepwise logistic multivariate analysis of patients responding versus non-responding to NTP

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Coefficient</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.1653</td>
<td>NS</td>
<td>0.891</td>
<td>0.470 - 1.439</td>
</tr>
<tr>
<td>Gender</td>
<td>0.1082</td>
<td>NS</td>
<td>0.521</td>
<td>0.591 - 1.266</td>
</tr>
<tr>
<td>COPD status</td>
<td>0.6321</td>
<td>&lt; 0.05</td>
<td>1.829</td>
<td>1.129 - 2.695</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0.1852</td>
<td>NS</td>
<td>0.694</td>
<td>0.774 - 1.337</td>
</tr>
<tr>
<td>Precordial scar</td>
<td>0.2184</td>
<td>NS</td>
<td>0.897</td>
<td>0.896 - 1.067</td>
</tr>
<tr>
<td>Chest size</td>
<td>0.4609</td>
<td>&lt; 0.05</td>
<td>2.411</td>
<td>1.178 - 5.337</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>0.5037</td>
<td>&lt; 0.05</td>
<td>3.262</td>
<td>1.295 - 5.316</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.6168</td>
<td>&lt; 0.05</td>
<td>2.624</td>
<td>1.106 - 4.497</td>
</tr>
<tr>
<td>LV end-diastolic</td>
<td>0.4816</td>
<td>&lt; 0.05</td>
<td>1.592</td>
<td>1.072 - 2.139</td>
</tr>
<tr>
<td>Pacing Device</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CardioMaster</td>
<td>0.1659</td>
<td>NS</td>
<td>0.614</td>
<td>0.754 - 1.367</td>
</tr>
<tr>
<td>CardioLife</td>
<td>0.1781</td>
<td>NS</td>
<td>0.827</td>
<td>0.804 - 1.169</td>
</tr>
<tr>
<td>Pacing Device</td>
<td>0.1509</td>
<td>NS</td>
<td>0.711</td>
<td>0.178 - 1.437</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease, CI = confidence interval, LV=left ventricle, NS = not significant

Fig. 3: Receiver operating characteristic (ROC) curve data of LVEF and serum (K+) for prediction of non-responders to transcutaneous external pacing: 100% sensitivity has 40% error for (EF) and 100% sensitivity has 55% error for (K+).
We found that hypokalemia, impaired left ventricular function, chest size, and dilated cardiomyopathy were independent variables associated with failure of NTP to capture the heart. NTP stimulates effective ventricular beats, when the heart is capable of responding, without the complications of an invasive procedure, electrocardiographic responses are clearly recognized and it is well tolerated by most conscious patients. Skeletal contractions were thereby diminished to a usual range of 40 to 60 mA. Intolerable stinging pain was described by only ten patients and four developed skin burns. Relocation of the electrode over the skin eliminated the stinging or burning pain from stimulation of cutaneous nerves that previously rendered external stimulation intolerable at about 20 mA. Intolerable stinging pain was described by only ten patients and four developed skin burns. Relocation of the electrode over the skin eliminated the stinging and permitted comfortable stimulation in one of these. Shaving or applying and removing sensing electrodes may damage the skin or leave salt deposit with resulting areas of high electron density that produce sting during stimulation. When time permits, the skin should be examined to avoid traumatized areas and washed to remove salt.

A second type of discomfort resulting from contraction of local skeletal muscles was primarily related to current amplitude. Modifications of the stimulus duration and shape have reduced the threshold for stimulation to a usual range of 40 to 60 mA. Skeletal contractions were thereby diminished and were usually well tolerated. Although occasionally uncomfortable, they infrequently required termination of stimulation. In several instances, misplacement of the back electrode, old pacing devices over bone or at a level other than that of the anterior electrode increased the threshold for stimulation and consequently the muscular contractions. Apprehension, which often increased discomfort, was usually allayed by explanation of the procedure and by increasing amplitude gradually. Occasionally, rapidly acting analgesic or tranquilizing agents were used with benefit. Thus, external cardiac stimulation has been comfortably continued for prolonged intervals of up to 25 hours and intermittently up to 17 days in conscious patients.

Table 9: Haemodynamic changes to NTP in responders

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b/m)</td>
<td>46 ± 11</td>
<td>70 ± 6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>74 ± 11</td>
<td>95 ± 8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Arterial O₂ saturation (%)</td>
<td>85 ± 5</td>
<td>88 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (l/m)</td>
<td>3.2 ± 0.3</td>
<td>3.6 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>CVP (cmH₂O)</td>
<td>14 ± 2.4</td>
<td>12 ± 3.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

CVP = central venous pressure, O₂ = oxygen, l/m = liter/minute, SBP = systolic blood pressure

Table 10: Complications of NTP

<table>
<thead>
<tr>
<th>Complications</th>
<th>Threshold</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pectoral muscle contractions</td>
<td>60 mA</td>
<td>22</td>
</tr>
<tr>
<td>Prickly sensation of the skin</td>
<td>20 mA</td>
<td>14</td>
</tr>
<tr>
<td>Painful sensation of the skin</td>
<td>40 mA</td>
<td>10</td>
</tr>
<tr>
<td>Skin burns or redness</td>
<td>60 mA</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>60 mA</td>
<td>0</td>
</tr>
</tbody>
</table>

In our study, repetitive ventricular responses, tachycardia or fibrillation were not observed with use of the NTP, and this is in agreement with Madsen et al. The usual stimulation at currents just above threshold for capture, together with the demand mode of stimulation, appear to have been effective in preventing these ventricular arrhythmias, even in high-risk patients. Zoll et al. reported that the ease and safety of non-invasive stimulation encouraged application of the NTP in standby readiness in very ill, weak or unstable patient (such as those with acute myocardial infarction) when border-line indications for temporary pacing existed or when endocardial pacing was contraindicated, delayed, caused complications or failed.

No serious side effects were seen; in particular, no arrhythmias were induced. The median stimulation threshold was 50 mA in the study patients, with a range of 40 to 60 mA and this is in agreement with results of Zoll et al. The main advantage of the transcutaneous pacemaker is that it can be activated within less than a minute by persons who have had only a brief period of instruction. It can, therefore, be used until a transcutaneous catheter can be inserted. This is particularly important in hospital without facilities for transvenous pacing and transportation to other hospitals. Another important application for transcutaneous pacing is in patients in whom temporary pacing by transvenous insertion of a pacing catheter is not possible or is contraindicated.

Limitations of the study:
1. Relatively small number of patients
2. Only two center experience
3. Chest impedance parameters were not included in the study
4. There were 17 cases (2 false positive and 15 true negative), who did not respond well to intravenous temporary pacing and this could affect the results of agreement.

CONCLUSIONS

Inspite of limitations and confounders, NTP can be applied without delay following only simple instructions for all patients with bradycardia. Dilated cardiomyopathy, hypokalemia and impaired LV function are considered as a negative predictors for failure of NTP to capture the ventricle.
REFERENCES

Clinical Characteristics and Outcome of Acute Decompensated Heart Failure (ADHF) Patients in Adan Hospital, Kuwait

Mustafa Ridha, Ihab Hamdy, Amin AlSayed, Boby Cherian, Sathyan H Cherian
Department of Internal Medicine, Cardiac Unit, Adan Hospital, Ministry of Health, Kuwait

ABSTRACT

Objectives: To determine the prevalence of acute decompensated heart failure (ADHF) among the acute medical admissions in Adan Hospital, Kuwait, and describe their clinical characteristics and in-hospital mortality

Design: Prospective study

Setting: Medical wards and coronary care unit at Adan Hospital, Kuwait

Subjects: All adult patients admitted from 18th of September to 17th of November 2008 with the diagnosis of ADHF

Intervention: Echocardiography

Main Outcome Measures: Determination of the prevalence of ADHF among medical admissions, their clinical features, and their in-hospital mortality.

Results: The prevalence of ADHF was 14.5%. The mean age of our patients was 60.3 ± 13.2 years. There was a male preponderance (71.8 Vs 28.2%). There was a high percentage of co-morbidities among our patients. The average length of stay was 8.5 days. The in-hospital mortality was 4.9%. Beta-blocker use was relatively less than other studies. 88.5% patients had echocardiography done and 47.3% of them had preserved left ventricular ejection fraction (LVEF > 45%).

Conclusion: The clinical profile of this sample of ADHF reported from Kuwait is different from that observed in other clinical studies. These findings might have implications in the need for a nationwide database for future investigation and comparison.

INTRODUCTION

Acute heart failure is defined as the rapid onset of signs and symptoms secondary to abnormal cardiac function. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and afterload mismatch[1,2]. The patients with acute heart failure may present with one of several distinct clinical conditions as acute decompensated heart failure (ADHF) (either de-novo or as decompensation of chronic heart failure), hypertensive heart failure, severe pulmonary edema, cardiogenic shock, high-output heart failure, or right sided heart failure[2].

Heart failure is one of the most important causes of mortality and morbidity in the industrialized world[3]. The prevalence of symptomatic heart failure is estimated to range from 0.4 - 2% in the general European population[4].

Very limited information is available on the characteristics and outcomes of ADHF patients in Kuwait. The aim of the present study was to identify the magnitude of the problem and to clarify the clinical features and the care given to this category of patients and to study their in-hospital outcome at Adan Hospital, Kuwait during two consecutive months.

PATIENTS AND METHODS

The study population consisted of patients in whom the diagnosis of ADHF was made by the patient’s medical team, and who were admitted through the emergency department at Adan hospital to either the coronary care unit (CCU), or directly to the medical ward in the period from September 18 to November 17 of 2008. The final diagnosis of ADHF was based on the criteria derived from the executive summary of the guidelines on the diagnosis and treatment of acute heart failure - The Task Force on Acute Heart Failure of the European Society of Cardiology[2].

The clinical features, hospital course, and echocardiographic findings were described and compared. Standard echocardiographic techniques were used by an experienced cardiologist and the left ventricular ejection fraction (LVEF) was recorded. Preserved LVEF was defined as those patients with LVEF > 45% by M-Mode echocardiography.

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Dr Mustafa Ridha, Department of Internal Medicine, Cardiac Unit, Adan Hospital, Ministry of Health, Kuwait. ridha3@hotmail.com
(in those patients with no regional wall motion abnormalities), and by modified Simpson’s technique (in those with significant regional wall motion abnormalities)\(^5\).

It was assumed that patients had coronary artery disease (CAD) if they met any of the following criteria:

1. History of acute coronary syndrome (ACS i.e., unstable angina, Non-ST elevation myocardial infarction - NSTEMI, or ST elevation myocardial infarction - STEMI)
2. Established CAD by coronary angiography (i.e., > 50% stenosis in at least one coronary artery)
3. Anginal chest pain with evidence of stress inducible ischemia through plain exercise stress test, stress echocardiogram, or stress Thalium 201 chloride scintigraphy
4. Previous coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)

Detailed data on patient features, in-hospital course, and management were recorded after obtaining written informed consent from the patient or his / her legal representative. The study was approved by the research and ethics committee at the Ministry of Health, Kuwait.

**Statistical Analysis**

The data were analyzed using SPSS version10.1 (Chicago IL, USA) software package. Continuous variables were recorded as mean ± SD, and were compared using the paired two tailed student t-test. Qualitative (categorical) data were compared using Fishers exact test. A probability level of < 0.05 was considered statistically significant.

Table 1: Baseline clinical features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) ± SD</td>
<td>60.3 ± 13.2</td>
</tr>
<tr>
<td>Male gender</td>
<td>74 (78.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78 (75.7)</td>
</tr>
<tr>
<td>DM</td>
<td>76 (73.8)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>60 (58.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>33 (32.0)</td>
</tr>
<tr>
<td>COAD</td>
<td>16 (15.5)</td>
</tr>
<tr>
<td>CRI</td>
<td>30 (29.1)</td>
</tr>
<tr>
<td>ESRD</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>44 (42.7)</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>11 (10.7)</td>
</tr>
<tr>
<td>CAD</td>
<td>61 (59.2)</td>
</tr>
<tr>
<td>Old HF</td>
<td>75 (72.8)</td>
</tr>
<tr>
<td>ALOS (days) ± SD</td>
<td>8.46 ± 5.65</td>
</tr>
</tbody>
</table>

DM = Diabetes mellitus, COAD = Chronic obstructive airway disease, CRI = Chronic renal impairment, ESRD = End stage renal disease, CAD = Coronary artery disease, HF = Heart failure, ALOS = Average length of stay

**Results**

The prevalence rate of patients admitted with ADHF was 14.5% (103 patients out of total 711 patients admitted during the study period). Sixty-two patients (60.2%) were admitted to the CCU (representing 30% of the total CCU admissions). The remaining 41 patients were admitted directly to the medical wards. The baseline clinical characteristics are shown in Table 1. 71.8% of the patients were male. The mean age of the patients with ADHF was 60.3 ± 12.2 years. There was a high rate of co-morbid conditions among the patients with ADHF (hypertension 75.7%; diabetes mellitus (DM) 73.8%; hyperlipidemia 58.3%; chronic obstructive airway disease(COAD) 15.5%; chronic renal impairment (CRI) with serum creatinine level > 150mg/dl 29.1%; end stage renal disease (ESRD) on dialysis

1.9%; old non-hemorrhagic stroke 10.7%; history of CAD 59.2%; and finally history of prior admission due to heart failure (HF) 72.8%). The average length of stay (ALOS) was 8.46 ± 5.65 days.

Table 2 shows comparison between the clinical features of male and female patients with ADHF. As indicated previously, the majority of patients were of male gender (71.8%). The co-morbid conditions were high in both genders. However, significantly more females had history of prior admission for

<table>
<thead>
<tr>
<th>Feature</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) ± SD</td>
<td>59.7 ± 13.2</td>
<td>61.72 ± 13.1</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55 (74.3)</td>
<td>23 (79.3)</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>51 (68.9)</td>
<td>25 (86.2)</td>
<td>0.08 (NS)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>46 (62.2)</td>
<td>14 (48.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>33 (44.6)</td>
<td>00 (0.0)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>COAD</td>
<td>16 (21.6)</td>
<td>00 (0.0)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>CRI</td>
<td>24 (32.4)</td>
<td>06 (20.7)</td>
<td>0.18(NS)</td>
</tr>
<tr>
<td>ESRD</td>
<td>01 (1.4)</td>
<td>01 (3.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Anemia</td>
<td>26 (35.1)</td>
<td>18 (62)</td>
<td>0.016</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>09 (12.2)</td>
<td>02 (6.9)</td>
<td>NS</td>
</tr>
<tr>
<td>CAD</td>
<td>47 (63.5)</td>
<td>14 (48.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Old HF</td>
<td>49 (66.2)</td>
<td>26 (89.7)</td>
<td>0.025</td>
</tr>
<tr>
<td>ALOS (days) ± SD</td>
<td>08.28 ± 5.96</td>
<td>08.86 ± 4.85</td>
<td>NS</td>
</tr>
</tbody>
</table>

DM = Diabetes mellitus, COAD = Chronic obstructive airway disease, CRI = Chronic renal impairment, ESRD = End stage renal disease, CAD = Coronary artery disease, HF = Heart failure, ALOS = Average length of stay

Table 3: Precipitating factors for old heart failure

<table>
<thead>
<tr>
<th>Factor</th>
<th>N = 75 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet non-compliance</td>
<td>55 (73)</td>
</tr>
<tr>
<td>Drug non-compliance</td>
<td>41 (55)</td>
</tr>
<tr>
<td>Infection</td>
<td>29 (39)</td>
</tr>
<tr>
<td>ACS</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

ACS = Acute coronary syndrome
heart failure as compared to males (89.7% Vs 66.2%, p value = 0.025). Moreover, there were more females with anemia as compared to males (p < 0.05). Significantly more males were smokers and had COAD as compared to females. The ALOS was similar between the two groups.

We analyzed the possible cause of decompensation among patients with chronic heart failure (Table 3). Both diet and drug non-compliance (dietary non-compliance was assumed if the patient, or relative, confirmed that the patient did not comply with the low-salt diet prescribed by our hospital dietitian) represented the major cause of decompensation (73% and 55% respectively). Acute infection was responsible for 39% of the decompensation, ACS for 27% (35% of whom were transferred urgently to the heart center for urgent coronary angiography, i.e., 7 out of 20 patients), uncontrolled blood pressure for 20%, worsening anemia for 8%, and new arrhythmia (mainly atrial fibrillation) for 7%.

In-hospital and discharge medications are shown in Table 4. The majority of patients received either ACEI and / or angiotensin receptor blockers (ARB). On the other hand, a much less percentage of admitted patients received beta-blockers during their hospital stay or upon discharge (20.4 Vs 19.4%). All patients received loop diuretics in the form of furosemide. Less than 40% of the patients received spironolactone, and at least 65% of them received digoxin both during their in-hospital course and at discharge.

Echocardiography was done in 88.5% of our enrolled patients (91 patients). 47.3% of them had preserved LVEF > 45%, 12% of the total patients had normal left ventricular systolic function, i.e., LVEF > 55%.

The total in-hospital mortality for our ADHF patients was 4.9% (one female, and four male patients).

**DISCUSSION**

The characteristics and outcomes of ADHF patients in Kuwait are poorly defined despite the public health importance of this problem which

**Table 4: Inpatient and discharge medications**

<table>
<thead>
<tr>
<th></th>
<th>Medication %</th>
<th>Medication %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>54.4</td>
<td>52.4</td>
</tr>
<tr>
<td>ARB</td>
<td>11.7</td>
<td>11.7</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>20.4</td>
<td>19.4</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>17.5</td>
<td>28.1</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>35.9</td>
<td>39.8</td>
</tr>
<tr>
<td>Furosemide</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>65.0</td>
<td>69.0</td>
</tr>
</tbody>
</table>

ACEI = Angiotensin converting enzyme inhibitors, ARB = Angiotensin receptor blockers

**Table 5: Comparison between the current study and ADHERE and EHFS**

<table>
<thead>
<tr>
<th></th>
<th>EHFS (%)</th>
<th>ADHERE (%)</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>53</td>
<td>48</td>
<td>71.8</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71</td>
<td>72</td>
<td>60.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53</td>
<td>72</td>
<td>75.7</td>
</tr>
<tr>
<td>DM</td>
<td>20</td>
<td>44</td>
<td>73.8</td>
</tr>
<tr>
<td>CAD</td>
<td>68</td>
<td>58</td>
<td>59.2</td>
</tr>
<tr>
<td>Echo performed</td>
<td>66</td>
<td>----</td>
<td>88.5</td>
</tr>
<tr>
<td>LVEF &gt; 45%</td>
<td>55</td>
<td>----</td>
<td>47.3</td>
</tr>
<tr>
<td>ACEI use</td>
<td>62</td>
<td>55</td>
<td>54.4</td>
</tr>
<tr>
<td>Beta-blocker use</td>
<td>37</td>
<td>59</td>
<td>20.4</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>6.9</td>
<td>4.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>

EHFS = Euro Heart Failure Survey, ADHERE = Acute Decompensated Heart Failure National Registry, DM = Diabetes Mellitus, CAD = Coronary artery disease, LVEF = Left ventricular ejection fraction, ACEI = Angiotensin converting enzyme inhibitor

constituted 14.5% of the total medical admissions in one of the general hospital in the country as compared to 6.2% from the Scotland study[6]. The present study highlighted several important features of our patients as compared to some major registries and studies [7-10]. Our patients tended to be younger, and the male percentage was much higher. We conducted a simple comparison shown in Table 5 between our findings and the two major studies i.e., ADHERE and Euro-Heart survey[6,9]. It is clear that some of our co-morbidities like DM and systemic hypertension were more prevalent. Echocardiography was performed more frequently in our study as compared to the other two registries. This could be secondary to the fact that our study was done in one center while the other studies were multicenter studies. A comparable percentage of our patients had preserved LVEF as compared to the other registries. The in-hospital mortality in our study was comparable to the ADHERE study, but lower than the Euro-Heart survey.

A lower percentage of our patients received beta-blockers as compared to the other two studies. This reflects the need for more adherence to guideline recommendations. The percentage of patients receiving either ACEI or beta-blockers in patients with preserved left ventricular systolic function in other landmark trials, (e.g., Euroheart failure survey) was high (58 and 39% respectively)[9]. Moreover, in this study the 12 week mortality benefit extended to this category of patients despite having preserved left ventricular systolic function[9]. This should be taken cautiously due to the lack of randomized controlled trials. The ALOS was similar in our study and the EHFS II study (roughly 9 days)[11].

Renal impairment is considered a predictor of mortality in patients with heart failure. Although 31% of our patients had mild to severe renal impairment, this remains relatively lower than other studies[12].
Study Limitations:
The study period (two months) does not necessarily reflect the true heart failure population during the whole year as seasonal variations may occur. Moreover, a multicenter representation is required. This necessitates the performance of a large multicenter registry nationwide to obtain a better idea about the heart failure population in Kuwait.

CONCLUSION
The prevalence of ADHF in our study was high, although the study was performed only over two months, and in one center. The study showed that we need to adhere to practice guidelines more closely as regards the use of different heart failure medications in the ADHF patients. The study also indicates the need for a nation wide study for better characterization of such an important diagnosis.

Overall, we believe that the current study is the first study of its kind to describe the clinical features of patients with ADHF in Kuwait.

ACKNOWLEDGMENT
This study was supported by the Research Committee of the Ministry of Health, Kuwait.

REFERENCES
INTRODUCTION
Thoracic traumas comprise 10 - 15% of all traumas and are the causes of death in 25% of all fatalities due to trauma[10]. Seventy percent of thoracic traumas are blunt and the remaining are penetrating injuries. Despite timely and aggressive management of blunt and penetrating thoracic trauma, patients with blunt trauma still have a significantly higher mortality than penetrating trauma[1-3]. The management of thoracic injuries are often by tube thoracostomy. However, in many patients these injuries must be treated surgically in one of the three time periods: immediate, urgent, or delayed thoracotomy[5-8]. In this article, we sought to review our experience with blunt and penetrating chest trauma that required surgical intervention.

PATIENTS AND METHODS
This is a retrospective review of all thoracic traumas in six general hospitals in Kuwait city and surrounding regions that required surgical intervention in the form of thoracotomy, sternotomy or other surgical approaches during the period from January 1995 to December 2006. A total of 159 patients were reviewed. All these patients initially presented to emergency departments and following initial assessment and chest radiograph, tube thoracostomy was performed, if indicated, according to the standards of Advanced Trauma life Support (ATLS) guidelines. Fiber-optic bronchoscopy was performed when airway injuries were suspected in the presence of persistent air leak. Computed tomography (CT) of the chest was performed in some cases as indicated by the individual case scenario. Patients were then transferred to the operating room or intensive care unit according to their hemodynamic status and a detailed assessment was carried out by a thoracic surgeon. Indications for urgent surgery include initial chest tube drainage of 1000 ml or consecutive drainage of 200 ml of blood per hour for three consecutive hours; persistence of hypovolemic shock despite aggressive resuscitation in penetrating injuries, massive air leak without lung expansion, evidence of bronchial rupture on bronchoscopy, cardiac tamponade, proven diaphragmatic rupture and endoscopic or radiographic evidence of esophageal injury.

ABSTRACT
Objectives: To review our experience with blunt and penetrating chest injuries that required surgical interventions
Design: Retrospective case series
Settings: Six general hospitals in Kuwait
Subjects: One hundred fifty nine patients who underwent emergency surgery for thoracic trauma
Intervention: Urgent thoracic surgical procedures (thoracotomy or sternotomy)
Main Outcome Measures: Pattern of injuries, indications for surgery, surgical approaches, short-term morbidity and mortality
Results: One hundred fifty-nine patients (68 with blunt and 91 with penetrating injuries) underwent thoracotomy or sternotomy between January 1995 and December 2006. The mean age was 27 years (range: 2 - 70 years). The causes of penetrating injuries were stab wounds (n = 65), gunshot wounds (n = 19) and iatrogenic (n = 7). The causes of blunt thoracic injuries were motor vehicle accidents (n = 63) and fall from height (n = 5). The indications for thoracotomy were hemorrhage (n = 115), airway disruption (n = 14), pericardial tamponade (n = 5), clotted hemothorax (n = 8) and diaphragmatic rupture (n = 17). Major lung resections were performed in four patients (2.5%). The morbidity was 10 / 159 (6%) and the mortality was 7 / 159 (4.4%). The majority of deaths were due to adult respiratory distress syndrome (ARDS).

Conclusion: Prompt thoracotomy can be performed with minimal morbidity and mortality in cases of blunt and penetrating thoracic injuries. The complex pattern of such injuries requires a detailed assessment and management by a thoracic surgeon.

KEY WORDS: blunt thoracic trauma, penetrating injury, sternotomy, thoracotomy

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Demographic data collected included age, sex, specific thoracic injury, time from admission to operative intervention, and outcome. Ethical committee approval was obtained for this study.

RESULTS

There were 159 patients included in this study out of which, 140 patients were male (88%) and 19 were female (12%). The mean age was 27 years (range: 2 - 70 years). Patients' demographics, pattern of injury, mechanism of injury and breakdown of surgical procedures are summarized in Table 1. The operative findings and injury pattern of both groups are summarized in Table 2. As shown, lung was the most frequently injured organ. Out of the study population, 136 patients (86%) underwent urgent thoracotomy/sternotomy within 20 minutes and two hours of admission. The remaining 23 patients (14%) underwent surgical intervention between two hours and 21 days after admission and the breakdown for such cases is depicted in Table 3.

The majority of lung, vascular, cardiac and diaphragmatic injuries were repaired primarily. Lung resection was necessary in two patients with central laceration beyond repair.

A total of 14 patients had traumatic intrathoracic major bronchial disruption (Table 4). Tachypnea and subcutaneous emphysema is the most common findings in these patients. Ten patients out of 14 had pneumothorax and air leak after tube thoracostomy (Fig. 1). The diagnosis was confirmed by bronchoscopy in all patients. The majority of injuries were repaired primarily. Lung resection was necessary in two patients.

In-hospital mortality was 4% (7 patients), out of which three died intra-operatively from cardiac arrest and four postoperatively due to adult respiratory distress syndrome (ARDS). Morbidity was seen in 10 cases (6%) out of which three (2%) were re-operation

<table>
<thead>
<tr>
<th>Table 1: Demographics and distribution of variables in the study population (n = 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Pattern of injury</strong></td>
</tr>
<tr>
<td>Penetrating</td>
</tr>
<tr>
<td>Blunt</td>
</tr>
<tr>
<td><strong>Penetrating injury</strong></td>
</tr>
<tr>
<td>Stab</td>
</tr>
<tr>
<td>Gunshot</td>
</tr>
<tr>
<td>Iatrogenic</td>
</tr>
<tr>
<td><strong>Blunt injury</strong></td>
</tr>
<tr>
<td>Motor vehicle accident</td>
</tr>
<tr>
<td>Fall from height</td>
</tr>
<tr>
<td><strong>Type of surgical approach</strong></td>
</tr>
<tr>
<td>Thoracotomy</td>
</tr>
<tr>
<td>Sternotomy</td>
</tr>
<tr>
<td>Thoracoscopy</td>
</tr>
<tr>
<td>Thoracoabdominal</td>
</tr>
<tr>
<td>Collar</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Prominent thoracic injuries blunt and penetrating (n = 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injury</strong></td>
</tr>
<tr>
<td>Isolated lung</td>
</tr>
<tr>
<td>Lung and combined</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Cardiac injuries</td>
</tr>
<tr>
<td>Diaphragmatic</td>
</tr>
<tr>
<td>Major airway</td>
</tr>
<tr>
<td>Other*</td>
</tr>
</tbody>
</table>

*Includes trachea-esophageal injury and clotted hemothorax

<table>
<thead>
<tr>
<th>Table 3: Delayed thoracotomies / sternotomies (&gt; 2 hours) performed for thoracic injuries (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injury</strong></td>
</tr>
<tr>
<td>Clotted hemothorax</td>
</tr>
<tr>
<td>Unrecognized Diaphragmatic injury</td>
</tr>
<tr>
<td>Missed major airway injuries</td>
</tr>
<tr>
<td>Late bleeding</td>
</tr>
<tr>
<td>Tracheo-esophageal injury</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Infected intra pulmonary hematoma</td>
</tr>
<tr>
<td>Thoracic duct injury</td>
</tr>
<tr>
<td>Valve injury</td>
</tr>
</tbody>
</table>

Fig. 1: Posteroanterior chest radiograph of a child with right pneumothorax despite two chest tubes due to rupture right main bronchus
for bleeding, three patients (2%) had postoperative atelectasis requiring bronchoscopy and suction, two patients (1%) required prolonged mechanical ventilation and two patients (1%) had prolonged air leak that was treated conservatively.

DISCUSSION

Penetrating and blunt thoracic injuries frequently cause serious injuries to pulmonary, cardiac and thoracic vascular structures. Most chest trauma victims can be successfully managed without operation[3,7,8]. Penetrating injuries to the chest in a civilian practice result mainly from stab injuries or gunshot wounds[8] (Fig. 2, 3). In patients who require operative intervention, complex investigations are usually not needed to arrive at a diagnosis and prompt surgery is all that is needed. Delaying urgent surgery and ongoing blood loss are associated with the occurrence of ARDS that will lead to a higher mortality[9]. In this article, we review our experience with blunt and penetrating chest injuries in patients who underwent surgical interventions with emphasis on surgical approaches and postoperative outcome. Our preoperative management strategies include draining pleural collection of blood and air, aggressive resuscitation and when indicated, urgent surgery without resorting to unnecessary investigations.

Most patients sustaining blunt thoracic injuries reaching alive in the emergency department can be managed non-operatively[1-3]. Diagnosis of blunt injuries may be more difficult and require additional investigations such as CT scan. Delayed diagnosis usually reflect concealed injuries such as those depicted in Table 3 and these in turn are associated with delayed operative approach due to failure to recognize them at an early stage. Massive air leak usually denotes tracheo-bronchial injury or massive pulmonary laceration. Early diagnosis and surgical intervention can improve the prognosis[1-3,6]. The diagnosis of major airway injury depends first, on physical examination and then, on findings on chest radiography. Accurate interpretation of the chest radiograph is essential in the diagnosis of bronchial injury. Subcutaneous emphysema and pneumothorax was present in 10 patients in this series. Liberal use of bronchoscopy is important to make the diagnosis. Majority of these injuries can be repaired primarily. We tried to avoid lung resections in patients with lung lacerations. Resections are only resorted to when there is a complex bronchial injury beyond repair. This is to avoid subsequent high morbidity and mortality[3, 6].

Thoracotomy was the principal procedure used in our series, being done in 87% of cases (Table 1). This is in contrast to video-assisted thoracoscopy (VATS) which was done in 8% of cases. VATS can be used safely in hemodynamically stable patients with no cardiovascular or great vessel injury, sparing many patients the pain and morbidity associated with a thoracotomy incision[7]. In addition, VATS can allow visualization of all lung fields. Its use in our series was low due to the emergency nature of our patients. VATS use tends to be reserved for hemodynamically stable patients provided adequate equipment is available. This was not the case since our series encompassed patients operated upon in six different general hospitals, most of which lacked appropriate instruments required for VATS. The use of other techniques such as sternotomy or thoraco-abdominal approach was only limited to some cases (Table 1) as dictated by the initial presentation and assessment of these individualized cases.

Delayed surgical intervention can result in a high mortality. In our series, overall mortality was only 4% (7 patients), three of which died intra-operatively from cardiac arrest and four had developed ARDS postoperatively. Overall morbidity in this series occurred in 10 patients (7%). Only three patients required re-exploration for bleeding. The remainder were due to postoperative atelectasis and prolonged ventilation or prolonged air leak that settled conservatively. Certainly, the complexity of most of these cases necessitates...
management by a dedicated thoracic surgeon. The achievement of low postoperative mortality was the direct result of prompt diagnosis and operative intervention as 86% of the patients in our series had surgery performed within two hours of presentation.

In the emergency department, chest radiography was the most commonly used investigation\(^1,2,8,9\). Fiber-optic bronchoscopy was performed when airway injuries were suspected in the presence of persistent pleural leak\(^1,2\). Echocardiography was done in patients suspected of valve injury or pump failure due to cardiac tamponade\(^10\). CT of the chest is of great value in aiding the diagnosis of blunt trauma\(^11\).

Our criteria for exploration is somewhat more aggressive than the criteria suggested by other authors\(^1,2\) because we found intra-operatively that blood collection in the pleural cavity varied between 300 ml to 3000 ml in all bleeding patients with good functioning and well positioned chest tube. If the decision to perform surgery is based on the bleeding volume, then an unacceptable delay in the treatment will result.

Penetrating injuries under the nipple anteriorly and scapula posteriorly can involve the abdominal cavity and abdominal examination can be unreliable in the presence of great thoracic injury\(^9,10\). It has been stated that gunshot wounds of the thorax can involve the abdominal cavity in 30-40% of cases\(^9\).

We advocate preservation of thoraco-abdominal barrier to prevent thoracic contamination and to preserve the diaphragmatic function. We had to resort to thoraco-abdominal approach in two patients only and they had blunt chest trauma. Most patients with penetrating injuries had primary repair using techniques specific to the injury except for one patient who underwent cardiopulmonary bypass and mitral valve replacement after the primary surgery.

CONCLUSION

Our results indicate that all thoracic injuries that required urgent surgical intervention should be managed by a thoracic surgeon rather than a trauma or general surgeon because of the complexity of the injuries involved. In the timely management of patients with thoracic injuries undue delay should be avoided. Our results suggest that early surgery decreased the morbidity and mortality.

REFERENCES

INTRODUCTION

Although the small intestine constitutes one of the largest surface areas in the human body, less than 3 - 6% of gastrointestinal malignancies occur in the small bowel[1-4]. The tumors may be found (in order of increasing frequency) throughout the duodenum, jejunum, and ileum. Clinically, small bowel tumors are characterized by a lack of identifying symptoms. Abdominal pain is the most common clinical symptom in patients with a tumor of the small bowel[5,6]. On the other hand, bleeding is the most common presenting complaint in patients with benign tumors; obstruction and perforation were found to be associated with malignant tumors[7].

An appreciable number of small bowel tumors apparently cause no serious symptoms during a lifetime. Diagnosis is delayed or missed in many clinical cases because symptoms may be absent or vague and non-specific until significant complications develop. Many small bowel tumors are diagnosed during emergent surgery. Attention to vague symptoms and an aggressive diagnostic evaluation are important for diagnosis and treatment.

MATERIAL AND METHODS

Medical records of 45 patients who were operated on for small bowel tumors at the Department of Surgery, Izmir Bozyaka Teaching and Research Hospital, Turkey from January 1990 to January 2005 were reviewed. The data obtained from the medical records included clinical features, diagnostic workups, operative procedures and pathologic diagnoses. All cases underwent surgery and were confirmed by histopathology. Periampullary tumors were excluded.
The main objective of this retrospective study was to assess the prevalence and clinical importance of small bowel tumors in our medical practice. This study was approved by the ethical committee.

RESULTS

Incidence and demographic features:

Forty-five patients, 38 with malignant and eight with benign tumors of the small bowel were operated on during this 15 year period. During the same period 7,820 patients were operated on in our Department of Surgery giving our clinic an incidence of approximately 5 / 1,000 patients. Multiple tumors were encountered in one patient.

The median age of the patients was 53 years (range, 30 - 83 years) at the time of diagnosis. While mean age at presentation was 63.5 years (range, 59 to 83) in patients with malignant tumors, it was found to be 51.5 years (range, 30 to 62) with benign tumors. There were 26 (57.7%) male and 19 (42.3%) female patients in our series. The male-to-female ratio was 1.4:1.

Symptomatology:

The most frequent complaints were intermittent abdominal pain and nausea-vomiting in 45 (100%) and 33 (73.3%) patients, respectively. Weight loss was found in 16 (35.5%) patients.

The majority of patients had no physical sign of the disease. Abdominal distension, abdominal tenderness and mass were the most common clinical signs, and were found in 23 (51.1%), 18 (40%) and nine (20%) patients, respectively.

Non-urgent presentations were found in 15 (33.3%) patients. Urgent presentations in the form of intestinal obstruction were present in 18 (40%) patients. They were due to simple obstruction in 13 and intussusception in five patients. Intraluminal simple obstructions of the jejunum and ileum were found in three and ten patients, respectively. Intussusceptions were found in the jejunum and ileum in one and four patients, respectively. The initial presentation was acute perforation in 11 (24.4%) patients, seven of whom had an ileal perforation and four of whom had jejunal perforation. Gastrointestinal bleeding was present in one (2.2%) patient with a duodenal tumor (Table 1). Two patients had a history of another primary malignancy (lung cancer). The secondary tumors turned out to be metastases from lung cancer in these patients.

Diagnosis:

Preoperative diagnosis was made by enteroclysis, gastro-duodenoscopy, ultrasonography (US) and computed tomography (CT). Evidence of an intestinal obstruction was demonstrated in 17 (37.7%) patients by plain abdominal X-ray. Pneumoperitoneum was noted in eight (17%) patients. Small bowel series (enteroclysis) were used as diagnostic investigations in four (8.8%) cases with suspected clinical findings. Enteroclysis revealed small bowel abnormalities in all patients. The male-to-female ratio was 1.4:1.

Table 1: Preoperative condition of patients with respect to the biological nature of the tumor

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Malignant n (%)</th>
<th>Benign n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>30 (66.6)</td>
<td>15 (33.3)</td>
</tr>
<tr>
<td>Nausea-vomiting</td>
<td>27 (60.0)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>1(2.2)</td>
<td>-</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>12 (26.6)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>19 (42.2)</td>
<td>4 (8.8)</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>4 (8.8)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Weakness</td>
<td>13 (28.8)</td>
<td>3 (6.6)</td>
</tr>
<tr>
<td>Non-urgent</td>
<td>12 (26.7)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Urgent (Obstructive)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple obstruction</td>
<td>11(24.4)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Intussusception</td>
<td>3 (6.7)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Perforation</td>
<td>10 (22.2)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (2.2)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2: Distribution of the tumor location according to pathologic diagnosis

<table>
<thead>
<tr>
<th>Pathologic diagnosis</th>
<th>Duodenum n (%)</th>
<th>Jejunum n (%)</th>
<th>Ileum n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td></td>
<td></td>
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<td>Adenocarcinoma</td>
<td>1 (2.1)</td>
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<tr>
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<td>3 (6.5)</td>
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<td>9 (19.6)</td>
</tr>
<tr>
<td>Malignant GIST†</td>
<td>2 (4.2)</td>
<td>-</td>
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<td>7 (15.2)</td>
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<tr>
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<tr>
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<td>2 (4.3)</td>
<td>2 (4.3)</td>
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<tr>
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<tr>
<td>Leiomysma</td>
<td>-</td>
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<tr>
<td>Mesenchymal tumor</td>
<td>-</td>
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<td>-</td>
<td>1 (2.1)</td>
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<tr>
<td>Total</td>
<td>3 (6.5)</td>
<td>12 (26.1)</td>
<td>31 (67.4)</td>
<td>46 (100)</td>
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</table>

† Gastrointestinal stromal tumor, ‡ Neuroendocrine tumor
Treatment:
Thirty (66.7%) patients underwent emergency operations and 15 (33.3%) received elective surgical intervention. Segmental resection of the small bowel with end to end anastomosis was carried out in 41 (91%) out of the 45 patients. Among the malignant and benign tumors, segmental resections of the jejunum-ileum were performed in 40 (88.8%) patients and a duodenum resection was performed for one patient (Fig. 3A-B).

Four patients were deemed unresectable because of locally advanced disease of the ileum. In these cases, only biopsy was performed.

Anatomical distribution and characteristics of the tumors:
Thirty-one (68.8%) of the 46 lesions arose in the ileum, 12 (26.1%) arose in the jejunum and three (6.6%) occurred in the duodenum. Thirty-eight (82.6%) malignant and eight (17.4%) benign tumors were identified (malignant-to-benign ratio, 4.7:1). The anatomical distribution of the malignant tumors was as follows: the tumor presented in the ileum, jejunum and duodenum in 26 (57.7%), nine (20%), and three (6.6%) patients, respectively (Fig. 4 and 5). Benign tumors were found more commonly in the ileum and jejunum, with five and three patients presenting with a tumor in each region, respectively. In one case, a synchronous tumor, adenocarcinoma, was found in the duodenum and jejunum. The distribution of tumor locations in patients, as obtained via a pathologic diagnosis, is shown in Table 2. Lymph nodes were involved in the diagnosis of the tumors in seven (15%) patients, and the histological types of the observed tumors were adenocarcinoma, neuroendocrine tumor (NET), lymphoma and malignant melanoma in three, two, one and one patients, respectively. The histopathologic types of the unresectable tumors were adenocarcinoma and NET. There were two occurrences of each type. Two patients had secondary tumors from lung cancer presenting as small bowel malignancies.

DISCUSSION
The clinical presentation of small bowel tumors is frequently insidious and often overlooked by physicians[2]. This delay is probably due to the fact...
that patients are reluctant to go see a physician on account of indefinite symptoms. On the other hand, physicians may not recognize the importance of mild symptoms as they relate to small bowel tumors. Although, Rankin et al reviewed and analyzed the characteristics of these tumors 70 years ago[8], few advances have been made since.

Thus, in this article, we hope to highlight the seriousness and importance of small bowel tumors and to attract the attention of individuals who may interact with small bowel tumors.

Over 75 - 90% of small bowel tumors occur in patients between 45 and 60 years of age. In our study, the mean age was 53 years, which is comparable to that in other studies[9]. Our study reports the male-to-female ratio to be 1.4:1. The male-to-female ratio ranged from 1.4:1 to 3.1:1 in other series[9,10].

In our study, the most common symptoms were abdominal pain (100%), nausea-vomiting (73%) and obstruction (40%). These symptoms have been reported to occur in 8 - 80% of patients[11-13]. While in one series[14], intestinal obstruction, hemorrhage and pain were found to be the most common symptoms, we discovered similar findings in four previous studies[11-13,15].

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Other investigators have analyzed the correlation between the symptoms associated with and the types of the tumors[16]. While they have suggested that malignant tumors, typically scirrhoues and prone to result in a narrowing of the lumen, are associated with a higher proportion of symptoms, signs and episodes of obstruction[9], benign tumors are generally characterized by slow growth and a delayed clinical presentation. In one study, tumor size was reported to be associated with abdominal complaints while it was not found to be a factor according to another series (regardless of tumor type or tumor location)[17].

The malignant-to-benign tumor ratio is most commonly reported to be 4:1. In our series, the ratio was 4.7:1. Others showed an equal frequency of benign and malignant lesions[1,3,18].

In our study, obstruction and perforation were found to be the most common, while bleeding was only observed infrequently (40%, 24.4%, and 2.2%)[8,10,19]. Intestinal obstruction (34%) was more commonly associated with malignant tumors, while gastrointestinal bleeding occurred in 32% of patients[3]. In one series, perforation through small bowel malignant tumors was found in 5.1 - 30% of the cases[11].

In 1979, in a series of small bowel tumors, 50% of the tumors were reported to be present in the ileum, 41% in the jejunum, and 15% in duodenum[10]. In a final retrospective study, the most prevalent tumor sites were found, interestingly, to be the ileum (29%), duodenum (25%) and jejunum (15%)[20]. In our series, tumors were found to occur 68.8% in the ileum, 26.1% in the jejunum and rarely, 3.3% in the duodenum. However tumors may be found (in order of increasing frequency) throughout the duodenum, jejunum and ileum[1,18,21].

Histologically, adenocarcinoma was found to be the most common type of malignant tumor in multiple series[22]. The remaining tumors were NETs, gastrointestinal stomal tumors (GISTs) and lymphomas[3,4,23]. In our group, 28.3% of the cases were reported to be (in order of decreasing frequency) adenocarcinoma, lymphoma, GISTs and NETs. In a clinical study, the most prevalent histologic type was identified as NET(33%), followed by adenocarcinoma and lymphomas[20]. On average, adenocarcinomas are distributed most frequently in the duodenum followed by the jejunum and ileum, whereas lymphomas are more common in the jejunum and the ileum. In our study, adenocarcinomas and lymphomas were mostly located in the ileum. Interestingly, lymph node metastases have been reported in approximately half of the patients at the time.
of operation, while we found metastasized lymph nodes in 15% of the patients. Secondary tumors may involve the small bowel by hematogenous, direct, or intraperitoneal seeding. In our data, two of the observed secondary tumors metastasized from lung cancer. In some cases, the clinical manifestations of metastases are observed before those of the primary tumor.

Diagnostic accuracy has been enhanced via diagnostic imaging methods such as small bowel series (enteroclysis), US, and CT. Abdominal US is generally not helpful in the diagnosis of small bowel tumors, as was the case in our series. CT findings are used to diagnose small bowel obstruction with a dilated proximal small bowel and a collapsed distal small bowel and colon. The “small bowel feces” sign is present in half of patients. CT-enteroclysis findings analyzed in patients who were suspected of having a small bowel tumor showed a sensitivity and a specificity of 100% and 95%, respectively. Gastro-duodenoscopy is not available for jejunum and ileum lesions, but resulted in a sensitivity of 90% for the diagnosis of duodenal tumors. Over the last few years capsule endoscopy has been used to provide a more detailed inspection of the small intestine. In one study, the incidence of small bowel tumors was found to be 8.9% in patients who underwent capsule endoscopy for bleeding. Capsule endoscopy can be performed safely in almost all clinical settings. Complete intestinal obstruction and pregnancy are the only true contraindications to capsule endoscopy.

Recently, laparoscopy is being used more frequently as a diagnostic tool. The indications have varied from acute or chronic abdominal pain to intestinal obstruction. Laparoscopy not only provides a visualization of the small bowel but also provides cure by resection of the tumoral lesion. Laparoscopic resection was found to have favorable short-term outcome for tumors in selected cases but it is not appropriate for oncologic treatment. Elective surgical intervention was performed more frequently than the emergency intervention in some series. Surgery is usually the cornerstone of small bowel tumor therapy. Surgical resection of the tumor is the recommended therapy in case of small bowel tumors. In one study, significantly longer median survival was found for the resected group (26 months versus 11 months). Both segmental resection and enterotomy / polypectomy have been used for lesion removal.

Tumors discovered incidentally during a laparotomy should be removed to prevent future symptom development and secondary complications. If the pathology cannot be established at the time of resection, full segmental resection with adequate margins is recommended. In our study, 66% of the patients were operated on urgently, and adequate segmental resection was performed in 41 (91%) patients. The best outcome for patients with a non-metastatic disease occurred when oncologic surgery was performed. Surgical intervention, if done early, results in a better long-term prognosis.

Our observations suggest that diagnosis is delayed or missed in many clinical cases because the symptoms may be vague and non-specific until significant complications develop. A preoperative diagnosis remains difficult, and it is almost impossible to distinguish between malignant and benign tumors. Due to the unusual symptoms, the rarity of the disease, and the difficulty of small bowel imaging, a correct diagnosis is often delayed. Aggressive evaluation must be carried out for subtle symptoms and non-specific clinical presentations.

CONCLUSION
Our results are in agreement with those reported literature and support the conclusion that a high index of suspicion together with diagnostic imaging methods are useful in improving the diagnostic accuracy in patients with non-specific, vague, and variable symptoms and signs. In the event of negative findings, we believe that early laparotomy is necessary because of a likelihood of a small bowel tumor and the risk of tumor progression.

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Clinical and Radiological Aspects of Closed Reduction in Developmental Dysplasia of the Hip Treated in the First Six Months

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¹Department of Orthopedics, Al-Razi Hospital, Kuwait
²Department of Pediatric Orthopedics, Altona Children Hospital, Hamburg, Germany

ABSTRACT

Objective: To evaluate the success rate and subsequent restoration of normal acetabular angle (AC°), and associated growth changes secondary to avascular necrosis of the proximal femur in cases of developmental dysplasia of the hip (DDH) treated during the first six months of life

Design: Retrospective study from 1998 to 2006

Setting: Department of Pediatric Orthopedics, Altona Children Hospital, Hamburg, Germany

Subjects: Twenty six patients with twenty nine dysplastic hips were evaluated regarding grade of hip dysplasia. The success rate of closed reduction, postoperative restoration of normal acetabular coverage (AC angle) and associated complication were noted.

Intervention: Closed reduction of DDH with intraoperative arthrogram followed by spica cast

Main Outcome Measures: Success rate of closed reduction and restoration of normal acetabular index.

Results: Closed reduction could be achieved in twenty two hips (76%). Out of those twenty two hips fifteen (68%) developed normal acetabular index, six (27%) showed persistent acetabular dysplasia and one (5%) had borderline measurement. Closed reduction was not successful in seven hips. Those seven hips were treated by open reduction and capsulorrhaphy.

Conclusion: Closed reduction of DDH in the first six months of life was achieved in (76%) of dislocated hips, and did not show any significant growth changes in the proximal femur. The early changes in the ossific nucleus of capital femoral epiphysis (CFE) alone were found to be of very little value in predicting the nature of development of the hip.

INTRODUCTION

In developmental dysplasia of the hip (DDH) early reduction is the main goal of treatment to make use of the greatest potential for acetabular remodeling. The cartilaginous femoral head in the early months of life is extremely vulnerable to avascular necrosis (AVN). Indeed this is the period during which the results of closed reduction treatment can and virtually be perfect[1].

In the presence of ossific nucleus of capital femoral epiphysis (CFE) hips can be evaluated radiographically but before ossification cartilaginous femoral heads are evaluated using ultrasound. The Graf method focuses on the evaluation of anatomic characteristics of the hip[2]. This is accomplished by measuring the alpha angle, a measure of the slope of the superior aspect of the acetabulum, and beta angle, which evaluates the cartilaginous component of the acetabulum. With the Graf classification morphological features of the anatomy are converted into hip types.

The aim of this study was to evaluate the success rate and subsequent restoration of normal acetabular angle (AC°), and associated growth changes secondary to avascular necrosis of the proximal femur in cases of DDH treated in first six months of life.

PATIENTS AND METHODS

The records of children with DDH admitted and treated in the Pediatric Orthopedic department in Altona Children Hospital, Hamburg, Germany between June 1998 and January 2007 were reviewed. Only cases of DDH that satisfied our criteria were included. Inclusion criteria were cases treated by closed reduction in the first six months

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of life with Graf sonographic classification II D and
higher or Tonnis radiographic classification type
2 and higher and a minimum of two years follow
up. The exclusion criteria included all cases with
insufficient data or incomplete follow up, cases
with epiphyseal dysplasia, arthrogryposis or caudal
regression syndrome, all neuromuscular cases or
cases complicated by septic arthritis of the hip.

The final study group included 26 patients (29
hips). In cases where capital femoral epiphysis
(CFE) had not yet appeared Graf sonographic
hips). In cases where capital femoral epiphysis
was used in six hips after
the mean ± 2SD of normal. Any acetabular angle

Table 1: Patient data, pre-reduction evaluation and post reduction findings

<table>
<thead>
<tr>
<th>Sex</th>
<th>Affected hip</th>
<th>Age at reduction (months)</th>
<th>Pre-reduction U/S (Graf)</th>
<th>Pre-reduction radiograph Tonnis</th>
<th>Normalization of AC*</th>
<th>Changes in CFE</th>
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O.R = open reduction, SD = standard deviation, CFE = capital femoral epiphysis, D = decentered hip

intra-operative arthrogram (Fig. 1) was used in all
cases to confirm concentric reduction[4]. Reduction
was defined as concentric if the hip was located
anatomically with minimal medial dye pooling.
Clinical stability was assessed according to the
safe zone of Ramsey[5]. The reinforcement of tactile
sensation of the hip stability by visualization during
arthrography is invaluable in the management of
DDH[6]. Hips requiring more than 60° of abduction
were considered unstable and booked later for
open reduction. Post reduction, all cases were kept
in spica cast in the human position[6]. After four to
six weeks all cases underwent removal of spica cast,
re-arthrography and examination under anesthesia.
The plaster (POP) was kept for an average period
of 8.3 weeks (range: 4 -12 weeks). After removal of
spica cast all cases were kept in abduction brace
for an average period of three to six months. The
average period of follow up was 42.4 months (range:
24 – 93 months).

Avascular necrosis of the femoral head was
defined according to the radiographic criteria of
Bucholz & Ogden[7] which includes criteria of AVN
described by Salter[8] supplemented by criteria of
partial AVN of Gag & Winter\cite{8} (Table 1). This study was approved by the hospital ethical committee.

RESULTS

Out of the 29 hips there were 21 female and five male patients. The left hip was involved in 14 patients, the right side in nine and three patients had bilateral involvement.

The average age at intervention was 2.6 months (range: 1 – 6 months). Closed reduction was achieved in 22 hips (76 %). Although three hips showed initial irreducibility they were successfully reduced after traction.

Cases in which closed reduction was achieved successfully were followed radiographically every three to five months. Fifteen hips (68%) showed normal AC angle after an average period of 13 months (range: 6 – 20 months); six hips (27%) although kept reduced and stable showed persistent acetabular dysplasia and pelvic surgery (extra-articular Salter or Dega) was later performed after an average period of 24 months (range: 18 - 28 months) with the exception of one hip which was operated upon after 48 months. One hip (5%) had borderline measurement.

On the other hand, closed reduction was not successful in seven hips (24%). Out of these, three failed even after two attempts at closed reduction. Failure to achieve closed reduction was either due to irreducibility (three hips) or instability (four hips). These seven hips were treated with open reduction (Table 2).

During follow up there were minor abnormalities of the femoral head in eight cases of which four showed mottling or rarefaction and four were smaller. At latest follow up all had recovered to normality without growth disturbance or evidence of AVN.

DISCUSSION

Early closed reduction of DDH makes use of the greatest remodeling potential in this age group. The success to achieve closed reduction with or without traction and the incidence of AVN was studied by many authors. Pre-reduction traction is described by some authors to be of value to facilitate closed reduction\cite{9,10} or decrease incidence of growth disturbance of proximal femur\cite{11}. However, other authors deny this\cite{12}. AVN is a well known complication of DDH treatment that adversely affects the function of the affected hip in spite of good containment.

Quinn et al, after a routine use of traction reported a success rate of (58%)\cite{13}. In the older age group using guided abduction traction Tavares et al were able to achieve closed reduction in a higher percentage of hips (74%) and they reported a 7.4% incidence of AVN\cite{14}. In our study although traction was applied only in five cases, closed reduction was achieved in 76% of hips and no significant growth disturbances were reported.

Kalamchi and MacEwen reported that the most severe form of AVN occurred in cases that received treatment in the first six months and they found

| Table 2: Summary of the results |
|------------------|------------------|------------------|------------------|
| Age at reduction (months) | No. of pts. | Total No. of hips | Successful closed reduction (CR) 76% | Failed (CR) 24% |
|                    |                  |                  | Normal AC° n %  | Abnormal AC° n %  | Borderline n % | n |
| 2.6                | 26               | 29               | 15 68           | 6 27             | 1 5            | 7 |
that changes in the CFE alone were found to be of very little significance in predicting the nature of the development of the hip. In our study the eight cases with mottling and smaller CFE had grown normally during follow up and matched the results of Kalamchi et al although no cases reported with significant growth changes (AVN).

CONCLUSION
Closed reduction of DDH for children between one and six month old could be achieved in 76% of cases but the method was overall successful in only 68% in which normal AC° was restored.

The early changes in the ossific nucleus of CFE alone were found to be of very little value in predicting the nature of development of the hip as all these changes resolved and the CFE grew to normal size without significant growth disturbance (AVN). Pre-reduction traction did not significantly affect the success rate of closed reduction or the incidence of AVN.

ACKNOWLEDGEMENT
The author would like to thank Dr. Ralf Stuecker and the staff of Altona Children Hospital for the help offered in the preparation of this manuscript.

REFERENCES
INTRODUCTION

Antipsychotic medications are the mainstay of treatment for psychotic illnesses. The conventional or first generation antipsychotics (FGAs) were introduced in 1950 and are effective in treating positive symptoms of psychosis. FGAs do not, however, adequately alleviate negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment, and affective symptoms. With the introduction of the atypical antipsychotics in late 1980s, the use of these medications has soared. These newer antipsychotics have many notable benefits compared with their earlier counterparts, but their use has been associated with reports of dramatic weight gain, diabetes mellitus, even acute metabolic decompensation, e.g., diabetic ketoacidosis (DKA) and atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol). There are few reports in the literature indicating that olanzapine, a newer antipsychotic agent is associated with new onset or worsening of pre-existing diabetes mellitus, weight gain and metabolic syndrome. With the introduction of the atypical antipsychotics in late 1980s, the use of these medications has soared. These newer antipsychotics have many notable benefits compared with their earlier counterparts, but their use has been associated with reports of dramatic weight gain, diabetes mellitus, even acute metabolic decompensation, e.g., diabetic ketoacidosis (DKA) and atherogenic lipid profile (increased LDL cholesterol and triglyceride levels and decreased HDL cholesterol). There are few reports in the literature indicating that olanzapine, a newer antipsychotic agent is associated with new onset or worsening of pre-existing diabetes mellitus, weight gain and metabolic syndrome. However, severe DKA as presenting manifestation is very rarely reported in the literature. Increased physician awareness about the emergence of insulin resistance syndrome / metabolic syndrome and precipitation of life threatening side effects like DKA with atypical antipsychotic agents is of great importance.

KEY WORDS: atypical antipsychotics, diabetic ketoacidosis, olanzapine

Case Report

Severe Diabetic Ketoacidosis Precipitated by an Atypical Antipsychotic Drug

Mohammad Naeem Niazy, Thomas Isaac Neyyarapally, Ghassan Baidas
Department of Internal Medicine, Al-Sabah Hospital, Kuwait

ABSTRACT

We report a case of a young Kuwaiti gentleman who presented with severe diabetic ketoacidosis (DKA) associated with atypical antipsychotic drug olanzapine. The current medical literature suggest that atypical antipsychotic drugs, including olanzapine lead to weight gain, insulin resistance, impaired glucose tolerance (IGT), diabetes mellitus (DM) and rarely patient may presents with serious side effects like DKA. Clinicians are urged to monitor the emergence of metabolic risk factors periodically and remain aware of potentially serious effects like DKA in schizophrenic patients taking olanzapine.

INTRODUCTION

A 28-year-old Kuwaiti patient is diagnosed to have schizophrenia for the last eight years. He was on conventional antipsychotic drugs, but his symptoms were not fully controlled. He was initiated on olanzapine eighteen months ago. There was no past and family history of diabetes mellitus, hypertension, dyslipidemia or ischemic heart disease. He was brought in a state of stupor and confusion to emergency and was found to be severely dehydrated. He had significant osmotic symptoms (polyuria, polydipsia) for the last 20 days.

On examination, the patient was drowsy but arousable, had sinus tachycardia and tachypnea. Oxygen saturation was normal on room air. He was obese (BMI 37.7 kg/m²) and had normal BP (130/90). Systemic examination (CNS, CVS, respiratory system and abdomen) was unremarkable. Baseline investigations (Table 1) demonstrated DKA. Calculated anion gap was 27.8 mmol (normal range = 10-18 mmol). ECG revealed sinus tachycardia and CT brain, USG abdomen, ECHO and chest X-ray were normal.

DKA induced by olanzapine was diagnosed; he was treated with insulin, IV fluids and potassium supplements and the antipsychotic drug was stopped. Following withdrawal of olanzapine, hyperglycemia and acidosis improved gradually and ketonuria disappeared over next seven days. He was discharged on two doses of insulin mixtard. Later in view of recurrent hypoglycemic symptoms,
insulin was tapered and he was normoglycemic without insulin after one month of discharge. Olanzapine was replaced with risperidone for the treatment of worsening of his negative schizophrenic symptoms.

**DISCUSSION**

Data from most studies suggest that the prevalence of both DM and obesity among individuals with schizophrenia and schizoaffective disorders is 1.5 – 2.0 times higher than in the general population\(^1,2\). In the treatment of schizophrenia, atypical antipsychotics are preferred over conventional antipsychotics due to lack of adequate response of negative symptoms and high rate of extra-pyramidal side effects of conventional antipsychotics\(^3\). Atypical antipsychotic drugs especially olanzapine and clozapine have been found to induce weight gain, hypercholesterolemia, hypertriglyceridemia and DM. However DKA is extremely rare as a
presenting manifestation. Patients developing secondary diabetes mellitus following olanzapine are about 10 years younger than what is seen in the community[4]. The relative risk (RR) of olanzapine induced DM is 4.2 compared to the risk associated with conventional antipsychotics and 5.8 compared to those patients with no treatment[5]. Hyperglycemia and DKA related to olanzapine may occur approximately 10 days to 18 months following the initiation of the drug[6].

The temporal relationship of secondary DM and precipitation of DKA from olanzapine is confirmed in this case as the patient became normoglycemic spontaneously after one month of cessation of the drug (Fig. 1). Secondary DM and other metabolic abnormalities like weight gain, obesity, hyperlipidemia and hypertriglyceridemia were present in our case at the time of presentation and improved remarkably after cessation of olanzapine.

The most likely mechanisms of abnormal glucose homeostasis with olanzapine and other atypical antipsychotics are probably through weight gain and obesity, mediated by central nervous system blockade of the serotonin receptor 5HT2C[7,8] (Fig. 2). Olanzapine also induces hyperinsulinemia and insulin resistance[9]. Recent postulate denotes that olanzapine has an inhibitory role in insulin secretion through potent anticholinergic activity at the islet cells of pancreas[10]. Although patients similar to our case are reverted to an euglycemic state and regression of hyperlipidemia, the negative symptoms worsens on cessation of atypical antipsychotics. It has been suggested to continue on atypical antipsychotic olanzapine with regular monitoring and control of the blood sugar with appropriate anti-diabetic treatment under the guidance of specialists[11].

Recent guidelines for prevention and treatment of associated risks in patient using atypical antipsychotic drugs suggest a close monitoring of the patients about the emergence of metabolic risk factors, such as dyslipidemia, IGT, insulin resistance, DM and potentially serious metabolic side effects like DKA[1].

**CONCLUSION**

This case highlights the need for increased physician awareness about the serious side effects like DKA with olanzapine. Atypical antipsychotic induced metabolic side effects like insulin resistance, weight gain, IGT / DM and rarely DKA needs specialist supervision.

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**REFERENCES**

Case Report

Acquired Hemophilia in a Child: Response to Rituximab

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ABSTRACT

Acquired hemophilia, secondary to factor VIII inhibitors, is very rare especially in childhood. We present the case of an otherwise healthy Kuwaiti boy who presented with spontaneous factor VIII inhibitors at the age of two years, making him one of the youngest to be reported. There was no associated acute illness, recent vaccination or drug intake except a history of mild bronchial asthma. He presented with multiple ecchymoses, but no frank bleeding. His lowest factor VIII level was 8% and highest inhibitor level was 400 Bethesda units (BU)/ml. He initially responded to a combination of intravenous immunoglobulin, prednisolone and azathioprine. However he relapsed and later became refractory to treatment. He had a trial of mycophenolate, to which he did not respond. He eventually received rituximab 375 mg/m² as a six-week IV course, to which he had a prompt response without any major side effects. More than two years later, his factor VIII level is about 150% and inhibitor is not detectable. It appears therefore, that even in childhood, rituximab is useful for the management of acquired factor VIII inhibitors.

INTRODUCTION

Acquired inhibitors of coagulation may be alloantibodies or autoantibodies. The former are well-recognized in patients with severe congenital coagulation factor deficiencies, especially of factors VIII and IX. They are clotting factor-specific and generally retained for variable periods of time. Autoantibodies are seen in non-hemophiliacs and are of two general types - specific (directed against a single clotting factor) and non-specific inhibitors (interfering in some fashion with clotting factor interaction). The lupus antagonist (LA) is the most common non-specific inhibitor; it occurs in approximately 10% of adult patients with systemic lupus erythematosus. Specific inhibitors of coagulation are monofactor-specific and are directed at specific regions of the coagulation factor molecule[1-3].

Acquired factor VIII inhibitors are uncommon in adults and even rarer in children[2]. They have been reported in patients with underlying disorders like lymphoproliferative disorders, leukemia and autoimmune diseases; following vaccination, ingestion of drugs (e.g., penicillins) and postpartum[4-5]. The presence of these inhibitors has been associated with serious and life-threatening bleeding. Treatment is mainly directed at controlling the bleeding and eliminating the inhibitors. Spontaneous disappearance of the inhibitors has also been reported[5]. Here we report the case of acquired factor VIII inhibitor in a boy who presented at the age of two years, making him probably the youngest such patient in literature.

Case Report

A two-year old Kuwaiti boy presented for the first time in April 1995 with multiple bruises, mainly on his chest. There was no history of significant trauma, infection, recent vaccination or drug intake. There was no previous history of prolonged bleeding or excessive bruising. He had normal perinatal and developmental history and he had been quite well except for mild bronchial asthma. His parents were well and there was no family history of a bleeding disorder.

Physical examination was unremarkable except for significant ecchymosis. There was no lymphadenopathy and no hepatosplenomegaly. Imaging studies including X-ray and CT chest and abdomen were normal. Complete blood count (CBC), bleeding time and prothrombin time were normal, but activated partial thromboplastin time (APTT) was prolonged (82 seconds; control 31 seconds) and INR was 1.1. Factor VIII level was 8% and inhibitor screen showed the presence of a time-dependent inhibitor. Anti-nuclear and anti-dsDNA antibodies were negative. He was referred to the Royal Free Hospital London, UK in June 1995. Repeat investigations showed a normal PT, APTT was 91 seconds (control 28-38 seconds), factor VIII bioassay was < 1 u/dl and investigations confirmed the presence of type II acquired factor VIII inhibitors at a level of 14-24 Bethesda Units (BU)/ml.

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He received intravenous immunoglobulin (IVIG) at a dose of 1 g/kg for two days to which he showed no response. Another course of IVIG was given two weeks later without any significant change. His FVIII inhibitor level increased to 258 BU/ml and he was started on oral prednisolone 1 mg/kg in addition to further courses of IVIG. He responded with a decline in inhibitor level to 50-60 BU/ml. Unfortunately, in February 1996, while still on prednisolone, he had a rebound in his inhibitor level to 400 BU/ml and he was started on azathioprine 3 mg/kg per day, in addition to prednisolone. He responded well and was maintained on this regimen till inhibitors were no longer detected by June 1997. Prednisolone was tapered over six months and azathioprine was continued for about ten months (until April 1998).

He was in full remission till November 2000, when his factor VIII level dropped to 9%. He was asymptomatic; there was no history of preceding infection, vaccination or drug ingestion. His physical examination was normal. Repeat CBC, serum immunoglobulins, ESR, ANA, anti dsDNA were negative. So he was given IVIG and restarted on oral prednisolone and azathioprine. Factor VIII level normalized after two months. He was tapered off his medication slowly over a one year period and he was in remission for a year until November 2002 when he had another relapse and since then he could not be weaned off prednisolone. He continued to have ecchymoses and had bleeding into the right thigh muscles on two occasions with no sequelae and no life-threatening bleeding. In 2004 he was given a two-month trial of mycophenolate, to which he did not respond. In June 2005 he was evaluated in St. Louis, MO, USA and given a six-week course of rituximab 375 mg/m² dose, to which he responded promptly. He did not develop any adverse side effects. When he was last evaluated in June 2007, he remains well and currently his factor VIII level is about 150% and his inhibitor level is undetectable.

**DISCUSSION**

Acquired hemophilia is uncommon and most of the published data is on adults. To the best of our knowledge there are only twenty reported cases in children, the youngest being a three year old boy[2]. Our patient was only two years old at initial presentation, and he had one of the highest reported levels of inhibitors. He had bronchial asthma during early childhood, which is one of the conditions that have been associated with acquired inhibitors[2-3]. However, we could not establish a causal relationship and the bronchial asthma could have been simply coincidental.

Our patient presented with spontaneous soft tissue bleeding (subcutaneous and intramuscular), which is the usual mode of presentation in acquired hemophilia, though serious bleeding episodes have been reported in some patients[1-3]. The treatment options are directed at controlling the bleeding as a first and urgent step and eliminating the inhibitors[3]. For controlling bleeding, human factor VIII concentrate in high doses or desmopressin acetate is effective in patients with low titers of inhibitors and measurable factor VIII levels[4]. Porcine factor VIII is another effective alternative[2,3,5], but the development of heteroantibodies to porcine factor VIII has been reported. Therefore, it is recommended to check for porcine factor VIII inhibitor titers prior to porcine factor VIII administration. In patients presenting with severe bleeding or very low FVIII level and very high inhibitor titers, other alternatives should be used[6]. Activated prothrombin complex concentrate, with factor VIII inhibitor-bypassing activity, has proved to be effective in controlling episodes of bleeding[7]. Recombinant activated factor VII is effective and it is not associated with the development of antibodies but it is expensive and has a short plasma half life requiring frequent or continuous infusions[8].

Plasmapheresis or immunoadsorption can rapidly reduce inhibitor levels but the effect is transient[9,10]. IVIG at a dose of 1 g/kg/day for two consecutive days or 400 mg/kg for five consecutive days, has been used with varying results[11,12]. Immunosuppressive therapy with corticosteroids and cytotoxic drugs alone or in combination, is regarded as the mainstay of treatment[13]. In most of the published data prednisolone at a dose of 1 mg/kg per day was used initially and cyclophosphamide, at a dose of 2 mg/kg/day, was added later; or treatment was initiated with both drugs at the same time[14]. Several other immunosuppressive agents, including azathioprine, mycophenolate, cyclosporine, tacrolimus and sirolimus have been used with varying success rates[3]. Our patient responded to prednisolone initially but relapsed seven months later leading to the addition of azathioprine. Remission was subsequently achieved, but his course was variable with relapses. He did not respond to mycophenolate. We were wary of using cyclophosphamide because of his age and also since he never had life-threatening bleeding.

Rituximab, a chimeric anti CD 20 monoclonal antibody, depletes B-cells and has shown dramatic success in the treatment of lymphoma. It has been tried in the treatment of several diseases with an autoimmune basis both in adults and in children with very encouraging results[15]. Recent studies have proved its efficacy in adults with acquired hemophilia either as a monotherapy or combined with an immunosuppressive agent in patients with partial response or high antibody titers[16-18]. To the best of our knowledge, rituximab had not been tried for acquired
hemophilia in the pediatric population. Our patient showed dramatic response with no significant side effects. It appears, therefore, that the drug may be a useful addition to the treatment regime in childhood acquired hemophilia.

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REFERENCES


Case Report

Short QT Syndrome: A Case Report and Review of Literature

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ABSTRACT

Short QT syndrome (SQTS) was described for the first time in 2000. This report describes a case of SQTS in a 29-year-old male patient with resuscitated cardiac arrest in whom the diagnosis was missed in the first instance due to a lack of suspicion. Characteristic electrocardiographic findings provided the diagnosis. The patient was referred for the definitive implantable cardioverter defibrillator (ICD).

KEY WORDS: atrial fibrillation, short QT syndrome, sudden cardiac death, ventricular fibrillation, ventricular tachycardia

INTRODUCTION

Short QT syndrome (SQTS) is a recently described familial disorder. The real incidence and prevalence of this disorder is not known. Patients with this syndrome have a high risk for cardiac arrhythmias\(^1\). Mutations in genes encoding for cardiac potassium channels have been identified to cause SQTS\(^3\). The diagnosis depends on a combination of one or more symptoms of syncope, cardiac arrest, palpitation, family history of sudden cardiac arrest, and the characteristic electrocardiographic (ECG) findings. The mainstay of treatment is the implantable cardioverter defibrillator (ICD)\(^4\).

CASE REPORT

A 29-year-old male presented to the emergency department (ED) with sudden collapse and loss of consciousness of 20 minutes duration. Basic life support was initiated by a bystander. In the emergency room patient had decreased level of consciousness, blood pressure (BP) 100/70, pulse 110/min regular and a respiratory rate of 16/min. Examination of other systems was normal. The patient was intubated for airway protection and ventilated and then transferred to the intensive care unit (ICU). In the ICU the patient developed many attacks of ventricular tachycardia (VT) in the form of polymorphic ventricular tachycardia (Fig. 1) which was treated successfully with direct current (DC) shock and intravenous (IV) amiodarone. Further history obtained from the patient confirmed the absence of any symptoms before the collapse, as well as the absence of any past medical or drug history. Family history revealed that his sister died suddenly at the age of 35 years. Investigation showed a normal complete blood count, erythrocyte sedimentation rate (ESR), renal, liver and thyroid function tests. Glucose and electrolytes including sodium, potassium, calcium, magnesium, phosphorous and arterial blood gases (ABG) were normal. Toxicology screen was negative. Electrocardiogram (Fig. 2) showed normal sinus rhythm with a short QT interval; absolute QT = 280 ms, corrected QT = 285 ms and peaked, symmetrical T wave in the precordial leads. Echocardiography was normal. The patient was treated with loading dose of intravenous amiodarone followed by a maintenance dose of 200 mg twice daily and did not show any recurrence of arrhythmias, but the QT interval was persistently short. He was referred to a tertiary hospital for the insertion of an automatic ICD.

DISCUSSION

SQTS was first described as a new congenital clinical syndrome by Gussak et al in 2000\(^1\). It has been described to have an autosomal dominant inheritance due to repolarization abnormalities involving plateau phase of the action potential as a malfunction of potassium channels\(^3\). Three different mutations in genes encoding for cardiac potassium channels (KCNH2, KCNQ1 and KCNJ2) have been identified\(^3\). All mutations lead to abnormal function of the affected current IK(r), IK(s), IK(1). The possible substrate for the development of VTs may be a significant transmural dispersion of the repolarization due to a heterogeneous abbreviation of the action potential duration\(^10\). This lead to a high risk for an arrhythmia such as ventricular tachyarrhythmia. Furthermore,
episodes of AF are very frequent due to affection of atrial myocytes. The arrhythmia in SQTS can occur at any age but usually earlier in life. The ECG in SQTS is characterized by absolute QT interval less than or equal to 320 ms and a corrected QT less than or equal to 340 ms. Another peculiar ECG finding seen in at least half of the patients is a tall, symmetrical peaking T wave in the precordial leads. Finally, a further relevant feature is the lack of adaptation of the QT interval to the heart rate. The invasive electrophysiological findings showed very short atrial and ventricular effective refractory period.

The treatment of choice in patients with SQTS is ICD. Pharmacologic therapy may serve as an adjunct to ICD therapy to prevent ventricular tachyarrhythmia or may constitute an alternative to ICD therapy in very young patients and patients declining ICD therapy. In patients with KCNH2 mutation, quinidine was able to prolong the QT interval into the reference range. Furthermore, quinidine prolonged the effective ventricular refractory period. A preliminary data suggest amiodarone combined with B-blockers may be helpful in treating episodes of polymorphic ventricular tachycardia for patients with unknown genotype.

Our patient presented for the first time with resuscitated cardiac arrest. ECG was not available during the first event, but subsequent in-hospital events revealed a polymorphic VT shown on the monitor during cardiopulmonary resuscitation (CPR). His ECG showed an absolute QT interval of less than 320 ms and a corrected QT of less than 340 ms along with peaked, symmetrical T waves in the precordial leads and lack of adaptation of the QT interval to the heart rate. There was a history of sudden death of his elder sister at the age of 35 years. The patient was treated with amiodarone, as it was effective in one study. He remained in the hospital for a long observational time without any recurrence of arrhythmias. He was then referred for ICD therapy.

CONCLUSION

With this case report we intend to promote awareness among physicians about the presence of this new syndrome, characteristic ECG findings and management of this disorder. As the SQTS often involves young patients with apparently normal heart, it is imperative for physicians to recognize the clinical features of the SQTS in making a timely and correct diagnosis.

REFERENCES

Case Report

Hair - Thread Tourniquet Syndrome

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ABSTRACT

Hair tourniquet syndrome is a known but rare entity which may have unpleasant consequences if not recognized promptly. We present a case of a three month old boy who was noticed to have a strange looking swelling of his distal right ring finger. Prompt recognition lead to a timely decision for surgical intervention. The cause was a hair causing a tourniquet like effect. This was released without consequences. We report this case to increase the awareness of this entity because if it is not recognized, ischemia and then necrosis will lead to amputation.

KEY WORDS: acquired constricting syndrome, hair

INTRODUCTION

Hair tourniquet syndrome is a known but rare entity. It involves the entrapment of fibers around appendages leading to ischemic changes and necrosis[1]. It is considered an emergency because any delay would lead to amputation of the appendages involved.

This entity crosses cultural, economic and gender barriers. It has been reported in several different countries[2].

The age group is not confined to pediatrics which however is the most commonly involved segment. Cognitively impaired elderly patient can also be affected[3].

The cause is usually a human hair fiber but other types of fibers have been implicated as a cause of this entity. Once recognized, emergency treatment has to take place without a delay. Some advocate conservative medical treatment which has a high failure rate. The surgical option is most favored and this involves surgical release of the knotted fibers.

CASE REPORT

We present this case of a three month-old boy who was noticed to have a right ring finger swelling of one days’ duration by his mother. There was no history of trauma or an insect bite. The family seemed reliable and there were no signs indicating the possibility of child abuse. Systemic examination was unremarkable. Locally, there was a red and tender swelling confined to the distal phalanx of the right ring finger (Fig. 1). The passive as well as the active movements were intact (Fig. 2). Once the high index of suspicion regarding the possibility of hair tourniquet syndrome was entertained, the child was sedated with chloral hydrate. Proper examination revealed formed epithelial debris over the hair. Removal of the debris was achieved and the hair was identified and released (Fig. 3). The redness resolved almost instantaneously. On follow up the child showed no residual deficit.

DISCUSSION

Hair tourniquet syndrome is a phenomenon caused by a loose fiber that gets wrapped tightly around appendages. It is also known as acquired constricting syndrome[1]. It is considered relatively uncommon but if passed unrecognized, devastating consequences would occur. This phenomenon is mainly caused by human hair fibers in 95% of the reported cases[4]. Any fiber that can go around any appendage can cause such an entity. It is noticed frequently in the post-partum period where mothers experience increase loss of hair. Another entity is the Telogen effluvium which is a form of alopecia which is characterized by loss of more than 100 hair per day[4]. Chemotherapy and its consequence of hair loss is also implicated as a risk factor[5]. For fibers other than human hair, mittens and frequent cloth washing are considered to increase the risk.

Subsets are based on the appendages involved. Subsets are toes, fingers, genitals and others such as uvula and neck[4]. In a review of 66 cases, it was found that 28 (43%) cases involved toes, 16 (24%) involved fingers and 22 (33%) involved genitals[1]. The age group was mainly the infants and the pediatric. However, it is also described in adults with reduced mental capacity[3]. It has some differences according
to the appendage involved; for toes, the median age was four months (range 20 days to 15 months), for fingers, the median age was three weeks (range 4 days to 19 months), for genitals, the median age was two years (range 4 months to 6 years)[1]. Genitals were usually involved in the older age subgroup. These patients may be irritable or display no unusual behavior. Child abuse has to be considered in such a group and a thorough search in history and physical examination is mandatory to rule out this possibility. Accidental fiber entrapment is the most common form compared with the child abuse form.

Once diagnosed, it is considered an emergency. Lymphatic drainage is impaired initially leading to swelling. This is followed by venous impairment and more edema which later affects the arterial supply leading to ischemia and then necrosis. This will lead to auto-amputation[4]. It has to be considered that epithelium might cover the fiber making it difficult to recognize. On other extreme, it might cut through the skin.

The hair is extremely thin and therefore is overlooked especially with the edema. It stretches when wet and contracts when it dries causing a more tight constriction[4]. With regards to management, a high index of suspicion is required. If the clinician is not alert to this possibility, the diagnosis is missed and devastation is the rule. To avoid circulatory embarrassment, an immediate conservative management in the form of soaking the appendages in a depilatory cream is required. Two problems arises here: first, the cream will not reach the fibers if epithelium has been established and second, the cream will act mainly on the human fibers. Due to the high failure rate of this line of management, the surgical approach is advocated by many authors. It could be simply done with a fine scissor and forceps under magnification or a deep longitudinal incision reaching the bone could be made. This ensures the complete release of all fibers[5]. This entity is also reported in animals[6].

Awareness of such entity is required to prevent the delay and miss appropriate management.

CONCLUSION

Hair–thread tourniquet syndrome is a rare emergency resulting from circumferential strangulation of appendages by hair or fibers. If passed unrecognized, devastating consequences would almost occur. A high index of suspicion for this condition is mandatory to avoid unpleasant consequences of delayed treatment.

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Case Report

Neurosarcoidosis as a First Presentation of Systemic Sarcoidosis: Case Report

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ABSTRACT

Neurosarcoidosis (NS) is a well-recognized complication of systemic sarcoidosis, but it is an uncommon first presentation of the disease. Moreover, seizure disorder is a much less common presentation of this subset. We report a case of a 30-year-old male admitted with status epilepticus due to NS. Magnetic resonance imaging (MRI) of the brain demonstrated multiple nodular lesions. Chest radiograph showed bilateral hilar lymphadenopathy that proved by histopathological examination to contain non-caseating granulomas (NCG). Other causes of granulomatous lesions were excluded by relevant investigations. Corticosteroids (CS) markedly improved the clinical and radiological findings. Seizures were well controlled by antiepileptic drugs.

KEY WORDS: corticosteroids, magnetic resonance imaging, neurosarcoidosis, sarcoidosis, status epilepticus

INTRODUCTION

Sarcoidosis is an enigmatic multi-system granulomatous disease of unknown etiology that was first described in the nineteenth century[1]. It affects people of all racial and ethnic groups and occurs at all ages with a peak incidence at 20 to 39 years[2].

Sarcoidosis usually involves the lungs in up to 90% of patients[1]. Neurosarcoidosis (NS) as a first presentation of sarcoidosis with no prior evidence of systemic involvement is extremely uncommon and difficult to diagnose due to the long list of differential diagnoses that range from tumors to multiple sclerosis[3]. Only 5 to 10% of all patients with systemic sarcoidosis manifest neurological complications out of which about 50% were previously diagnosed when the nervous system gets involved[4,5]. Seizures are estimated to occur in 5 to 20% of NS patients[5]. Most reports indicate a poor prognosis with severe progressing or relapsing course when seizures complicate NS[5]. We describe an unusual case of NS with status epilepticus as the first presentation and illustrate the brain imaging, histology results and response to treatment.

CASE REPORT

A 30-year-old male patient was brought to the accident and emergency department of Mubarak El-Kabeer hospital by ambulance in an unconscious state after a sudden onset of three consecutive tonic-clonic seizures witnessed by his wife. Few minutes after arrival to the resuscitation room, the patient sustained another fit witnessed by the attending medical personnel. Accordingly, he was sedated, intubated, mechanically ventilated, loaded with diphenyl hydantion, and shifted to the intensive care unit (ICU). He was pyrexial at 39 °C, tachycardiac at 120 beats / min, normotensive, with no skin rash or palpable lymphadenopathy. Both pupils were dilated but reactive to light and fundi showed no papilledema. Except for leucocytosis, his hemogram as well as biochemistry including random blood sugar, calcium, magnesium, renal and liver functions were all within normal limits. The patient was immediately shifted to radiology department for brain CT scan that showed a one cm non-enhancing cystic lesion with adjacent hyperdensity in the right temporal lobe surrounded by vasogenic edema (Fig. 1). A portable chest X-ray (CXR) showed bilateral hilar lymphadenopathy (Fig. 2). A contrast enhanced brain magnetic resonance imaging (MRI) done the next day revealed a non-enhancing well-defined one cm cystic lesion in the right hippocampus with surrounding vasogenic edema and minimal mass effect, as well as a nodular enhancement of the suprasellar cistern and pituitary stalk. There was also multiple enhancing parenchymal nodular areas...
A thick nodular leptomeningeal enhancement at the right temporal lobe was also noted. These findings, together with the CXR were suggestive of neurosarcoidosis versus brain metastasis.

A chest / abdomen CT scanning showed multiple enlarged pre-tracheal, para-tracheal, anterior mediastinal, aorto-pulmonary, sub-carinal, and hilar lymphadenopathy with few smaller ones in the anterior aorta adjacent to the celiac trunk. These nodes showed no evidence of caseation or calcification (Fig. 4).

The differential diagnoses included: metastatic malignancy, lymphoma, leukemia, cysticercosis, tuberculosis, sarcoidosis, fungal or human immune deficiency virus infection (HIV). However, HIV, VDRL, and cystiocercosis serology, Mantoux test and blood film were all negative. At this stage, the seizure activity was well controlled by antiepileptic drugs. Therefore, video-assisted cervical mediastinoscopy was performed and multiple lymph node biopsies were obtained, the histopathological examination revealed extensive hyalinization with focally preserved lymphoid cells associated with multiple non-caseating compact granulomas (NCG) (Fig. 5). Stain for acid fast bacilli (AFB) and later the culture were negative.

The patient was then extubated and became fully conscious. He was shifted to the general medical ward and commenced on oral corticosteroids (CS) in a dose of 1 mg / kg body weight (prednisolone 80 mg daily). He showed marked improvement in his general condition and remained fit- free. Consequently, he was discharged home. Regular out-patient follow-up visits were arranged which
included CXR, brain MRI, and gradual reduction of the steroid dose.

A follow-up brain MRI done 12 weeks post-discharge showed, in comparison to the previous study, a reduction in the leptomeningeal enhancement, and in the number and size of the parenchymal sarcoid nodules. The non-enhancing one cm cystic lesion in the right hippocampus remained the same but with almost disappearance of the surrounding vasogenic edema and the midline shift, (Fig. 6). In addition to the radiographic improvement, the patient remained fit-free, the steroid dose was reduced to 5 mg daily, but the dose of the antiepileptic drugs remained unchanged.

DISCUSSION

NS may affect virtually any part of the nervous system, resulting in widely variable clinical presentations. Cranial neuropathy is the most common with the frequency of peripheral seventh cranial nerve paresis reaching 40 to 60%[3,6]. Neurological involvement precedes systemic manifestations in 31 to 74% of patients, but it may be the only manifestation in 10 to 17% of patients[2,4].

NS is a diagnostic consideration in patients with known sarcoidosis who manifest neurological complications and in patients presenting de novo with constellations of symptoms and signs consistent with the disease. There is no definite imaging technique or laboratory test that can prove the diagnosis of sarcoidosis beyond doubt and a definite diagnosis requires extensive work up that utilizes radiological, histopathological and serological tests collectively.

Contrast-enhanced brain CT scan is insensitive, with normal appearances in up to 30% of cases with definite NS. Conversely, gadolinium-enhanced brain MRI is the diagnostic investigation of choice in suspected case of NS with leptomeningeal involvement being the most frequent feature[7].

Despite the emergence of new technologies, a conventional CXR continues to have a crucial role for the diagnosis, prognosis, and follow-up of sarcoidosis. The CXR is abnormal in more than 90% of patients at some point and is often the first investigation to suggest the diagnosis. Typical abnormalities (i.e., bilateral hilar lymphadenopathy with or without parenchymal involvement) are noted in 50 to 80% of patients[7]. Cerebrospinal fluid (CSF) analysis maybe normal or may show non-specific abnormalities like elevated proteins and lymphocytic pleocytosis. It is helpful in ruling out other CNS diseases like infections and multiple sclerosis[8]. The role of CSF angiotensin converting enzyme (ACE) is unclear since it is neither sensitive nor specific for the disease[2].

In all cases, a biopsy specimen should be obtained from the involved organ that is most easily accessible. Lung tissue is usually sampled by means of fibro-optic bronchoscope with a diagnostic yield of about 85%[2]. The finding of typical NCG that stain negatively for AFB is highly suggestive in the appropriate setting; however, careful further evaluation is needed to rule out other causes of granulomatous diseases[8].

Seizures in NS are estimated to occur in up to 20% of cases and maybe the heralding manifestation of sarcoidosis[4]. Some series consider seizures a poor prognostic indicator and associate it with high mortality[4]. It is worth mentioning that seizure types affected survival with death being more frequent (about double) in those with generalized tonic-clonic (40%) seizures compared with focal variety (20%)[5]. The use of conventional antiepileptic medications alone is considered ineffective[5].

CS therapy for NS has been the mainstay of treatment for half a century. The rationale behind its use was to treat the possible subclinical endocrine impairment, particularly in the pituitary...
and adrenal gland\textsuperscript{[1]}. The adverse effects of CS are prominent due to the high dose required (40 to 80 mg prednisolone)\textsuperscript{[8]}; pulse therapy with methyl prednisolone maybe used in certain cases. Scott et al\textsuperscript{[9]} recently advocated early intervention with immunosuppressive agents in patients who present with disabling symptoms with favorable outcomes and minimal treatment related toxic effects. Hydroxychloroquine has been used for hypercalcemia, skin and neurological involvement\textsuperscript{[2]}. Chlorambucil, cyclophosphamide, cyclosporine and azathioprin have all been used as steroid sparing agents with variable degrees of success. Radiation therapy also has been tried in refractory NS. A recent article described a case of steroid refractory NS with marked clinical and radiological response to infliximab; a chimeric monoclonal human-murine antibody directed against tumor necrosis factor alpha\textsuperscript{[10]}. Neurosurgical intervention is indicated for selected cases such as ventriculo-peritoneal shunting for obstructive hydrocephalus or resection of intracranial granulomas causing raised intracranial pressure\textsuperscript{[9]}.

In our case, in spite of the dramatic presentation that was suggestive of meningo-encephalitis due to the high grade fever, leucocytosis and diminished sensorium, an urgent brain CT scan insinuated a plethora of differential diagnoses and a simple CXR limited them to only a few. However, the definitive diagnosis was offered by the histopathological examination of a cervical lymph node coupled by brain MRI findings and confirmed by the good response to steroids.

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Case Report

Urosepsis Simulating Congenital Adrenal Hyperplasia in an Infant

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ABSTRACT

Urinary tract infection in infants simulating congenital adrenal hyperplasia is rarely reported in literature. We report a case, which was misdiagnosed as a case of congenital adrenal hyperplasia. A three-month old female infant was admitted to a local hospital for persistent vomiting and severe dehydration. Her biochemical profile revealed hyponatremia, hyperkalemia and metabolic acidosis. She was initially misdiagnosed as congenital adrenal hyperplasia (CAH). Her urine examination revealed a urinary tract infection. Upon investigation there was no evidence of an obstructive uropathy. A full septic work up was performed and she was treated for a suspected urosepsis. Her electrolytes imbalance improved to normal and she had a complete recovery after antibiotic therapy. This case demonstrates the importance of urine culture and ultrasound examination in suspected case of pseudo-hypoaldosteronism.

KEY WORDS: congenital adrenal hyperplasia, pseudo-hypoaldosteronism, transient pseudohypoaldosteronism, urosepsis

INTRODUCTION

Pseudo-hypoaldosteronism (PHA) was described as a salt losing condition seen in infants with vomiting, dehydration, hyponatremia, hyperkalemia, metabolic acidosis, and increased plasma aldosterone concentration with normal adrenal function and normal renal anatomy[1]. In addition to sporadic cases, familial, recessive and dominant inheritance has been described[2]. PHA is a rare salt wasting syndrome of infancy and is postulated to be caused by renal tubular insensitivity to mineralocorticoids. It may be an isolated condition or may be associated with renal disease[3]. A wide variety of urologic lesions have been reported in association with transient pseudo-hypoaldosteronism (TPHA), these include obstructive and non-obstructive lesions[4].

The prompt diagnosis of the potentially fatal congenital adrenal hyperplasia (CAH) in neonate is critical. However, neonatal infection is actually more common. Early onset neonatal infection occurs within the first five days of life.

Infection is caused by organisms acquired during intra-uterine or intra-partum stages. Late onset neonatal infection occurs after seven days and frequently results from colonization. Escherichia coli is one of the most important pathogen of newborn and young infants causing sepsis, meningitis, and urinary tract infection[5].

We report an unusual case of neonatal urosepsis secondary to E.coli, with clinical presentation simulating CAH. We will review the literature with emphasis on the differential diagnosis and treatment of this condition.

The purpose of this communication is to report the apparent association of urinary tract infection in a female neonate who had multiple electrolytes abnormalities and the adrenogenital syndrome.

CASE HISTORY

A three-month-old girl born at term by spontaneous vaginal delivery was seen in a community hospital with a one week history of persistent vomiting, increased irritability and decrease feeding. She had previously been fit and well. On the day of admission the parents reported that the baby was lethargic and difficult to arouse. On assessment at the community hospital, the infant was found to be severely dehydrated. Physical examination revealed a heart rate of 190 beats/min, a respiratory rate of 48 breaths/min, capillary refill of five seconds, a blood pressure of 84/54 mmHg and a temperature of 37.2 °C. Chest and abdominal examinations were unremarkable, and the infant had normal external genitalia with no clitoromegaly and no hyperpigmentation. She was initially treated with a 20 ml/kg bolus of intravenous saline (0.9 %
The initial blood work is shown in Table 1. The patient had hyponatremia with a sodium of 109 mmol/l, hyperkalemia with a potassium of 9.0 mmol/l and a metabolic acidosis with a pH of 7.31. The patient was given sodium polystyrene sulfonate (Kayexalate ® 1 gram/kg rectally and was started on a dextrose and insulin infusion. A 12-lead electrocardiogram (EKG) showed peaked T-wave.

The patient received 1 ml/kg of 10% calcium gluconate. The patient was subsequently transferred to The Hospital for Sick Children (Toronto; Canada) with a possible diagnosis of CAH.

On arrival at the Emergency Department, the patient had a generalized stiffness and her eyes were rolled upwards. A 6 ml/kg bolus of 3% NaCl was given after which the seizure stopped. A full septic work-up including a lumbar puncture, blood cultures and catheterization to obtain urine for culture was commenced and various imaging techniques were employed. The patient was then admitted to the general pediatric ward.

Lumbar puncture was negative for meningitis. Urinalysis revealed a large number of leukocytes, RBCs and bacteria, and was also positive for nitrites. She was started on intravenous ampicillin (100 mg/kg/day) and gentamycin (2.5 mg/kg q8h).

The urine culture was positive for Escherichia coli (more than 100 x 106 organisms), which was sensitive to ampicillin. The patient had a voiding cystourethrogram (VCUG) which was normal with no evidence of urinary reflux. She had a normal renal ultrasound examination.

Work up for CAH showed a serum 17-Hydroxy-progesterone (17-OH-P) of 5 nmol/l (normal range: < 15.3 nmol/l) and an elevated serum aldosterone of 6 nmol/l, (normal range: 0.7-2.0 nmol/l). A CT scan of her head was unremarkable.

The patient had a final diagnosis of urosepsis with hyponatremia and hyperkalemia secondary to mineral corticoid resistance. The patient continued to improve clinically and biochemically and was discharged from the hospital after seven days without any medication. At follow-up, the patient was well, and had a normal electrolyte profile.

**DISCUSSION**

This is the first reported case of a urinary tract infection in an infant with clinical presentation of CAH that did not have an obstructive uropathy.

CAH is an inherited, born error of metabolism with an incidence 1 in 10,000 births in the Caucasian population[8]. Nearly 95% of cases of CAH are a result of 21-hydroxylase deficiency. The salt-wasting form of “classic” 21-hydroxylase often leads to acute adrenal insufficiency in the first weeks of life and necessitates prompt evaluation and treatment[7].

<table>
<thead>
<tr>
<th>Table 1: Laboratory-test results at time of admission</th>
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<tbody>
<tr>
<td><strong>Value</strong></td>
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<tr>
<td>Sodium mmol/l</td>
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<tr>
<td>Potassium mmol/l</td>
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<tr>
<td>Urea mmol/l</td>
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<td>Creatinine umol/l</td>
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<td>pCO₂ mm Hg</td>
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<td>pO₂ mm Hg</td>
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<tr>
<td>Bicarbonate mmol/l</td>
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<td>Base excess</td>
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Girls with CAH are identified by masculinization of their external genitalia. Boys, however, may be overlooked, as they have either normal genitalia or bilateral cryptorchidism and hypospadias.

The renal causes for these electrolyte abnormalities include vesicoureteral reflux (VUR) with infection, obstructive uropathy with or without infection, polycystic disease, and end stage renal disease. These renal diseases have been reported to cause TPHA[9]. The explanation provided by Melzi et al[9] and Rodriguez-Soriano et al[10] for this constellation of symptoms is that infant’s urinary tract infection results in pseudo-hypoaldosteronism. Infant urinary tract infection affects renal tubular function, possibly through a bacterial endotoxin, such as E. coli lipopolysaccharide, and interstitial inflammation, which leads to increased sodium excretion and elevated aldosterone[11]. The result of this nephrotoxic effect includes renal tubular resistance to aldosterone and pseudo-hypoaldosteronism that include hyponatremia and hyperkalemia. Treating the urinary tract infection reverses the TPHA and normalizes electrolyte and hormonal values.

In view of the rarity of TPHA it is likely that CAH is the first diagnosis in infants presenting with severe hyponatremia and hyperkalemia.

However, before initiating hydrocortisone and fludrocortisone therapy, blood samples for plasma 17-OH-P, renin, aldosterone and ACTH should be obtained. These results will help differentiate between CAH and TPHA.

Our case illustrates the importance of performing urine culture and renal ultrasonography in the evaluation of any infant with electrolyte disturbances and possible CAH to exclude urine infection or obstructive uropathy. In the patient presented here the underlying pathology for her electrolyte abnormalities was severe urinary tract infection without any signs of obstruction. Previously reported cases of TPHA with urinary tract infections had an obstructive or a VUR lesion.

**CONCLUSION**

While CAH could present with dehydration, metabolic acidosis, hyponatremia and hyperkalemia, urinary tract infection (with or without accompanying electrolyte abnormalities) could be the first presenting symptom.
reflux or obstruction) should be kept in mind and urine culture with renal ultrasound should be performed promptly. This approach could prevent complications and inappropriate use of medications.

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Case Report

Rituximab in Severe Refractory Autoimmune Hemolytic Anemia in Children

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ABSTRACT

Rituximab, an anti-CD20 monoclonal antibody, is a relatively new drug for autoimmune diseases, and its use in childhood autoimmune hemolytic anemia (AIHA) is still limited. We report our experience with two children who presented with acute severe AIHA not responding to standard treatment modalities. The first patient was a 4-month-old infant with severe AIHA who did not respond to steroids, intravenous immune gammaglobulin (IVIG), cyclophosphamide and plasmapheresis, but responded well to rituximab. The second patient was an 8-year-old with a similar presentation who did not respond to all modalities of treatment including rituximab. He eventually required a splenectomy to control his hemolysis. While rituximab is a useful addition to the treatment regime in AIHA, it is not always effective and the occasional patient may still require splenectomy.

KEY WORDS: autoimmune hemolytic anemia, children, plasmapheresis, rituximab

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a rare disorder in children in whom the most common variant is the warm antibody type characterized by IgG auto-antibodies (mainly IgG1) directed against most red cell antigens (pan-agglutinins). The disorder is acute in the majority of children with hemolysis developing over hours to days[1-3]. Most cases are associated with viral (cytomegalovirus, parvovirus B19) or bacterial infection and, less frequently, with malignancy (Hodgkin disease) or immunodeficiency states (HIV infection, common variable immunodeficiency). Although the disorder generally responds well to corticosteroid therapy, patients with a severe and refractory course may require intravenous immunoglobulin (IVIG), cytotoxic drugs or splenectomy[1-3]. Recently, rituximab, an anti-CD 20 monoclonal antibody, has emerged as a promising agent in refractory cases of AIHA in children[4]. Here we discuss the management of two children with severe AIHA who showed different responses to rituximab.

CLINICAL PRESENTATION

Patient 1

A 4-month-old Egyptian female infant was admitted with a 2-day history of pallor, lethargy, and difficulty in feeding. Her parents had noted red-brown staining of the diaper from urine. She had recently recovered from an upper respiratory tract infection and was otherwise well. On admission, she was febrile and irritable with marked pallor and jaundice. Physical examination revealed an enlarged spleen with a normal liver span and there was no skin rash, lymphadenopathy or bone tenderness. Physical examination revealed an enlarged spleen with a normal liver span and there was no skin rash, lymphadenopathy or bone tenderness.

Initial investigations showed: hemoglobin 28 g/l, hematocrit 0.095, white blood cells 10.4 x 10⁹/l, platelets 163 x 10⁹/l, reticulocyte count of 28.4%, MCV 109.7 fl and MCH 37 pg. Total serum bilirubin (94 μmol/l), conjugated bilirubin (8 μmol/l) and serum LDH (543 IU/l) were elevated. The peripheral blood film showed severe anisopoikilocytosis with macro-ovalocytes, polychromasia, nucleated red cells, increased rouleaux formation and a few spherocytes. Occasional activated and atypical lymphocytes were also seen. Urine examination showed hemoglobinuria.

The direct antiglobulin test (Coombs’ test) was positive; sickling test was negative and glucose-6-phosphate dehydrogenase was normal. Antibody studies confirmed the diagnosis of warm antibody-type hemolytic anemia with panreactive IgG antibodies. Computed tomography scan of abdomen and chest showed no lymphadenopathy, thymic hyperplasia or other masses.

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She received washed filtered packed red cell transfusions cross-matched against the mother’s serum. Initial treatment was started with oral prednisolone, 2 mg/kg/day. She did not require another transfusion in the first week of treatment. However hemolysis worsened over the next two weeks, with hemodynamic instability, requiring repeated transfusions and ICU care. IVIG was added at 1 g/kg at weekly intervals but she remained transfusion dependent. Therefore methylprednisolone pulse therapy, 30 mg/kg/day for three days, was given with poor response. High dose cyclophosphamide, 50 mg/kg/day over five days, was added to control the persistent hemolysis. She subsequently developed severe febrile neutropenia and enterocolitis, which were treated with antibiotics and granulocyte-colony stimulating factor (G-CSF), (Neupogen, Filgrastim®, Hoffman-La-Roche, Ltd., Basel, Switzerland) at a dose of 6 mcg/kg subcutaneously 12 hourly for six days. Her renal function remained normal throughout this period.

As transfusion requirements persisted, rituximab (at a weekly dose of 375 mg/m²) was commenced with plasmapheresis (using a Prisma 4 hemodialysis machine fitted with a Gambro membrane filter) as additional supportive treatment. Prednisolone was gradually tapered and withdrawn. Hemolysis abated after three doses of rituximab with the hemoglobin rising to 60-80 g/l and no further transfusions were required. Plasmapheresis had to be discontinued after two sessions because of technical difficulties. However, the patient’s improvement was rather slow and rituximab was continued for a total of eight weeks after which the hemoglobin increased and finally at about six weeks after the initial presentation, splenectomy was carried out and steroid therapy was gradually withdrawn. His hemoglobin stabilized at about 70g/l.

However, hemolysis started afresh soon after the third weekly dose of rituximab with Hb dipping again below 40 g/l. This time he underwent three sessions of plasmapheresis with only partial response. Transfusion requirements increased and finally at about six weeks after the initial presentation, splenectomy was carried out and steroid therapy was gradually withdrawn. His hemoglobin stabilized at about 110 g/l and he has suffered no recurrences in the subsequent nine-month follow up period. There was only slight fall in his serum IgG, which normalized after six months. He did not have any infections.

**DISCUSSION**

AIHA has an estimated annual incidence of 0.2 per 100,000 individuals below 20 years of age. The highest incidence is seen in children below four years of age[1,2]. In about half of these patients the disorder has an acute presentation with hemolysis worsening over days. Among young children it can be frequently life-threatening, with a mortality rate of approximately 10%[3]. When it occurs in infants, as in our first patient, the disorder tends to be severe and refractory to treatment and often results in transfusion dependency[1,2]. Rare familial variants of AIHA present with similar acute hemolysis[11].

Most cases of AIHA in children are due to the warm IgG autoantibodies directed against almost all red cell surface antigens. These antibodies are bound to the red cell membrane and have a variable capacity to fix complement. Most of the hemolysis occurs in the spleen as the IgG-coated red cells are bound to the Fcγ receptors of the splenic macrophages with
fixation of complement and are cleared from the circulation\cite{1}. Some of these autoantibodies are also bound to the reticulocytes in the bone marrow often resulting in reticulocytopenia and acute anemia with a normal bone marrow reserve. Both our patients presented with primary autoimmune hemolysis with no evidence of underlying disorders.

Most children with AIHA recover spontaneously; however, treatment is required in severe cases. A short course (4-6 weeks) of oral prednisone induces remission in the majority of patients (~80\%)\cite{1}. The second-line of treatment in refractory cases includes IVIG and cytotoxic drugs like cyclophosphamide. IVIG has been used with limited success in children with AIHA\cite{5,6}. It acts by blocking the Fc receptors on macrophages and thereby enhances the survival of red cells coated with antibodies. The effect is temporary and repeated doses are necessary every 3-4 weeks. IVIG produced no apparent benefit in either of our patients.

Response to cytotoxic drugs may be slow since these drugs probably induce remission by suppressing the autoimmune response and antibody production. High-dose cyclophosphamide has been used with success in refractory AIHA, but there is a high risk of severe bone marrow suppression\cite{7,8}. Cyclophosphamide induced severe neutropenia in our first patient and had to be stopped before completing the full course. Considering the toxicity and narrow therapeutic window especially in very small children, these drugs should probably be used less often.

Plasmapheresis is aimed at the removal of autoantibodies thereby enhancing red cell survival\cite{9}. Plasmapheresis may help as an additional measure to control hemolysis before other drugs begin to act. Although 5-6 alternate-day sessions were planned, this could not be completed in our first patient due to problems with venous access while in the older boy no favorable response was observed after three sessions.

Rituximab is a promising alternative to splenectomy, particularly among young children. It is a chimeric, anti-CD20 monoclonal antibody, which is selective against active B-lymphocytes. It causes antibody-mediated and complement-mediated cytotoxicity with depletion of B-lymphocytes. Thus it abolishes antibody production and consequently, immune-mediated hemolysis. Due to the specificity of rituximab to B-lymphocytes, toxicity is minimal. However, prolonged hypogammaglobulinemia may follow rituximab therapy and replacement therapy with IVIG may be indicated\cite{10}. Several case series and reports have documented the safety and effectiveness of rituximab in children\cite{4,11,12}.

Both our patients responded well to the initial doses of rituximab. However, the response was rather slow in the first patient and she had eight weekly doses before the response was sustained. The second patient also showed an initial response, but this was temporary. There was a relapse of severe hemolysis after the third dose and he, eventually, had to be splenectomized. There is no reliable predictor of response to rituximab in children. In general, the response is favorable in acute fulminant, steroid-refractory cases especially in very young children. This is consistent with the similar experience reported by Zecca et al in their series of children treated with rituximab\cite{12}. Neither of our patients suffered any infections resulting from treatment-induced hypogammaglobulinemia.

Splenectomy is the ultimate treatment for patients who fail to respond to all the above lines of treatment. The response rate to splenectomy is as high as 56-70\% and is especially effective for IgG-mediated hemolysis\cite{1,3}. Splenectomy is effective because it not only eliminates the actual site of hemolysis but it also removes a substantial pool of active B-lymphocytes curtailing antibody production. However the risks of splenectomy in a young infant far outweigh the benefits. Hence we were reluctant to consider splenectomy in our first patient. However, the older patient did require splenectomy once his disease became protracted and unresponsive to rituximab.

**CONCLUSIONS**

The management of AIHA that is refractory to corticosteroid therapy and IVIG, presents challenging problems, especially in children. Cytotoxic drug therapy is unsafe and difficult to monitor in very young infants. With the availability of rituximab and its relative safety and efficacy, its use should now be probably considered before the use of cytotoxic drugs. Plasmapheresis remains a useful therapeutic option in selected cases. However, as our second case illustrates, splenectomy may still be required in some patients.

**ACKNOWLEDGEMENTS**

Several colleagues contributed to the care of these patients and we particularly thank the following: Prof. Zeinat Hijazi, Dr. Najwa Akar and Dr. Abdulkhaleq of Unit B in the department of general pediatrics, the staff of the pediatric intensive care unit, especially Dr. Maria van der Vorst and the pediatric nephrology unit (Dr. Faisal Al-Kandari and Dr. Aisha Al-Terkait); all from the Mubarak Al Kabeer Hospital, Kuwait.
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Th1 Cell Reactivity and HLA-DR Binding Prediction for Promiscuous Recognition of MPT63 (Rv1926c), A Major Secreted Protein of Mycobacterium Tuberculosis

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MPT63 (Rv1926c), a major secreted protein of Mycobacterium tuberculosis, is immunoreactive in antibody assays in humans and animals and provides protection as a combined DNA vaccine in mice. This study was undertaken to determine the reactivity of MPT63 in T helper 1 (Th1) cell assays, i.e. antigen-induced proliferation and interferon-gamma secretion, using peripheral blood mononuclear cells (PBMCs) obtained from 72 Mycobacterium bovis Bacille Calmette-Guérin vaccinated healthy subjects. PBMCs were tested with complex mycobacterial antigens and pools of synthetic peptides corresponding to MPT63, MPB70, MT24, PPE68, CFP10 and ESAT-6. The results showed that MPT63 induced moderate Th1 cell reactivity which was equivalent to the reactivity induced by other secreted antigens of M. tuberculosis, i.e. MT24 and MPB70. Furthermore, human leucocyte antigen (HLA) heterogeneity of the responding donors suggested that MPT63 was presented to Th1 cells promiscuously. Analysis of the MPT63 sequence and its peptides for binding to 51 alleles of 9 serologically defined HLA-DR molecules, using a virtual matrix-based prediction program (ProPred) showed that MPT63 sequence could bind to all the 51 alleles, whereas 9 of the 10 peptides of MPT63 were also predicted to bind promiscuously. When tested with PBMCs of HLA-DR heterogeneous donors that responded to MPT63 in interferon-gamma assays, at least 9 of the 10 peptides of MPT63 were recognized by PBMCs from HLA heterogeneous donors. These results suggested that promiscuous Th1 cell reactive epitopes are scattered throughout the sequence of MPT63, and further support the inclusion of this protein in an antigen cocktail to develop a new anti-tuberculosis vaccine.

Multilevel Modeling of Household Contextual Determinants of Tuberculin Skin Test Positivity among Contacts of Infectious Tuberculosis Patients, Umerkot, Pakistan

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This cross-sectional study sought to identify household contextual determinants that might be associated with Mycobacterium tuberculosis infection as assessed by tuberculin skin test (TST) positivity among familial contacts of index patients of infectious pulmonary tuberculosis (TB) while controlling for the effects of individual-level factors. We analyzed data on TST results on 359 household contacts of 77 index cases of acid-fast bacilli (AFB) sputum smear-positive pulmonary TB using multilevel logistic regression analysis with characteristics of household contacts at the first level and that of households at the second level. The prevalence of M. tuberculosis infection as assessed by TST positivity among household contacts...
of index TB patients was 49.9% (179/359). After taking into account the individual-level risk factors, household-level contextual determinants significantly associated with contact’s TST positivity were gender of index TB patient (adjusted odds ratio [OR] = 2.2; 95% confidence interval [CI]: 1.3-3.9%) and density of AFB sputum smear (adjusted OR = 3.2; 95% CI: 1.9-5.5%). Household variances in multilevel models indicated significant inter-household heterogeneity in TST positivity among contacts. This study provided the evidence for substantive effects of household-level contextual variables on the TST positivity among contacts of index TB patients. Thus, both individual-level and household-level characteristics need to be taken into account while prioritizing contacts for investigations to improve TB control and prevention in resource-constrained countries such as Pakistan.

Severity of Liver Disease Predicts the Development of Glucose Abnormalities in Patients with Chronic Hepatitis B or C following Achievement of Sustained Virological Response to Antiviral Therapy

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A higher prevalence of glucose abnormalities has been reported in patients with hepatitis C virus (HCV) infection compared to patients with hepatitis B virus (HBV) infection. However, previous studies considered some confounding factors and ignored others, which might influence the comparative risk assessment between HBV and HCV infections. Fasting plasma glucose concentration, severity of liver disease and viral load were determined in 220 patients with HCV genotype 4 infection, and 200 patients with HBV infection. Patients completing antiviral therapy were followed-up, and the fasting plasma glucose levels were determined in patients with and without sustained virological response. The prevalence of glucose abnormalities in HCV infection (41%) was significantly higher than that in HBV infection (16%). However, when controlling the severity of liver disease and other risk factors, the prevalence of glucose abnormalities in patients with HCV infection was comparable to that in patients with HBV infection. After attaining of sustained virological response, a decrease of the median fasting plasma glucose value was observed only in chronic hepatitis C. In the group of patients with normal fasting plasma glucose levels, an association of nonsustained virological response with the development of impaired fasting glucose was only observed in chronic hepatitis C. The severity of liver disease was a common predictor of impaired fasting glucose in hepatitis B and C infections. These results indicate that high prevalence of glucose abnormalities can be associated with HBV- and HCV-related liver disease, and that clearance of HCV, but not HBV, may improve glucose metabolism.

The Prevalence of Antimicrobial Resistance and Carriage of Virulence Genes in Staphylococcus Aureus Isolated from Food Handlers in Kuwait City Restaurants

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Background: Staphylococcus aureus is a major cause of food poisoning due to their ability to produce enterotoxins which if ingested in sufficient amounts results in sickness. Food handlers carrying enterotoxin-
producing S. aureus in their noses or hands can contaminate food leading to food poisoning. We characterized 200 S. aureus obtained from food handlers in different restaurants for antibacterial resistance and the carriage of virulence genes.

Findings: Susceptibility to antibacterial agents was determined by disk diffusion and Etest. PCR was used to detect genes for accessory gene regulator (agr); capsular polysaccharide (cap) 5 and 8, staphylococcal enterotoxins (SE), toxic shock syndrome toxin-1 (TSST-1) and Panton-Valentine leukocidin (PVL). Isolates were typed using pulsed-field gel electrophoresis. In total 185 (92.5%) of the 200 isolates expressed resistance to antibacterial agents. They were resistant to penicillin G (82.0%), tetracycline (19.0%), erythromycin (2.5%), clindamycin (2.0%), trimethoprim (7.5%), kanamycin (2.5%), streptomycin (1.5%), ciprofloxacin (1.5%), fusidic acid (1.0%) and cadmium acetate (68.0%). Seventy-six (38.0%) and 114 (57.0%) isolates had type 5 and type 8 capsular polysaccharides respectively. The agr types I, II and III alleles were detected in 50.5%, 20.0% and 23.5% of the isolates respectively. They contained genes for SEI (38.5%), SEG (24.0%), SEC (23.0%), SEB (12.5%), SEH (21.5%), SEA (11.0), SED (1.5%), SEE (1.5%), TSST-1 (4.0%) and PVL (9.0%).

Conclusion: This study revealed a high prevalence of antibacterial resistance and virulence determinants in S. aureus from food handlers in Kuwait restaurants justifying the screening of food handlers to detect and treat carriers and protect restaurant customers from staphylococcal food poisoning.

Closed Percutaneous Pleural Biopsy. A Lost Art in the New Era

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Objective: To assess the association between size and number of biopsy specimens obtained by percutaneous closed pleural biopsy, with overall diagnostic yield in general, and histopathological evidence of tuberculosis pleurisy, in particular.

Methods: One hundred and forty-three patients, with a high index of clinically having tuberculous pleurisy, were referred to the respiratory division of Mubarak Al-Kabeer Hospital in Kuwait during a 9-year period (January 1999 to December 2007). All subjects with exudative lymphocytic predominant effusion underwent percutaneous closed pleural biopsy, looking for tuberculous granulomas. The clinical diagnosis and pathological characteristics (number and size of biopsy samples) were analyzed.

Results: Overall diagnostic yield of percutaneous closed pleural biopsy in all cases was noticed to be 52%. The larger biopsy sample size of 3 mm and more, and the higher number of specimens (> or = 4) were significantly associated with an increased diagnostic yield for tuberculous pleurisy (p=0.007 and 0.047).

Conclusion: Obtaining 4 or more biopsy samples, and larger specimens of 3mm and more for histopathological evaluation, through percutaneous pleural biopsy, results in a better diagnostic yield for tuberculous pleurisy.

Short-Term and Long-Term Outcome in Low Body Mass Index Patients undergoing Cardiac Surgery

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Objective: We sought to assess the effect of low body mass index (BMI) on short- and long-term outcomes following cardiac surgery.
Methods: This is a retrospective review of a prospectively collected departmental database over a 6-year period. Patients were eligible for the study if the BMI was <25 kg/m(2). All morbidities, length of hospital stay, and short- and long-term mortality were reviewed.

Results: There were 704 patients divided into low (n = 71) and normal (n = 633) BMI. Postoperative pulmonary complications were higher in the low BMI group compared to the normal BMI group (24% vs. 11%, P < 0.001) with a higher incidence of in-hospital mortality (10% vs. 5%). Using multiple logistic regression, low BMI was an independent risk factor for in-hospital mortality. The 1-, 3-, and 5-year survivals for the low group were 90%, 78%, and 70% compared to 94%, 86%, and 81% in the normal BMI group.

Conclusions: Low BMI is associated with increased morbidity and mortality following cardiac surgery. Risk scoring systems should utilize the BMI in the preoperative risk assessment with special attention to low BMI.

Tetracycline Resistance is Frequent among Campylobacter Jejuni Isolates from Kuwait

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Microb Drug Resist 2009; 15:115-120

Campylobacter jejuni is a major cause of diarrhea worldwide, including Kuwait. Kuwait is an important destination for commerce, employment for expatriates, and stationing of multinational troops. Knowledge about antimicrobial susceptibility of C. jejuni will be helpful for empirical treatment of infection. Tetracycline is one of the antibiotics recommended for treatment, but no data exist for tetracycline resistance in C. jejuni for the Arabian Gulf region. We characterized the tetracycline susceptibility of 85 C. jejuni isolates from diarrheal stools of patients seen at a teaching hospital in Kuwait during 2003-2006. Thirty-four (40%) isolates were tetracycline resistant (minimum inhibitory concentration \( \geq 16 \text{ microg/ml} \)), with 30 isolates carrying the tet(O) gene, including 19 isolates that carried the gene on a 35 kb plasmid. Four selected tetracycline-resistant donor strains transferred the plasmids and tetracycline resistances to a tetracycline-susceptible C. jejuni strain on conjugation. Tetracycline-resistant C. jejuni isolates were genetically unrelated to each other by pulsed-field gel electrophoresis. Thus, tetracycline resistance is common in C. jejuni isolates from Kuwait with the resistance determinant carried on transmissible plasmids. We conclude that tetracycline resistance is a feature of C. jejuni in Kuwait as in other parts of the world and that empirical therapy with tetracycline will yield variable results in Kuwait.

Mucoepidermoid Thymic Carcinoma: A Challenging Mediastinal Aspirate

Kapila K, Pathan SK, Amir T, Joneja M, Hebbar S, Al-Ayadhy B
Cytology Unit, Department of Pathology, Faculty of Medicine, Kuwait University, Kuwait

Diagn Cytopathol 2009 Feb 13 [Epub ahead of print]

Primary thymic carcinoma-mucoepidermoid cell (MEC) type is rare and only one report describing the cytologic features of this neoplasm in the metastatic site is described. We describe the cytological features of poorly differentiated carcinoma possibly MEC in a 54-year-old man who presented with cough, weight loss, and puffiness of face for 3 months. The significance of this infrequently encountered neoplasm lies in its potential confusion of origin of the tumor-thymus or metastases from a primary bronchial MEC. Immunocytochemical profile was suggestive of a thymic carcinoma of the MEC type.
Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy


International Society of Cryosurgery: 15th World Congress of Cryosurgery
Oct 01 - 04, 2009
St. Petersburg, Russian Federation
Contact: Congress Secretariat
Phone: 78-125-544-950 Fax: 78-125-533-460
E-Mail: info@ societyofcryosurgery.org

4th Annual AAOS Orthopaedic Practice Management Course
Oct 02 - 04, 2009
Rosemont, IL, United States
Contact: Customer Service
Phone: 1-800-626-6726 / 1-847-823-7186; Fax: 847-823-8125
E-Mail: custserv@aaos.org

Mayo Cardiology Review: General Cardiology, Echo Focus Session, Electrophysiology, Interventional Cardiology
Oct 03 - 08, 2009
Rochester, MN, United States
Contact: Mayo Clinic Medical Education Office
Phone: 904-953-7114 / 507-284-2509 / 480-301-4580
Fax: 904-953-2954 / 507-284-0532 / 480-301-8323
E-Mail: cme-jax@mayo.edu / cme@mayo.edu / mcs.cme@mayo.edu

FIGO 2009: 19th World Congress of Gynecology and Obstetrics
Oct 04 - 09, 2009
Cape Town, South Africa
Contact: Conference Secretariat: FIGO 2009 Secretariat, Turners Conferences & Conventions, PO Box 1935, 4000 Durban
Phone: 27-313-321-451; Fax: 27-313-686-623
E-Mail: info@figo2009.org.za

Michigan Ear Institute Temporal Bone Surgical Dissection Course
Oct 05 - 09, 2009
Farmington Hills, MI, United States
Contact: Organiser
Phone: 248-865-4444; Fax: 248-865-6161

Endourological Society: 27th World Congress on Endourology and SWL (WCE 2009)
Oct 06 - 10, 2009
Munich, Germany
Contact: Meeting Organiser
Phone: 49-210-296-920; Fax: 492-102-969-230
E-Mail: beate.ruloff@ruloff.de

Western Neuroradiological Society’s 41st Annual Meeting
Oct 06 - 11, 2009
Napa, CA, United States
Contact: Susan Franzblau
Phone: 310-247-8004; Fax: 310-247-8457
E-Mail: susan@globaleventsweb.com

18th Congress of the European Academy of Dermatology and Venerology (EADV)
Oct 07 - 11, 2009
Berlin, Germany
Contact: EADV Office
Phone: 322-650-0090; Fax: 322-650-0098
E-Mail: office@eadv.org

2nd Epilepsy review, Cleveland clinic & Yeditepe Uni. Hospital
Oct 08 - 10, 2009
Istanbul, Turkey
Contact: MRS. GULIN KAYSERILI
Phone: 902-163-884-858; Fax: 902-163-880-354
E-Mail: epilepsy@trendturizm.com

2009 Breast Cancer Symposium
Oct 08 - 10, 2009
San Francisco, CA, United States
Contact: Meeting Organiser
Phone: 888-282-2552 / 571-483-1300
E-Mail: membermail@asco.org

Pediatric and Adolescent Medicine Update for the Primary Care Physician
Oct 09 - 21, 2009
Southampton, England, United Kingdom
Contact: Eileen Tener, ACC
Phone: 813-333-6878
E-Mail: ETener@CruisersParadise.com

9th European Peritoneal Dialysis Meeting
Oct 09 - 12, 2009
Strasbourg, France
Contact: In Conference Ltd
Phone: 44-0-1-313-399-235; Fax: 44-0-1-313-399-798
E-Mail: europd@in-conference.org.uk

Allergy and Immunology Conference Cruise
Oct 10 - 17, 2009
Honolulu, HI, United States
Contact: Continuing Education, Inc.
Phone: 1-800-422-0711; Fax: 727-522-8304
E-Mail: Sandra@continuingeducation.net
The Best of the Big Apple Ob-Gyn Ultrasound 2009
Oct 11 - 13, 2009
New York, NY, United States
Contact: Tim Blackwelder, MD
Phone: 888-207-9105 / 509-529-9202; Fax: 509-529-9650
E-Mail: office@worldclasscme.com

8th International Congress on Coronary Artery Disease - ICCAD 2009
Oct 11 - 14, 2009
Prague, Czech Republic
Contact: Liraz Bregman
Phone: 41-229-080-488; Fax: 41-227-322-850
E-Mail: coronary@kenes.com

American College of Surgeons 95th Annual Meeting
Oct 11 - 15, 2009
Chicago, IL, United States
Contact American College of Surgeons
Phone: 312-202-5000; Fax: 312-202-5001
E-Mail: postmaster@facs.org

16th International Meeting of the European Society of Gynaecological Oncology: ESGO 2009
Oct 11 - 15, 2009
Belgrade, Serbia
Contact: Natalie Shabi
Phone: 41-229-080-488; Fax: 41-227-322-850
E-Mail: wccs2009@kenes.com

37th Annual Meeting of the International Society for Pediatric Neurosurgery
Oct 11 - 15, 2009
Los Angeles, CA, United States
Contact: Gordon Mccomb
E-Mail: gmcomb@chla.usc.edu

19th Annual Current Concepts of Magnetic Resonance Imaging
Oct 12 - 15, 2009
Monterey, CA, United States
Contact: Stanford Radiology Continuing Medical Education Program 480 California Avenue, Suite 301, Palo Alto, CA 94306 USA
Phone: 1-888-556-2230 / 1 650 473-5052 Fax: 1 650 473-5062
E-Mail: radiologycme@med.stanford.edu

Macular Review
Oct 12 - 16, 2009
London, England, United Kingdom
Contact: Postgraduate Medical Education Office
Phone: 02-0-75-662-428
E-Mail: courses@moorfields.nhs.uk

The 4th International Congress on Pulmonary Diseases, Intensive Care and Tuberculosis
Oct 13 - 16, 2009
Middle East, Iran
Contact: Bitaraf
Phone: 982-120-109-507; Fax: 982-120-109-484
E-Mail: fc@nrtild.ac.ir

5th ECHO Singapore 2009 Conference
Oct 14 - 16, 2009
Singapore, Singapore
Contact: Meeting Organiser
Phone: 65-64-966-846 Fax: 65-64-966-853
E-Mail: pam_ml_wong@nhg.com.sg

Child Neurology Society (CNS) 38th Annual Meeting
Oct 14 - 17, 2009
Louisville, KY, United States
Contact: CNS National Office, 1000 West County Road E, Suite 290 Saint Paul, MN 55126 Phone: 651-486-9447; Fax: 651-486-9436
E-Mail: nationaloffice@childneurologysociety.org

Twenty-First Century Obstetrics and Gynecology (In Conjunction with the ACOG District I and III Annual Meeting)
Oct 16 - 18, 2009
Orlando, FL, United States
Contact: American College of Obstetricians and Gynecologists, 409 12th St., S.W., PO Box 9692 Phone: 202-638-5577
E-Mail: coding@acog.org / meetings@acog.org

Controversies in Breast Cancer: Adjuvant and Neoadjuvant Therapy 2009
Oct 16 - 18, 2009
New York, NY, United States
Contact: Physicians’ Education Resource, 3500 Maple Ave, Suite 700 Dallas, TX 75219 Phone: 888-949-0045; Fax: 214-367-3304
E-Mail: info@pergrouplp.com

American Society for Reproductive Medicine 65th Annual Meeting
Oct 17 - 21, 2009
Atlanta, GA, United States
Contact: American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, Alabama 35216-2809
Phone: 205-978-5000; Fax: 205-978-5005
E-Mail: asrm@asrm.org

Neuroscience 2009
Oct 17 - 21, 2009
Chicago, IL, United States
Contact: Society for Neuroscience, 1121 14th Street, NW, Suite 1010 Washington, DC 20005 Phone: 202-962-4000; Fax: 202-962-4941
E-Mail: info@sfn.org

WALA LASER 2009 Universal Conference and Exhibitions with Anti-Aging & Aesthetic Symposium
Oct 18 - 21, 2009
Manama, Bahrain
Contact: Prof. Farouk A.H. AL-Watban
Phone: 96-614-427-889 Fax: 96-614-547-272 ext 32-922
E-Mail: laser2009@laser-wala.com
4th Trends in Medical **Mycology**  
Oct 18 - 21, 2009  
Athens, **Greece**  
Contact: Rob Zikkenheimer  
Phone: 31-736-901-415 Fax: 31-736-901-417  
E-Mail: r.zikkenheimer@congresscare.com  

**2nd Paediatric Neuropsychology Symposium**  
Oct 19 - 23, 2009  
Centurion, **South Africa**  
Contact: Robbie Cameron  
Phone: 27-117-288-173; Fax: 27-117-281-675  
E-Mail: robbie@rca.co.za  

**Breast Imaging**  
Cairo  
Oct 20 - 22, 2009  
Cairo, **Egypt**  
Contact: Dr Norran H Said  
Phone: 20-123-938-584; Fax: 20-237-602-536  
E-Mail: contact@eswih.org  

**3rd Thyroid Neoplasms Conference**  
Oct 21 - 24, 2009  
Santa Fe, NM, **United States**  
Contact: Conference Management  
Phone: 713-792-2223; Fax: 713-794-1724  
E-Mail: register@mdanderson.org  

**The Dementia Summit**  
Oct 22 - 24, 2009  
Manila, **Philippines**  
Contact: Dr. Simeon Marasigan  
Phone: 63-27-409-725; Fax: 63-27-409-725  
E-Mail: dementia@ustn4s.org, rye1959-dementia@yahoo.com  

**Lymphoma & Myeloma 2009: An International Congress on Hematologic Malignancies**  
Oct 22 - 24, 2009  
New York, NY, **United States**  
Contact: Customer Service  
Phone: 770-751-7332; Fax: 770-751-7334  
E-Mail: meetings@imedex.com  

**8th Annual Symposium on Advances in Breast MRI**  
Oct 22 - 24, 2009  
Las Vegas, NV, **United States**  
Contact: Stanford Radiology Continuing Medical Education Program 480 California Avenue, Suite 301, Palo Alto, CA 94306 USA  
Phone: 1-888-556-2230 / 1 650 473-5052; Fax: 1 650 473-5062  
E-Mail: radiologycme@med.stanford.edu  

**AAOS Knee Arthroplasty: Uni, Total & Revision Insights, New Techniques - What You Need to Know**  
Oct 22 - 24, 2009  
Rosemont, IL, **United States**  
Contact: Customer Service  
Phone: 1-800-626-6726 / 1-847-823-7186; Fax: 847-823-8125  
E-Mail: custserv@aaos.org  

**3rd Annual Urology Today**  
Oct 22 - 25, 2009  
City: Asheville, NC, **United States**  
Contact: Office of Continuing Education, Medical Center Blvd, Winston-Salem, NC 27157 Phone: 336-713-7755; Fax: 336-713-7702  
E-Mail: rnhoc@wfubmc.edu  

The First Iranian National Congress on **Occupational Health**  
Oct 23 - 25, 2009  
Tehran, **Islamic Republic of Iran**  
Contact: M.Zargham  
Phone: 00-982-188-943-999 Fax: 00-982-188-943-991  
E-Mail: info@piho.org  

ACG 2009: American College of **Gastroenterology**  
Annual Scientific Meeting and Postgraduate Course  
Oct 23 - 28, 2009  
San Diego, CA, **United States**  
Contact: ACG Office  
Phone: 301-263-9000  

2009 American Academy of **Ophthalmology** Joint meeting with the Pan-American Association of Ophthalmology (PAAO)  
Oct 24 - 27, 2009  
San Francisco, CA, **United States**  
Contact: American Academy of Ophthalmology  
Phone: 415-447-0320  
E-Mail: meetings@aao.org  

The 3rd World Congress on Controversies in **Neurology**  
Oct 24 - 26, 2009  
Prague, **Czech Republic**  
Contact: Organizing Secretariat  
Phone: 00-97-235-666-166  
E-Mail: cony@comtecmed.com  

The 19th World Congress of **Neurology** (WCN 2009)  
Oct 24 - 30, 2009  
Bangkok, **Thailand**  
Contact: WCN 2009 Secretariat  
Phone: 46-84-596-600; Fax: 46-86-619-125  
E-Mail: wcn2009@congrex.com  

**Cardiology and Ophthalmology CME Cruise**  
Oct 24 - Nov 02, 2009  
Dubai, **United Arab Emirates**  
Contact: Dr. Martin Gerretsen  
Phone: 1-888-647-7327; Fax: 1-888-547-7337  
E-Mail: cruises@seacourses.com  

Central Association of **Obstetricians and Gynecologists**  
2009 Annual Meeting  
Oct 25 - 28, 2009  
Maui, HI, **United States**  
Contact: Rochelle Hickel  
Phone: 701-838-8323; Fax: 701-852-8733  
E-Mail: rhickel@caog.org
American Review of **Oral and Maxillofacial Surgery** 2009  
Oct 25 - 29, 2009  
Dubai, United Arab Emirates  
Contact: Imedex, 4325 Alexander Drive, Alpharetta, GA 30022-3740 USA  
Phone: 1-678-242-0906 / 1-800-233-0957; Fax: 1-678-242-0920  
E-Mail: meetings@imedex.com

Royal College of Physicians Conference: Acute and **General Medicine** for the Physician  
Oct 26 - 28, 2009  
London, England, United Kingdom  
Contact: Conference Organiser  
Phone: 02-072-241-539; Fax: 02-072-241-539  
E-Mail: conferences@rcplondon.ac.uk

**8th International Congress on Endocrinology and Metabolism**  
Oct 27 - 30, 2009  
Tehran, Iran  
Contact: Dr. H. Delshad  
Phone: 98-2-122-418-931; Fax: 98-2-122-418-931  
E-Mail: info@endocrine.ac.ir

**20th Annual Coronary Interventions**  
Oct 28 - 30, 2009  
San Diego, CA, United States  
Contact: Gretchen Ploen  
Phone: 858-652-5400; Fax: 858-652-5565  
E-Mail: Med.edu@scrippshealth.org

**JOPEOI European Indian Ocean Perinatology Congress / Journées Obstétrico-Pédiatriques Europe Océan Indien**  
Oct 29 - 31, 2009  
Antananarivo, Madagascar  
Contact: Dr. K. De Bargou  
Phone: 33-607-686-118; Fax: 33-143-839-985  
E-Mail: kambarg@orange.fr

**Pennsylvania Academy of Dermatology and Dermatologic Surgery 42nd Annual Meeting**  
Oct 29 - Nov 01, 2009  
Bedford, PA, United States  
Contact: Meeting Organiser  
Phone: 866-650-3376; Fax: 717-558-7841  
E-Mail: paderm@pamedsoc.org

**Michigan Ear Institute Temporal Bone Surgical Dissection Course**  
Nov 02 - 06, 2009  
Farmington Hills, MI, United States  
Contact: Meeting Organiser  
Phone: 248-865-4444; Fax: 248-865-6161

19th **Iranian Congress of Physiology and Pharmacology**  
Nov 03 - 06, 2009  
Tehran, Iran  
Contact: 19th Iranian congress of physiology and pharmacology, Shahid Beheshti University of Medical Sciences, Tehran, Iran. PO Box: 19615-1179  
Phone: 982-122-429-765  
E-Mail: sazai@gmail.com

**Middle East Congress on Age Ageing & Alzheimer’s**  
Nov 04 - 06, 2009  
Tripoli, Lebanon  
Contact: A. Abyad  
Phone: 00-96-13-201-901; Fax: 00-96-16-443-684  
E-Mail: aabyad@cyberia.net.lb

**Turkish Endourology Society: 8th Meeting of Turkish Endourology Society Under the Auspices of ESUT**  
Nov 04 - 07, 2009  
Antalya, Turkey  
Contact: Meeting Organiser  
Phone: 902-122-324-689; Fax: 902-122-339-804  
E-Mail: info@endo2009.org

**American Society for Mohs Surgery Fundamentals of Mohs Surgery**  
Nov 04 - 08, 2009  
San Diego, CA, United States  
Contact: Meeting Organiser  
Phone: 800-616-2767 Fax: 714-379-6272  
E-Mail: execdir@mohssurgery.org

**American College of Phlebology 23rd Annual Congress**  
Nov 05 - 08, 2009  
Palm Desert, CA, United States  
Contact: Meeting Organiser  
Phone: 246-6800; Fax: 510-346-6808  
E-Mail: ddeponzi@acpmail.org

**AAOS Spinal Surgery**  
Nov 05 - 07, 2009  
Rosemont, IL, United States  
Contact: Customer Service  
Phone: 1-800-626-6726 / 1-847-823-7186; Fax: 847-823-8125  
E-Mail: custserv@aaos.org

**International Society for Dermatologic Surgery 30th Annual Meeting of the ISDS**  
Nov 05 - 08, 2009  
Vienna, Austria  
Contact: Meeting Organiser  
Phone: 49-61-519-518-892; Fax: 49-61-519-518-893  
E-Mail: info@isdsworld.com
5th International Congress on Myeloproliferative Disorders and Myelodysplastic Syndromes
Nov 05 - 07, 2009
New York, NY, United States
Contact: Customer Service
Phone: 770-751-7332; Fax: 770-751-7334
E-Mail: meetings@imedex.com

Florida Society of Dermatologic Surgeons Advances in Dermatologic Surgery - 28th Annual Meeting of the FSDS
Nov 06 - 08, 2009
Orlando, FL, United States
Contact: Meeting Organiser
Phone: 904-292-0051 Fax: 904-886-0114
E-Mail: fsds82@aol.com

17th Annual Trauma/Surgical Critical Care Symposium
Nov 06 - 09, 2009
Indianapolis, IN, United States
Contact: Indiana University School of Medicine, Division of Continuing Medical Education, Attn: REGISTRAR, 714 N. Senate Ave, EF 200, Indianapolis, IN 46202
Phone: 317-274-8353 / 888-615-8013; Fax: 317-274-4638
E-Mail: marmin@iupui.edu

American College of Allergy, Asthma & Immunology Annual Meeting 2009
Nov 06 - 11, 2009
Miami Beach, FL, United States
Contact: Meeting Organiser
Phone: 847-427-1294; Fax: 847-427-1200
E-Mail: mail@acaai.org / meetings@acaai.org

Chemotherapy Foundation Symposium, Innovative Cancer Therapy for Tomorrow
Nov 10 - 14, 2009
New York, NY, United States
Contact: Jaclyn Silverman Phone: 212-866-2813; Fax: 646-215-7589
E-Mail: jaclyn.silverman@mssm.edu

Royal College of Physicians Conference: Medical Complications in Pregnancy
Nov 11 - 13, 2009
London, England, United Kingdom
Contact: Conference Organiser
Phone: 02-0-72-241-539; Fax: 02-0-72-241-539
E-Mail: conferences@rcplondon.ac.uk

Istanbul Multidisciplinary Breast Cancer Symposium
Nov 12 - 14, 2009
Istanbul, Turkey
Contact: Mrs. Gulin Kayserili
Phone: 902-163-884-858; Fax: 902-163-880-354
E-Mail: info@breastcancer2009.org

3rd Asia Pacific Congress on Controversies in Obstetrics, Gynecology and infertility
Nov 12 - 15, 2009
Bangkok, Thailand
Contact: Congress Secretariat
Phone: 97-235-666-166
E-Mail: cogi@comtecmcd.com

The Arthroscopy Association of North America 2009 Fall Course
Nov 12 - 15, 2009
Palm Desert, CA, United States
Contact: Arthroscopy Association of North America
Phone: 847-292-2262; Fax: 847-292-2268
E-Mail: info@aana.org

2nd International Congress on Exacerbations of Airway Disease (ICEAD2)
Nov 13 - 15, 2009
Los Cabos, Mexico
Contact: Cathryn Macrae
Phone: 212-988-7732; Fax: 212-717-1222
E-Mail: themacraegroup@comcast.net

Emergency Medicine Update
Nov 15 - 22, 2009
Miami, FL, United States
Contact: Eileen Tener, ACC
Phone: 813-333-6878
E-Mail: ETener@CruisersParadise.com

The 3rd Iranian Asthma Meeting
Nov 17 - 19, 2009
Tehran, Iran
Contact: Iranian Society of Asthma & Allergy
Phone: 982-166-938-545; Fax: 982-166-428-995
E-Mail: isaacong@tums.ac.ir

11th World Congress on Pediatric Dermatology (WCPD 2009)
Nov 17 - 20, 2009
Bangkok, Thailand
Contact: Liraz Bregman
Phone: 00-41-229-080-488; Fax: 00-41-227-322-850
E-Mail: wcpd@kenes.com

Allergy, Asthma and Clinical Immunology Symposium
Nov 17 - 18, 2009
Riyadh, Saudi Arabia
Contact: Ms Ghalya Al Otaibi
Phone: 96-614-647-272 ext. 31-912; Fax: 96-614-424-153
E-Mail: gotaibi@kfsrhc.edu.sa
International Congress in **Aesthetic, Anti-aging Medicine**  
Nov 19 - 21, 2009  
Dubai, United Arab Emirates  
Contact: Omair Khan  
Phone: 00-97-143-365-161 Fax: 00-97-143-364-021  
E-Mail: omair.khan@iirme.com

**6th Annual International Pediatric Orthopaedic Symposium** presented by POSNA and AAOS  
Dec 02 - 06, 2009  
Lake Buena Vista, FL, United States  
Contact: American Academy of Orthopaedic Surgeons  
Phone: 847-823-7186; Fax: 847-823-8125  
E-Mail: meeting@aaos.org

**Update on Cervical Diseases**  
Dec 03 - 05, 2009  
New York, NY, United States  
Contact: American College of Obstetricians and Gynecologists, 409 12th St., S.W., PO Box 9692  
Phone: 202-638-5577  
E-Mail: coding@acog.org / meetings@acog.org

**The 8th International Symposium in Ocular Pharmacology and Therapeutics**  
Dec 03 - 06, 2009  
Rome, Italy  
Contact: Hila Vakrat  
Phone: 41-0-225-330-948 Fax: 41-0-225-802-953  
E-Mail: oishay@isopt2009.com

**40th Union World Conference on Lung Health**  
Dec 03 - 07, 2009  
Cancun, Quintana Roo, Mexico  
Contact: Conference Unit  
Phone: 33-143-299-087; Fax: 33-153-108-554  
E-Mail: cancun2009@theunion.org Quintana Roo

**Pain Management Conference Cruise**  
Dec 05 - 12, 2009  
Honolulu, HI, United States  
Contact: Continuing Education, Inc.  
Phone: 1-800-422-0711; Fax: 727-522-8304  
E-Mail: Sandra@continuingeducation.net

**XXI World Allergy Congress**  
Dec 06 - 10, 2009  
Buenos Aires, Argentina  
Contact: Mariu Denovi  
Phone: 541-147-779-449; Fax: 541-147-711-536  
E-Mail: info@worldallergy2009.com

**2009 Annual Meeting of the American College of Neuropsychopharmacology**  
Dec 06 - 10, 2009  
Hollywood, FL, United States  
Contact: American College of Neuropsychopharmacology, 545 Mainstream Drive Suite 110, Nashville TN 37228  
Phone: 615-324-2360; Fax: 615-324-2361  
E-Mail: acnp@acnp.org

**Mayo Clinic 4th Annual Practical Course in Dermoscopy and Update on Malignant Melanoma**  
Dec 04 - 06, 2009  
Scottsdale, AZ, United States  
Contact: Meeting Organiser  
Phone: 480-301-4580; Fax: 480-301-8323  
E-Mail: king.staci@mayo.edu

**26th Annual Advances in Heart Disease**  
Dec 11 - 13, 2009  
San Francisco, CA, United States  
Contact: UCSF Office of Continuing Medical Education, 3333 California Street, Room 450, San Francisco, CA 94118  
Phone: 415-476-4251 / 415-476-5808; Fax: 415-476-0318 / 415-502-1795  
E-Mail: info@ocme.ucsf.edu

**Rheumatology for the Primary Care Physician**  
Dec 12 - 20, 2009  
Fort Lauderdale, FL, United States  
Contact: Eileen Tener, ACC  
Phone: 813-333-6878  
E-Mail: ETener@CruisersParadise.com

**Orthopaedics for the Primary Care Physician**  
Dec 20 - 27, 2009  
Port Canaveral, FL, United States  
Contact: Eileen Tener, ACC  
Phone: 813-333-6878  
E-Mail: ETener@CruisersParadise.com

**68th AIOS Annual Conference**  
Jan 21 - 24, 2010  
Kolkata, India  
Contact: Parminder Singh  
Phone: 1-800-102-2220  
E-Mail: confsales@saharaglobal.in

**The Society of Thoracic Surgeons 46th Annual Meeting**  
January 25 - 27, 2010  
Fort Lauderdale, FL, United States  
Contact: The Society of Thoracic Surgeons, 633 N. Saint Clair Street, Suite 2320, Chicago, IL 60611  
Phone: 312-202-5800; Fax: 312-202-5801  
E-Mail: sts@sts.org

**Obs-Gyne Middle East Meeting**  
Feb 14 - 16, 2010  
Dubai, United Arab Emirates  
Contact: Eben Botha  
Phone: 00-97-143-365-161; Fax: 00-97-143-364-021  
E-Mail: eben.botha@iirme.com

**The 5th International Conference on Ocular Infections**  
Feb 18 - 21, 2010  
Palm Beach, FL, United States  
Contact: Hila Dayan  
Phone: 41-225-330-948  
E-Mail: hdayan@paragon-conventions.com
Multidisciplinary *Head and Neck Cancer Symposium*
Feb 25 - 27, 2010
Chandler, AZ, United States
Contact: Meeting Organiser
Phone: 703-502-1550; Fax: 703-502-7852

American Academy of *Allergy, Asthma and Immunology* (AAAAI) Annual Meeting
Feb 26 - Mar 02, 2010
New Orleans, LA, United States
Contact: AAAAI Education Manager
Phone: 414-272-6071
E-Mail: cme@aaaai.org

**NYSORA World Anesthesia Congress**
Mar 07 - 12, 2010
Dubai, United Arab Emirates
Contact: Jo Watling
Phone: 00-441-462-441-166; Fax: 00-441-462-452-562
E-Mail: jo.watling@choicelive.com

**29th Annual Dialysis Conference**
Mar 08 - 10, 2010
Houston, TX, United States
Contact: Office of Continuing Medical Education, University of Missouri
Phone: 573-882-4105; Fax: 573-882-5666
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Mar 11 - 13, 2010
Abu Dhabi, United Arab Emirates
Contact: Prof. Mohamed Al-Hajjaj
Phone: 00-966-505-419-532; Fax: 0096-14-679-496
E-Mail: msalhajjaj@yahoo.com

**1st International (ADDC) Abu Dhabi Diabetes Congress**
Mar 12 - 14, 2010
Abu Dhabi, United Arab Emirates
Contact: Congress Manager
Phone: 44-0-1-903-288-288; Fax: 44-0-1-903-520-520
E-Mail: secretariat@addc.gr

**Innovations in Plastic Surgery**
Mar 19 - 21, 2010
Fort Lauderdale, FL, United States
Contact: Diana Sheffey
Phone: 954-659-5490 Fax: 954-659-5491
E-Mail: dheffed@ccf.org

**41st Annual Meeting of the Society for Paediatric Nephrology**
Mar 25 - 27, 2010
Hamburg, Germany
Contact: Jutta Vach
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**Hair and Scalp Diseases in Clinical Practice. International Course and Symposium**
Mar 26 - 28, 2010
Warsaw, Poland
Contact: Lidia Rudnicka
Phone: 48-225-081-480; Fax: 48-225-081-492
E-Mail: lidiarudnicka@yahoo.com

**British Renal Society: BRS Conference 2010**
Apr 26 - 29, 2010
Manchester, England, United States
Contact: Conference Secretariat
Phone: 44-1-483-764-114; Fax: 44-1-483-727-816
E-Mail: brs@britishrenal.org

The 4th International Conference of *Biomarkers in Chronic Diseases*
May 04 - 06, 2010
Riyadh, Saudi Arabia
Contact: Conference Secretariat
Phone: 00-96-614-675-939; Fax: 00-96-614-675-931
E-Mail: biomarkers@ksu.edu.sa

FIP World Congress of *Podiatry*
May 13 - 15, 2010
Amsterdam, Netherlands
Contact: Wendy van Buren
Phone: 31-0-348-443-251; Fax: 31-0-348-446-920
E-Mail: fip2010@mccm.nl

**10th International Congress of Immunology and Allergy of Iran**
May 18 - 20, 2010
Tehran, Islamic Republic of Iran
Contact: Dr. Mandana Sattari
Phone: 982-123-872-573; Fax: 982-122-439-952
E-Mail: info@icia2010.com

**International College of Neuropsychopharmacology 2010 Congress**
Jun 06 - 10, 2010
Hong Kong, China
Contact: Organiser
Phone: 0-1-355-244-966; Fax: 0-1-355-249-959
E-Mail: cinp2010@congrex.com

**16th World Congress of Basic & Clinical Pharmacology**
Jul 13 - 23, 2010
Copenhagen, Denmark
Contact: Prof. Kim Brøsen / Tina Ludvig
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**14th International Congress of Immunology**
Aug 22 - 27, 2010
Kobe, Japan
Contact: Prof. Masayuki Miyasaka
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E-Mail: mmiyasak@orgctl.med.osaka-u.ac.jp
1. GLOBAL USE OF ROTAVIRUS VACCINES RECOMMENDED

Vaccines can protect millions of children from diarrhoeal disease

WHO has recommended that rotavirus vaccination be included in all national immunization programmes to provide protection against a virus that is responsible for more than 500,000 diarrhoeal deaths and 2 million hospitalizations every year among children. More than 85% of these deaths occur in developing countries in Africa and Asia. This new policy will help ensure access to rotavirus vaccines in the world’s poorest countries.

The new recommendation by WHO’s Strategic Advisory Group of Experts (SAGE) extends an earlier recommendation made in 2005 on vaccination in the Americas and Europe, where clinical trials had demonstrated safety and efficacy in populations with low and intermediate mortality. New data from clinical trials, which evaluated vaccine efficacy in countries with high child mortality, has led to the recommendation for global use of the vaccine. This is reported in the Weekly Epidemiological Record published on 5 June 2009.

“This is a tremendous milestone in ensuring that vaccines against the most common cause of lethal diarrhoea reach the children who need them most,” noted Dr Thomas Cherian, Coordinator of the Expanded Programme on Immunization in the WHO Department of Immunization, Vaccines and Biologicals.

Clinical trials

The GAVI Alliance, vaccine manufacturers, and the public health community made an unprecedented commitment to understand how these vaccines would work in developing-world conditions. The clinical trial, funded in part by GAVI and conducted by PATH, WHO, GlaxoSmithKline (GSK) and research institutions in high-mortality, low-socioeconomic settings of South Africa and Malawi, found that the vaccine significantly reduced severe diarrhoea episodes due to rotavirus.

In 2006, the GAVI Alliance added rotavirus vaccines to its portfolio of vaccines for which it provides financial support to developing countries, underscoring GAVI’s commitment to reduce the traditional 15-year to 20-year lag between the introduction of new vaccines in developed countries and their availability in the developing world. WHO’s global recommendation now paves the way for low-income countries in Africa and Asia to apply to GAVI for introduction of rotavirus vaccines—just three years after new rotavirus vaccines became available in the United States of America, Europe and Latin America.

Because oral vaccines can have variable efficacy in different populations, it was important to demonstrate vaccine performance in high-mortality settings. The studies in Africa were conducted among populations with high infant and child mortality, poor sanitary conditions, high diarrhoeal disease mortality and high maternal HIV prevalence.

“The new evidence and the WHO recommendation are major breakthroughs for the health of our children,” said Dr Oyewale Tomori, Vice-Chancellor of Redeemer’s University, Nigeria, who has served as Regional Laboratory Coordinator for WHO in the African Region.

“Too many of our children are dying from rotavirus and other causes of diarrhoea. We urgently need these lifesaving vaccines against rotavirus.”

Vaccine efficacy valid for all regions

The clinical trial investigators from Malawi and South Africa will present and publish their data on the GSK RotarixTM vaccine later this summer. While efficacy data from Asian countries are forthcoming, SAGE recommended rotavirus vaccines for all populations, including Asia, since available evidence indicates that efficacy data can be extrapolated to populations with similar mortality patterns regardless of geographic location.

Because there are many causes of diarrhoeal disease, SAGE emphasized the importance of providing rotavirus vaccination in the context of a
comprehensive diarrhoeal disease control strategy, including improvement of water quality, hygiene, and sanitation; provision of oral rehydration solution and zinc supplements; and overall improved case management.

WHO, UNICEF and other GAVI partners are working together in a new accelerated and integrated approach to combat rotavirus diarrhoea and pneumonia, the two biggest vaccine-preventable diseases which together account for more than 35% of all child deaths every year, the majority of which are in the developing world.

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2. FOOD STANDARDS COMMISSION TARGETS DANGEROUS BACTERIA, CHEMICALS

Measures to Make Food Safer Dominate Agenda of Codex Alimentarius Commission

The Codex Alimentarius Commission, (CAC) concluded a week-long meeting and adopted more than 30 new international standards, codes of practice and guidelines to improve worldwide food safety and protect the health of consumers.

New standards adopted by the Commission include:
Reduction of acrylamide in foods

The Commission approved measures for reducing the formation of acrylamide in foods. The Code of Practice will provide national and local authorities, manufacturers and others with guidance to prevent and reduce formation of acrylamide in potato products during all phases of the production process. The guidance includes strategies for raw materials, the addition of other ingredients; and food processing and heating. The chemical acrylamide, first identified in food in 2002, is produced during frying, roasting and baking of carbohydrate-rich foods, such as French fries, potato crisps, coffee, biscuits, pastries and breads. Acrylamide is considered a possible human carcinogen.

Reduction of contamination with Polycyclic aromatic hydrocarbons

The Commission adopted the first guidelines for reducing Polycyclic aromatic hydrocarbons (PAH) intake through final food preparation. Because smoking and direct drying processes are used both in industry and in private households, the guidance can also form the basis of consumer education programs. Parts of PAH are possible human carcinogens formed during the combustion of fuel both in the smoking and in the direct drying processes involved in the preparation of foods.

Prevention of Ochratoxin A contamination in coffee

The Commission adopted guidance to enable coffee producing countries to develop and implement their own national programmes for the prevention and reduction of Ochratoxin A (OTA) contamination. OTA is a fungal toxin also considered a possible human carcinogen.

Powdered follow-up formulae

The Commission adopted criteria for salmonella and other bacteria in powdered follow-up formulae for children six months of age or older and for special medical purposes for young children. A bacterium of special concern is E. sakazakii, for which Codex adopted specific criteria for powdered formula for infants (0 to 6 months) in 2008. The Commission decided that in countries with particular risk for E. sakazakii from consumption of follow-up formulae (i.e., countries with substantial populations of immunocompromised babies) similar criteria for E. sakazakii could be introduced for follow-up formula as for powdered formula for infants.

Follow-up formulae should only be used for the intended target population. Unfortunately, they are often consumed by babies younger than six months of age. The standard stresses the need to address such product misuse issues through education campaigns and training.

Listeria monocytogenes in ready-to-eat foods

The Commission adopted parameters for microbiological testing and environmental monitoring for Listeria monocytogenes in ready-to-eat foods. A maximum level was set for certain foods where the bacteria cannot grow, while in ready-to-eat products where growth is possible, no Listeria monocytogenes will be allowed. The parameters will help producers control and prevent contamination of ready-to-eat foods with this bacterium that can result in listeriosis, a potentially fatal disease. While healthy people rarely contract listeriosis, it can cause miscarriages and stillbirths, as well as serious and sometimes fatal infections in those with weakened immune systems, such as infants, the elderly and persons with HIV infection or undergoing chemotherapy.

The Commission also adopted regional standards for ginseng products, fermented soybean paste and gochujang.

Ezzeddine Boutrif, FAO Director, Nutrition and Consumer Protection Division, noted that Codex
membership now represents 99 percent of the world’s population. “Applying Codex standards and guidelines are an important part of ensuring that consumers in every part of the world can be protected from unsafe food,” he said.

The Commission also launched new work projects, among them establishing maximum levels for melamine in food and feed. In the last few years, high levels of melamine have been added illegally to food and feed products, causing illness and death. Because it has many industrial uses, melamine may be found in trace amounts in the food chain due to its presence in the environment. Setting maximum limits will help governments differentiate between unavoidable melamine occurrence and the deliberate adulteration of food and feed.

Other new work proposals adopted by the Commission include:

- Principles and guidelines to assist governments in the development and operation of comprehensive national food control systems that protect the health of consumers and ensure fair practices in the food trade;
- Practices to control viruses in food, especially noroviruses (NoV) and hepatitis A (HAV) in fresh produce, mulluscan shell fish and ready-to-eat foods;
- Prevention of aflatoxin (toxic substances produced by moulds and known to cause cancer in animals) contamination of Brazil nuts;
- Setting maximum levels and defining sampling plans for Fumonisins, (toxic substances produced by fungi) in maize and maize products.

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3. INFECTION PREVENTION AND CONTROL IN HEALTH CARE FOR CONFIRMED OR SUSPECTED A(H1N1) SWINE INFLUENZA PATIENTS

Background
The current situation regarding the outbreaks of A(H1N1) swine influenza is evolving rapidly, and countries from different regions of the globe have been affected.

Based on epidemiological data, human-to-human transmission has been demonstrated along with the ability of the virus to cause community-level outbreaks which together suggest the possibility of sustained human-to-human transmission. Health-care facilities now face the challenge of providing care for patients infected with A(H1N1) swine influenza. It is critical that health-care workers use appropriate infection control precautions when caring for patients with influenza-like symptoms, particularly in areas affected by outbreaks of A(H1N1) swine influenza, in order to minimize the possibility of transmission among themselves, to other health-care workers, patients and visitors.

As at 29 April, human-to-human transmission of A(H1N1) swine influenza virus appears to be mainly through droplets. Therefore, the infection control precautions for patients with suspected or confirmed A(H1N1) swine influenza and those with influenza-like symptoms should prioritize the control of the spread of respiratory droplets. The precautions for influenza virus with sustained human-to-human transmission (e.g., pandemic-prone influenza) are described in detail in the document “Infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in health care WHO Interim Guidelines” (Available at http://www.who.int/csr/resources/publications/WHO_CD_EPR_2007_6/en/index.html). This guidance may change as new information becomes available.

Fundamentals of infection prevention strategies
1. Administrative controls are key components, including: implementation of Standard and Droplet Precautions; avoid crowding, promote distance between patients (≥ 1 m); patient triage for early detection, patient placement and reporting; organization of services; policies on rational use of available supplies; policies on patient procedures; strengthening of infection control infrastructure.
2. Environmental/engineering controls, such as basic health-care facility infrastructure, adequate ventilation, proper patient placement, and adequate environmental cleaning can help reduce the spread of some respiratory pathogens during health care.
3. Rational use of available personal protective equipment (PPE) and appropriate hand hygiene.

Critical Measures:
- Avoid crowding patients together, promote distance between patients
- Protect mucosa of mouth and nose
- Perform hand hygiene

SUMMARY PRECAUTIONS
For staff providing care to patients with suspected or confirmed A(H1N1) swine influenza infection and for patients with influenza-like symptoms:
Standard Precautions (basic precautions designed to minimize direct unprotected exposure to potentially infected blood, body fluids or secretions (www.who.int/csr/resources/publications/standardprecautions/en/index.html) and Droplet Precautions (health-care workers to wear medical mask if working within 1 m of the patient) should be strengthened when working in direct contact with suspected or confirmed A(H1N1) swine influenza infected patients.

Key elements:
• use a medical or surgical mask
• emphasize hand hygiene and provide hand hygiene facilities and supplies.

As per Standard Precautions (basic precautions designed to minimize direct unprotected exposure to potentially infected blood, body fluids or secretions (www.who.int/csr/resources/publications/standardprecautions/en/index.html), if there is a risk of splashes onto face:
• use face protection Use either (1) a medical or surgical mask and eye-visor or goggles, or (2) a face shield and,
• use a gown and clean gloves.
• Do not forget hand hygiene after PPE removal

Aerosol generating procedures (e.g., aspiration of respiratory tract, intubation, resuscitation, bronchoscopy, autopsy) are associated with increased risk of infection transmission, and the infection control precautions should include using:
• particulate respirator (e.g., EU FFP2, US NIOSH-certified N95);
• eye protection (i.e., goggles);
• a clean, non-sterile, long-sleeved gown;
• gloves (some of these procedures require sterile gloves).

KEY ELEMENTS FOR HEALTH CARE
1. Basic infection control recommendations for all health-care facilities
   Standard and Droplet Precautions when caring for a patient with an acute, febrile, respiratory illness.

2. Respiratory hygiene/cough etiquette
   Health-care workers, patients and family members should cover mouth and nose with a tissue when coughing and perform hand hygiene afterwards.

3. Infection control precautions for suspected and confirmed A(H1N1) swine influenza infection
   Place patient in adequately-ventilated room. If single rooms are not available, cohort patients in wards keeping at least 1 metre distance between beds. Standard, and Droplet Precautions for all persons entering the isolation room.

4. Triage, early recognition and reporting of A(H1N1) swine influenza infection
   Consider A(H1N1) swine influenza infection in patients with acute, febrile, respiratory illness who have been in an affected region within the one week prior to symptom onset and who have had exposure to an A(H1N1) swine influenza infected patient or animal.

5. Additional measures to reduce nosocomial A(H1N1) swine influenza virus transmission
   Limit numbers of health-care workers/family members/visitors exposed to the A(H1N1) swine influenza patient.

6. Specimen collection/transport/handling within health-care facilities
   Use Standard, and Droplet Precautions for specimen collection. Use Standard Precautions for specimen transport to the laboratory. Health-care facility laboratories should follow good biosafety practices.

7. Family member/visitor recommendations
   Family members/visitors should be limited to those essential for patient support and should use the same infection control precautions as health-care workers.

8. Patient transport within health-care facilities
   Suspect or confirmed A(H1N1) swine influenza patients should wear a medical/ surgical mask.

9. Pre-hospital care
   Infection control precautions are similar to those practiced during hospital care for all involved in the care of suspected A(H1N1) swine influenza patients. (e.g., transportation to hospital).

10. Occupational health
    Monitor health of health-care workers exposed to A(H1N1) swine influenza patients. Antiviral prophylaxis should follow local policy. Health-care workers with symptoms should stay at home.

11. Waste disposal
    Treat any waste that could be contaminated with A(H1N1) swine influenza virus as infectious clinical waste, e.g., used masks.

12. Dishes/eating utensils
    Wash using routine procedures with water and detergent. Use non-sterile rubber gloves.
13. Linen and laundry
Wash with routine procedures, water and detergent; avoid shaking linen/laundry during handling before washing. Use non-sterile rubber gloves.

14. Environmental cleaning and disinfection
Clean soiled and/or frequently touched surfaces regularly with a disinfectant. e.g. door handles.

15. Patient care equipment
Dedicate separate equipment to A(H1N1) swine influenza patients. If not possible, clean and disinfect before reuse in another patient.

16. Duration of A(H1N1) swine influenza infection control precautions
For the duration of symptoms.

17. Patient discharge
If the A(H1N1) swine influenza patient is discharged while still infectious (i.e. discharged within the period of infection control precautions: see 16 above), instruct family members on appropriate infection control precautions in the home.

18. Prioritization of PPE when supplies are limited
Medical/surgical mask for the care of all A(H1N1) swine influenza patients and hand hygiene are priorities.

Pandemic influenza prevention and mitigation in low resource communities
This summary guidance is derived from the WHO document Pandemic influenza preparedness and mitigation in refugee and displaced populations: WHO guidelines for humanitarian agencies, Second edition, 2008

Key principles
1. Public health measures taken by individuals and communities, such as social distancing, respiratory etiquette, hand hygiene, and household ventilation, are at present the most feasible measures available to reduce or delay disease (morbidity) caused by pandemic influenza.

2. In the case of mild illness, patients should be provided with supportive care at home by a designated caregiver and only referred to health care facilities if they deteriorate or develop danger signs. Separation of sick from well individuals, with rigorous respiratory etiquette and hygiene measures should be practised.

3. In health-care settings, a system of triage, patient separation, prioritization of use of antiviral medicines and personal protective equipment (PPE) according to risk of exposure, and patient management should be in place to focus efforts on the most effective interventions to reduce mortality and any further morbidity.

1. Key prevention measures for individuals and communities
Social distancing (keeping at least an arm’s length distance from others, minimizing gatherings), respiratory etiquette (covering coughs and sneezes), hand hygiene, and household ventilation, are likely to be the most effective public health measures and are highly recommended.

Once cases of pandemic influenza in a community are widespread, evidence and experience suggest that interventions to isolate patients and quarantine contacts would probably be ineffective, not a good use of limited health resources, and socially disruptive.

Ill people should as far as possible be cared for at home by a designated caregiver (with appropriate home-care instructions communicated in advance) and advised not to attend health-care facilities unless they deteriorate or develop danger signs so as not to overwhelm health facilities (see guidance note below). Supportive care entails bed rest, fluids, medication for fever, antibiotics if prescribed, and good nutrition.

WHO recommends that mask use should be based on risk, including frequency of exposure and closeness of contact with potentially infectious people. Routine mask use in public places should be permitted but is not expected to have an impact on disease prevention.

2. Management of patients
• The objectives of patient management are to provide supportive health care to decrease mortality and to minimize disease transmission.

• Given limited resources, it will be necessary to triage patients for treatment during a pandemic to maximize the impact of available treatment capacity.

• Essential medical services should be continued, while elective and non-essential medical services should be temporarily suspended.

• Patients are most likely to be managed in two distinct settings: in the health-care facility and at home.

Patient management in the health-care facility
Admission criteria may change depending on bed availability, but should be reserved for severe cases most likely to benefit from treatment.

For milder cases presenting to the outpatients department, a caregiver, preferably an available family member, should be identified if possible to manage care of the ill patient in the home if the patient is being discharged.
Health facilities should anticipate a very high demand for treatment with supportive care, and should plan accordingly. Based on current estimates, agencies should anticipate that up to 10% of those who fall ill may require inpatient treatment. In a population of 10 000, this could mean 500–600 persons requiring inpatient care for influenza alone over a period of 2–3 months, or approximately 6–10 patients per day. These figures are an average to assist calculations. Note that the number of patients affected per week may not be constant over the pandemic period: it is likely that there will be increasing numbers affected per week, reaching a peak in the middle of the pandemic (weeks 4–8) with decreasing numbers thereafter.

Ensure:
• separation of patients with respiratory symptoms from those presenting with other symptoms at both the outpatient and inpatient level;
• availability of admission and discharge criteria (these may change depending on treatment capacity);
• availability of case-management protocols; referral protocol, if feasible (with appropriate infection control during the transfer);
• confinement in a separate respiratory ward for patients admitted with suspected pandemic influenza;
• maximum separation of beds and head-to-toe positioning of patients in inpatient wards if space is limited;
• good ventilation of outpatient and inpatient areas;
• adherence to Standard and Droplet Precautions; use of PPE according to risk of exposure.

Inpatient treatment in low resource settings should include:
• treatment of dehydration with IV or oral rehydration fluids;
• supplemental oxygen therapy (if available) by face mask rather than nasal prongs;
• antibiotics (oral or parenteral) for secondary bacterial infections;
• non-aspirin antipyretics for pain and fever; nutritional supplementation as needed.

Note: in HIV-infected individuals, a distinction between opportunistic pneumonia and secondary pneumonia from pandemic influenza may be difficult. Antiviral medicines decrease the duration of virus excretion and the severity of illness when used for treatment of ill patients, and may also prevent illness when used for prophylaxis. If only limited quantities are available, prioritization of use should be in place according to national protocol.

In general, the order of priority for antiviral use should be:
• treatment of sick health-care and other essential staff;
• treatment of sick individuals from the community;
• post-exposure prophylaxis for essential staff with unprotected, high-risk exposure;
• pre-exposure prophylaxis for critical staff with anticipated high-risk exposure.

Patient management at home
During a pandemic, very high numbers of patients presenting to the health-care facility will necessitate home treatment. Trusted community leaders should be identified in advance for crowd control at the health-care facility and to address concerns among health-seekers and their caregivers.

All people not exhibiting severe symptoms and signs of influenza should be encouraged (through health messaging) to stay at home, institute respiratory etiquette (cover coughs and sneezes or cough/sneeze into sleeve) and hand hygiene, and restrict close contact (within approximately 1m) with others as much as possible.

Home confinement of ill people in crowded settings may not be practicable. However, restricting contact with others should be encouraged as much as possible.

Adequate supervision within the household of the ill person should be ensured with preferably only one caregiver to limit potential exposure.

Patients and caregivers should be trained to wear and dispose of masks during the infectious period of the patient, if supplies are available. Where supplies are limited, it is more important in the home that the patient wears the mask than the caregiver. The mask need not be worn all day and only when close contact (within approximately 1m) with the caregiver or others is anticipated. Masks should be disposed of safely if wet with secretions. Tightly-fitting scarves or a reusable mask made of cloth covering the mouth and nose could be used if masks are unavailable. They should be changed if wet and washed with soap and water.

If enough masks are available, caregivers should also use them to cover their mouth and nose when in close contact with ill persons. The caregiver should always wash hands after patient contact.

General support and advice should be given to caregivers on the use of antipyretics (acetylsalicylic acid should be avoided in children), oral fluids, nutrition and bed rest.

Instructions must be provided on the use of antibiotics (if necessary) for bacterial complications of influenza when prescribed.

Instructions for further care in case of deterioration (if capacity exists) should be given (i.e., when there
are symptoms of severe illness or dehydration – see guidance note below).

Those who have recovered are no longer infectious and can be considered immune (usually 2–3 weeks after the onset of illness).

Proper respiratory etiquette and hand hygiene must be promoted for all household members.

Keep windows open and allow ventilation of the room/tent. Household surfaces should be cleaned regularly with soap and water or disinfectant.

GUIDANCE NOTE

Referral to health-care facilities:
The majority of influenza cases may be cared for at home with the simple supportive care outlined above. However, if there is deterioration or severe symptoms, then patients may need to access a health-care facility. These symptoms may include: weakness/not able to stand, lethargy, unconsciousness, convulsions, very difficult/obstructed breathing or shortness of breath, inability to drink fluids and dehydration, high fever. It is important that specific instructions are provided according to the local context.

Protection of staff

Rigorous attention to Standard Precautions (basic measures to minimize direct unprotected exposure to blood and body fluids) and Droplet Precautions (medical masks when close to patients with respiratory symptoms) is required to reduce the opportunities for transmission in the health-care setting. Mechanisms for procuring (and/or stockpiling) antibiotics, PPE, antiviral medicines and vaccines (when/if available) should be considered, with protocols and prioritization for their use.

Priority recipients will include those involved in direct clinical contact with patients, and those staff required to maintain essential functions who anticipate close contact with potentially ill people.

Source control (i.e. of the ill person) is crucial, as this can prevent opportunities for transmission; the patient must be encouraged at all times to cough/sneeze into a tissue/cloth or into their sleeve and to practice frequent hand hygiene.

Masks

Use of masks should be prioritized to ensure that those at highest risk of exposure have access to available protection. Masks do not have to be worn at all times as they may become uncomfortable, particularly in hot climates. They should be worn as a priority by health-care workers and caregivers, and other essential staff when in close contact (within approximately 1 m) with sick patients.

Antibiotics and antivirals

Antibiotics: Consideration should be given to stockpiling quantities of antibiotics sufficient to treat secondary bacterial pneumonia in at least 5–10% of total staff and dependents.

Antivirals: If feasible and where quantities are available, agencies should stockpile sufficient oseltamivir to provide treatment of ill staff and post-exposure prophylaxis of essential staff.

Self-monitoring: Health staff should monitor their temperatures twice daily. Fevers should be reported and the staff member should confine themselves at home. If a staff member becomes unwell, treatment with antivirals as well as supportive care as for other patients should be provided at home by a caregiver.

For more information: