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EDITORIAL

REVIEW ARTICLE

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Continued inside

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CONTENTS

Continued from cover

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INTRODUCTION

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Book chapter

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Weblinks

U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed June 4, 2003, at http://www.house.gov/reform/min/inves.tobacco/index_accord.htm.)

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Editorial

Good for Old As Well As Young: Oral Rehydration Therapy (ORT)

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Kuwait Medical Journal 2011; 44 (1): 1 - 2

Oral Rehydration Therapy (ORT) is based on the discovery of "carrier-mediated transport" published in the Journal of General Physiology in the 1960's[1]. Its discovery and application demonstrates that the "translation" of basic science to patient care is important and effective. In 1978, the journal Lancet noted that "the discovery that sodium transport and glucose transport are coupled in the small intestine, so that glucose accelerates absorption of solute and water was potentially the most important medical advance this (20th) century"[2].

When 9 million refugees poured out of East Pakistan into India and cholera broke out in the Kolkata camps, application of ORT reduced mortality in cholera patients from 30 - 40% to less than 3%, even when intravenous therapy was not possible[3]. This demonstration of the power of ORT in the chaotic setting of a refugee camp indicated that ORT was ready for major global use. The careful clinical and laboratory studies which were accomplished in Dhaka, Bangladesh and Kolkata, India proved that the glucose-sodium carrier-mediated transport system of the small intestine remained robust and fully functional even in cholera, the most severe of diarrhoeal diseases[4]. Realizing that diarrhea was responsible for 7 - 8 million deaths of children from birth until the age of four years, the World Health Organization (WHO) and UNICEF then initiated a global program for the control of diarrheal diseases (CDD) and used ORT as a backbone of this program. In a report in 2010, it was estimated that deaths of children due to diarrhea which had been an estimated 8 million each year before ORT was reduced to 1.3 million in 2008 – a decrease of 5 - 6 million deaths each year[5].

The original studies on ORT in cholera included both adults and children, so starting in the 1960's, there has been evidence of the efficacy of ORT in adults as well as children. It is important then 50 years later to ask, why this inexpensive and effective treatment has not moved into the mainstream of adult and geriatric medical practice?[6] We know that as one ages and immunity wanes, diarrhea reemerges as a major cause of morbidity and mortality[7]. However, we recognize that there are certainly medical issues in older patients that may differ from those in children. These include, the risk of congestive heart failure and renal failure which are more frequent with increasing age. Few of the conditions affecting older individuals, however, would preclude the timely use of ORT especially early in the course of diarrhea before serious volume depletion ensues. At home or in an outpatient setting, it's use would be most appropriate, were this practice widely adopted. If application of this proven modality were introduced, it could result in substantial reduction of hospital admissions and the associated costs. In an older population in which atherosclerosis compromised the arterial blood supply to vital organs such as the brain, heart, kidney and intestines, volume depletion increases the risk of infarctions or death. The risk of overdose with ORT solutions is less than with intravenous fluid since it is not so tasty as to be imbibed casually as a pleasant refreshment. Hence the risks of fluid overload would be less with ORT than with the use of intravenous hydration. Furthermore there are serious hazards associated with intravenous therapy beyond the risk of over hydration. These include bloodstream infection, and complications of central line insertion, or the less serious but important considerations of discomfort and immobility.

Several steps are needed to validate the widespread use of ORT in geriatric practice to confirm efficacy and rule out hazards in adults and the elderly. Well-

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designed prospective studies and careful balance studies in patients with high output ostomies are certainly indicated. We know from case reports that with chronic intestinal fluid loss patients can be freed from intravenous therapy by substituting ORT. Careful balance studies in patients with daily fluid losses could define the power of ORT in a relatively small series of cases. A second approach would be to assess potential risks of hyperkalemia that might occur with current ORT solutions all of which have 20 mEq/L of potassium. In patients with marginal renal function where hyperkalemia may be a hazard, a potassium free ORT may be needed. A third area needing investigation would be studies to compare the currently published advantage of rice-based ORT with the WHO low osmolarity glucose ORT[8].

I would suggest that application ORT in older individuals is likely to be highly effective and could potentially save the costs and risk of hospitalizations. The principal challenge beyond research to document safety and efficacy is that of educating not only physicians and health workers but also the public who are currently bombarded with the importance and power of life saving centralized high technology medicine with its sophisticated intravenous methods. Why would anyone think that drinking a simple solution would be better than a trip to the emergency room and intensive care units with the mystique of intravenous fluid therapy? Although the health care systems of my own country favors such high technology approaches and would not reimburse for simply giving patients drinks of ORT, most countries have an overall concern for better health care at lower costs. Thus, it may be, and is perhaps even likely, that countries other than the US would take leadership in doing the research needed to put ORT on the map and prove that it is an effective, accessible and inexpensive way to repair the solute and water losses incurred by diarrhea or short bowel syndromes in adults and older populations.

Conflict of interest

Dr. Greenough was an original and current shareholder of Cera Products, Inc. and chairs the company's scientific advisory committee.

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Review Article

New Approaches in the Diagnosis and Treatment of Susceptible, Multidrug-Resistant and Extensively Drug Resistant Tuberculosis

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ABSTRACT

Tuberculosis (TB) is killing nearly two million people worldwide every year. The current global burden of TB is mainly due to the expanding human immunodeficiency virus infection and its association with active TB disease and increasing resistance of *Mycobacterium tuberculosis* strains to most-effective (first-line) anti-TB drugs. Incomplete/ improper treatment of TB patients leads to evolution of drug-resistant *M. tuberculosis* strains as a result of chromosomal mutations in genes encoding drug targets. Sequential accumulation of mutations in target genes generate multidrug-resistant (resistant atleast to rifampin and isoniazid) *M. tuberculosis* (MDR-TB) and extensively drug-resistant (additionally resistant to fluoroquinolones and an injectable anti-TB agent) *M. tuberculosis* (XDR-TB) strains. While proper treatment of susceptible TB has > 95% cure rate, effective treatment of MDR-TB is difficult in developing countries as it is heavily dependent on rapid diagnosis, supervised aggressive therapy with several (5 - 6) expensive, toxic and less efficacious drugs for 18 - 24 months and regular monitoring for bacteriological and clinical improvement. Treatment of XDR-TB is far more difficult even in developed countries. Several anti-TB drugs with novel mechanism of action are under clinical development, which may shorten treatment duration of susceptible TB to around three months and also help in effective treatment of MDR-TB / XDR-TB.

KEY WORDS: diagnosis, MDR-TB, treatment, tuberculosis, XDR-TB

INTRODUCTION

Despite concerted worldwide efforts, tuberculosis (TB) remains a major infectious disease and a formidable public health challenge as it contributes considerably to illness and death around the world. In humans, TB is caused overwhelmingly by *Mycobacterium tuberculosis* while some disease cases are also caused by two other closely related species, *Mycobacterium bovis* and *Mycobacterium africanum*[1]. Current TB epidemic is being sustained by two major factors; global human immunodeficiency virus (HIV) infection and its association with active TB disease and increasing resistance of *M. tuberculosis* strains to most effective (first-line) anti-TB drugs[2-5]. Other contributing factors include inadequate TB control programs in developing countries, active transmission in overcrowded prisons, hospitals, and other public places, poor case detection / cure rates in impoverished countries, wars, famine, homelessness and poorly controlled diabetes mellitus[2,3,6].

Active disease patients with sputum-positive pulmonary or laryngeal TB are the main source of infection in a community. Primary infection with *M. tuberculosis* leads to clinical disease in only ~ 10% of exposed individuals. In the remaining cases, the ensuing immune response arrests further growth of *M. tuberculosis*. However, complete eradication of the pathogen occurs in ~ 10% people while immune response in the remaining ~ 90% individuals only succeeds in containment of infection as some bacilli escape killing and remain in non-replicating (dormant or latent) state in granulomatous lesions[7]. The bacilli can remain dormant for a long time (lasting up to a life time) but retain the ability to resuscitate and to cause active TB if a disruption of immune response occurs (such as in HIV infection)[8-11]. The World Health Organization (WHO) has estimated that one-third of the total world population is latently infected with *M. tuberculosis* and 5 - 10% of the infected individuals will develop active TB disease during their life time[2,3,12].

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However, the risk of developing active disease greatly increases in HIV-infected and other immune-compromised individuals[2,3]. The annual risk of active TB is 5 - 15% and the lifetime risk is nearly 50% in HIV-seropositive persons[2,3,9].

GLOBAL EPIDEMIOLOGY OF TB AND DRUG-RESISTANT TB

The current global burden of active TB disease is based on the results of surveys conducted by the WHO for the prevalence of infection and disease. Recent data showed that 9.4 million new active disease cases corresponding to an estimated incidence of 139 per 100,000 population occurred throughout the world in 2008[3]. Only 5.7 million of 9.4 million cases (including new cases and relapse cases) of TB were actually notified to national tuberculosis programs of different countries while the rest were based on assessments of effectiveness of surveillance systems. Nearly half of the total TB cases were sputum-smear positive, representing the infectious form of the disease. The highest number of TB cases occurred in Asia (55%) followed by Africa (30%). The 22 high TB burden (11 Asians, nine Africans, one East European and one South American) countries accounted for ~ 80% while the six most populous countries of Asia (China, India, Indonesia, Pakistan, Bangladesh and Philippines) accounted for > 50% of all estimated TB cases worldwide. The highest incidence rate (351 per 100,000 population) was recorded for the African region, mainly due to high prevalence of HIV infection. The incidence rates of 31, 48 and 115 per 100,000 population were recorded for the Americas, European region and Eastern Mediterranean region, respectively in 2008[2,3]. Globally, an estimated 1.4 million (15%) of incident TB patients were co-infected with HIV and prevalent TB cases totaled 11.1 million (corresponding to 164 cases per 100,000 population) that resulted in 1.8 million deaths in 2008 (including 0.5 million TB patients co-infected with HIV)[2,3].

In several African and Asian countries, the incidence rates are highest among young adults, with most cases resulting from recent episodes of infection or re-infection. On the contrary, in low TB incidence countries of Western Europe and North America, a higher proportion of active TB cases occur in older patients or among immigrants from high TB incidence countries[1-3]. Pulmonary TB accounts for > 85% of active TB cases in high TB incidence countries while extra-pulmonary TB is more common in low TB incidence countries, particularly among HIV infected individuals and immigrants originating from TB endemic countries[2,3,13-15]. In Kuwait, TB accounts for > 90% of all mycobacterial infections and similar to many low TB incidence countries but unlike high TB incidence countries, pulmonary TB accounts for only 55% of TB cases while the rest involve extrapulmonary sites[15,16]. Furthermore, nearly 80% of active TB cases occur among expatriate workers or their family members many of which originate from high TB incidence countries while ~ 20% of active TB cases occur in the native population[15-17].

Several successive reports of 'Global Projects on Antituberculosis Drug Resistance Surveillance' sponsored by WHO have been published since 1997. The latest reports gathered drug susceptibility testing (DST) data from ~ 91,000 patients representing 93 settings in 83 countries and territories between 2002 and 2007 for isoniazid (INH), rifampin (RMP), ethambutol (EMB) and streptomycin (SM)[4,5]. The data showed that resistance to at least one anti-TB drug (any resistance) among new TB cases was 11.1% (varying from 0 - 56%). The prevalence of resistance to any drug was higher than 30% in 13 settings. The prevalence of resistance to any drug among previously treated TB patients was much higher (25.1%, varying from 0 - 86%). The worldwide average for any resistance, INH resistance and multidrug-resistance (MDR) (defined as infection with *M. tuberculosis* strains resistant at least to INH and RMP) among all TB cases were higher in previously treated TB cases compared to new cases (35, 27.7 and 15.3% versus 17, 10.3 and 2.9%, respectively). As expected, monoresistance to RMP was rare except in HIV-infected individuals and resistance to RMP was a good surrogate marker for MDR-TB[4,5]. The highest percentage of MDR-TB cases were estimated for countries of Eastern Europe (19.2%) followed by Western Pacific region (7%) and Southeast Asia (4.3%). Overall, ~ 440,000 cases of MDR-TB occurred in 2008 that resulted in 150,000 deaths[18]. Although 50% of all MDR-TB cases occurred in the two most populous countries of the world, *i.e.*, China and India, the highest proportion of MDR-TB cases (among both, new and previously treated TB cases) were reported from countries of the former Soviet Union. Nine countries reported > 12% of all new TB cases infected with MDR-TB strains[18]. In Kuwait, the incidence of MDR-TB among all TB cases over a 10-year period was reported to be ~ 1.2%[15].

The MDR-TB is a major threat to global public health, as it is more difficult to treat and often results in relapse or treatment failure[18-20]. It is also a risk factor for the emergence of extensively drug-resistant (XDR) (defined as infection with MDR-TB strains additionally resistant to a new generation fluoroquinolone and an injectable anti-TB agent such as kanamycin, amikacin, capreomycin or viomycin) TB[18,21]. The XDR-TB is even more difficult to treat than MDR-TB even in developed countries and is virtually untreatable in developing countries as reflected from very high fatality rates by a recent outbreak of XDR-TB in South Africa[22]. By 2009, XDR-TB has been found in 58 countries and 5.4% of MDR-TB cases were found to have XDR-TB while

no information exists for several other countries that have a high incidence of MDR-TB[18]. Eight countries, six of them located in the Eastern Europe and Central Asia, reported XDR-TB in > 10% of all MDR-TB cases. With many countries reporting a high incidence of additional resistance to fluoroquinoloes among MDR-TB cases, the incidence of XDR-TB is likely to climb further[18].

DIAGNOSIS OF ACTIVE TB DISEASE AND DRUG-RESISTANT TB

The diagnosis of active disease (both, pulmonary and extra-pulmonary TB) is usually based on clinical suspicion, chest radiographs, microscopic examination for acid-fast bacilli (AFB), solid and liquid culture as well as hybridization - and PCR amplification-based molecular methods for the detection of *M. tuberculosis* nucleic acid in clinical specimens[20,23,24]. Microscopic examination of smears for acid-fast bacilli is a rapid and inexpensive test. However, positivity in expectorated sputum samples is highly variable (34 - 80%)[23]. Recent application of fluorescence microscopy with light emitting diode (LED) technology has improved the sensitivity of *M. tuberculosis* detection by ~ 10%[25]. However, microscopy is often negative in HIV-coinfected TB patients due to atypical presentation and paucibacillary load[23,26]. The sensitivity of smear examination for non-sputum samples is, even less and the test does not differentiate TB from infections caused by non-tuberculous mycobacteria (NTM). The gold standard for TB diagnosis is culture of *M. tuberculosis*. The culture also allows species-specific identification and drug sensitiviy test (DST) to guide therapy. Culture on solid media is slow and may take 4 - 6 weeks while liquid media-based culture systems yield faster (7 - 12 days) growth of *M. tuberculosis* but are expensive[23]. Recently, phage-based culture systems have also been developed that offer rapid detection of *M. tuberculosis* in resource-poor settings[27].

Molecular methods have also been developed and are mostly used in smear-positive samples to rapidly differentiate *M. tuberculosis* from NTM but have not yet been able to replace microscopy and culture due to simplicity, rapidity and accurate DST by the latter methods[24]. Molecular methods have also been useful in smear-negative specimens when the organism could not be grown in culture[24,28]. Two commercial molecular tests are approved by FDA for respiratory specimens and several in-house developed PCR assays, despite variations in their choice of amplification target, detection platforms, and performance, are also available[28,29]. Two reverse hybridization-based macroarray (line probe) assays are also available commercially and allow identification of *M. tuberculosis* and several NTM species, both in cultured isolates and clinical specimens[16,24,28].

Rapid DST of *M. tuberculosis* strains ensures effective treatment of TB patients and also limits emergence of additional drug resistance, MDR-TB and XDR-TB. The Center for Disease Control and Prevention (CDC) strongly encourages reporting of DST results within 30 days of specimen collection[30]. Conventional phenotypic DST requires culture and detects the growth of *M. tuberculosis* in the presence of anti-TB drugs on solid media, usually within three weeks[23]. The broth-based semiautomated, radiometric BACTEC 460 TB system (Becton Dickinson) is regarded as the gold standard for culture and DST of *M. tuberculosis*[31,32] and reports DST results within 4 - 12 days from primary cultures. Non-radioactive, fully automated liquid culture systems such as BACTEC MGIT 960 TB system have also been developed for culture and DST of *M. tuberculosis*[31-33]. Although MGIT 960 system may be used directly on sputum samples, additional time and labor is needed for identification of *M. tuberculosis*. The automated liquid culture systems are expensive and are not suitable for resource-poor settings. Several cost-effective methods have recently been developed for poor, developing countries[32,34].

The liquid media-based microscopic observation drug susceptibility (MODS) test is a low-cost, rapid and direct assay for simultaneous detection and DST of *M. tuberculosis* in sputum specimens and results are usually available within two weeks[35-37]. Another low-cost method for detection and DST of *M. tuberculosis* is growth on thin layer agar (TLA) and results are usually available within 10 days[37-39]. Limitations of MODS and TLA tests include indirect identification of *M. tuberculosis* and requirement for frequent microscopic observations for cording morphology. The colorimetric assays are based on reduction of redox indicators such as tetrazolium salt, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) or resazurin that are added to culture medium during *in vitro* growth of *M. tuberculosis* and detect drug-resistant and multidrug-resistant *M. tuberculosis* strains usually within 10 days[34,40]. The colorimetric nitrate reductase assay (NRA) is based on the ability of *M. tuberculosis* to reduce nitrate to nitrite when grown in the presence or absence of drug and the results are usually available within 10 days[41,42]. This simple assay provides rapid, accurate and cost-effective detection of MDR-TB and has performed well with smear-positive sputum samples; however, false-positive detection of *M. tuberculosis* due to growth of other organisms is a possibility[41]. Phage-based methods are other alternatives for detection of drug-resistant *M. tuberculosis* in resource-poor settings. Two alternative protocols are available. One assay is based on phage amplification by using D29 phages while the second assay is based on detection of light by using luciferase reporter mycobacteriophages (*e.g.*, phAE142)[43,44]. A commercial, FAST Plaque

TB-Response (Biotec Laboratories Ltd.) assay is also available that detects drug resistance of *M. tuberculosis* directly in sputum specimens.

Molecular methods have also been developed for DST for first-line and many second-line anti-TB drugs and detect resistance associated mutations in target genes of *M. tuberculosis*, provide results within 1 - 2 days and can be performed on both, clinical isolates as well as smear-positive clinical samples[20,28]. Molecular detection of RMP resistance is most feasible since 90 - 95% RMP-resistant strains contain mutations in a small (81-bp) hot-spot region of a single (*rpoB*) gene[20,45-48]. Furthermore, detection of RMP resistance is a surrogate marker for MDR-TB since monoresistance to RMP occurs infrequently except in patients with HIV-coinfection or some other underlying conditions[20,49-52]. However, 5 - 10% RMP-resistant strains either contain mutations in other regions of the *rpoB* gene or in some other genes[53-55]. For other first-line drugs (INH, EMB and pyrazinamide, PZA), the sensitivity of resistance detection by molecular methods varies considerably due to involvement of many gene loci and / or diversity of mutations[20,49,56-63]. Despite these limitations, drug-resistant *M. tuberculosis* strains isolated from TB patients of different ethnic background or from different geographical locations have exhibited few dominant mutations[20,50,64-70]. Research has, therefore, led to development of region-specific molecular diagnostic methods. Alternatively, assays targeting entire gene or multiple gene loci in a single test have been developed for these drugs[20,71-74]. Similar strategies have also been applied for second-line drugs[20,75-77].

Several different types of molecular methods have been developed and evaluated for the detection of resistance conferring mutations in drug-resistant and multidrug-resistant *M. tuberculosis* strains. The PCR-restriction fragment length polymorphism (PCR-RFLP) analysis has been developed as a simple, rapid and low-cost method to detect polymorphisms at *katG* codon 315 and *embB* codons 306 / 497 that are frequently mutated in INH- and EMB-resistant strains, respectively[78-80]. The DNA sequencing provides unambiguous detection of mutations. Direct DNA sequencing is most practical if majority of drug-resistant strains contain mutations in a limited region of a single target gene (hot-spot region of *rpoB* for RMP resistance), a single dominant codon (*katG* codon 315 for INH resistance) or the target gene is relatively small (~ 0.6 kb) (*pncA* for PZA resi stance)[20,45,46,57,63-66]. A commercial real-time PCR-based assay (Xpert MTB, Cepheid, Sunnyvale, CA, USA) has also recently become available for RMP resistance detection in smear-positive specimens[20,28].

The reverse hybridization-based macroarrays have been developed for simultaneous detection of mutations in several target genes for the diagnosis of MDR-TB and XDR-TB in cultured isolates and clinical specimens[72,77,81-84]. Two line probe macroarray assays are commercially available for detection of RMP-resistant and MDR *M. tuberculosis*. The INNO-LiPA Rif. TB assay (Innogenetics) detects mutations in hot-spot region of *rpoB* gene[20-85]. Since RMP resistance is a surrogate marker for MDR-TB, the positive result may also predict MDR status of ~ 90% *M. tuberculosis* strains in HIV-seronegative individuals[20,49,85]. The GenoType MTBDRplus (Hain Lifesciences) assay detects MDR-TB by simultaneously detecting mutations in HSR of *rpoB* gene for RIF resistance and mutations at *katG*315 and *inhA* regulatory region for INH resistance[72,81,86,87]. Further detection of resistance of MDR-TB strains to fluoroquinolones and injectable agents like kanamycin or capreomycin by GenoType MTBDRsl identifies XDR-TB strains[77]. These simple and rapid assays have performed fairly satisfactorily in high incidence countries for detection of MDR *M. tuberculosis* in clinical samples, usually within one working day[84,85]. Despite their simplicity and ease of use, these assays, however, have limited use in resource-poor developing countries due to their high-cost. Other low-cost, culture-based methods such as MODS, TLA and NRA described above are more suitable for these settings.

TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS

The chemotherapy for TB is different than for other bacterial infections. Short-course chemotherapy with multiple drugs was developed in 1960s and 1970s due to several reasons[88]. The *M. tuberculosis* has a long generation time, higher capacity for dormancy and ability to localize in different environments (*e.g.*, pulmonary cavities, pus, solid caseous material, immune cells) that make it a difficult target for therapeutic drugs[89,90]. Different drugs selectively target different bacterial populations. Actively growing bacilli are mainly killed by INH and RMP, those in immune cells (such as inside macrophages) are susceptible to PZA followed by RMP and persisters (semi-dormant bacilli in solid caseous lesions) are mainly killed by RMP[89]. Combination therapy also kills *M. tuberculosis* strains monoresistant to one drug that evolve spontaneously at a predictable rate (varying from 10^{-3} for PZA to 10^{-10} for RMP per cell division) in patients with cavitary TB due to high bacterial load (10^{7} to 10^{9})[91,92]. However, the probability of two independent mutations resulting in resistance to two anti-TB drugs is rather low (~ 10^{-14} per cell division) and most treatment naïve patients are effectively cured with therapy with multiple drugs as all bacilli are eliminated in all cell types, including monoresistant strains, as they are killed by other drugs[88,90].

Treatment for TB, particularly the infectious pulmonary form, occurs in two stages. In the first stage, actively growing extracellular bacilli in the lung

Table 1: Important first-line, second-line and third-line antitubercular agents currently in use for the treatment of drug-susceptible and drug-resistant tuberculosis

Category and drug	Chemical description	Cellular process inhibited	Efficacy
Group I: First-line oral drugs			
Isoniazid, INH	Nicotinic acid hydrazide	Mycolic acid synthesis	Bactericidal
Rifampin, RMP	Rifamycin derivative	Protein synthesis	Bactericidal
Ethambutol, EMB	Ethylene diimino di-1-butanol	Lipid / cell wall synthesis	Bacteriostatic
Pyrazinamide, PZA	Nicotinamide derivative	Unknown	Bactericidal
Rifabutin, RBU	Rifamycin derivative	Protein synthesis	Bactericidal
Rifapentine, RPE	Rifamycin derivative	Protein synthesis	Bactericidal
Group II: Second-line, injectable agents			
Streptomycin, SM	Aminoglycoside	Protein synthesis	Bactericidal
Kanamycin, KAN	Aminoglycoside	Protein synthesis	Bactericidal
Amikacin, AMI	Aminoglycoside	Protein synthesis	Bactericidal
Viomycin, VIO	Polypeptide	Protein synthesis	Bactericidal
Capreomycin, CAP	Polypeptide	Protein synthesis	Bactericidal
Group III: Second-line, fluoroquinolones			
Ofloxacin, OFX	Fluoroquinolone	DNA replication	Bacteriostatic
Levofloxacin, LFX	Fluoroquinolone	DNA replication	Bactericidal[a]
Gatifloxacin, GFX	8-Methoxy-fluoroquinolone	DNA replication	Bactericidal
Moxifloxacin, MFX	8-Methoxy-fluoroquinolone	DNA replication	Bactericidal
Group IV: Second-line, oral agents			
Ethionamide, ETA	Isonicotinic acid derivative	Mycolic acid synthesis	Bacteriostatic
Prothionamide, PTA	Isonicotinic acid derivative	Mycolic acid synthesis	Bacteriostatic
D-Cycloserine, CS	Alanine analogue	Cell wall synthesis	Bacteriostatic
Terizidone, TRD	Cycloserine analogue	Cell wall synthesis	Bacteriostatic
Para-amino salicylic acid, PAS	Para-amino salicylic acid	Unknown	Bacteriostatic
Group V: Third-line agents			
Clofazimine, CFZ	Iminophenazine derivative	Cell membrane function	Bacteriostatic
Clarithromycin, CLR	Erythromycin derivative	Protein synthesis	Bactericidal
Amoxycillin-clavulanate, AMX- CLV	β–lactam with β–lactamase inhibitor	Cell wall synthesis	Bactericidal
Thiacetazone, THZ[b]	Thiacetazone	Mycolic acid synthesis	Bacteriostatic
Meropenem-clavulanate, MEP- CLV	Carbapenem with β–lactamase inhibitor	Cell wall synthesis	Bactericidal
Linezolid, LZD	Oxazolidinone derivative	Protein synthesis	Bactericidal

[a]Likely bactericidal
[b]Not recommended for HIV-infected TB patients

are rapidly killed to attain non-infectious (negative sputum-smear) status to prevent further transmission of the disease (conversion of culture-positive to culture-negative sputum within two months). The second stage requiring complete sterilization and elimination of less actively growing or semi-dormant bacilli persisting intra-cellularly in other cell types is achieved during extended therapy duration[30,88-90]. Positive sputum cultures after three months of multidrug therapy indicate treatment failure, mostly due to incomplete or inappropriate therapy or poor adherence to treatment and the disease persists due to emergence of drug resistance (acquired resistance)[30,90]. When the resulting *M. tuberculosis* strain is transmitted to a new host, it causes TB that is already resistant to the indicated drug(s) (primary resistance)[4,5]. Emergence of resistance in some TB patients is related to *M. tuberculosis* strain or co-infection with HIV. Simultaneous treatment of HIV-infected patients on anti-retroviral therapy with protease and non-nucleoside reverse transcriptase inhibitors leads to malabsorption and suboptimal therapeutic blood levels of rifamycins (despite compliance to therapy) and facilitates the development of RMP-resistant TB and MDR-TB[30,51,93,94]. For instance, improper treatment of an HIV-seropositive patient, infected with an INH-resistant *M. tuberculosis* strain, with INH and RMP alone may lead to further development of resistance to RMP (= MDR-TB) due to spontaneous mutation in *rpoB* gene in few bacilli and their selection during therapy. Similar sequence of events leads to resistance to additional drugs, and eventually to all first-line anti-TB agents[20,49].

The most important drugs currently in use for the treatment of drug-susceptible TB, MDR-TB and XDR-TB are listed in Table 1. These drugs are categorized as first-line (most effective), second-line and third-line (reinforcing) agents based on efficacy, tolerability and clinical trial data. First-line (Group I) drugs (INH, RMP, EMB and PZA) are highly efficacious, and relatively less toxic bactericidal agents that facilitate oral formulations for combination therapy in both, hospital and community settings[30,90]. Newer rifamycins (rifabutin and rifapentine), though more expensive, may be used in place of RMP in select patient populations. Rifabutin has fewer problematic drug

interactions with antiretroviral agents and is used in HIV-seropositive patients concomitantly treated with protease and non-nucleoside reverse transcriptase inhibitors[95]. Rifapentine has much longer half life and is being evaluated with higher or daily dosing in low-risk HIV-seronegative individuals for shortening treatment duration[96].

Second-line agents are less efficacious than first-line anti-TB drugs and have been further divided as injectable (Group II) agents, fluoroquinolones (FQs) (Group III agents) and other oral (Group IV) agents (Table 1). Injectable agents include aminoglycosides (streptomycin, kanamycin, KAN and amikacin, AMI) and polypeptides (viomycin, VIO and capreomycin, CAP). The streptomycin (SM) is now regarded as a second-line drug since and its use has declined in recent years due to much higher rates of resistance of clinical *M. tuberculosis* isolates to SM in high TB incidence countries and the availability of more effective anti-TB drugs[4,5,20]. Cross-resistance between SM and other aminoglycosides (KAN or AMI) or polypeptides (CAP or VIO) is not reported. However, cross-resistance between KAN and AMI or between CAP and VIO is observed frequently and some *M. tuberculosis* strains also exhibit cross resistance between KAN/AMI and CAP/VIO[98]. The oral FQs used for the treatment of TB include ofloxacin (OFX), levofloxacin (LFX), moxifloxacin (MFX) and gatifloxacin (GFX). The new-generation FQs (MFX and GFX) are bactericidal with good central nervous system penetration and are undergoing clinical trials for use as first-line agents to shorten treatment duration[98-100]. Other oral agents are bacteriostatic, less efficacious, costly and more toxic and include ethionamide (ETH), prothionamide (PTH), cycloserine (CS), terizidone (TZN) and para-amino salicylic acid (PAS)[30]. Group IV agents are added to therapy regimens for treatment of MDR-TB and XDR-TB based on actual or projected susceptibility, cost, and side-effect profiles.

Group V (third-line or reinforcing agents which are not recommended by WHO for routine use due to variable efficacy) drugs include clofazimine (CFZ), amoxicillin-clavulanate (AMX-CLV), clarithromycin (CLR), thiacetazone (THZ), meropenem-clavulanate (MEP-CLA) and linezolid (LZD) that have been used for the treatment of MDR-TB and XDR-TB with varying degree of success[30,101-107]. There are some differences in the treatment of TB patients in low incidence, high-income industrialized countries compared to their treatment in high incidence, low-income countries.

Tuberculosis caused by an *M. tuberculosis* strain susceptible, *in vitro*, to all first-line drugs is regarded as drug-susceptible TB. The recommendations of American Thoracic Society (ATS) / Center for Disease Control and Prevention (CDC) / Infectious Disease Society of America (IDSA) for treatment regimens (also applicable for other rich industrialized countries with < 4% INH resistance rates) for culture positive (smear positive or smear negative) pulmonary or extra-pulmonary TB are based on evidence from clinical trials, universal availability of mycobacterial cultures, DST, and radiographic facilities for all TB patients[30]. Although WHO also strongly recommends culture and DST wherever possible to guide therapy, these facilities are not routinely available in developing countries[4,5]. Both WHO and ATS / CDC / IDSA treatment guidelines are built around directly observed therapy short-course (DOTS) strategy and both recommend a two-phase treatment regimen[30,108,109].

Standard initial treatment phase of two months comprises daily or thrice weekly therapy with all first-line drugs (EMB may be omitted for children if DST results are known). Although efficacy of SM is nearly same as EMB in the initial phase, EMB is preferred as oral formulations in multidrug regimens are feasible while use of SM requires frequent patient's visit to health care facilities. Furthermore, highest levels of resistance to an anti-TB drug worldwide are generally observed for SM[4,5,30,110]. Standard continuation phase of four months includes daily or thrice weekly therapy with INH and RMP. The continuation phase should be extended (up to 7 months) for patients with cavitary pulmonary TB whose sputum culture remains positive after two months of initial phase to minimize relapse of TB[30,108,109]. Treatment of drug-susceptible TB with properly implemented DOTS has a cure rate > 95%, reduces relapse and emergence of drug-resistant TB and MDR-TB and treatment-limiting drug adverse reactions are usually not severe[30,111]. However, treatment of HIV-TB co-infected patients is complicated by drug-drug interactions of RMP with antiretroviral agents (mainly protease and non-nucleoside reverse transcriptase inhibitors)[30,94,109,112]. Rifabutin, though more expensive than RMP, is equally effective against *M. tuberculosis* but has fewer drug interactions with antiretroviral agents and thus may be substituted for RMP[30,95,112]. Another problem associated with anti-TB therapy in HIV-TB co-infection is a temporary exacerbation of symptoms, signs or radiographic manifestations of TB in patients on antiretroviral therapy due to immune reconstitution inflammatory syndrome (IRIS)[30,113,114]. The drug regimens may be altered with other drug combinations with less problematic drug-drug interactions[95,115,116].

TREATMENT OF DRUG-RESISTANT TB, MDR-TB AND XDR-TB

Monoresistance of *M. tuberculosis* strains to PZA is either rare or is not determined routinely. Monoresistance of *M. tuberculosis* strains occurs frequently for INH, less frequently for EMB and infrequently for RMP. In fact, detection of resistance

Table 2: Potential drug combinations and treatment duration for patients with drug-susceptible, drug-resistant, multidrug-resistant and extensively drug-resistant tuberculosis

Resistance of *M. tuberculosis* strain to anti-TB drug(s)[a]	Drugs to be included in appropriate therapy regimens	Desirable number of active drugs for effective treatment	Minimum treatment duration (months)
None	INH, RMP, PZA, EMB	4	6
EMB	INH, RMP, PZA, Group II	4	6
PZA	INH, RMP, EMB, Group II	4	6
INH	RMP, PZA, EMB, Group II or III	4	6 to 9
RMP	INH, PZA, EMB, Group II + III	4 to 5	9 to 12
INH, SM	RMP, PZA, EMB, Group II + III	4 to 5	6 to 9
INH, EMB	RMP, PZA, Group II + III	4 to 5	6 to 9
INH, RMP	PZA, EMB, Group II + III + IV	5 to 6	18 to 24
INH, RMP, EMB	PZA, Group II + III + IV	5 to 6	18 to 24
INH, RMP, PZA	EMB, Group II + III + IV	5 to 7	24
INH, RMP, PZA, EMB	Group II + III + IV + V	5 to 7	24
INH, RMP, PZA, EMB, Group II	Group III + IV + V + surgery	5 to 7	>24
INH, RMP, PZA, EMB, Group III	Group II + IV + V + surgery	5 to 7	>24
INH, RMP, PZA, EMB, Group II + III	Group II[b] + III[c] + IV + V + surgery	5 to 7	>24

[a]SM, streptomycin; EMB, ethambutol; PZA, pyrazinamide; INH, isoniazid; RMP, rifampin; Group II, second-line injectable agents like kanamycin, amikacin, capreomycin or viomycin; Group III, fluoroquinoles like ofloxacin, levofloxacin, moxifloxacin or gatifloxacin; Group IV, second-line bacteriostatic oral agents like ethionamide, prothionamide, D-cycloserine, terizidone or para-amino salicylic acid; and Group V, third-line reinforcing agents like clofazimine, clarithromycin, amoxicillin with clavulanate, thiacetazone, meropenem with clavulanate or linezolid

[b]Injectable agent not used previously

[c]FQ agent not used previously

of *M. tuberculosis* strains to RMP is a good marker for MDR-TB[4,5,18,110]. However, monoresistance to RMP may occur more frequently in TB patients with other underlying conditions such as HIV-co-infection and diabetes mellitus due to drug-drug interactions[51,52,110,117]. Although monoresistance to SM also occurs frequently, it is not routinely used now in treatment regimens. The infections caused by monoresistant *M. tuberculosis* strains to most of the first-line drugs and SM can be managed effectively as the available first-line and some bactericidal second-line agents ensure effective cure. However, treatment of MDR-TB is difficult, particularly in resource-poor settings while treatment of XDR-TB is much more difficult even in developed countries. The available drugs and minimum duration of treatment for various combinations of drug-resistant TB, MDR-TB and XDR-TB are listed in Table 2.

The treatment duration, risk of treatment failure and mortality rates are nearly same for EMB- or PZA-monoresistant TB as susceptible TB[30,118]. Although some studies suggested that treatment failure is more likely for INH-monoresistant TB[30,118], a meta-analysis has recently shown that oral daily therapy with regimens containing RMP and 3 - 4 other effective drugs including an effective injectable agent was associated with lower rates of failure, relapses or acquired resistance to additional drugs[119]. Similarly, infection with *M. tuberculosis* strains resistant to two (INH and EMB or INH and SM) drugs that occur frequently can also be successfully treated. However, treatment duration of even nine months with 4 effective drugs for infections caused by RMP-resistant *M. tuberculosis* strains has poor prognosis mainly because RMP is most effective drug against persisters which are mainly responsible for clinical relapse. Increasing treatment duration to 12 months resulted in better prognosis[30,118,120].

Treatment of MDR-TB is problematic in developing countries mainly due to delayed diagnosis and in HIV-TB co-infected patients due to undesirable drug-drug interactions that occur with concomitant antiretroviral therapy[19,20,104]. Both CDC and WHO recommend DST for first-line and important second-line drugs and treatment regimens, based on the results of DST and/or previous treatment history, should include all available first-line and several most active second-line drugs[30,121]. Rapid diagnosis of MDR-TB is crucial for improved outcome and molecular methods may be employed for early detection and DST to guide therapy. For effective treatment, 5 - 6 drug regimens should include all available first-line drugs, an effective Group II (injectable) agent, a Group III (preferably a new generation FQ) agent and one to several second-line oral Group IV agents[19,121-124]. Successful management of MDR-TB patients requires specialized treating centers to be equipped with rapid diagnostic procedures and universal DST for first- and second-line drugs. These facilities, however, are seldom available to most patients in resource-poor settings where majority of MDR-TB cases occur[19,20,122-124]. Rapid diagnosis of MDR-TB and universal DST for first- and second-line drugs, though challenging,

is even more crucial in HIV-seropositive patients for improved outcome[94,112,125]. Two treatment approaches are currently being used. Standardized treatment regimens are designed based on representative drug-resistance surveillance data from respective settings / countries or individualized regimens are tailored on the basis of prior treatment history, results of individual DST and inclusion of bactericidal drugs likely to be effective[19,122-124,126,127].

Treatment for MDR-TB usually lasts for 18 to 24 months or even longer and is complicated by higher cost, poor drug tolerance and higher toxicity with greater tendency for adverse drug-drug interactions, and higher relapse and fatality rates[19,104,127,128]. The DST profile is crucial for monitoring response to treatment during therapy for MDR-TB. Regular (at least once a month) monitoring of sputum for smear microscopy, culture and DST is required to assess response to treatment and should be carried out until sputum culture conversion (indicating non-infectious state) has been achieved. Early sputum culture conversion (within two months of initiating therapy) is associated with better clinical outcome while patients who remain sputum culture positive even after three months of multidrug therapy are more likely to have poor prognosis[129]. Continued sputum smear microscopy and culture positivity without clinical improvement indicates ineffective / improper therapy or poor adherence to treatment warranting fresh DST and reassessment of treatment strategies[122,129]. The duration of treatment is generally guided by sputum culture conversion. For improved outcome, the injectable agent should be used for > 6 months (at least four months after sputum culture conversion) and oral therapy should be continued for another 18 months (24 months for chronic cases with extensive pulmonary damage) after culture conversion[149]. Directly observed therapy (DOT) support for MDR-TB patients ensures adherence to treatment regimens and rapid adjustments to avoid adverse drug reactions[122,129-131]. Pulmonary TB patients may also be evaluated for resection surgery after two months of therapy to improve outcome[131,132].

Successful treatment of XDR-TB is much more difficult than MDR-TB even in developed countries while in developing countries / resource-poor settings, XDR-TB is virtually an untreatable disease[18,105,106,128,133-135]. Programmatic management of XDR-TB is extremely complex and no single strategy is likely to be successful in all situations. For effective treatment of XDR-TB, treating physicians must use any effective first-line drug, an injectable agent never used before and a new generation FQ (such as MFX or GFX) (even if *M. tuberculosis* isolate exhibits *in vitro* resistance to FQs and injectable agents), all Group IV agents that have not been used extensively in previous regimens or those that are likely to be effective (if susceptibility data are not available) and two to several reinforcing Group V agents[126,105,106,133-135]. If the isolate exhibits only low-level resistance to INH and no cross resistance is observed between RMP and rifabutin, high dose INH and rifabutin may also be used as second-line drugs for therapy[134,135]. Similar to MDR-TB treatment, close monitoring of patients for clinical improvement and management of adverse drug reactions, complete adherence to treatment and surgical resection in case of localized disease are crucial for improved outcome[105,128,132,134-136]. Patients who fail to undergo sputum culture conversion within 2 - 4 months of starting treatment are likely to fail therapy[134,135].

Treatment of MDR-TB and XDR-TB in HIV-TB co-infected patients presents with additional challenges due to intolerability of some second-line agents (such as thiacetazone), poor absorption of drugs (due to vomiting and diarrhea) and drug-drug interactions[105,111,112]. Emergence of IRIS in HIV-TB co-infected patients under concomitant treatment with antiretroviral drugs and potentially severe drug-drug interactions between RMP and protease / non-nucleoside reverse transcriptase inhibitors pose even more serious challenges to effective treatment of drug-resistant TB than drug-susceptible TB. New treatment combinations have recently been used to minimize drug interactions in HIV-TB co-infected patients[115,116,137]. Substitution of rifabutin for RMP has fewer problematic drug interactions. However, the regimen becomes prohibitively expensive for resource-poor settings[95]. Despite these limitations, recent developments in rapid diagnosis of MDR-TB, prompt institution of aggressive therapy with several active drugs, close radiological and bacteriological (for sputum smear and culture) monitoring of patients have considerably improved clinical outcome and reduced mortality rates in both HIV-negative and HIV-infected TB patients[127,138,139]. However, the prognosis of XDR-TB in HIV-co-infected TB patients is extremely poor, with fatality rates varying from ~ 30% in developed countries to nearly 100% in developing countries[22,128,133-136]. More effective drugs are urgently needed for proper treatment of MDR-TB and XDR-TB patients.

NEW ANTI-TB DRUGS IN CLINICAL DEVELOPMENT

Since the discovery of RMP and its inclusion in combination therapy regimens nearly forty years ago, no new TB specific drug has been developed[88,89]. Addition of RMP (highly effective against persisters which are mainly responsible for relapse), to therapy regimens was instrumental in reducing the duration of treatment to six months which has remained unchanged till today[89,140]. Non-adherence to therapy due to long duration of treatment is mainly responsible for incomplete cure and evolution of drug-resistant,

Table 3: Potential drugs in various stages of clinical development for the treatment of active tuberculosis

Potential drug	Chemical description	Biological process inhibited	Stage of development	Drug company or sponsor(s)
TMC207	Diarylquinolone	ATP synthesis	Phase II	Tibotec & TB Alliance
PA-824	Nitroimidazo-oxazine	Mycolic acid synthesis	Phase II	TB Alliance
OPC-67683	Nitroimidazo-oxazole	Mycolic acid synthesis	Phase II	Otsuka Pharma
SQ109	Ethylenediamine derivative	Cell wall synthesis	Phase I	Sequella
PNU100480	Oxazolidinone derivative	Protein synthesis	Phase I	Pfizer
AZD5847	Oxazolidinone derivative	Protein synthesis	Phase I	Astra-Zeneca
FAS 20013	Unknown	Cell wall synthesis	Phase I	FASgen Inc.

multidrug-resistant and extensively drug-resistant strains of *M. tuberculosis*[2-5]. To alleviate these problems, existing and new drugs are being developed and evaluated with the aim to shorten treatment duration of drug sensitive active TB to ~ 3 months in the short-term and to only two weeks eventually[141-145].

Among the drugs already in use for the treatment of TB, rifamycins are key drugs in the current treatment regimens. The currently used dose (600 mg) of RMP chosen in the 70s appears to be rather low. Results of an initial study suggest that high-dose RMP (1200 mg) given daily has markedly increased activity against TB and the drug may also be well-tolerated by most patients[146]. Further phase II clinical trials are underway to evaluate drug tolerance and the efficacy of high-dose RMP in TB patients for the possibility of shortening treatment duration to four months. Daily administration of another rifamycin (rifapentine), due to much better pharmacokinetic properties, was recently shown to be superior to RMP in curing TB in a mouse model and is also tolerated well even at higher doses[96,147]. Phase II clinical trials are underway with daily, high-dose therapy with rifapentine for shortening treatment duration to four months in HIV seronegative TB patients. High-dose RMP or rifapentine-based regimens, however, will be problematic in HIV-infected individuals on antiretroviral therapy.

New generation FQs (MFX and GFX) have potent activity against *M. tuberculosis*[148]. Phase II trials of MFX- or GFX-containing regimens (substituted for EMB and/or INH), however, yielded variable results[149-151]. Phase III trials to evaluate the efficacy of replacement of EMB by MFX and GFX and of INH by MFX in first-line TB treatment and to shorten therapy duration to four months are currently being carried out. Although FQs have potential to contribute to chemotherapy of TB, resistance of *M. tuberculosis* strains to FQs is becoming more common[18] and will probably increase further if these drugs are used indiscriminately. Another drug already approved for human use, meropenem (in combination with clavulanate) is also being used for the treatment of some TB patients even though parenteral administration of the drug is a disadvantage[107]. However, to shorten treatment duration to three months or less, new drugs with novel mode of action and bactericidal activity greater than INH against actively dividing bacteria and potency greater than RMP against non-replicating persisting bacilli in anerobic environment are needed. The search for these agents has accelerated more recently due to several worldwide outbreaks of MDR-TB and XDR-TB that were associated with high mortality rates[22,132-135,141-145]. Several new classes of anti-TB drugs are at various stages of development for the treatment of drug sensitive active TB, MDR-TB and XDR-TB and are listed in Table 3.

The first anti-TB drug developed recently with a novel mechanism of action is a diarylquinoline known as TMC207 (also called R207910). TMC207 inhibits ATP synthase and is highly potent against both, replicating and anerobic non-replicating persistent bacteria[152-154]. Cross-resistance between TMC207 and other commonly used first- and second-line anti-TB drugs is not described suggesting that TMC207 is a useful drug for the treatment of both, drug sensitive as well as drug-resistant and MDR *M. tuberculosis* strains[155-157]. Although its relatively longer half-life in tissues and detrimental drug interactions with RMP are potential limitations, the drug appears suitable to simplify / shorten the current treatment duration for drug susceptible TB and also shows promise for the treatment of MDR-TB[154,157-160]. The drug is in Phase II trials for safety, tolerability and efficacy (measured by sputum conversion rates) in combination with standardized second-line treatment regimen for MDR-TB with encouraging initial results[157]. Other derivatives of TMC207 have also been synthesized recently and exhibit potent (submicromolar) activity against actively dividing bacteria and micromolar activity against nonreplicating persistent tubercle bacilli[161].

Two new, potent drugs of the nitroimidazole class that affect mycolic acid synthesis have recently been developed. Both compounds are prodrugs that require nitroreductive activation and exhibit activity against both, actively dividing and non-replicating persistent bacteria. The nitroimidazo-oxazine (PA-824) has excellent activity against drug sensitive and drug-resistant (including multidrug-resistant) strains of *M. tuberculosis*[162-164]. Oral doses of PA-824 are tolerated well and maximum bactericidal activities are achieved at low drug concentrations

in sputum-positive pulmonary TB patients[165,166]. Phase II clinical trials are currently underway to shorten treatment duration of drug sensitive TB. The nitroimidazo-oxazone (OPC-67683), the second member of nitroimidazole class, is nearly 20 times more potent than PA-824[167]. Due to common activation mechanism, cross-resistance to both PA-824 and OPC-67683 occurs through mutations in *ddn* gene that encodes the enzyme responsible for drug activation[164]. However, the cellular targets of PA-824 and OPC-67683 appear to be different since mutations in a conserved hypothetical protein (Rv3547) of *M. tuberculosis* confer resistance to PA-824 but not to OPC-67683[168]. The OPC-67683 is also currently undergoing Phase II clinical trials for the treatment of MDR-TB. Other derivatives of OPC-67683 have also been synthesized recently and exhibit potent (submicromolar) activity against actively dividing bacteria and micromolar activity against non-replicating persistent tubercle bacilli[169].

Another novel drug, SQ109 (ethylenediamine derivative) is chemically related to first-line drug EMB and inhibits cell wall synthesis but appears to differ in its mode of action because it has bactericidal activity against EMB-resistant strains of *M. tuberculosis*[170,171]. The drug exhibits synergistic activity with other first-line drugs, RMP and INH[170-172]. The phase I clinical trials for safety and tolerability yielded encouraging results and multi-dose escalation studies are now being initiated. Other derivatives of SQ109 have also been synthesized and are being evaluated for efficacy against drug-resistant TB[173].

Broad-spectrum antibiotic, linezolid, belonging to the class oxazolidinones is also active against *M. tuberculosis* and has been used occasionally in the treatment of some MDR-TB/XDR-TB patients[103,174,175]. However, duration of linezolid therapy is limited by adverse side effects (peripheral neuropathy, bone marrow suppression). Half-dose therapy reduces the incidence of hematologic toxicity without adversely affecting potency and appears to have some benefits for the treatment of MDR-TB/XDR-TB[176-178]. Recently, other safer and more potent oxazolidinones (PNU-100480 and AZD5847) have also been developed. PNU-100480 is active against *M. tuberculosis* including MDR-TB/XDR-TB strains[179]. The drug is more potent and well-tolerated than linezolid and showed sterilizing activity in a murine model of TB suggesting a role in shortening treatment duration for both, drug-susceptible TB and MDR-TB/XDR-TB[180,181]. The drug is currently in Phase I and multi-dose studies for safety, tolerability and pharmacokinetics are in progress. AZD5847 is also undergoing phase I clinical trials, however, much less information is currently available for its safety, tolerability or pharmacokinetic properties.

Another promising and highly potent anti-TB drug (effective at submicromolar levels) against *M. tuberculosis* is FAS 20013. The target of FAS 20013 is mycolic acid / cell wall synthesis and the drug appears to kill *M. tuberculosis* more rapidly than any other anti-TB drug currently in use. The manufacturer, FASgen Inc., has listed this project on its website (http://www.fasgen.com/pubs-fr.html accessed on Nov. 8, 2010 by S. Ahmad). This oral drug is non-toxic to mammalian cells in culture and is effective against both actively dividing *M. tuberculosis* as well as non-replicating bacilli in anerobic environment suggesting that it possesses sterilizing activity similar to that of first-line drugs RMP. Similar to PZA, FAS 20013 is also effective against *M. tuberculosis*-infected macrophages. Cross-resistance to first-line drugs is not reported, thus suggesting its potential for the treatment of both drug-susceptible TB and MDR-TB and for shortening the treatment duration of current therapy regimens.

Several other novel compounds have also been synthesized that show promising results for the treatment of both, drug sensitive as well as drug-resistant TB and are in various stages of preclinical development. Some of these compounds (*e.g.*, BTZ043, methylbenzothiazole derivatives and salicylanilide derivative) have exhibited submicromolar and micromolar bactericidal activities against actively dividing *M. tuberculosis* as well as non-replicating persistent bacteria, respectively. Furthermore, these agents appear not to be affected by resistance of *M. tuberculosis* to first-line drugs, prerequisite for any new drug to be effective in chemotherapy of TB in a time-frame shorter than the current duration of treatment[141-145,182-185]. The ideal new drug should also be able to replace RMP from the current therapy regimens to avoid interactions with antiretroviral drugs during concomitant treatment of HIV-TB co-infected patients. A new pathway for α-glucan synthesis has also been described in *M. tuberculosis* recently and compounds that inhibited the activity of maltosyltransferase (GlgE) caused rapid killing of tubercle bacilli *in vitro*, thus providing a novel drug target for designing anti-TB drugs with a novel mechanism of action[186]. These drugs / target add to the existing new drugs that are already in various stages of clinical development and it is expected that at least some of these novel agents will soon become available for the treatment and proper management of MDR-TB and XDR-TB.

CONCLUSION

The current TB epidemic is partly due to decades of neglect and poor management of an important infectious disease in much of the developing world and partly due to the emergence of global pandemic of HIV infection and its strong association with active TB disease and complications associated with concomitant

treatment of dual infections. The problem has been further compounded by the emergence of MDR-TB and then XDR-TB that remain virtually untreatable in much of the resource-poor developing countries. The inadequate allocation of resources for national TB control programs over several decades, poor case detection and cure rates due to poor quality of anti-TB drugs and inappropriate / improper therapy regimens are mainly responsible for the problem of drug resistance in high TB incidence countries. The limitations of TB control programs are clearly evident by extremely high mortality rates in sub-Saharan Africa where high incidence of HIV infection and MDR-TB occur in the same setting. Recent advances in development of simple cost-effective methods for rapid diagnosis and DST for first- and second-line drugs and greater availability of second-line and other drugs may translate into greater availability and adoption of new treatment regimens for MDR-TB / XDR-TB even in resource-poor settings. New drugs under development are urgently needed for synergistic and complementary activities to shorten the duration of current TB treatment and to be effective against MDR-TB / XDR-TB. Although several new classes of anti-TB drugs are in various stages of clinical development, new drug combinations must be carefully tested for most effective treatment of TB patients in the shortest possible time and to avoid emergence of novel resistance.

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Original Article

The Microbiology of Vaginal Discharge and the Prevalence of Bacterial Vaginosis in a Cohort of Non-pregnant Women in Kuwait

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ABSTRACT

Objective: To examine the microbiology of vaginal discharge and to estimate the prevalence of bacterial vaginosis and its association with sexually transmitted infections in a cohort of non-pregnant women in Kuwait
Design: Retrospective study conducted during a six-month period (November 2009 – April 2010).
Setting: The gynecology outpatient clinic at the South Ardyia Health Unit, Farwania, Kuwait
Subjects And Methods: Retrospective evaluation of medical records of 668 women, who attended the gynecology outpatient clinic at the South Ardyia Clinic, Farwania, Kuwait complaining of vaginal discharge during the study period
Interventions: Retrospective review of the files for complaints, history, clinical examination and investigations of the vaginal discharge
Main Outcome Measures: A retrospective microbiological study of the infective etiology of vaginal discharge, the prevalence of bacterial vaginosis and its association with sexually transmitted infections
Results: Microbiological causes of vaginal discharge accounted for 43.4% of cases. The commonest causes were bacterial vaginosis (prevalence = 18.9 %) and Candida infections (prevalence = 11.8%). There was no significant association of bacterial vaginosis and sexually transmitted infections.
Conclusion: Bacterial vaginosis is the commonest microbiological cause of vaginal discharge. Bacterial vaginosis is not a sexually transmitted disease.

KEY WORDS: bacteria, candida, chlamydia, gardnerella

INTRODUCTION

Vaginal discharge is a common complaint in gynaecology outpatient clinics[1]. The common causes of vaginal discharge are physiologic, infective non-sexually transmitted infections (bacterial vaginosis, and candida), infective sexually transmitted infections (*Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoea*) or non-infective causes (foreign bodies *e.g.*, tampons, condoms, cervical polyps and ectropion, genital tract malignancy, fistulae and allergic reactions)[2].

Bacterial vaginosis (BV) is the commonest cause of vaginal discharge in women of childbearing age[3]. It is a polymicrobial disorder characterized by an increase in the vaginal pH over 4.5, a reduction in / or absence of lactobacillus colonization, and overgrowth of several facultatively and obligately anerobic bacteria (*Gardnerella vaginalis, Prevotella species, Mycoplasma hominis, Mobiluncus species*)[4]. The commonest complaint is a fishy smelling offensive vaginal discharge. BV is associated with an increased risk of sexually transmitted human immunodeficiency virus infection[5,6], urinary tract[7] and upper genital tract infections, pelvic inflammatory disease and endometritis[8]. It may cause adverse pregnancy outcomes and premature labour[9,10]. It is reported to cause post-gynecologic-surgery infections[11]. The reported prevalence of BV varies between 6 - 37.5%[12-15]. Prevalence is statistically reduced in postmenopausal women[16].

The association between BV and sexually transmitted infections is still controversial. It is not yet clear, if BV is a risk factor which predispose to sexually transmitted infections, or if it is a sexually transmitted disease by itself. Sexual behaviour (a new or multiple sex partners) may change the balance of

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the vaginal flora and predispose to BV. However, other factors not related to sexual activity are also important for the development of BV infection (*e.g.*, psychosocial stress, ethnicity and age)[17,18]. Center for diseases control, USA classifies BV under sexually transmitted diseases. Paradoxically, they state that women who have never had sexual intercourse may also be affected[3]. United Kingdom text books[19, 20] and family planning publications[2] do not classify BV as a sexually transmitted disease but recognize that it is more common with pelvic inflammatory disease[2,19,20].

The aim of this work was to evaluate the microbiology of vaginal discharge, prevalence of BV in a cohort of non-pregnant women in Kuwait complaining of vaginal discharge and its association with sexually transmitted diseases.

SUBJECTS AND METHODS

Study population

The files of all 668 non-pregnant women aged 19 to 45 years, complaining of vaginal discharge who attended the Gynaecology outpatient clinic at the South Ardyia health unit, Farwania, Kuwait, during a six months period (November 2009 – April 2010) were retrieved off the clinic registration book, the computer data base and cross checked against the laboratory data base. The files were retrospectively reviewed and included in this study. The data from reviewed files included present complaints, history (age, marital and socio-economic status, hygienic habits, contraception, recent and regular medications, past medical, surgical, obstetric and menstrual history), clinical examination findings and results of investigations for the microbial causes of vaginal discharge.

This study was approved by the institutional review board.

Exclusion criteria

To avoid compounding factors, after careful retrospective review of the patient files, we excluded 61 files of women with severe medical illnesses (4 files) , on hormonal or intrauterine contraception (11 files), who were bleeding (6 files), had douching or used vaginal suppositories in the past three days or had used antibiotics in the past two weeks (14 files). Women who had obvious non-infective causes of vaginal discharge (tampons, foreign body or cervical lesions) were also excluded (9 files). For homogeneity of the patients included in the study, 11 files of post menopausal women or women who had total or subtotal hysterectomy were also excluded (the prevalence of BV is statistically significantly reduced in post menopausal women[16]). Files with incomplete information were also excluded (6 files).

The files of the remaining cohort of 607 patients were retrospectively rechecked for complaints, history, clinical examination and microbiology findings of the vaginal discharge.

Sample collection

According to the retrospective review of the patient files, samples were collected from the posterior fornix or lateral vaginal wall and the endocervix of non-bleeding women. Samples were labelled and colour coded (red for endocervix, blue for vaginal samples) for identification and sent to the laboratory according to the clinic guidelines. The samples were processed in the following way:

1. A wet preparation in saline mount to check for clue cells and *Trichomonas vaginalis* infection
2. Tested for odour by adding 10% potassium hydroxide to a wet preparation.
3. Measurement of vaginal pH with Whatman™ Acid-Alkali Test Papers (Whatman plc, UK) which changes colour around pH 5 to 8.
4. Smeared on a glass slide, and the smear was stained according to the Gram procedure. The vaginal flora was evaluated on the Gram-stained smear according to the Nugent score[21].
5. Swabs in agar gel transport medium (Copan Italia) were cultured on blood agar, chocolate agar and Sabouraud's agar. The cultures were checked after 48 hours.
6. The presence of *Gardnerella vaginalis, Candida species* and *Trichomonas vaginalis* was also detected by the BD Affirm VP111TM" Microbial identification test kit. It is based on the principles of nucleic acid hybridization. A positive result for *Gardnerella, Trichomonas vaginalis* and / or *Candida*, means nucleic acid of the particular organism is present in the sample[22].
7. The BD Probe TecTM ET System was used to detect the presence of *Neisseria gonorrhoea* and *Chlamydia trachomatis* in the endocervical specimen[23,24].

Statistical analysis

The data are presented as mean ± standard deviation (SD), median, range, and percentage. Comparison between variables was made using the Chi square test. Receiver operator characteristic curves (ROC) were constructed to detect the relevance of age and parity in the prediction of occurrence of BV.

A p-value of less than 0.05 was considered significant. Statistical analysis was made using the MedCalc computer program (MedCalc Software, Ghent, Belgium).

RESULTS

The majority of our patients, 522 (85.9%), were of Kuwaiti origin. None of our patients ever smoked. All were normally menstruating women. The age of patients ranged from 19 to 45 years. The mean was

28.82 (SD 6.73) and the median was 28. The parity range was 0 - 8, with a mean of 2.9 (SD 1.67) and a median of three.

Out of the 607 patients complaining of vaginal discharge, 282 patients' (46.4%) sole complaint was vaginal discharge and had no other associated symptoms. The remaining 325 patients (53.5%), also complained of other different symptoms (foul or fishy smelling, greenish, yellowish or white curdy vaginal discharge, vulval soreness, itching, dyspareunia, or symptoms of urine infection) (Table 1).

Table 1: Associated main complaints (325 cases)

Complaint	Number	Percentage
Change of color or odour	103	31.6
Vulval itching	82	25.2
Soreness	82	25.2
Superficial dyspareunia	32	9.8
Deep dyspareunia	11	3.4
Symptoms of urine infection	15	4.6

Out of the 607 patients, there was no microbial abnormality in 343 patients (56.5%). Eight different organisms were isolated in the remaining 264 (43.4%) patients (Table 2). Out of these 264 positive microbiology

Table 2: Microbiology organisms in 264 positive cases

Organism	Cases (n)	%
Gardnerella vaginalis	122	46.2
Candida albicans.	72	27.2
Gardnerella vaginalis + Candida albicans	31	11.7
Gardnerella vaginalis +Streptococcus agalactiae	15	5.68
Gardnerella vaginalis + Streptococcus agalactiae + Candida albicans	2	0.75
Gardnerella vaginalis + Trichomonas vaginalis	1	0.38
Trichomonas vaginalis	6	2.3
Chlamydia trachomatis	6	2.3
Escherichia coli	5	1.9
Klebsiella pneumoniae	2	0.75
Neisseria gonorrhoea	2	0.75
Total	264	

cases, *Gardnerella vaginalis* was detected in 122 patients (46.2%). According to the Nugent scoring and Amsel's clinical criteria[21,25] BV was diagnosed in 115 cases of those with Gardnerella positive culture samples. This accounts for an overall BV prevalence of 18.9%. In our cohort of 607 women, BV was the commonest cause of microbial vaginal discharge (115 cases, 18.9%), followed by candidal infection (72 cases, 11.8%). Symptoms associated with BV are shown in Table 3.

All 115 women with proven BV had release of fishy odour on adding 10% potassium hydroxide. All 72 women who were proven to have *Candida albicans* infection demonstrated the typical Candida curd-white discharge.

Table 3: Symptoms associated with BV

Symptom	Cases (n) N= 115	%
Thin discharge	54	46.9
Fishy odor	34	29.5
Burning micturition	12	10.4
Soreness	9	7.8
Itching	4	3.4
Dyspareunia	2	1.7

According to the microbial findings, there was only one case of BV associated with sexually transmitted infections (*Chlamydia trachomatis*).

Table 4: Prevalence of BV according to ethnicity

Ethnicity	Bacterial vaginosis	No bacterial vaginosis	p-value
Kuwaitis	99	421	0.94
Asians	13	60	
Others	3	11	
Total	115	492	

The prevalence of BV in the 115 women according to ethnicity is not significant as shown in Table 4. According to ROC, both age (AUC = 0.60, p = 0.02) and parity (AUC = 0.73, p = 0.0001) were statistically significant predictors for the occurrence of BV (Fig. 1).

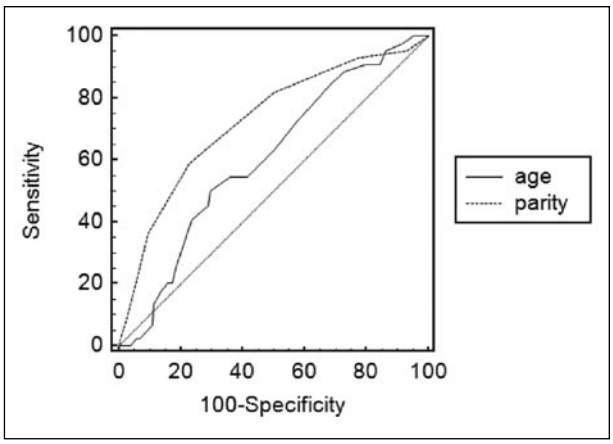

Fig. 1: Prediction for age and parity

Parity of three has 59% sensitivity and 77% specificity for prediction of BV. Age of 30 years has sensitivity of 50% and specificity of 70% to predict BV (Table 5).

Retrospective review of patient files indicated that on clinical examination, four women had clinical evidence of mild pelvic inflammatory disease (tender adnexae, cervical excitability and tender lower abdomen). Two of these four women showed copious purulent vaginal discharge.

There were 14 cases of sexually transmitted infections, two cases of *N. gonorrhoea* and six cases each of *Chlamydia trachomatis* and *Trichomonas vaginalis* (Table 2). In both cases where *N. gonorrhoea* was found,

Table 5: BV correlation with age and parity

Variable	Area Under the Curve (AUC)	Criterion	Sensitivity	Specificity	p - value
Age (years)	0.604	30	50%	70%	0.0241
Parity	0.726	3	59%	77%	0.0001

only one patient explained she may have had it from her husband who had just come from a long trip abroad. She also volunteered that her husband is receiving treatment for a urine infection. The second patient was completely reluctant to discuss any sexual history. Patients with *N gonorrhoea* and *Chlamydia trachomatis* were referred to the genitourinary medicine unit. All other patients with positive microbiology received the appropriate treatment.

Male partners of those who were diagnosed with BV were asymptomatic and were not given any treatment[2,26,27].

DISCUSSION

The present study is to our knowledge the first study for the microbiology of vaginal discharge, the prevalence of BV, and its association with sexually transmitted infections in a cohort of non-pregnant women in Kuwait. BV was confirmed using the clinical criteria of Amsel *et al*[25] and laboratory score of Nugent *et al*[21]. The Amsel clinical criteria for the diagnosis of BV are the presence of three out of four conditions, namely, homogeneous vaginal discharge (colour and amount may vary), amine fishy odour when potassium hydroxide solution is added to vaginal secretions, the presence of clue cells (greater than 20%) on microscopy and a vaginal pH greater than 4.5[19,20,25,28]. Culture of *Gardnerella vaginalis* without the above Amsel criteria is not diagnostic of BV [19,20,25,28].

The Nugent scoring is a Gram stain scoring system to diagnose BV. It is derived from estimating the relative proportions of bacterial morphotypes to give a score between zero and 10. A score of < 4 is normal, 4 - 6 is intermediate, and > 6 is BV[21].

The Gram stain is reported as being 100% accurate[29]. It has a 91% sensitivity (significantly higher than that of the clinical criteria (46%), (sign test p = 0.0023, < 0.01).The Gram stain method also has both a low false-negative (4%) and high negative predictive value (96%), making it an ideal diagnostic test[30].

According to the above criteria, BV was diagnosed in 115 cases of those with *Gardnerella* growth (122 cases). This accounts for an overall BV prevalence of 18.9%. This prevalence is within the range of different prevalence reported in different studies from different countries[12-15]. However, a previous study in Kuwait on the prevalence of BV in a pregnant population reported a higher prevalence of 28%, in marked contrast with their control of 30 non-pregnant women in whom the prevalence was 0%[31]. This difference in the prevalence may be explained because their control cases of non-pregnant women were a small number of asymptomatic women.

In our study, there was no statistical significance in the prevalence of BV according to ethnicity. Parity had better sensitivity and specificity for prediction of BV compared to age. Parity of three and age of 30 was a significant predictor for the occurrence of BV. There were repeated complaints of symptoms of irritation, discharge, or odour in 81 women in whom even repeated microbial workup did not reveal any abnormality, confirming other reports that normal vaginal discharge may still cause symptoms and complaints[32,33].

In this study, details of sexual activity and behaviour were not available. It is of note that all patients in the study were married women who were, for social and religious reasons, reluctant to discuss details of sexual activity and behaviour. Consequently, it is difficult in this study to assess the effect of sexual behaviour on the incidence and association between BV and sexual activity. However by assessment according to microbial cultures, BV was associated with only one case of *Chlamydia trachomatis*. Consequently, it is not possible to conclude any statistical significance for the association between BV and sexually transmitted infections.

Out of the 115 cases of BV, forty eight women came back for follow-up and requested repeat work up which did not show recurrence of infection. As the male partners were not given any treatments, it may suggest that BV is not a sexually transmitted disease in agreement with United Kingdom sources[2,19,20].

Our study confirms other reports, that the commonest causes of microbial vaginal discharge are BV and Candida[34,35].

Limitations of this study

Among the limitations of the present study is the lack of information on body mass index, age of sexual debut, frequency of sexual intercourse, other sexual behaviour, and hygienic and alimentary habits. This study does not have enough power to correlate to the causes of association of BV with sexually transmitted infections.

The study was not planned to relate any history of premature birth to BV.

CONCLUSION

Our study agrees with the opinion that the commonest cause of vaginal discharge is physiological.

Our data reveal that the commonest cause of microbial vaginal discharge is BV and *Candida*. The prevalence of BV in this cohort of non-pregnant women in Kuwait is 18.9% and BV responds well to standard treatments. BV is not a sexually transmitted infection.

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Original Article

Clinical and Bacteriologic Correlates of the PapG Alleles among Uropathogenic *Escherichia Coli* Strains Isolated from Cases of Adult Urinary Tract Infection

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ABSTRACT

Objectives: To study the distribution of papG gene in uropathogenic *Escherichia coli* (*E.coli*) strains isolated from adult urinary tract infection (UTI) and the relationship between the different classes of papG gene and patients, sex, hospitalization and their clinical forms of UTI
Design: Laboratory study
Setting: Inpatient and outpatient settings with laboratory investigation
Subjects and Methods: Genotyping of papG, the adhesin gene of *E. coli* P fimbriae, may predict clinical outcomes of UTI. A total of 182 urinary *E .coli* strains were analyzed by multiplex PCR method for detection of papG gene. Patients, sex, hospitalization and their clinical forms of UTI were also evaluated.
Intervention: The distribution of papG gene in uropathogenic *E.coli* strains and the relationship between papG gene and clinical features of the patients
Main Outcome Measures: Multiplex PCR method was performed for detection of papG gene in uropathogenic *E.coli* strains isolated from adult urinary tract infections
Results: The prevalence of pap operon in the uropathogenic isolates was 36.2%. The prevalence of papG gene classes II and III in uropathogenic isolates was 23.1% and 6.6% respectively. None of the isolates had class I genotype. PapG classes II and III were predominant in patients with pyelonephritis and cystitis respectively. There was no significant relationship between the presence of papG alleles, sex and hospitalization of the patients.
Conclusions: PapG gene is likely to play an important role in pathogenesis of uropathogenic strains of *E.coli* in adult nosocomial UTIs. Detection and genotyping of this gene may contribute to improving the management of UTI.

KEY WORDS: *Escherichia coli*, multiplex PCR, pap operon, urinary tract infection

INTRODUCTION

Virulent *Escherichia coli* (*E. coli*) strains are the most frequent etiological factor of urinary tract infections (UTIs). Several virulence factors including adhesins, invasins, toxins, and secretion systems are involved in *E. coli* pathogenic mechanisms. Strains of the same pathotype are genetically similar and carry the same genetic virulence determinants involved in the infection. These virulence genes are targets for the determination of the pathogenic potential of any given *E. coli* isolate[1,2]. The ability of bacterial pathogens to bind to the host tissues is a critical step in the pathogenesis of many bacterial infections. P-fimbrial adhesions, as the important virulence factors in uropathogenic *E.coli* strains, enable the colonization of host tissues by mediating attachment to P-blood group antigens on uroepithelial cells. It mediates specific binding via the adhesin molecule PapG[2-4].

Previous studies have shown the association of the three alleles of papG with specific clinical syndromes, *e.g.*, allele II with pyelonephritis[5,6] and allele III with cystitis[7,8]. Furthermore, some studies showed the role of allele II and III in *E. coli* bacteremia independent of the source of the bacteremia[6,9]. On the contrary, other studies reported that, the class III G adhesin is associated with cystitis, although it has been found in pyelonephritis and bacteremia while papG I strains might have a larger prevalence among fecal isolates[8]. Tseng and co-workers also concluded that, although most human pyelonephritogenic *E. coli* strains express the papG II adhesion, the role of the papG II adhesin in enhancing the establishment and persistence of *E. coli* infection in the kidney is controversial[10]. The aim of this study was to evaluate the prevalence of pap operon, coding for P fimbriae virulence factor among *E. coli* strains isolated from the urine of adults with

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UTI and also to establish the relationship between the bacterial genotype and the type of UTI.

MATERIALS AND METHODS

A total of 182 strains of *E. coli* isolated from urine samples of 182 hospitalized and outpatient adults (34 male and 148 female) with different forms of UTIs were evaluated between May 2007 and December 2007 in Shahre-kord Teaching Hospital, Shahre-kord, Iran. The design of this study was approved by Shahre-kord university ethics committee. The isolates were screened by multiplex PCR for pap genotype. Specific primers were utilized to detect genes associated with outer membrane protein (papC), and papG allele's adhesin (papG I / papG II/ papG III). The diagnosis of UTI was established, based on clinical symptoms and laboratory investigations. The laboratory criterion for acute *E. coli* UTI was defined as the presence of a positive urine culture with at least 105 colony-forming units (CFU) / ml of clean voided urine[11]. Also, the clinical criteria for cystitis, pyelonephritis and asymptomatic bacteriuria were defined as follows: cystitis (dysuria, with or without suprapubic pain, with no fever), pyelonephritis (flank pain, fever, with or without chills, nausea, vomiting) and asymptomatic bacteriuria (the presence of at least 105 CFU / ml in a culture of clean-voided midstream urine from an individual without symptoms of a UTI)[11].The isolation and identification of *E.coli* strains was performed by standard bacteriological tests[12].

Molecular methods for detection of pap operon and papG alleles

DNA extraction: *E. coli* strains were grown in Luria-Bertani (LB) broth at 37 °C for 18 hours. Bacteria were pelleted from 1.5 ml LB broth, suspended in 200 µl of sterile distilled water and boiled at 100 °C for 15 min. Following centrifugation (7000 G for 10 min) of the lysate, a 150 µl sample of the supernatant was stored at – 20 °C as a template DNA stock[1].

Detection of papC gene and papG alleles by PCR: The information on genes targeted, *E. coli* strains used as positive controls, the sequences of forward (F) and reverse (R) primers and the expected size of amplified DNA for each target is given in Table 1. The primers were synthesized commercially (TAG Copenhagen Co., Denmark). PCRs were carried out in a total volume of 25 µl containing 4 µl of template DNA, 0.1-0.5 µM of each of the F and R primers, the four deoxynucleoside triphosphates (each at 200 µM), PCR buffer with 1.6 mM of MgCl2, and 1.5 U of Taq DNA polymerase (Fanavaran,Tehran-Iran)[13]. The amplification procedure consisted of an initial denaturation at 94 °C for 5 min, followed by 30 cycles of denaturation at 94 °C for 30 sec, annealing at 65 °C for 30 sec, and extension at 72 °C for one minute[1].

Table 1: Genes targeted, primer sequences, size of the amplified DNA and *E. coli* strains used as positive controls in PCR amplification

Gene Targeted	Size (bp) of amplified DNA	*E.coli* strain	Reference
pap C	328	FVL2	(2,13)
papG I	461	O4K12J96	(2)
papG II	190	1A2	(2)
papG III	258	O4K12J96	(2,13)

The primers' sequences for papC gene:
Forward primer: 5′-GACGGCTGTACTGCAGGGTGTGGCG-3′
Reverse primer: 5′-ATATCCTTTCTGCAGGGATGCAATA-3′
The primers' sequences for papG alleles:
Allele I, Forward primer: 5′-TCGTGCTCAGGTCCGGAATTT-3′
Reverse primer: 5′-TGGCATCCCCCAACATTATCG-3′
Allele II, Forward primer: 5′-GGGATGAGCGGGCCTTTGAT-3′
Reverse primer: 5′ CGGGCCCCCAAGTAACTCG-3′)
Allele III, Forward primer: 5′-GGCCTGCAATGGATTTACCTGG-3′
Reverse primer: 5′ CCACCAAATGACCATGCCAGAC-3′

Aliquots (10 µl) of the final reaction mixture underwent gel electrophoresis in 8% poly acrylamide gel. The 100-bp ladder (Gene Phanavaran Co., Tehran, Iran) was used as a molecular size marker. Strain O4K12J96 was used as positive control for papG classes I and III and the strain IA2 was the positive control for papG class II[2] (Gene phanavaran Co., Iran).

Statistical analysis

Comparisons of proportions were tested by Chi-square test. A p-value < 0.05 was considered significant.

RESULTS

Out of 182 cases with UTI, 124 (68.1%) were diagnosed as cystitis, 44 (24.2%) as pyelonephritis and 14 (7.7%) as asymptomatic bacteriuria. Ninety (49.5%) of the studied cases had previous history of symptomatic UTI. Twenty-eight (15.4%) patients were hospitalized and 154 (84.6%) of them were outpatients. Ninety-two (5.5%) cases had no history of previous UTI.

Pap operon (papC gene) was detected in 66 out of the 182 (36.3%) uropathogenic *E. coli* strains isolated from the patients. There was no significant relationship between presence of pap operon in these strains and sex and hospitalization of the patients ($p > 0.05$, data not shown). On the contrary, pap operon was detected more frequently in the strains isolated from the patients with pyelonephritis (35 / 44, 80%) compared with strains isolated from the cystitis cases (31 / 124, 25%, ($p < 0.01$). None of the strains isolated from the patients with asymptomatic bacteriuria had papC gene.

Examples of multiplex PCR results for papG genotyping in uropathogenic *E. coli* strains are shown in Fig. 1, and the distribution of papG alleles in papC

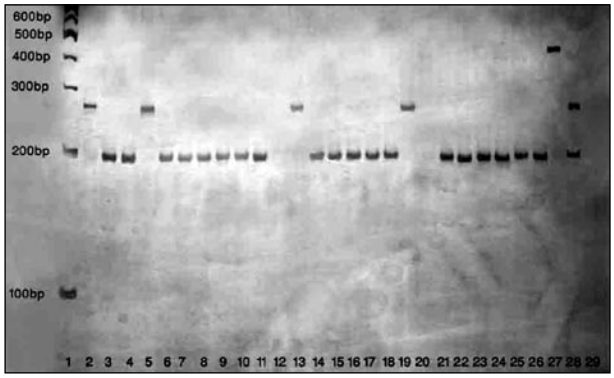

Fig. 1: Multiplex PCR reults for papG genotyping. The PCRs to detect papG alleles in *E. coli* were performed as described in the materials and methods. The PCR products were electrophoresed through 8% polyacrylamide gel. Lane 1: DNA ladder; Lanes 2- 26: *E. coli* isolates from patients; Lane 27: Positive control papG class I (*E.coli* strain O4K12J96); Lane 28: Positive control papG classes II and III (*E. coli* strains IA2 and O4K12J96, respectively) Lane 29: Negative control (Distilled water).

positive *E. coli* strains (n = 66) is shown in Table 2. The papG I allele was not detected in any clinical strain, whereas papG II and III alleles were detected in 42 / 66 (63.6%) and 12 / 66 (18.2%) cases of the uropathogenic *E. coli* strains, respectively ($p < 0.05$, Table 2). Although, papG II allele was predominant in *E. coli* strains from pyelonehritis than cystitis and reverse was the case for papG III allele (Table 2), no significant correlation was observed with clinical types of UTI and the occurrence of papG II and III alleles ($p > 0.05$). Furthermore, no significant relationship was found between the presence of different classes of papG gene in bacterial isolates and sex and hospitalization of the studied patients ($p > 0.05$, data not shown).

DISCUSSION

Based on the fact that urinary signs and symptoms are not often useful to reliably distinguish upper and lower UTIs, proper management of UTIs to prevent urinary tract complications is critical[14]. In this study, 182 strains of *E.coli* isolated from urine samples of hospitalized and outpatient adults were examined for detection of pap operon (papC gene) using PCR. The prevalence and distribution of papG gene classes were also assessed using multiplex PCR. The prevalence of papC gene in urinary isolates was 36.3%. Forty-two (63.6%) of pap-positive E.coli strains, had allele II only, twelve (18.2%) had allele III only, and seven (10.6%) had both alleles II and III. None of the isolates had papG class I. In general, the prevalence of pap operon (papC gene) in uropathogenic *E.coli* strains has been reported in ranges of 23 - 57% by other investigators[1,3,5]. In the present study, the distribution of the papC gene was in agreement with the published data. Our study also showed that, the prevalence of pap operon in the strains isolated from the patients with pyelonephritis was

Table 2: The distribution of papG gene classes in 66 papC positive uropathogenic *E. coli* isolates according to the clinical type of UTI

Clinical forms of UTI	PapG gene classes (%)				
	I	II	III	II,III	Negative
Pyelonephritis (35 cases)	0	28 (80)	2 (5.7)	3 (8.6)	2 (5.7)
Cystitis (31 cases)	0	14 (45)	10 (32.3)	4 (13)	3 (9.7)
Total (66 cases)	0	42 (63.7)	12 (18.2)	7 (10.6)	5 (7.5)

UTI: urinary tract infection

significantly higher than those isolated from cystitis cases ($p < 0.01$). These results have been similarly reported by some investigators[1,16]. Furthermore, although the prevalence of papC gene in patients with asymptomatic bacteriuria has been reported by some investigators[16], in our study, none of the isolates had papC gene. In general, we conclude that, since the ability of bacterial pathogens to bind to the host tissues is a critical step in their pathogenicity, P fimbriae has an important role in adhesion of the bacteria that invade upper urinary tract tissues and cause pyelonephritis. It is not probably highly critical for lower tract UTIs or asymptomatic bacteriuria. Some studies reported that, the class III G adhesin sequence is associated with cystitis, and also it has been found in pyelonephritis and bacteremia[8]. Tseng and co-workers concluded that, the role of the papG II adhesin in enhancing the establishment and persistence of *E. coli* infection in the kidney is controversial[10]. In one study[8], papG III was less prevalent than papGII in cystitis cases. In our study, class II predominated overwhelmingly over class III, occurring in 42 (63.6%) out of the 66 strains, versus only 12 strains (18.2%) for class III.

The prevalence of papG class II and III in our study was prevalent significantly in pyelonephritis and cystitis cases respectively. Similar results have been also reported by other investigators[5,7,8,17]. In general, we conclude that, the papG class II, specifically enables the uropathogenic *E.coli* to adhere to upper urinary epithelial cells and produce pyelonephritis.

Some reports have also shown the role of class II in the pathogenesis of bacteremia during UTI and other extraintestinal infections[4]. In fact, it seems that, papG class II, can be taken into account as an important virulence factor for invasion of uropathogenic strains to the kidney tissue and blood. On the contrary, according to our results, it seems that, papG class III plays a role in invasion of pathogenic bacteria into the lower urinary system.

In this study, none of the papG classes were found in the 5 / 66 strains (7.6%) of papC positive urinary bacteria. Juntunen[7] and co-workers concluded that such strains were found significantly more often in infants with major urinary tract abnormalities.

Therefore, it could be suggested that the presence of papG gene might play a role in renal tissue invasion and producing urinary infections.

CONCLUSION

It seems that the distribution of the papG classes in uropathogenic *E.coli* strains isolated from the UTI cases in Chahar- Mahal province of Iran is highly in agreement with published data. In addition, based on our results, we can conclude that uropathogenic *E.coli* strains with pap operon are more likely to be related with pyelonephritis than cystitis in UTI patients.

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Original Article

A Randomized Trial of Epidural Volume Extension by Sequential Combined Spinal Epidural Anesthesia using Three Different Techniques

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ABSTRACT

Objective(s): Sequential combined spinal epidural anesthesia (SCSEA) is gaining popularity in ASA grade III / IV, elderly, low cardiac output state and high risk patients. In view of contradicting results related to sensori-motor characteristics, we undertook this study with the null hypothesis that epidural volume extension (EVE) with local anesthetic or normal saline results in augmentation of initial intrathecal block.

Design: Prospective, randomized, double blind study

Settings: J N Medical College, Aligarh Muslim University, Aligarh, India

Subjects: Seventy-five ASA I/II patients divided into three groups and operated upon from September 2007 to January 2009

Intervention(s): Group I received 1.5 ml bupivacaine (0.5%) + 25 μg fentanyl in subarachnoid space and epidural catheter was inserted without any top ups. In group II & III with the same technique top ups were given after 10 minutes of the intrathecal block in the form of either 10 ml NS or 10 ml of 0.125 % bupivacaine.

Main Outcome Measure(s): Augmentation of initial intrathecal block

Results: Significant increase in height of block was seen after EVE by different techniques of epidural top up (T4.64 ± 0.86 & T3.92 ± 0.99 in group II & III respectively, p-value < 0.05) as compared to group I (T7.12 ± 0.83). The average increase was 3.12 ± 0.97 and 3.48 ± 1.35 segments in group II & III respectively as compared to 0.48 ± 0.51 segments in group I.

Conclusion: Height of low-dose intrathecal block can be enhanced by SCSE using EVE effect even with normal saline.

KEY WORDS: anesthesia, SCSEA, spinal-epidural

INTRODUCTION

The monumental popularity of sequential combined spinal epidural anesthesia (SCSEA) lies in its ability to combine the rapidity, density and reliability of the subarachnoid block with stable hemodynamic parameters. The flexibility of continuous epidural block makes the anesthesiologist more comfortable due to its ability to titrate the dose to achieve a desired sensory level, intensify a patchy block, control the duration of anesthesia, and deliver postoperative analgesia.

Single segment sequential combined spinal epidural (CSE) technique for cesarean delivery was described by Rawal *et al*[1], where an epidural catheter was used not only as a reserve, but to allow additional local anesthetics to be injected into the epidural space to gradually raise the level of an intentional low spinal block. This is especially important in obstetrics and high risk patients, as it allows the reduction of the local anaesthetic dose and consequently reduces the severity and frequency of maternal hypotension.

SCSEA technique is gaining popularity in obstetrics and in major orthopedic surgery, can also be applied in vascular, urological and lower abdominal surgery. Though CSE has secured its place well in the regional anesthetic armamentarium[1], its safety and efficacy is still questioned in comparison to single shot spinal anesthesia and extra expenditure involved in purchasing a CSE set.

Various studies have shown the advantages of this technique in ASA grade III/IV and elderly patients, low cardiac output state patients (MS or AS), patients with severe PIH and in high risk patients where avoidance of sudden changes in hemodynamics is of paramount importance. Epidural volume extension (EVE), when applied to intrathecal hyperbaric bupivacaine, fails to decrease the dose or raise the level of block.[2]

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Table 1: Comparative demographic profile of patients in three groups

Variables (Mean ± SD)	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)	p-value
Male to Female ratio	19:6	17:8	19:06	0.76
Weight (kg)	57.5 ± 10.60	64.24 ± 9.69	61.44 ± 7.85	0.58
Height (cm)	158.4 ± 8.36	158.2 ± 6.17	160.96 ± 4.72	0.28
Body Mass Index (BMI)	24.99 ± 4.06	25.67 ± 3.52	23.69 ± 2.64	0.13

In view of contradicting results related to block characteristics, we undertook this study with the null hypothesis that EVE with local anesthetic or normal saline results in augmentation of initial intrathecal block.

SUBJECTS AND METHODS

The study was conducted in a tertiary care teaching hospital from September 2007 to January 2009. Written informed consent was obtained from all patients and the study was approved by the Institutional Ethics Committee. 75 ASA I/II patients (20 - 60 years of age) undergoing surgery of the lower abdomen, pelvis, perineum, and lower limb were included in this study. The study design was prospective, randomized, double blind controlled study.

Statistical Analysis

Sample size was calculated on the assumption that the power of our study was 80% (1-β) with an alpha error of 0.05 for this study (Using PS software), estimated that 14 patients weres sufficient to detect a difference of two segment sensory block. We had taken 25 patients in each group to reduce the β error. Randomization into three groups was achieved using computer generated random numbers. In group I – 1.5 ml bupivacaine heavy + 25 μg fentanyl was injected into the subarachnoid space and a catheter was passed into the epidural space and no top ups were given. In group II & group III after 10 minutes of epidural catheterization either 10 ml NS (group-II) or 10 ml of 0.125 % bupivacaine plain (group-III) was injected through the epidural catheter. However, 1.5 ml bupivacaine heavy + 25 μg fentanyl was given in the subarachnoid space similar to group I.

In our study, we inserted epidural catheter in group I to eliminate any confounding factor caused by our failure to equilibrate the pressures in the epidural space. This catheter was later used to provide intra as well as postoperative analgesia.

Our exclusion criteria included patients having preoperative neurological deficits, coagulation disorders, hypotension or hemodynamic instability. Uncooperative patients, those who refused regional anesthesia, any anticipated difficulty in regional anesthesia, valvular heart disease and pediatric age along with other standard contraindications of central neuraxial blockade were also excluded from the study. A predetermined proforma-based evaluation was done according to the protocol of our institute.

Preloading was done with 10 ml / kg of lactated ringer solution over 20 minutes. No sedatives were given during intraoperative period. CSE was performed in sitting position *via* 18G Tuohy needle and 1.5 ml bupivacaine heavy 0.5% and 25 μg fentanyl was injected intrathecally *via* needle through needle technique. Sensory and motor blocks were assessed every 2.5 minutes by a blinded independent observer. Epidural top up was given according to the group assigned after 10 minutes of intrathecal injection. Sensory and motor characteristics, after EVE were assessed every 2.5 minutes by same blinded independent observer. Observations were carried out for next 30 minutes or until there was no change in the height of maximum sensory block for three consecutive reading.

RESULTS

The patients in the three groups were well-matched (Table 1) as regards their age, sex, weight, height, BMI distribution. Thus, the chances of biasing of results due

Table 2: Sensorimotor characteristics (Mean /Median (SD / Range)

Variables	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)	p-value
Height of block (achieved at 10 mins)	T7.64 ± 1.11	T7.76 ± 1.16	T7.48 ± 1.26	0.87
Height of block (achieved at 30 mins)	T7.12 ± 0.83	T4.64 ± 0.86	T3.92 ± 0.99	0.00*
Total no. of segments blocked	8.88 ± 0.83	11.36 ± 0.86	12.06 ± 0.99	0.0043*
Two segment regression time (minutes)	81.68 ± 9.1	79.4 ± 9.17	83.68 ± 6.63	0.36
Sensory block recovery time at L4 level (min)	130.6 ± 9.38	118 ± 8.90	122.4 ± 8.67	0.01*
Onset of motor block (min)	4.24 ± 0.61	4.5 ± 0.85	4.46 ± 0.73	0.414027
Bromage score at 10 min.	2.96 ± 0.2	2.84 ± 0.37	2.92 ± 0.28	0.34
Motor black recovery time (Bromage score 0) min.	107 ± 10.99	99.4 ± 6.66	100.4 ± 10.20	0.04*

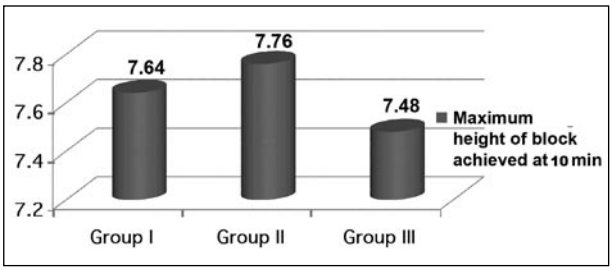

Fig. 1: Comparison of mean height of block achieved at 10 min

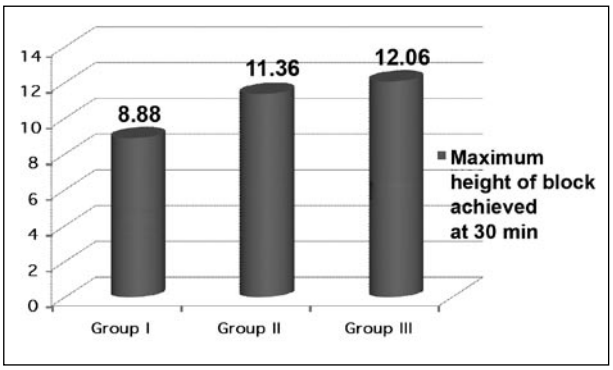

Fig. 2: Comparison of mean height of block achieved at 30 min

to demographic profile of the patient were minimized. The mean onset of sensory block, motor block and height of sensory blockade achieved at 10 minutes were comparable in three groups (Table 2). There was significant increase of sensory block after EVE with 10 ml of normal saline or 0.125% bupivacaine plain (T4.64 ± 0.86 & T3.92 ± 0.99 in group II & III respectively, p-value < 0.05) as compared to group I (T7.12 ± 0.83). There was an average increase of 3.12 ± 0.97 and 3.48 ± 1.35 segments in group II & III respectively as compared to 0.48 ± 0.51 segments in group I (Table 2). Two segment regression times were comparable in all the groups (81.68 ± 9.1, 79.4 ± 9.17 & 83.68 ± 6.63 minutes respectively). Total duration of sensory blockade was not comparable in three groups (130.6 ± 9.38, 118 ± 8.90 & 122.4 ± 8.67 minutes in group I, II & III respectively). There was faster sensory recovery in Group II & III as compared to group I (Table 2). There was statistically significant difference in motor recovery in group II & III as compared to group I (107 ± 11, 99.4 ± 6.66 & 100.4 ± 10.20 minutes in group I, II & III respectively, p-value < 0.05).

DISCUSSION

SCSEA enables low-dose spinal anesthesia without sacrificing the ability to extend the blockade through the epidural catheter and enables us to obtain a relatively controlled and graded sympathectomy. Thus, this technique avoids the adverse effects of sudden sympathectomy associated with spinal anesthesia providing stable hemodynamics.

Though in our study we could not get any statistically significant difference between group II & III (p > 0.05), it may be due to very low concentration of plain bupivacaine as opposed to higher concentrations used in other studies. This finding is supported by Stienstra *et al*[3], as 25 mg of bupivacaine was insufficient to cause any appreciable increase in initial level of intrathecal block.

In 1998, Mardirosoff *et al*[4] observed failure of epidural volume extension in augmenting sensory block when patients were asked to sit for five minutes after intrathecal deposition of hyperbaric bupivacaine. This failure may be attributed to the restricted spread of local anesthetic to lumbar and sacral roots only during the sitting position.

The role of intrathecal drug baricity alteration on cephalad augmentation of spinal block after EVE was studied by Yamazaki *et al*[5] in the lateral position after 20 minutes of the intrathecal injection, and no difference was found, as the hyperbaric local anesthetic would not be confined to caudad space and hence no question of enhancement. Moreover, as EVE is a time dependent phenomenon, it may not be able to cause its effect after 20 minutes.

Furthermore, very low dose of drug (5.1 mg and 6.1 mg in Group EVE & NEVE respectively) could not be augmented by EVE[6]. In this study, they have not mentioned the timing of EVE. Horstman *et al*[7] measured CSF pressures in single-shot spinal (SSS) versus CSE and concluded that there was no correlation between extent of sensory blockade and CSF pressures. The SSS and CSE techniques were performed in lateral decubitus position and resulted in similar extent of sensory blockade and CSF pressure. Initial higher spread in both the groups might be due to lateral decubitus position as enhancement of intrathecal block by EVE depends on initial levels of sensory block.

Lew *et al*[8] demonstrated significantly faster motor recovery to modified Bromage score of zero (73 ± 33 min versus 136 ± 32 min; p < 0.05) in the EVE group. They used 9 mg and 5 mg of bupivacaine heavy in two groups respectively. This large difference in the initial intrathecal doses might have accounted for this major difference in motor recovery times. We have used 7.5 mg of bupivacaine in each group, which accounted for minor differences in motor recovery times. If Lew *et al* had taken a control group, they might not have noticed such a large difference in motor recovery times.

Tyagi *et al*[2] were not able to detect any significant effect of dose reduction on EVE {10.0 mg (8.7 - 11.5 dermatomes); 9.7 mg (8.8 - 10.7 dermatomes)}. Though they have found significant dose reducing effect of EVE with normal saline when intrathecal plain bupivacaine was used {8.1 mg (7.5 - 8.6 dermatomes): 7.0 mg (6.0 - 8.2 dermatomes)}. We were not able to find out any reason to explain why their results have not shown any EVE

effect in the bupivacaine heavy group. One plausible cause of these results may be due to additional sedative effects of diazepam or even intrathecal fentanyl. All these factors must have hampered the assessment of sensory block to pinprick. This impairment of assessment of sensory block may vary from patient to patient due to different level of sedation score achieved in each individual. However, they have not mentioned any sedation scores in their study, which might have affected their results. In our study, we have not used any sedatives to avoid any impairment of sensory assessment. All the block characteristics were assessed by same observer blinded to group of patient to avoid observer to observer variations.

However, one limitation of our study was that we have not included control group with SSS using higher dose of drug to produce equivalent level of sensory block as achieved in Group II & III. By using this control group, we may be able to compare the efficacy of SSS anesthesia over SCSEA in term of hemodynamic stability. We could also have better elucidated the benefits gained in terms of faster recovery of sensory and motor block.

In our study, we have given epidural top up in supine position which might have lead to better cephalad spread of CSF causing enhancement of initial intrathecal anesthesia. Further studies are required to prove whether EVE in supine as compared to sitting position has any dissimilar effect on the spread of initial intrathecal block.

During thorough review of literature, we have come across various interesting findings. The studies done in parturient undergoing cesarean section have contradictory outcomes. There are a few studies which showed augmentation effect of EVE[2,3,9-15] while some studies were unable to elucidate any significant augmentation effect[16-18]. In non- parturients, most of the studies have elucidated the augmenting effects of EVE[3,18-20] whereas only few were unable to show similar effects[12]

One of the probable explanations for these conflicting results in parturients may be due to variable epidural pressures which lead to unpredictable spread.

CONCLUSION

The present study concluded that in CSE anesthesia, the low dose of bupivacaine heavy (1.5 ml) with addition of 25 μg of fentanyl intrathecally, with epidural catheterization without any top up is sufficient to produce desired surgical analgesia. The presence of epidural catheter in epidural space might have volume effect on subarachnoid space and the breach of ligamentum flavum leading to equalization with atmospheric pressure with better dispersion of drug causing higher level of analgesia.

There was clinically significant increase in the initial intrathecal block after epidural top up of 10 ml of normal saline (group II). However, no additional enhancing effect of 10 ml of 0.125% plain bupivacaine over normal saline was evident when used in EVE.

There was statistically significant faster recovery of sensory block in group II & III as compared to group I. Similarly there was statistically significant faster motor recovery in group II & III as compared to group I. This faster recovery may be due to dilution effect of epidural normal saline as well as higher spread in group II & III leading to more diffusion and faster metabolism of the drug.

In conclusion, we can say that low doses of bupivacaine heavy with the addition of intrathecal opioids can be used successfully to attain adequate levels of sensory block which can be enhanced by EVE with either normal saline or plain bupivacaine in non-parturient patients.

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Original Article

Total Hip Replacement after Hip Fracture: Primary or Secondary Surgery? A Comparison of Clinical and Radiological Results

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ABSTRACT

Objective: To compare clinical and radiological results of primary and secondary total hip replacement (THR) after displaced fracture of the femoral neck
Design: Retrospective review of a cohort of 47 patients
Setting: All surgeries were performed by the senior author in Al Razi Hospital, Kuwait between 2002 and 2007. Follow- up assessment was done in Al Razi and in Farwaniya Hospital, Kuwait by all authors.
Subjects: Twenty-nine cases of primary THR compared with 18 cases of secondary THR
Interventions: Cementless, cemented and hybrid implants were used for total hip relacements
Main Outcome Measures: Clinical assessment was done using Merle D'Aubigne hip score and radiological assessment was done using standard criteria of geometry of the implant and its stability
Results: Clinical results were better in the primary THR group but radiological results were equivocal. There was tendency to position the cup horizontally in the secondary surgery group. Cementless, cemented and hybrid implants did equally well in our cohort.
Conclusion: Primary THR seems to be a better option in displaced fracture of the femoral neck. Cemented cementless and hybrid hip can be used in these cases.

KEY WORDS: hip fracture, primary THR, secondary THR

INTRODUCTION

Hip replacement after hip fracture has been used for more than six decades. Controversy as to fix or replace the displaced hip fracture is still not settled. However, there is more scientific evidence that for medical and economical reasons replacement is superior to fixation above the age of 60 years in displaced fractures[1-4]. Fixation failure and avascular necrosis of the femoral head are the main reasons for secondary procedures (Fig. 1). Shortening of the femoral neck in united fractures may result in painful hip for biomechanical reasons (Fig. 2)[5,6]. The question, which type of prosthesis to use is the subject of controversy that still continues and there is no clear guideline regarding when to use cemented, cementless, unipolar, bipolar or total hip replacement in cases of a displaced femoral neck fracture[7,8]. In our retrospective analysis, we present results of primary and secondary hip replacement for displaced fracture of the femoral neck. We compare the clinical and radiological outcomes and discuss the problems related to these cases.

SUBJECTS AND METHODS

Forty-seven patients with primary and secondary total hip replacement (THR) for hip fracture are the subjects of this retrospective study. The material reflects patients treated by one of the units and patients referred from other units if they were candidates for THR. Most of the admitted patients with femoral neck fracture in Al Razi hospital were treated by non-modular (Thompson) or modular (unipolar cemented or cementless Smith&Nephew- Plus Orthopedics) implants and are not the subject of this study. All surgeries were performed by the senior author in Al Razi Hospital between 2002 and 2007. Follow-up assessment was done in Al Razi and in Farwaniya Hospital, Kuwait by authors not involved in surgical procedures. In primary cases, the THR was performed as the first operation for displaced fracture and in secondary cases the THR was done for fixation failure, non- union or both. Displaced hip fracture was defined as Garden type III and Garden type IV femoral neck fracture[9]. THR was done as the initial operation in 29

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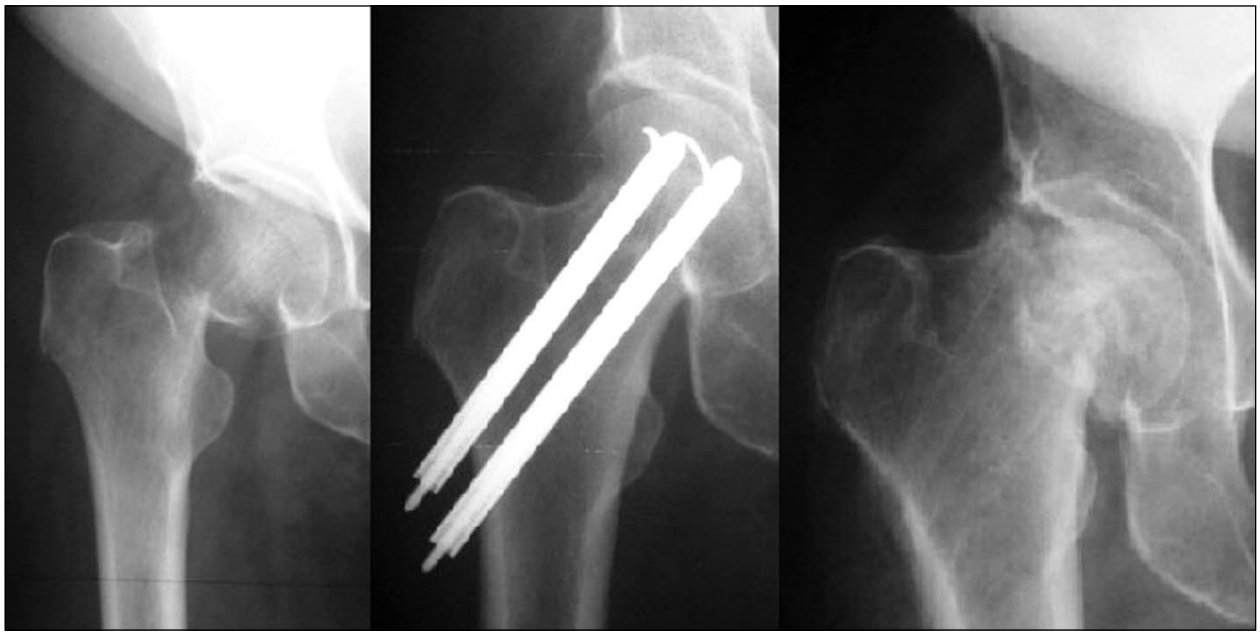

Fig. 1: Failure of fixation with non-union and avascular necrosis of the femoral head

patients and secondary THR done as the secondary surgery in 18 patients. Cementless implants used were Bicon Cup, EPF Cup and SL Stem (Smith & Nephew-Plus Orthopedics) and cemented implants used were Exeter (Stryker). In two hybrid type implants, Bicon Cup was combined with Exeter stem in one case and in other case Exeter PE Cup was combined with CBH stem (Mathys) (Fig. 3 - 5). In all cases, 28 diameter chrome-cobalt or ceramic head was used. Clinical assessment was done using Merle d'Abigne clinical score[10] and radiological results were assessed using standard criteria for implant geometry and assessment of implant / bone or bone / cement interface according to the type of implant. Inclination of the cup was defined as optimum (between 30 and 50 °), horizontal (below 30 °) or vertical (above 50 °). The stem position was defined as neutral, varus or valgus. Integration of the cup and stem was defined as integrated if no lucent lines were found and there was no migration, possibly loose when lucency did not exceed 2 mm, and loose if the lucency exceeded 2 mm and there was migration of the implant[11]. The patients were followed up for a average period of 48.5 months (36 - 61 months) after surgery. The details of the patients, type of pathology, implant used and follow-up are shown in the Table 1. Student t-test was used to compare clinical results of primary and secondary hip replacement. Seven patients died during the follow up for causes not related to surgery, but case information was sufficient to include them in the study.

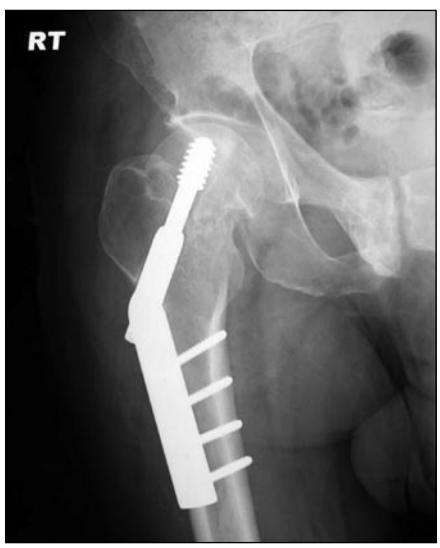

Fig. 2: Femoral neck shortening in united fracture

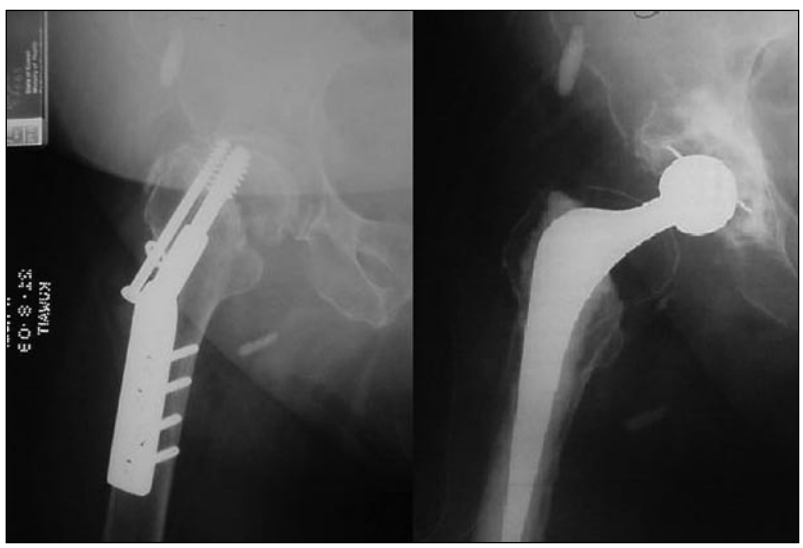

Fig. 3: Cemented THR after failed fixation

Table 1: Demographic and clinical data of patients in the two groups

Data	Primary THR n (%)	Secondary THR n (%)
No. of patients	29 (62)	18 (38)
Age in years (range)	66.5 (54 - 104)	58.8 (54 - 68)
Male	10 (34)	9 (50)
Female	19 (66)	9 (50)
Follow-up in months	48.3 (36 - 62)	48.8 (36 - 62)
Type of implant		
Cemented	16 (55)	4 (22)
Cementless	12 (42)	13 (72)
Hybrid	1 (3)	1 (6)

Five patients were in the primary arthroplasty group and two were in secondary arthroplasty group.

RESULTS

Clinical and radiological results are shown in Table 2 and 3.

Clinical results show that the primary hip replacement was better than secondary cases with difference that was statistically significant. There were no significant differences in radiological results.

DISCUSSION

The concept of optimum treatment for displaced fracture of the femoral neck underwent evolution during the last century and is still under scrutiny[12]. Choice between replacement and fixation followed changes in implant technology and outcome of clinical studies. Economic aspect of hip fracture treatment, has been stressed in different geographical locations[13-15]. Unipolar or bipolar hip replacement has been a preferred alternative to fixation in displaced fractures in many published studies. However, THR gains popularity, especially in generally fit patients with longer life expectancy[3,16]. Our cases with average age of 63.6 (54 - 104) years were in the group of relatively active individuals. Patients with low activity level and poor health condition were

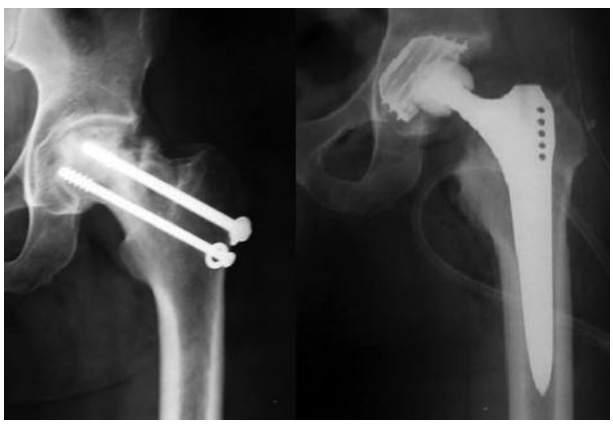

Fig. 4: Cementless THR after failed fixation and avascular necrosis of the femoral head

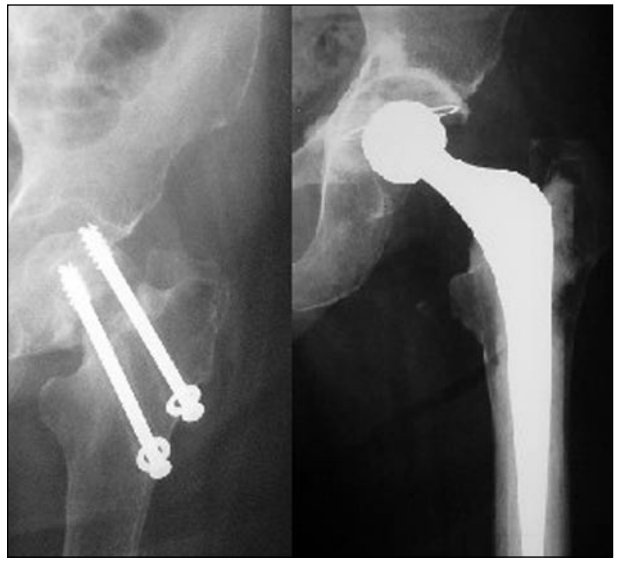

Fig. 5: Hybrid THR after failed fixation and avascular necrosis of the femoral head

Table 2: Clinical results

Clinical result	Primary THR	Secondary THR
Initial clinical score	8.3 pt	10.4 pt
Final clinical score	16.7 pt	15.6 pt
	$p < 0.01$	

qualified for less invasive unipolar hip replacement[17]. Results of hip replacement as a primary or secondary procedure have been reported but no evidence as to which procedure is superior has been provided. In some studies, no difference in results has been demonstrated[18]. In other reports primary replacement was better[19]. Our results of primary hip replacement were better than secondary cases ($p < 0.01$). However,

Table 3: Radiological results

Radiological result	Primary THR n (%)	Secondary THR n (%)
Cup inclination		
optimal (30 - 50 º)	24 (8)	9 (50)
horizontal (< 30 º)	4 (14)	7 (39)
vertical (> 50 º)	1 (3)	2 (11)
Cup version: anteversion	29 (100)	18 (100)
Stem position		
neutral	27 (93)	16 (88)
varus	2 (7)	2 (12)
Cup integration		
integrated	28 (96.5)	17 (94)
possible loosening	1 (3.5)	1(6)
Stem integration: integrated	29 (100)	18 (100)

with a rather small series, we consider this result with caution. In our study, cemented, cementless and hybrid hip replacement were used. The selection of implant depended on pre-morbid clinical assessment of the patient's condition and radiological assessment

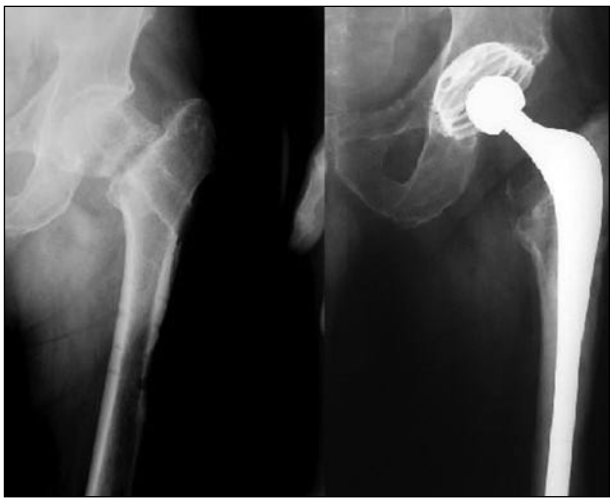

Fig. 6: Horizontal cup position in a case of secondary THR after failed fixation and avascular necrosis

of bone quality using Singh index[20] and also on implant availability. Although the reliability of Singh Index has been put into question, there is no other method to determine the bone quality at the time of decision making process. In some cases decision was taken during surgery according to clinical assessment of bone quality. Cemented hip replacement was done for most of the primary cases reflecting poorer bone quality in this group. In the secondary hip replacement group, cementless implants were frequently used, as the bone quality in those patients was better, justifying initial decision to fix the fracture. There was a tendency to position the cup more horizontally (Fig. 6) in the group of secondary cases. We considered it as a factor of stability in the revision situation. There were no significant differences in other radiological aspects. We observed three cases of dislocation in the early postoperative period (6.6%) in the group of primary hip arthroplasty that is consistent with bibliographical data[21]. In two cases, dislocation occurred in posterolateral approach and in one case in direct lateral approach. In two primary cases with posterior approach there was significant delay in surgery because of logistic problems with implant delivery. In all three cases, position of the cup was within optimal limits. Weakening of the muscles due to prolonged bed rest might be a reason for instability. It may also be partially attributed to the head diameter (only 28 mm head was used). A striking feature of our material is the relatively low number of cases of hip fracture and subsequently low number of hip replacement for hip fracture treatment and also for other indications[22]. This fact reflects the structure and average age of the population of Kuwait as well as other Middle-East societies. Although the hip fracture incidence is relatively high in Kuwait[23] the actual number of population at risk is low. Genetic, environmental and socio-cultural aspects play a role and should be a subject of further studies.

CONCLUSION

The following conclusions may be drawn:

1. Total hip replacement is a viable option in treatment of displaced fracture of the femoral neck.
2. Clinical results of primary cases in our material are better than results of secondary cases.
3. Radiological results of primary and secondary cases are similar

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Original Article

More Expensive Surfaces are Not Always Better

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ABSTRACT

Objectives: To assess efficacy of two support surfaces RIK® gel mattress and a Power Air® overlay in preventing and healing pressure ulcers
Design: Retrospective analysis of patient records
Setting: An academic affiliated 240-bed long-term care facility in Baltimore, MD, USA
Subjects and Method: All patients with pressure sores at the start of the study were included. One hundred and twenty-two patient records and weekly wound measurements on 173 pressure ulcers done by a dedicated team of wound nurses and technicians were retrospectively analyzed. The two surfaces studied were assigned by the respective physicians and nurses of each unit.
Intervention: None
Results: The two patient groups were comparable at the start of the study. One third of all patients developed one or more wounds during the study period or 48% of all ulcers studied. Healing rates were similar for both surfaces. New stage II ulcers were most common. There was a trend toward higher risk in patients assigned to the Power Air overlay mattress. Patients assigned to the gel mattress developed pressure ulcers less frequently than those on the Power Air overlay; however, the Power Air overlay tended to heal more ulcers. Controlling for the total amount of time each group spent on the respective mattresses, the efficacy of the gel surface in preventing new ulcers equaled or outweighed the benefit of the Power Air overlay. Since the gel fluid mattress is less costly we would favor the use of the gel mattress system.

KEY WORDS: gel fluid surfaces, power air surfaces, pressure sores

INTRODUCTION

Pressure ulcers are common in long term care among elderly patients. Acute care settings generate 60 - 70% of all pressure ulcers, the remainder occurring in long-term facilities and in community settings[1-4]. They are estimated to affect 7 - 11% of the adult population. Pressure ulcers are costly, painful, and result in deformity as well as loss of dignity[3, 5-8]. They can also serve as reservoirs for antibiotic resistant bacteria and lead to outbreaks of serious nosocomial infections[2, 9-13].

Pressure ulcers are due to many factors including severity of disease, immobility, pressure, shear, friction, skin moisture and nutrition, but inadequate repositioning is a central factor[2,10,14]. The common denominators are unrelieved pressure or shearing forces over bony prominences, resulting in damage to underlying tissues. As a person ages, there is a general loss of fat from the subcutaneous tissue that normally cushions the bony protuberances. Unrelieved pressure on these bony prominences compresses underlying blood vessels thereby compromising blood flow and oxygen delivery to surrounding tissues[6,15]. As little as 32 mmHg of constant pressure over a two-hour period can lead to ischemic tissue breakdown[2, 6, 15]. Within days of this initial mishap, necrosis ensues and an eschar may develop over the infarcted area.

Usually, a healthy person can sense pain due to pressure and even the slightest changes in body position increases blood flow. However, when a patient cannot position himself or herself, a caregiver must turn and reposition the immobile patient[16]. Patient repositioning every two hours is the standard of prophylactic care; but unfortunately limited staff, excessive documentation tasks and lack of supervision often prevent this[3, 11,17]. Health care facilities have long been concerned about preventing pressure ulcers, not only because of the costs and suffering that result from them[17] but because pressure ulcers have traditionally been thought to reflect quality of nursing care.

Despite mandated two-hour turning schedules and use of assessment tools to identify those at risk for skin breakdown, individuals still enter nursing homes with pressure ulcers or develop them during their

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stay[1,18]. Often because of shorter stays in the acute care setting, pressure ulcers induced in the acute hospital are not recognized until the patient is in the nursing home[3]. A wide variety of support surfaces promise an environment to prevent injury and promote healing, but there is little clinical evidence that one support surface is consistently superior[15,18,19,19]. The decision by a care provider on which support surface to use is often based on who is detailing the various products to a given facility[18,19].

Current data favors the low air loss bed, which decreases skin breakdown and shortens healing time compared to conventional hospital mattresses[1,2,9,10, 20-22]. The drawback to the use of this low air loss mattress system is the cost and upkeep it requires[10]. The average cost of renting the low air loss bed at the time of this study was averaging $70 per day. Third party payers favor lower costing products[23]. However, there are many other quality pressure reducing support surfaces offered as intermediary steps between the conventional and low air loss mattress at more affordable prices[1,7,14,19,24,25]. Pressure-reducing mattress overlays such as foam, air, and gel products are used most commonly to prevent pressure ulcers[15,18,22,24,26]. Two such products are the RIKTM fluid mattresses and the First Step Power Air Overlay™. The power air overlay provides a circulating air interface between the patient and the mattress. When properly inflated the air overlay's interconnecting chambers, which allow air exchange between compartments when compressed, are superior to the traditional hospital mattress[14, 15]. The disadvantage for the power air overlay is that the dynamic alternating air pressure requires a relatively noisy electric motor and maintenance is necessary to insure that the device remains properly inflated[15,27]. The RIKTM mattress is a gel-foam subsurface divided into independently compressible oversized fluid pad pillars. Each pillar conforms to overlying bony prominences and reduces shearing forces. The gel overlay is a cumbersome product to transport, but requires no extra maintenance.

The few studies comparing the performance of these products have not shown any significant clinical differences between the two mattresses[15,19]. Data suggests that they are useful for prevention, but to what degree is not known[26]. The Johns Hopkins Geriatric Center at the time of this study offered both mattress types for physicians to order at their discretion. However, since no concrete clinical information existed to support either type, physicians made a choice based on convenience and cost. Clinical evaluation of these surfaces for prevention of pressure sores and their healing rates is needed. Therefore, the purpose of this study was to determine the efficacy of the gel-fluid support surface and the power air overlay surface in preventing and healing pressure ulcers in a teaching long-term care facility.

SUBJECTS AND METHODS

The study was a retrospective chart review of inpatients admitted to John Hopkins Geriatrics Center from 7/1/01 through 6/30/02. The patients studied were those in the chronic hospital beds of this facility. The study protocol was reviewed and approved by the Institutional Review Board at Johns Hopkins Bayview Medical Center, MD, USA. On admission to the facility, all patients were assessed by a registered nurse for risk of developing a pressure ulcer using the Braden Score risk assessment tool. The Braden Scale is based on risk factors known to predispose an individual to pressure ulcers which include mobility, activity, sensory perception, skin moisture, nutritional status, friction and shear[16,17]. A score of 16 or less (indicating high risk), or a patient presenting with an existing pressure ulcer required the institution of an appropriate pressure reduction product. Facility guidelines at that time allowed physicians to choose one of two available surface support interventions, the RIK gel fluid mattress or the First Step power air overlay. Patient assignment to either test group was according to the physician's decision, and was not done following any formal guidelines or protocol.

Product-billing lists from the mattress rental company Kinetic Concepts Incorporated (KCI technologies) identified all patients on support surfaces during their stay for the last year. In addition to identifying the patient on a given mattress type, the lists also included the start and stop dates that a given patient was on the support surface. Since literature suggests that the given time frame for a pressure ulcer to reveal itself is approximately 7 - 10 days, we excluded anyone who did not stay at the facility or on the mattress for more than 10 days. Additionally, if during their stay the patient developed a severe stage III or IV pressure ulcer, they were removed from the mattress and the study at that time and placed on a Low Air Loss (Kinair) bed. The number of patients on each mattress type during the time period determined sample size yielding a study population of 122 patients.

Data collection for demographics of the patient population was performed by a patient chart abstraction and we compared the two groups using independent t-tests. Demographic data collection included age, gender, race, Braden Score, primary diagnosis upon admission, total number of medical problems, and patient death during period.

We obtained pressure ulcer data from skin care flow sheets included in each patient chart. The standard care guidelines at Johns Hopkins Geriatric Center require that the skin care flow sheets be maintained on every patient in the facility that presents with or acquires a pressure ulcer during his or her stay. A team of trained nursing staff performs these weekly assessments on every patient with a pressure ulcer. The nursing staff recorded the start and heal dates of each ulcer and

Table 1: Demographic data

Data variables	Gel mattress (n = 55)	Power air overlay (n = 67)
Age (years)	65.7 ± 14	69.5 ± 16
Gender		
Male	17	26
Female	38	41
Race		
Caucasian	42	52
African American	13	15
Braden Score	12.9 ± 2.9	13.5 ± 2.5
Number of co-morbidities*	9.3 ± 2.2	8.3 ± 2.7
Expired	17	18
Primary diagnosis		
Paraplegia/quadriplegia	1	2
Pressure ulcer	4	4
Amyotrophic lateral sclerosis	1	0
Cerebrovascular accident/ brain neoplasm	13	15
Respiratory failure	15	4
Infection	8	15
Osteomyelitis/osteoarthritis	1	7
Nutrition/failure to thrive	1	2
Heart disease	2	2
Pneumonia	3	3
Fracture	0	4
Cancer	3	4
Multiple Sclerosis	1	2
Surgery	1	3
Burn	1	0

evaluated site and stage by direct observation. The size of each ulcer (length and width) was assessed by using paper tape measurements. Between-group comparisons were done using t-tests and Chi Square (χ^2).

RESULTS

Table 1 shows the demographic data of the two study groups. The patients placed on the gel-fluid mattress were on average 65.7 ± 14 yrs of age. The group consisted of 38 female and 17 male patients with an average Braden score of 12.9 ± 2.9. In the Power air overlay group, there were 41 female and 26 male patients with an average age of 69.5 ± 16 yrs and a Braden Score average of 13.5 ± 2.5.

In both groups there were more than 75% Caucasians compared to African-Americans with no between-group differences observed. The total number of problems (referring to co-morbidities) between the two groups was significant ($p < 0.03$) with patients on the gel mattress averaging 9.3 ± 2.2 and the power air overlay 8.3 ± 2.7. There were 17 deaths in the gel mattress group and 18 in the power air overlay group.

A total of 122 patients having 173 pressure ulcers were studied (Table 2). The gel mattress group had 22 (40%) of the total 55 patients present with at least one pressure ulcer on admission while 32 (48%) of the 67 patients placed on the power air overlay had a pressure ulcer on admission. The overall percentage of patients developing a new pressure ulcer during their stay when placed on the gel mattress was 25% compared to 40% when placed on the power air overlay ($p = 0.118$).

Table 2: Comparative length of stays for patients on gel or air overlay mattresses

Mattress	N	Length of stay (days)	Standard error of mean
Gel	55	133	± 16.7
Air Overlay	67	83	± 13.6

Table 3 shows that out of 55 patients placed on the gel mattress, there were 63 pressure ulcers, 36 on admission, and 27 (43%) that developed during stay. The power air overlay group of 67 patients had 110 pressure ulcers, 54 present at admission and 56 (51%) developing during stay. One third of all of the patients in the study developed one or more pressure ulcers during the study year, generating 48% of the total pressure ulcers examined. There were no significant differences between the two surfaces used.

Table 3: Number of patients with pressure ulcers (presenting with a pressure ulcer Vs developing a pressure ulcer during stay)

	Gelmattress n (%)	Power air overlay n (%)
All patients with pressure ulcers	55	67
Ratio of developing a new pressure ulcer	14/55 (25)	27/67 (40)

$\chi^2 = 2.44$, $p = .118$

Fig. 1 illustrates that pressure ulcers most commonly developed on the sacrum, ischium and heels, respectively. There was no difference in the severity of pressure ulcers that developed, but stage II ulcers were generated at the highest proportion on both mattresses. Fig. 2 shows that there was a significant ratio ($p < 0.05$) of developing a stage II ulcer in patients assigned to the power air overlay mattress as compared to those on the gel fluid mattress.

We determined that 27of the 63 pressure ulcers healed on the gel mattress (27%) while 47 of the 110 ulcers healed on the power air overlay (42%). Logistic regression was used to explore the rate of healing per week (SI-SF/SI*#weeks) in relation to overall healing rate. Overall, of the pressure ulcers that showed healing, the lesions healed at simultaneous rates on both mattresses (at a mean rate of 31.9 ± 15.4 cm^2/week on the gel mattress and 31.3 ± cm^2/week on the air overlay). It should be noted that the total time that the patients were exposed to the gel support surface averaging 115.8 ± 133.3 days was significantly higher

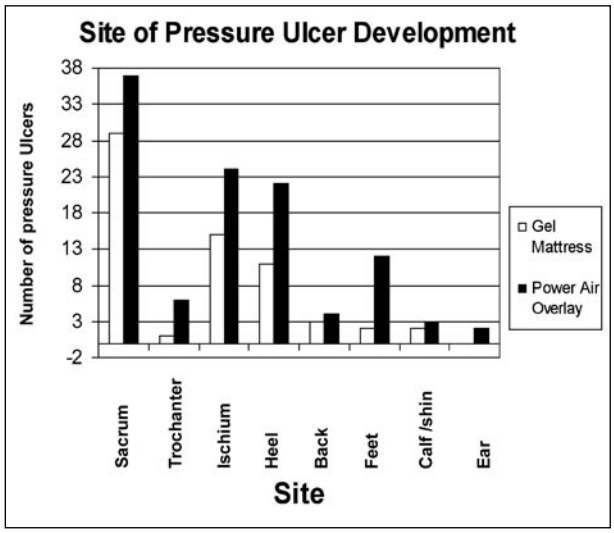

Fig. 1: Showing that pressure ulcers most commonly develop on the sacrum, ischium and heels, respectively

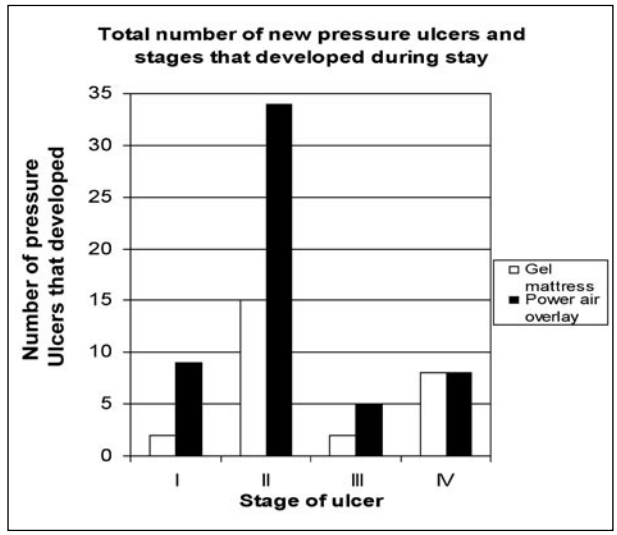

Fig. 2: Showing that there was a significant ratio ($p < 0.05$) of developing a stage II ulcer in patients assigned to the power air overlay mattress as compared to those on the gel fluid mattress

($p < 0.003$) than the average 55.5 ± 80.0 days patients spent on the power air overlay. An Analysis of Covariance controlled for the effects time exposed to the support surface found that the number of pressure ulcers that healed on the gel mattress was greater than on the air overlay ($p < 0.05$).

DISCUSSION

Pressure sores remain a refractory and increasing problem especially in frail elderly individuals[4, 5,10, 28]. At the long-term ventilator and chronic hospital unit of the Johns Hopkins Geriatric Center we have used a power air overlay as the standard support surface for patients determined to be at risk for skin breakdown as well as patients with known pressure ulcers. Kinetic Concepts Incorporated introduced the RIK gel mattress in 1995 with claims that an improved quality gel-fluid mattress might substitute for the high-maintenance, more complex air overlay. Before substituting the gel fluid system in our facility we compared the efficacy of each system in our unit.

The first question we addressed was which support surface showed improved healing rates of pressure ulcers. Since both mattresses are pressure-reducing surfaces, meaning that they reduce the surface pressure below 32 mmHg, ideally they both would create an environment that would enhance tissue viability. Our findings indicated that healing did occur on both mattresses. The rates of healing between the mattress types were not significantly different. Although different brands of mattress were used, this finding supports the investigation by Lazzara and Buschmann 1991, in which they also found no difference in healing rates between an air and gel support surface[15].

The second issue was to determine which system best protected patients from new pressure sores. We found that the power air overlay was associated with the generation of a higher proportion of stage II lesions as compared to the gel-fluid mattress. Since, stage II ulcers are historically known to be a result of shearing forces, specifically on the sacrum which is exposed to the most shear[30], it is likely that the gel may better prevent ulcers resulting from shear. This parallels the claims made by the distributing company for the RIK mattress.

The nurses performing the assessments were specially trained to ensure that data are collected in a reproducible manner, at regular intervals, and that all pressure ulcers, even stage I would be

Table 4: Percentages of pressure ulcers present

	Gel mattress	n (%)	Power air overlay	n (%)	Total N
Total number of patients	55		67		122
Pressure ulcer present at admission	30	30/55 (55)	48	48/67 (72)	78
Pressure ulcer present on admission that healed	5	5/30 (17)	13	13/58 (27)	18
Pressure ulcer that developed during stay	14	14/55 (20)	26	26/67 (39)	40
Pressure ulcer that developed during stay that healed	6	6/55 (11)	15	15/67 (22)	21

detected. Consequently, studies that involve direct examination of patients by such wound teams usually report the highest rates of pressure ulcer incidence and prevalence[31]. However, these high rates are of great concern, especially in a teaching facility where standards of care are thought to be superior.

Our study had limitations in that it was retrospective, and the decision for patient placement on a support surface was not randomized but by choice of the nursing and care teams. This was reflected in Table 1 where several patients were on the gel fluid mattress for longer periods than on the power air overlay. There was also a trend for patients with more medical problems to be placed on the gel fluid system. This evident selection bias however tended to place patients with more problems for longer periods on the gel fluid system which would have a propensity to place higher risk individuals on this surface. A randomly assigned prospective controlled study to examine similar findings would be needed to fully control other variables which have implications for skin breakdown, such as incontinence, nutrition, medications, and ulcer treatments.

We would also have liked know when and in what setting pressure ulcers present on admission developed. Out of the 122 patients admitted to the facility, 47 presented from the acute hospital with a lesion present. Whether or not it developed during the hospital stay or prior to admission could not be determined. Infection also has a role in healing of wounds[9-12] and obtaining cultures of the presenting ulcers particularly for *Staphylococcus aureus*[13] or other invasive organisms should be the target of future investigations.

This study showed that despite recent control efforts and the use of advanced support, pressure ulcers occurred frequently and need to be critically compared for constant efficacy. Since the use of the gel-fluid mattress system is intrinsically simpler, less costly, and requires little or no special care to maintain, we would favor this system and encourage further comparisons.

It is evident that the only truly robust solution to prevention and healing of pressure ulcers is adequate bedside nursing. Patient turning schedules need to be adhered to, and implementation of costly pressure relieving surface technology is never a complete answer. Although helpful, support surfaces alone cannot prevent pressure ulcers. Recent nursing shortages across the country might play a part in the increasing trend in pressure ulcer incidence throughout the recent years. The task ahead is to determine whether it is more beneficial to take the costs of support surface rentals, or place them into programs which improve direct bedside care and staffing.

CONCLUSION

This study shows that the gel-fluid mattress is more cost-effective than the power air overlay mattress in prevention and healing of pressure sores.

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Original Article

Effect of Granulocyte Colony-Stimulating Factor on Liver Injury Induced by CCL4: A Correlation between Biochemical Parameters and Histopathology Results

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ABSTRACT

Objectives: To determine whether granulocyte colony-stimulating factor (G-CSF) could reverse liver damage in the model of acute liver injury induced by carbon tetrachloride (CCL4)
Design: Prospective, using experimental animal model of acute and chronic liver injury
Setting: Babol University of Medical Sciences, Babol, Iran
Subjects: We established an animal model of liver damage by administration of CCL4 (1 ml/kg, IP). Two hours later the animals were treated with G-CSF (100 μg /kg body weight, IP). On the 28th day, rats were scarified. Malondialdehyde (MDA) was determined using diagnostic kits following recommendations of manufacturer of the kits. Serial 5 μm thick liver sections were stained with haematoxylin-eosin and Masson,s trichrome and examined.
Main Outcome Measures: Reduction in serum albumin and total protein levels (1.24 ± 0.16 and 3.22 ± 0.21 g/dl, respectively) were 2.58 ± 0.19 and 6.82 ± 0.30 g/dl, respectively reversed by G-CSF treatment.
Results: CCL4-induced increase in serum AST, ALT, and ALP activities and MDA and hydroxyproline levels were significantly suppressed by G-CSF treatment.
Conclusions: G-CSF stimulates liver repair and may be clinically beneficial in restoring liver damage. There was a positive correlation ($p < 0.05$) between histopathological and biochemical parameters.

KEY WORDS: CCL4, hematoxylin-eosin, liver damage, masson's trichrome

INTRODUCTION

As reported by many investigators, administration of CCL4, induces liver damage[1]. In this study, measurement of the end products of hepatic synthetic activity was used to assess liver damage. Aminotransferase (AST, ALT and ALP) activity, albumin and total protein levels were used to assess liver damage[2]. Elevated aminotransferase activity suggests liver damage[3]. Low serum albumin levels reflect destruction of liver tissue. The diminution in albumin was paralleled by a fall in total serum protein. Many studies showed that, granulocyte-colony stimulating factor (G-CSF) is a cytokine that shows a variety of biological functions[4]. However, relatively little is known regarding the underlying mechanism of its action in liver cirrhosis[5]. In some experiments, serum AST,ALT and ALP activity, albumin and total protein, hydroxyproline, MDA levels and WBC count were determined as biochemical markers of hepatic damage[6]. G-CSF action ranges from mobilization of bone marrow-derived stem cells to immuno-modulation of a variety of host responses[7]. The objective of the present study was to investigate a possible protective role for G-CSF in the maintenance of liver structure after damage.

ANIMALS AND METHODS

Wistar rats each weighing 200 ± 40 g were purchased from animal section of Babol University of Medical Sciences, Iran. The approval of the Ethics Committee of Babol University was also obtained (# 381). Generally, animals were housed in cages under conditions of controlled temperature (22 - 28 °C) and a 12 h artificial light period for 10 days for this study. In

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Table 1: Effects of G-CSF treatment on biochemical parameters in rats with CCL4 - induced liver injury

Biochemical parameters	Group I (n = 6)	Group II (n = 6)	Group IV (n = 6)
MDA level of liver (μmol/g)	0. 19 ± 0.04	0.51 ± 0.06	0. 21 ± 0.06
Serum total protein level (g/dl)	7.34 ± 0.40	3.22 ± 0.21	6.82 ± 0.30
Serum albumin level (g/dl)	2.73 ± 0.22	1.24 ± 0.16	2.58 ± 0.19

Data are presented as mean ± SD, each data refer to day 28th, $p < 0.05$

addition, animals had free access to standard pellet rat chow and drinking water. The animals were randomly divided into four groups (each with six rats) and were kept in separate cages as follows:

Group I: Control group, controls received only PBS

Group II: Received CCL4, followed by administration of PBS 2 hr later

Group III: Received G-CSF only

Group IV: Received CCL4, and G-CSF 2 hr later

The experiments started between 8.00 and 10.00 AM on animals which were fasted for 12 hrs before any administration. Liver damage was induced by intraperitoneal injection of CCL4 (25% v/v) solution in olive oil at a dose of 1 ml/kg corresponding to 0.25 ml/kg of CCL4 (Sigma, St.,Louis, USA). Human recombinant G-CSF expressed in *E coli*, (Saint Louis, Missouri 63103, USA) was administered at a dose of 100 μg /kg, body weight in sterile PBS. Control animals received PBS in a similar manner under light ether anesthesia (diethyl ether per anesthesia, Sigma, USA).

The injection was given twice a week for four weeks to establish chronic liver damage. To determine the effects of G-CSF in healthy animals, we selected six rats that each received daily intraperitoneal injection of G-CSF for seven consecutive days. Two hours after CCL4 injection, the animals received intraperitoneal injection of G-CSF. The animals were sacrificed under general anesthesia after 28 days and blood and liver tissue samples were collected. Immediately after exsanguination, the livers were removed, cleaned, and weighed. One portion of the liver was separated and immersed in buffered formalin solution for histological examination. Serum albumin, and total protein levels were also measured using commercial kits following the manufacturer's protocols (Pars Azmoon, Tehran, Iran). Hydroxyproline levels in the liver were determined according to the Woessner method[8]. Malondialdehyde (MDA) levels were determined following the method of Buege and Aust[9]. Liver sections were fixed in 10% (v/v) phosphate buffered formalin solution and embedded in paraffin wax. Formalin fixed sections were stained with hematoxylin-eosin and Masson',s trichrome. All specimens were randomized and analyzed in a blinbeded fashion to eliminate bias. The histopathologic index was assayed as the number of cases observed per 10 high power fields (HPF) randomly.

Statistical analysis

All experiments were repeated at least for three times. Results are presented as means ± SD (n = 6). Statistical significance was determined using a one-way analysis of variance (ANOVA). A value with $p < 0.05$ was considered to be statistically significant.

RESULTS

The effects of G-CSF on serum parameters in the liver damage model are shown in Table 1. This study demonstrated that CCL4-induced slight to moderate increase in serum MDA and hydroxyproline levels (Group II). But, these alterations were remarkably reduced in the G-CSF treated rats (Group IV), ($p < 0.05$). Our histological results demonstrated low serum total protein levels in the liver damaged by CCL4 indicating tissue damage. A decreased serum albumin level may be due to reduced liver protein synthesis. The diminution in albumin is paralleled by a fall in total serum protein.

The effects of G-CSF on CCL4-induced liver injury were evaluated by histopathologic examination of the liver sections by hematoxylin-eosin and Masson's trichrome staining technique. The treatment with CCL4 for four weeks caused extensive hemorrhagic necrosis and disruption of liver tissue. Central vein liver cords and sinusoids were abnormal (Fig. 1, 2). These alterations were remarkably reduced in the liver sections of the G-CSF treated rats (Fig. 3 , 4). Assessment with regard to Masson's trichrome technique and

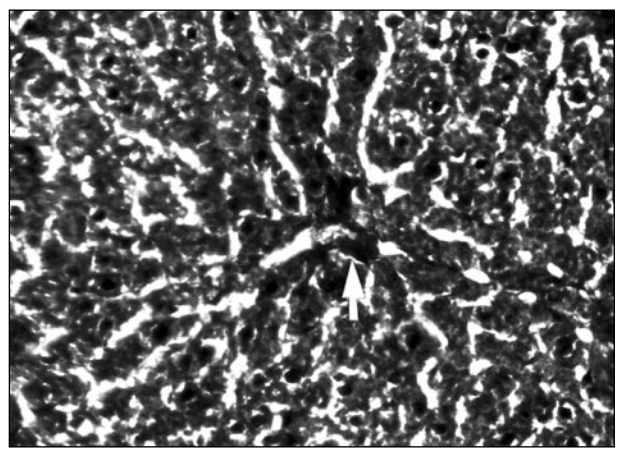

Fig. 1: A representative picture showing histological analysis of liver sections from 28th day after administration of CCL4 alone - treated group (Masson's trichrome staining, original magnification 100x).

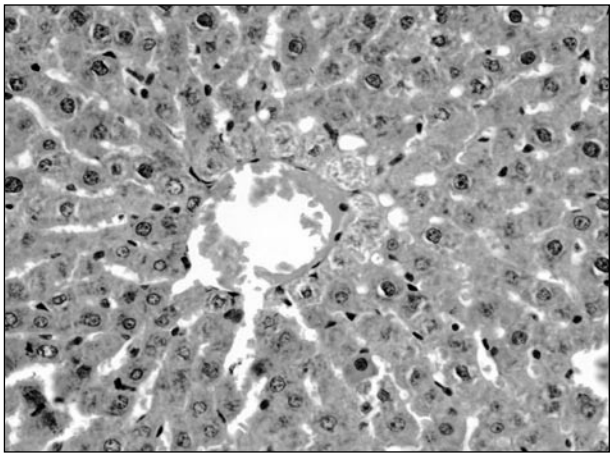

Fig. 2: A representative picture showing histological analysis of liver sections from 28th day after administration of CCL4 alone – treated group (hematoxylin-eosin staining, original magnification 100x).

hematoxylin-eosin staining showed that there was a correlation ($p < 0.05$) between the histological results and biochemical parameters.

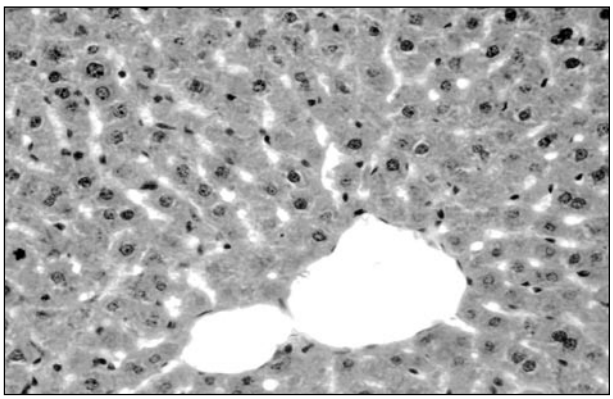

Fig. 3: A representative picture showing histological analysis of liver sections from 28th day after administration of CCL4 with G-CSF treated group (hematoxylin-eosin staining, original magnification 100x).

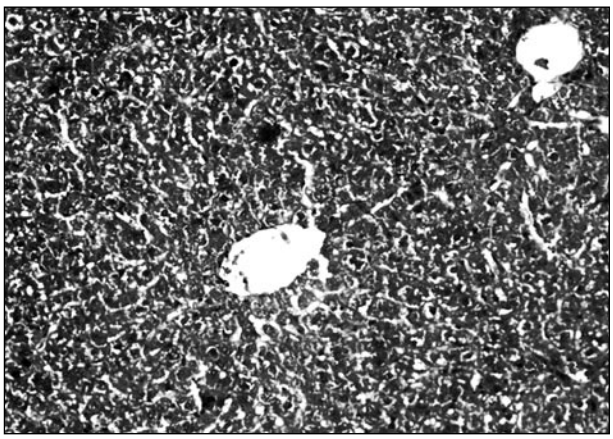

Fig. 4: A representative picture showing histological analysis of liver sections from 28th day after administration of CCL4 with G-CSF treated group (Masson's trichrome staining, original magnification 100x).

DISCUSSION

These results indicate that G-CSF protects the hepatocytes from injury and improves the liver function of the CCL4 damaged liver. These outcomes suggest that the mechanism for the hepato- protective effects of G-CSF in the development of liver injury may be related to the reduction of hepatic injury. In liver damage, the serum albumin levels are reduced due to protein synthesis disruption in the liver. The G-CSF treatment blocked the CCL4-induced reductions in serum albumin and total protein. These results also suggest that G-CSF administration improves the liver function of the CCL4-treated rats. Controversial experimental observations suggest different roles to G-CSF. In this regard many investigators demonstrated that G-CSF decreased transaminases activity[10]. Also, many investigators reported that G-CSF administration significantly improve survival of animals in the liver injury induced by chemical compounds[11]. Our results were in good agreement with those reported previously[11]. But this role of G-CSF in reducing damage effect of chemical toxin was challenged by other studies. Our observations represents some differences from the results obtained by other investigators[12,13]. In the present study, the CCL4 treatment after 28 days caused liver damage in rats, as evidenced by increase liver hydroxyproline and MDA level. This phenomenon was confirmed by histological changes observed in the liver such as extensive hemorrhagic necrosis and disruption. Liver hydroxyproline and malondialdehyde level as a marker of oxidation were raised due to liver injury. Treatment with G-CSF significantly decreased both liver hydroxyproline and MDA level elevated by CCl_4induced liver damage. This phenomenon also was confirmed by histological changes in the liver such as reduce incidence of liver lesions and necrosis induced by CCL4.

In addition, our results showed that evaluation effect of G-CSF *via* Masson's trichrome technique (Fig. 1and 4) and hematoxylin-eosin (Fig. 2, 3) staining could be considered as one of the complementary tests of liver injury. There was correlation between defects in liver stained by Masson's trichrome technique and hematoxylin-eosin staining and biochemical characteristics. There was good correlation between biochemical parameters and histological findings because our results revealed that the CCL4 treatment after 28 days caused liver damage in rats, as evidenced by increase in serum AST, ALT, and ALP activity and MDA and hydroxyproline levels. This phenomenon was confirmed by histological changes observed in the liver such as hemorrhagic necrosis and disruption. These alterations were remarkably reduced in the liver sections of the G-CSF treated group.

ACKNOWLEDGMENTS

We express our gratitude to the staff of the Departments of Biochemistry and Anatomical Sciences, Babol University School of Medicine for their assistance in blood collection and liver tissue sampling. This investigation was a collaborative work of the Cellular and Molecular Biology Research Center and the Faculty of Medicine.

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CONCLUSIONS

Investigations of potential treatment to address liver damage is still in the early stages. The results of this paper could encourage clinical studies to evaluate the potential benefit of G-CSF administration.

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Case Report

Subarachnoid Hemorrhage as a Rare Presentation of Cerebral Venous Sinus Thrombosis

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ABSTRACT

Cerebral (Dural) venous thrombosis can present with a variety of symptoms ranging from mild headache to altered level of consciousness and coma. Cerebral venous thrombosis is an uncommon clinical condition. It often affects young to middle aged patients and more commonly women. Subarachnoid hemorrhage is a rare presentation. In this report, we describe a case of cerebral venous thrombosis presenting with subarachnoid hemorrhage.

KEYWORDS: Confusion, headache, thrombosis

INTRODUCTION

Thrombosis of the venous system in the brain is an uncommon cause of cerebral infarction relative to the arterial disease, but it is important due to the need of early introduction of treatment and its long-term morbidity. It is difficult to diagnose, because of its large spectrum of clinical manifestations. It may vary, depending on the anatomical sites of the venous system involved. Cortical and sagittal sinus vein involvement may cause cerebral infarction (paresis 43%), lateral sinus thrombosis may be associated with headache (95%) and pseudotumour cerebri like picture (20%). Involvement of the jugular vein and the cavernous sinus may cause jugular foramen syndrome and cranial nerves palsies respectively. Other presentations are seizures (47%), coma (50%), and impaired level of consciousness (39%). Subcortical hemorrhage was reported in 38% of cases. However, subarachnoid hemorrhage was reported to be a rare presentation[1,2]. There is a verity of causes that might be in involved in the development of cortical venous thrombosis, namely, head trauma, infection of the paranasal sinuses, mastoiditis, bacterial meningitis, hypercoagulable states, either hereditary or secondary to connective tissue diseases, malignancies, drugs and others[3]. Anticoagulation with heparin has been advocated in most patients followed by oral anticoagulation therapy with warfarin for a period of 3 - 6 months.

CASE REPORT

A 39-year-old male patient presented to our medical department with sudden onset of acute confusional state. He was found by his family disoriented for which they brought him to the hospital. Prior to his presentation he complained of three days history of right-sided severe headache with repeated vomiting.

Upon arrival to the hospital he was confused and his Glascow coma scale (GCS) was 10. His vital signs and fundus examination were normal. He had normal pupillary size and reactivity. Signs of meningeal irritation were present in the form of neck rigidity. He was moving all his four limbs although there were signs of weakness involving the left side on day three, when he regained his alertness. Plantar responses were flexor bilaterally. There was also cranial nerve involvement. He had bilateral 6th nerve palsy and left lower motor neuron facial nerve palsy. The patient was also noticed to have difficulty in swallowing and he was kept on nasogastric feeding. Systemic examination was normal.

The patient was admitted to the intensive care unit. A non-contrast computed tomography (CT) brain was obtained immediately (Fig.1). It was reported as subdural hemorrhage along the posterior falx, and subarachnoid hemorrhage was noted in the ambient cistern and along the cerebellar tentorium. The patient was started on nimodipine and an urgent neurosurgical consultation was requested.

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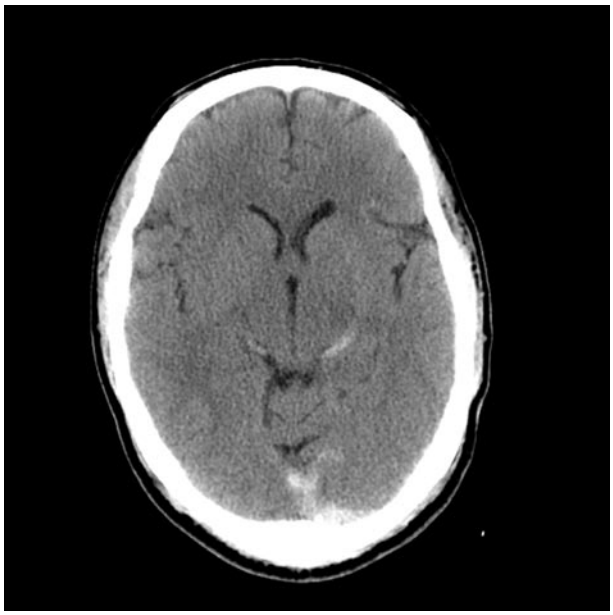

Fig. 1: Subarachnoid hemorrhage noted in the ambient cistern, and cerebellar tentorium

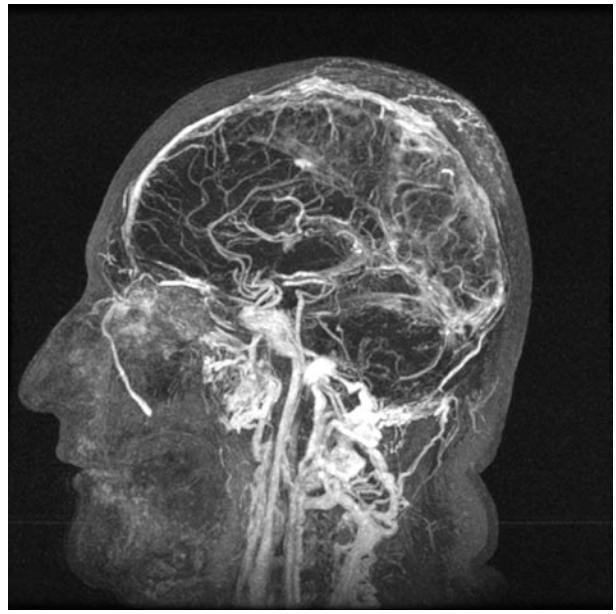

Fig. 2: Extensive thrombosis of the superior saggital sinus

Routine hematological examination revealed normal hemoglobin, white cell count and platelet count. His renal and liver function tests were normal. He had normal coagulation profile, and normal cholesterol levels. His d-dimer was 2918 (high). Further tests, protein C, protein S, antithrombin III, factor V leiden, antiphospholipid antibody and anticardiolipin antibody were normal. In addition blood cultures were negative.

Magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) were carried out next day. MRV (Fig. 2, 3) revealed extensive thrombosis in the superior saggital sinus, both the transverse sinuses and both sigmoid sinuses. There was also an extension of the thrombus into the straight sinus. Proximal portion of both jugular veins were not visualized suggesting the involvement of the deep venous system. MRA of the 'circle of Willis' did not show any evidence of significant stenosis or aneurysm. The neurologist was involved and the patient was started on unfractionated heparin, followed by oral anticoagulation.

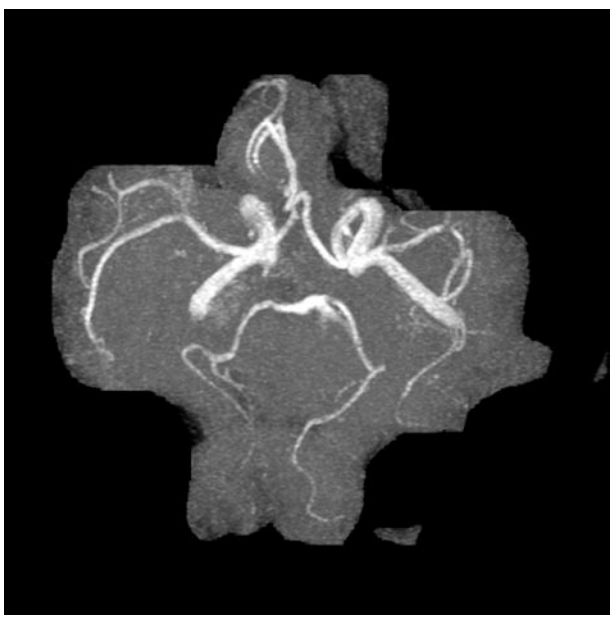

Fig. 3: Thrombosis of the transverse and sigmoid sinus

On taking further history from the family, there was a possibility that the patient had middle ear infection and was on antibiotics which were discontinued by the patient due to poor compliance.

The patient showed good recovery on day four, and was posted for a repeat CT scan to evaluate the subcortical hemorrhage and to look at the mastoids. It reported a low attenuation area suggestive of subacute infarction noted in the left parietal paraventricular area, opacification of the mastoid air cells with air fluid levels and the right mastoid septations were partially destroyed creating a coalescent area, the findings suggesting bilateral acute mastoiditis. The patient was kept on antibiotics. He showed good improvement over one week regarding his weakness. He had residual 6th and 7th nerve palsies, and was discharged on oral anticoagulant.

DISCUSSION

Cerebral sinus venous thrombosis (CSVT) is an infrequent condition commonly affecting young adults, predominately females. CSVT is difficult to diagnose due to the variety of clinical presentations. Headache is the commonest. Thunderclap headache of subarachnoid hemorrhage is reported in more than

10% of cases[1,4,5]. The exact cause of subarachnoid hemorrhage in patients with CSVT is unknown. It is postulated that the venous system dilates in response to the venous thrombus and reversed blood flow causes rupture of the fragile thin walled cortical veins. This leads to hemorrhage entering the subarachnoid space[6,7]. Another theory postulates that sinus venous thrombosis causes venous hemorrhagic infarct in which the blood enters the subarachnoid space[6]. Our case demonstrated CVST presenting as subarachnoid hemorrhage.

Clinical manifestation depends on the anatomical site of the thrombus. In addition, retinal hemorrhages and papilledema may be present. In our case, the extension of the thrombus to the superior sagittal sinus, both the transverse sinuses and sigmoid sinus resulted in paresis and jugular foramen syndrome respectively.

The patient's CT scan showed mastoiditis which was a relevant cause of his condition. It may predispose to CSVT. It has been reported to cause lateral venous sinus thrombosis[2]. *Streptococcus pneumonae* is the most likely organism.

Although the clinical presentation is variable, the diagnosis should be considered in middle-aged patients complaining of sudden severe headache, or presenting with neurological deficits in the absence of risk factors. Also due consideration should be given in patients with CT findings of hemorrhagic infarcts, which are not confined to a vascular territory.

The most sensitive investigation is the MRI coupled with MRV to reveal the underlying thrombosis, and occluded dural sinus[2,8]. CT is usually the first imaging study requested. It is normal in upto 30% of CSVT cases. CT of the sinuses is useful in evaluating sinusitis. Empty delta sign appears on contrast scans as enhancement of the collateral veins in the superior sagittal sinus (SSS) walls surrounding a non-enhanced thrombus in the sinus, representing thrombosed cortical vein and is extremely rare in 20% of cases[1]. CT angiography has also been used to visualize the cerebral venous system thrombosis.

An elevated D-dimer level supports the diagnosis of CSVT. 26% of the diagnosed cases have a normal D-dimer. Lumbar puncture may be useful to exclude meningitis in patients with CSVT. The cerebrospinal fluid abnormalities in CSVT are nonspecific and 30-50% may have lymphocytic pleocytosis, elevated red blood cell count, and elevated protein.

Anticoagulation has been recommended as the treatment of choice to arrest the thrombotic process[4], and continued for three to four months. Recanalization occurs in about 50% of the cases by four months[8,9].

CONCLUSION

Subarachnoid hemorrhage is a rare presenting manifestation of cerebral venous thrombosis. Venous hemorrhagic infarction can be responsible for secondary rupture into the subarachnoid space causing subarachnoid hemorrhage and / or rupture of the thrombosed cortical veins with blood leak into the subarachnoid space. Early evaluation and detection of the thrombus is important for early anticoagulation[10].

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Case Report

Persistent Junctional Reciprocating Tachycardia (PJRT)

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ABSTRACT

Persistent junctional reciprocating tachycardia (PJRT) is an arrhythmia mostly seen in infants and children, but is reported in the older age group as well. It is an easy diagnosis with "awareness of the mind". Once confirmed by electro-physiological study, the management is simplified. Radiofrequency ablation of the accessory pathway gives complete cure in almost all cases, especially so, for those with the persistent form. The tachycardia when untreated could induce the so called Tachycardia Induced Cardiomyopathy (TIC) which is reversible. We report the case of a 64-year-old lady with spontaneously relapsing and remitting PJRT which remained undiagnosed. Ultimately, a complete cure was achieved with the help of electro-physiology study and radiofrequency ablation.

KEY WORDS: inverted "P" waves, long RP tachycardia

INTRODUCTION

Persistent junctional reciprocating tachycardia (PJRT) occurs predominantly in infants and children and is limited to a small series in adults[1]. It is a form of supra-ventricular tachycardia which remains in most cases persistent but can present in paroxysms. There are certain specific features seen in the 12 lead surface electrocardiogram (ECG) helping to reach a correct diagnosis. Technological advances in electrophysiological studies (EPS) have lead to a faster diagnosis and management, leading to a cure in almost all cases.

CASE REPORT

A 64 year old lady presented in April 2006 with the history of palpitations and easy fatigability for six months. She also had shortness of breath on exertion for three to four months. She was seen by a physician in September 2005, when an ECG strip showed a persistent heart rate of 130 beats / minute suspecting sinus tachycardia. She was started atenolol 50 mg, which she was still continuing.

She was referred to the cardiologist by an internist on 21st of April for comments on an ECG done on the same day. Clinical examination was unremarkable. Her blood pressure was 130 / 80 mmHg. The ECG showed a narrow complex tachycardia at a rate of 132 beats / minute. There were inverted P waves in leads II, III, and aVF (Fig. 1).

A 24-hour Holter monitoring was done. It revealed more or less a continuous state of tachycardia at around 125 to 140 beats per minute with occasional short pauses with a tendency of the sinus node to capture a few beats (Fig. 2). An Echocardiogram showed good left ventricular ejection fraction. With the concluding remarks of a persistent state of tachycardia, needing further assessment for a more precise diagnosis and management, she was referred to the cardiac electrophysiologist at our tertiary cardiac center.

Based on a prolonged RP interval, inverted P waves in leads II, III, and aVF, located after the T wave, the differential diagnosis was atypical supraventricular tachycardia "long RP tachycardia", which included:

1. Persistent junctional reciprocating tachycardia (PJRT)
2. Atypical AV nodal tachycardia (fast-slow)
3. Slow atrial tachycardia

Patient underwent an electrophysiology study, using standard techniques, conscious sedation and local anesthesia. The right femoral vein was punctured in three locations and the left shoulder subclavian vein in one. Catheters were placed into the coronary sinus and RV along with an ablation catheter. The earliest activation was seen between 4 and 5 O'clock position of the tricuspid annulus. Pacing was started from the ventricle during tachycardia when the Bundle of His is refractory and the retrograde "A"

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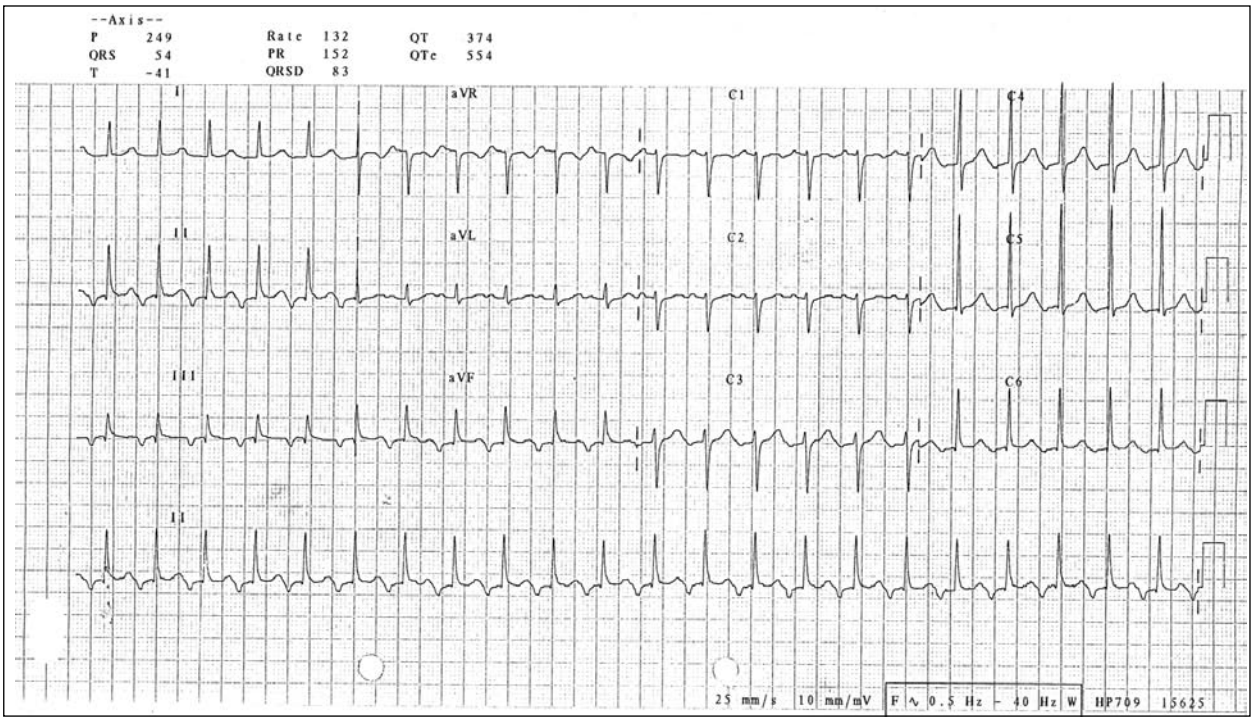

Fig. 1: 12 lead ECG showing the typical features of PJRT. Note: Inverted P waves in leads II, III, aVF appearing after the T waves with prolonged RP interval and a heart rate of 132 bpm

electrode was advanced to confirm the presence of retrograde accessory pathway with peculiar feature of decremental conduction. An ablation at that area during tachycardia caused an abrupt termination of the tachycardia. The burning application was maintained for one minute with a temperature of 55 degrees Celsius. Following the ablation, induction of the tachycardia was not possible. A twelve lead ECG showed a normal sinus rhythm with a rate of 67 beats / minute (Fig. 3).

A follow up ECG and Holter monitor at one month continued to show a normal sinus rhythm while the patient was off medication.

DISCUSSION

PJRT is an atrio-ventricular tachycardia where anterograde conduction occurs *via* the His purkinje and the retrograde conduction *via* an accessory pathway (AP) with slow conduction. The most common form is incessant tachycardia but a paroxysmal form also exists[2].

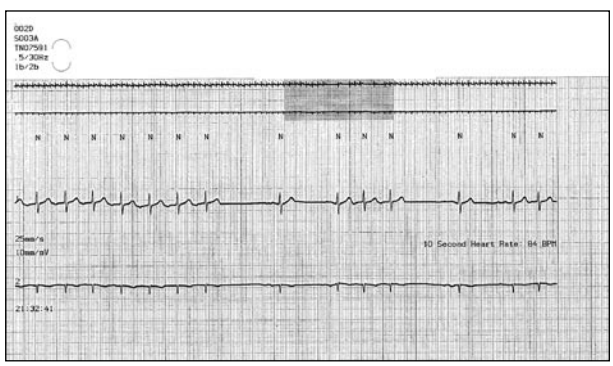

Fig. 2: ECG strip from a Holter recording showing PJRT and short sinus pauses and a tendency to revert to sinus rhythm

The ECG in PJRT usually shows an inscription of the retrograde P wave in late diastole or closer to the succeeding QRS than the preceding QRS. The finding of an RP interval > 50% of the RR tachycardia interval invokes the descriptor, "long RP tachycardia". Since the low atrial septum is the most frequent site of atrial activation, P waves during PJRT are typically negative in leads II, III, and aVF, indicating a low-to-high retrograde atrial activation sequence[3].

PJRT is reported to occur in fetuses[4] as well as in the elderly (our patient was 64 year old), but occurrence in the latter age group is unusual. PJRT is a potentially lethal arrhythmia in children with tachycardia induced cardiomyopathy (TIC). Spontaneous resolution of tachycardia is not uncommon. Antiarrhythmics are often effective. The use of propafenon alone or in combination with digoxin is safe and effective in young children with PJRT[5]. Radiofrequency ablation should be performed in older children or when rate is not controlled, especially in patients with persistent left ventricular dysfunction[6].

PJRT in adults is often paroxysmal and the retrograde slowly conducting, decremental AP is not infrequently seen in a non-posteroseptal location. Radiofrequency catheter ablation is highly effective and should be considered as the treatment of first choice in adult patients with PJRT[1].

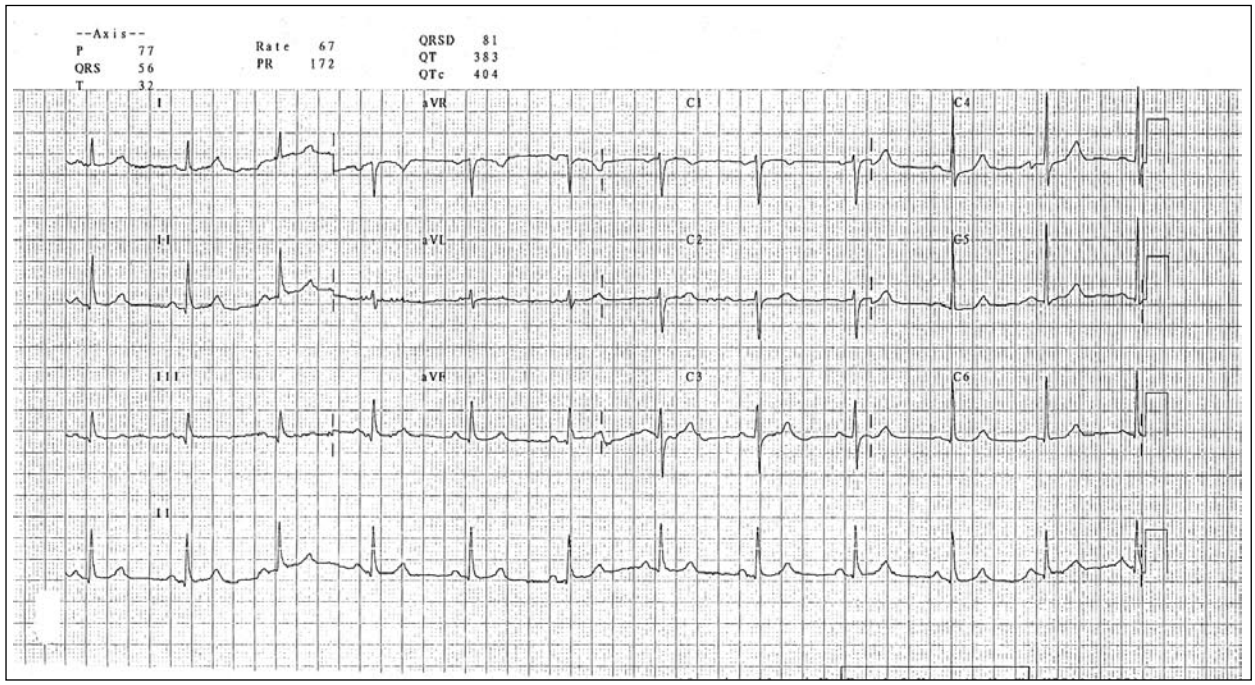

Fig 3: Post radiofrequency ablation 12-lead ECG showing normal sinus rhythm at the rate of 67 bpmg

The above referenced recent paper[1], has described the clinical presentation, electrophysiological characteristics, feasibility and safety of radiofrequency ablation and the long term prognosis in a large group of adult patients with PJRT.

The mean age was 43 ± 16 with 22 males and 27 females in a total of 49 electrophysiologically confirmed cases. Eight patients (16%) had a TIC. The ventricular rate was 146 ± 30 beats / minute. The arrhythmia was incessant or permanent in 23 / 49 cases (47%) and paroxysmal in 26 / 49 (53%). The AP was located in the right postero-basal region in 37 cases (76%) and in atypical sites in 12 cases (24%). Patients with the permanent form had more frequent TIC and a slower tachycardia rate. Radiofrequency ablation was initially successful in 46 cases (94%) without any serious complication. Regression of TIC was seen in all cases (8 / 8). Long term success rate was 100% in the absence of any anti-arrhythmic drugs. (Mean follow up of 49 ± 38 months).

CONCLUSIONS

Any tachycardia in the range of 120 to 140 beats per minute, with improperly located P waves, and seen inverted in leads II, III, and aVF, located after the T wave, with a long RP interval should not be taken lightly. PJRT is a curable condition and an effort made in treating the patient is worthwhile as it will avoid the development of TIC and its complications.

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Case Report

Bilateral Diffuse Mucinous Cystic Adenocarcinoma of the Lungs Complicated by Recurrent Pneumothorax in a Pregnant Woman

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ABSTRACT

The incidence of lung cancer continues to rise among young females. The pulmonary mucinous cystic tumor is very rare with few reported cases and it is an uncommon histological type of primary lung adenocarcinoma. The cystic nature of this type of carcinoma makes it unique radiologically. We report a very rare case of bilateral diffuse mucinous cystic adenocarcinoma of the lungs in a young pregnant woman.

KEY WORDS: CT scan, lung cancer, pregnancy

INTRODUCTION

Lung cancer is the most common cancer worldwide and its mortality is currently higher than either breast or cervical cancer among females[1]. The occurrence of lung cancer in pregnant women is rare. Unfortunately, most lung cancers in pregnancy are diagnosed at advanced stages with poor prognosis. We report a very rare case of mucinous cystic adenocarcinoma of the lungs with rare radiological appearance of diffuse bilateral cystic lesions in a young pregnant woman with recurrent pneumothoracis.

CASE REPORT

A 32-year-old pregnant woman at 24 weeks of gestation was brought to the emergency room with a history of slowly progressive breathlessness over a three-month period associated with dry cough and fatigue. She did not have fever, chest pain, wheezing or hemoptysis. She was a lifelong non-smoker. The patient was known to have Glucose 6 phophatase deficiency. She had three pregnancies with normal deliveries in the past.

On arrival to the emergency room, the patient had severe respiratory distress with oxygen saturation of 80% on room air. She had reduced breath sounds on the left and coarse crackles on the right side. The chest radiograph showed a large pneumothorax on the left side with extensive interstitial changes associated with widespread cystic lesions bilaterally (Fig. 1). Intercostal thoracostomy tube was inserted into the left hemithorax and the patient subsequently was transferred to the intensive therapy unit for further management. Thereafter, her oxygen saturation significantly improved to over 92% on 2 l / min of oxygen *via* nasal prongs. Initial laboratory data showed normal biochemistry and hypochromic, microcytic anemia with hemoglobin (Hb) level of 112 mg/dl. A low-dose high resolution computed tomography (HRCT) of the chest was done for further evaluation of the lung changes. The HRCT showed bilateral diffuse cystic lesions associated with multiple, small ill-defined nodules that were present predominantly in the middle and upper portions of both lungs (Fig. 2). The radiological differential diagnosis includes pulmonary histiocytosis X, lymphangiomyomatosis (LAM) and necrotizing sarcoidosis. Due to the mysterious nature of the clinical and radiological presentations, the general consensus was to start the patient on systemic steroids intravenously, especially since her pregnancy was nearing the third trimester. Unfortunately, systemic corticosteroids induced only mild improvement. In the meantime, the patient had a full battery of tests to assist our goal in diagnosing the lady as soon as possible. The patient had pulmonary function test,

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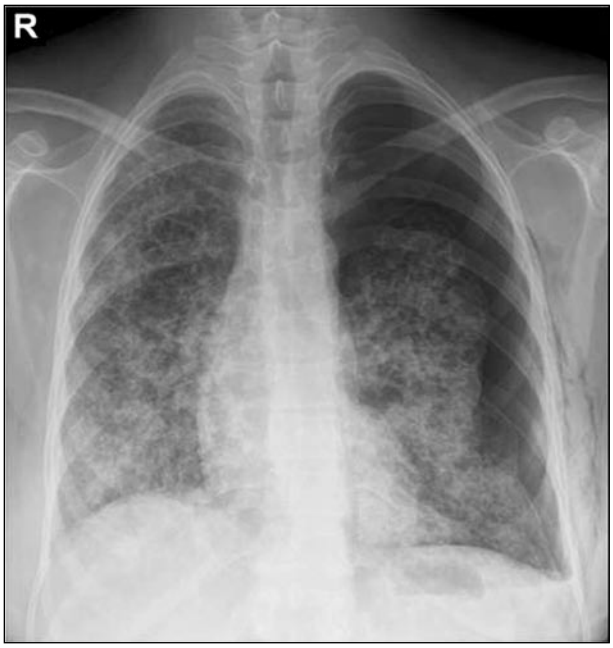

Fig. 1: Chest radiograph showing large left pneumothorax, bilateral interstitial pattern with cystic changes and subcutaneous emphysema

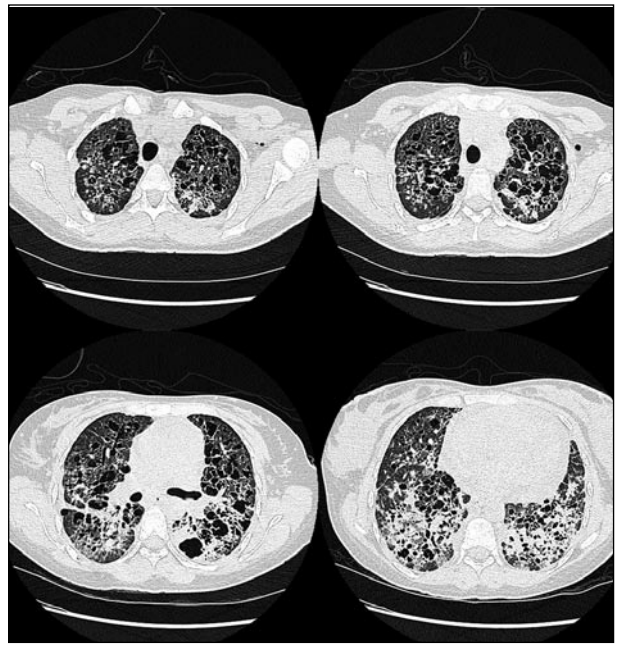

Fig. 2: CT scan of the chest showing extensive bilateral diffuse interstitial changes, cystic lesions and multiple ill defined nodules

which showed moderate restrictive pattern with diffusion lung capacity for carbon monoxide (DLCO) at 54% of predicted. Microbiological tests were negative and did not yield any organisms including acid fast bacilli from the sputum samples. Furthermore, she had negative serological tests effectively ruling out immune mediated lung diseases. Her human immunodeficiency virus (HIV) test was negative as well. Echocardiography and Doppler ultrasound of both legs were normal.

During the course of her illness, the patient developed dyspnea at rest with dry cough. Her oxygen saturation dropped to 84% on room air. A follow up chest radiograph revealed recurrent left-sided pneumothorax. Subsequently, intercostal thoracostomy tube drainage was inserted. Thereafter, a combined consensus between the respirologist, intensivist and obstetrician was made to deliver the fetus towards the end of 27th week of gestation. The issue was thoroughly discussed with the patient and her husband and consent was obtained for urgent cesarean section. The operation was uneventful and a preterm baby girl was born with a birth weight of 750 gm.

During the postpartum period, computed tomography (CT) scan of the chest, abdomen and the pelvis were done. The CT scan showed moderate left-sided pneumothorax with extensive bilateral, diffuse cystic lesions of varying sizes (Fig. 3). In addition, multiple sclerotic lesions were present in the dorsal

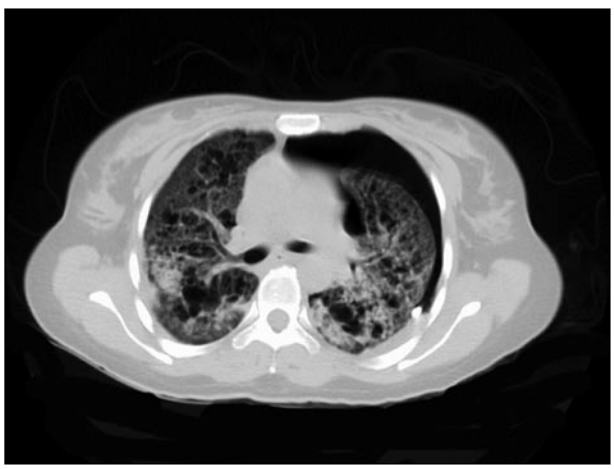

Fig. 3: Follow-up CT scan of the chest showing left pneumothorax and bilateral cystic lesions of varying sizes

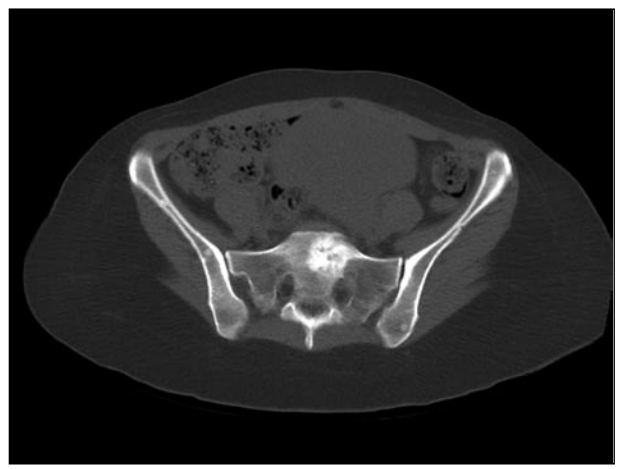

Fig. 4: CT scan of pelvis showing sclerotic lesions in sacrum and ilium

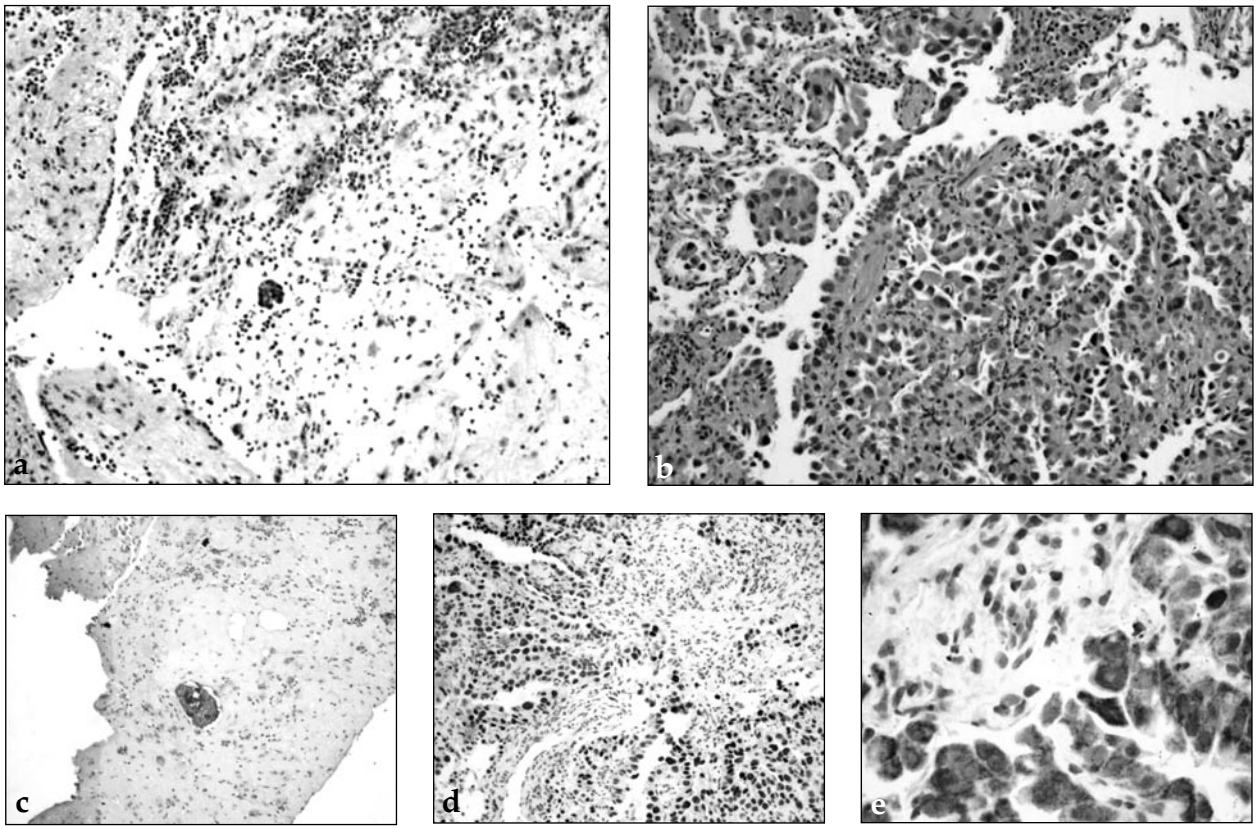

Fig. 5 (a, b, c, d, e): Histopathology slides from transbronchial biopsy showing islet of neoplastic cells with glandular formation (a, b), cytokeratin 7 (c), TTF-1 (d) and cytokeratin 20 (e)

vertebrae (D4, D7 and D8), left clavicle, sacrum and ilium (Fig. 4), which were suggestive of bony metastases. Bone scan showed hot spots suggestive of sclerotic metastases in thoracic and lumbar spine, pelvis and the rib cage. To obtain the definitive diagnosis, bronchoscopy with transbronchial biopsy was performed. The histopathology revealed the presence of neoplastic cells with abundant cytoplasm, some containing mucin and staining positive with mucicarmin stain. The final pathological diagnosis was mucinous cystic adenocarcinoma (MCA) as confirmed by positive immunohistochemical staining for TTF-1 and cytokeratin 7, and negative staining for cytokeratin 20 which helped to narrow the differential diagnosis and support the pulmonary origin of the tumor (Fig. 5). The patient also had bilateral mammography, colonoscopy, esophago-gastro-duodenoscopy and CT scan of brain, which were normal. The patient was transferred to the oncology center for further management.

DISCUSSION

The occurrence of cancer in pregnant women is not a common phenomenon. The incidence ranges from 0.07 to 0.1% of all malignant tumors[2]. However, given the recent increase in cigarette smoking among young women, the incidence of lung cancer in women of reproductive age is expected to increase[3]. Unfortunately, most lung cancers in pregnancy are diagnosed at advanced stages with poor prognosis. Only 19 cases of lung cancer associated with pregnancy have been reported[4]. Only 20 cases of pulmonary mucinous cystoadenocarcinoma have been reported[4].

Adenocarcinoma is classified into four types based on growth pattern, namely, papillary, tubuloacinar, bronchioloalveolar adenocarcinoma, and solid carcinoma with mucin production. MCA was initially described by Gower in 1978[5]. According to the WHO classification system, MCA is an adenocarcinoma variant with cystic component and copious mucin production. It may resemble tumors of the same name in the ovary, breast, or pancreas[6].

Radiological presentation of MCA varies from a solitary pulmonary nodule to a more extensive disease. From the literature review, most of the reported cases of pulmonary cystic adenocarcinoma originated from a pre-existing single cyst or a cavity in the lung, which could be congenital, a long standing benign cyst or a cavitary mass[7]. Furthermore, inflammatory cysts can present as a complication of bronchiectasis, cystic "honeycomb" pattern in interstitial fibrosis healed granulomatous diseases, post-infarction cysts and emphysematous bullae[8]. These patterens may

antedate the development of malignancy creating confusion in diagnosing the case.

Our patient had a three-month history of progressive shortness of breath associated with pneumothorax. She is a life-long non-smoker. Her radiological differentials including pulmonary hisiocytosis X, LAM and necrotizing sarcoidosis were ruled out clinically and through cytological examination of bronchoalveolar lavage and by immunohistochemical staining of biopsied lung samples. Therefore, it is fair to assume that the cystic changes in the lung developed as result of MCA. The most important evidence that carcinomas are not coincidentally associated with cysts, is the early age at which carcinoma has developed in many of the reported cases[4,5,7], as in our case. Our hypothesis is that, these cystic changes could be related to MCA tumor factors leading to extensive liquefaction and multifocal necrosis of lung tissue, resulting in a disease pattern of bilateral diffuse cystic disease.

CONCLUSION

The pulmonary mucinous cystic tumor is very rare with few reported cases. The cystic nature of this type of carcinoma makes it unique radiologically. We report this rare case of bilateral diffuse mucinous cystic adenocarcinoma of the lungs in a young pregnant woman. To the best of our knowledge this is the first report of cystic adenocarcinoma presenting as bilateral diffuse cystic lung disease.

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No disclaimers for any of the authors

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Case Report

Mucinous Cystadenoma in a Horseshoe Kidney : Report of a Case with Review of Literature

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ABSTRACT

Renal mucinous cystadenoma is very rare with five documented cases in medical literature. Out of these, two developed in horseshoe kidneys. The occurrence of mucinous cystadenoma in horseshoe kidneys is extremely rare and may represent a disorder, wherein such anomalous kidneys may have a tendency to have mucinous tumors taking origin from sequestrated segments of renal pelvic epithelium in the parenchyma. Surgical intervention and thorough histopathologic sampling is required for the diagnosis. It is important to be aware of mucinous cystadenomas while evaluating cystic masses occurring in horseshoe kidney. We report the case of a 52-year old lady who presented with vague abdominal discomfort and on evaluation was found to have a horseshoe kidney with left renal huge cystic lesion with wall enhancement on computerized tomography (CT) scan suggesting malignancy. She underwent left radical nephrectomy with excision of the isthmus. The histological examination revealed a mucinous cystadenoma.

KEY WORDS: horseshoe kidney, mucinous cystadenoma

INTRODUCTION

Mucinous cystadenomas of the kidneys are extremely rare tumors with only five cases on record so far. Out of these, two have occurred in horseshoe kidneys[1-3]. Herein we report an additional case of mucinous cystadenoma of renal parenchymal origin, arising in a horseshoe kidney and review clinico-pathologic findings of these unusual tumors.

CASE REPORT

A 52-year-old woman was admitted to the hospital with history of left-sided abdominal pain of three-month duration, without lower urinary tract symptoms or hematuria. Physical examination showed a large mass palpable in the left half of the abdomen of possible renal origin. . Her laboratory investigation revealed normal hemoglobin, blood urea and creatinine. Abdominal ultrasound showed horseshoe kidney with fusion of lower poles. A large hypoechoic mass lesion of 10.9 x 10.1 cm in size, was noted, arising from inferomedial aspect of the left portion of the horseshoe kidney. A computerised tomography scan (CT scan) confirmed the presence of horseshoe kidney with a fleshy isthmus connecting the lower poles and a left renal cystic lesion with contrast enhancing wall and calcification, raising suspicion of malignancy (Fig. 1). After completing the metatstatic evaluation and preoperative workup she underwent trans-peritoneal left radical nephrectomy including portion of isthmus under general anesthesia and recovered well (Fig. 2A).

Gross specimen showed left half of a horseshoe kidney 19 x 12 x 13 cm sectioned at isthmus. A monolocular well encapsulated large cyst measuring 14 cm in diameter was present, arising from infero-medial aspect of the kidney, in close proximity to the renal pelvis (Fig. 2B and 2C). The content of the cyst was mucinous. Inner aspect of the cyst was shaggy with friable areas. The cyst showed no connection with the pelvicalyceal system.

Microscopic examination of the sections from the cyst wall revealed a thick fibrotic cyst wall, inner surface of which was lined by mucinous epithelium with goblet cells (Fig. 3). Epithelial lining was attenuated and disintegrated at places and focally was thrown into short papillations. There was no evidence of mitotic activity, cytological atypia or stromal invasion. In some areas, cyst wall revealed atrophic renal tubules and glomeruli (Fig. 4) and small foci of

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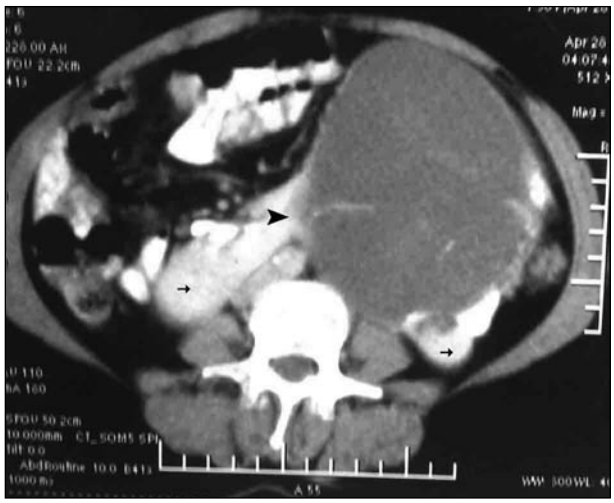

Fig. 1. Contrast enhanced CT of abdomen showing large cystic lesion in the left kidney with contrast enhancing wall and calcification. The isthumus of the horse shoe kidney crossing the aorta is clearly visualized (arrowhead) along with the right and left parts of the horse shoe kidney (arrows).

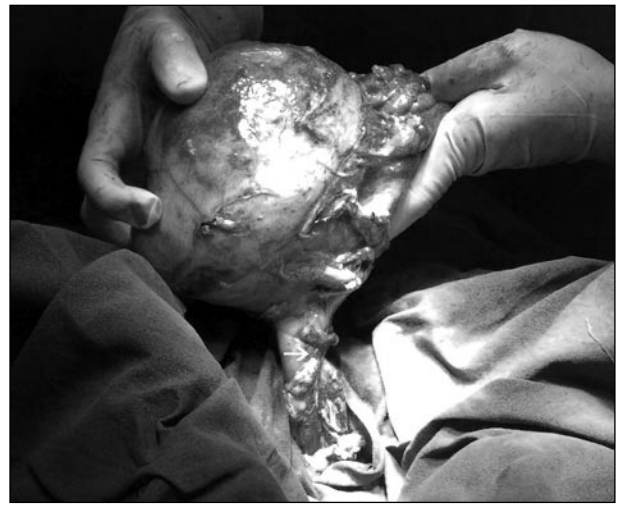

Fig. 2A: Intra-operative photograph of the left radical nephrectomy specimen with attachment to the isthmus of the horse shoe kidney (arrow)

dystrophic calcification. Rest of the renal parenchyma, renal pelvis and ureter revealed no specific pathology.

The final pathological diagnosis was mucinous cystadenoma in a horseshoe kidney.

DISCUSSION

Mucinous epithelial neoplasms of renal origin are exceedingly rare and constitute less than 1% of all primary tumors of renal origin. Out of these, the majority are mucinous cystadenocarcinomas of the renal pelvis[1]. Mucinous cystadenomas are very rare with only five cases reported in medical literature so far[2-6]. Out of these, two cases were discovered in horseshoe kidneys[3,4]. Our case is the third case of mucinous cystadenoma arising in a horseshoe kidney. In the case described by Haken Akan *et al*, the tumor was an incidental finding[4]. CT scan revealed no calcification and findings were in favor of a simple renal cyst. Preoperative cyst fluid aspiration was done under CT guidance and cytology of the fluid revealed no neoplastic findings. Cyst excision was carried out in this case. In the current case and the case reported by Ross *et al*[3], patients presented with left sided abdominal pain. In the case reported by Ross *et al*, CT scan revealed partial calcification of the cyst wall suggestive of malignancy and hence a partial nephrectomy was performed[3]. In the current case CT revealed cyst wall enhancement and calcification suggestive of malignancy and hence a radical nephrectomy was undertaken.

Macroscopically all these tumors, including our case, were monolocular cysts. Our case and the one reported by Haken Akan *et al* were lined by mucinous epithelium with goblet cells[4]. The cyst reported by Ross *et al* was lined by endocervical type mucinous epithelium[3]. All three tumors arose in close proximity

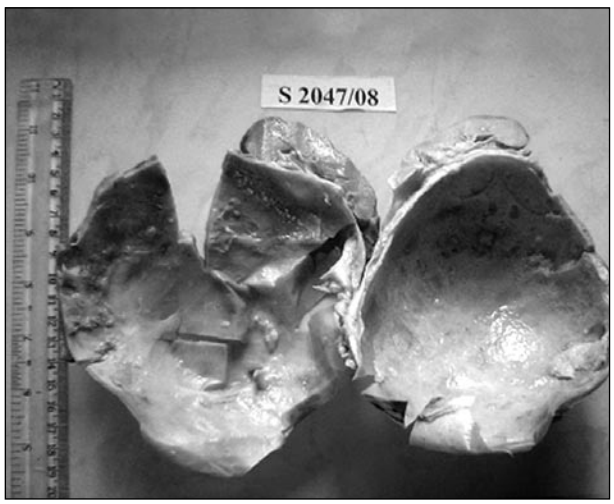

Fig. 2B: Left kidney with monolocular cyst

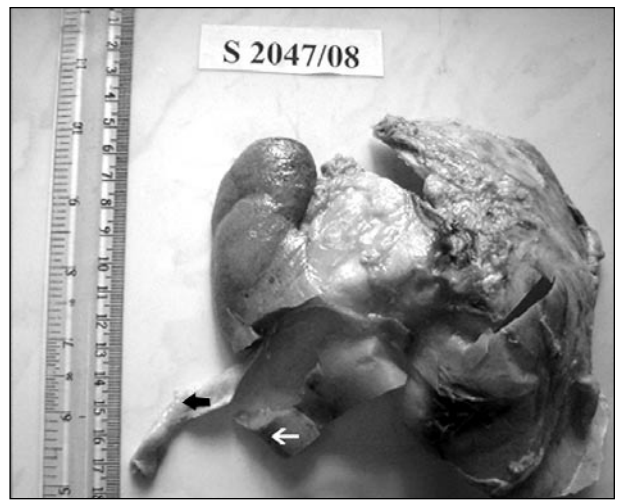

Fig. 2C: Cyst arising from left kidney and isthmus of horse shoe kidney (black arrow), ureter separate from cyst (white arrow)

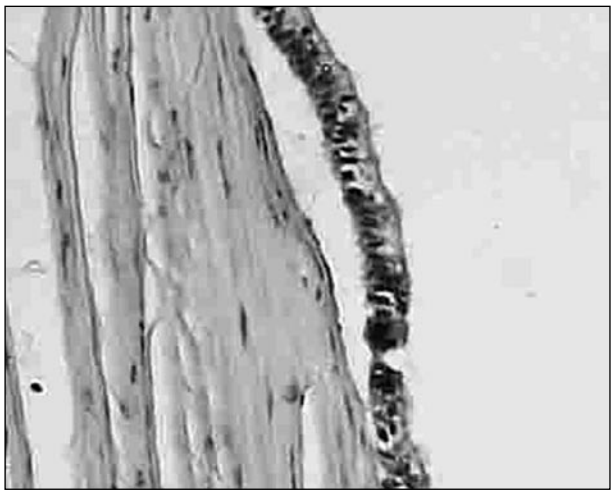

Fig. 3: Cyst wall lined by mucinous epithelium (Hematoxylin Eosin, 400x)

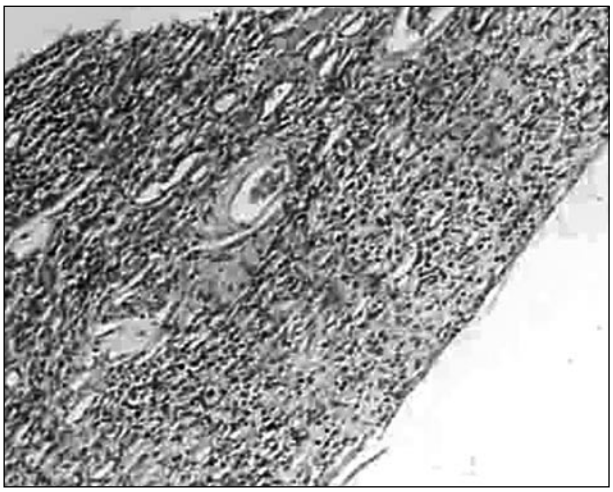

Fig. 4: Cyst showing atrophic renal tubules and glomeruli (Hematoxylin-Eosin, 4x)

to the renal pelvis but showed no connection with the collecting system. Atrophic renal tubules were present in the cyst wall in the case reported by Akan *et al*[4]. The case reported by Ross *et al* showed sclerotic glomeruli in the cyst wall[3]. The cyst wall showed atrophic tubules and glomeruli in some areas in the current case. Foci of dystrophic calcification in the cyst wall were present in the case described by Ross *et al* and in our case[3].

As regards to the histogenesis of mucinous cystadenomas in horseshoe kidneys, we agree with other authors that such anomalous kidneys may harbor sequestrated segments of renal pelvic epithelium which may give rise to these tumors[3,4]. This is in keeping with the renal parenchymal location of these tumors. Some investigators have speculated that glandular metaplasia in response to injury (urolithiasis) or chronic inflammation is a potential precursor for renal mucinous epithelial tumors[5]. Multiple sections from the collecting system did not reveal any foci of glandular metaplasia in our case and in the case described by Ross *et al*[3]. Hence, the theory of inflammation induced metaplasia is not likely to be a valid contributory factor in the development of mucinous tumors of renal parenchymal origin.

The three other reported cases of mucinous cystadenomas of the kidney were present in non-anomalous normal kidneys[2,5,6]. Interestingly, of these three cases, one was reported as mucinous cystadenoma with malignant transformation and another as mucin producing cystadenoma with borderline malignancy[2,5]. The inclusion of these two tumors in the category of truly benign mucinous cystadenomas of the kidney, is therefore, debatable when strict criteria for assessment of malignancy are applied. The third case was a composite tumor of mucinous cystadenoma and somatostatinoma[6]. We are lead to infer that benign renal mucinous cystadenomas are exceedingly rare neoplasms, with two of the reported cases occurring in horse shoe kidneys.

The data from the reported cases and our case indicate that there are no definite radiological criteria for the diagnosis of such tumors and that surgical intervention and histopathological examination is necessary to establish the benign nature of these tumors. If there is radiological suspicion of malignancy, as was encountered in our case, total or partial nephrectomy may be undertaken accordingly.

CONCLUSION

The development of mucinous cystadenomas in horse shoe kidney is unlikely to be a random occurrence, as review of literature revealed two similar cases. These tumors may take origin from sequestrated segment of renal pelvic epithelium in the renal parenchyma of anomalous kidneys. Therefore, awareness of this rare entity is critical for the evaluation of cystic masses arising in horseshoe kidneys.

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Case Report

A Case of Adult Botulism following Ingestion of Contaminated Egyptian Salted Fish ("Faseikh")

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ABSTRACT

Food-borne botulism is a rare and serious disease caused by potent neurotoxin of the *Clostridium botulinum* which is a Gram-positive strictly anerobic organism. It manifests clinically as descending paralysis characterized by prominent oculo-bulbar palsies and symptoms and autonomic signs in an afebrile patient with normal sensorium. If not promptly and aggressively treated it may lead to fatality. In this communication, we report a case of food poisoning resulting in adult botulism that responded to early and effective treatment with specific antitoxin and supportive therapy. The patient made a remarkable recovery and was discharged home three weeks after admission. This case is the first to be reported for adult variant botulism in Arabian Gulf States.

KEY WORDS: antitoxin, *Clostridium botulinum*, descending paralysis

INTRODUCTION

Although rare, food-borne botulism is a public health emergency because of the potential severity of illness and exposure of many individuals to contaminated food. The term botulism is derived from the Latin word for sausage coined after an outbreak of clostridial 'Sausage poisoning' in Europe in the late 1700s and was responsible for many deaths[1]. The scientific parameters of this disease began to unravel in 1895, when Emile Van Ermengem was summoned to investigate an epidemic in the small Belgian town of Ellezelles involving several people who had gathered at a funeral music festival and who developed botulism after consuming raw ham[2]. Ermengem was able to isolate an anerobic bacterium from the ham and then reproduce the disease in laboratory animals by injecting the toxin produced by the organism.

It is a paralyzing disease caused by the potent neurotoxin of a bacterium called *Clostridium botulinum*. The food-borne type is related to inappropriate food preparation and/or subsequent contamination especially with foods canned at home.

In this communication, we report the case of a 28-year-old female patient with clinical diagnosis of botulism to increase awareness for this rare and dangerous disease among our clinical colleagues.

CASE REPORT

A 28-year-old Egyptian lady presented in the emergency room with a 24-hour history of abdominal pain, nausea, repeated attacks of vomiting and mild difficulty in breathing. She was fully conscious, alert and oriented and hemodynamically stable. Her blood pressure (BP) was 130/80 mmHg and she was tachycardic with a pulse rate of 120/min but not dyspneic or febrile. Oxygen saturation was 99%. Physical examination revealed no abnormalities although there was epigastric tenderness and no focal neurological deficit at that point.

After three hours in the observation room, the patient suddenly became dyspneic, tachypneic and cyanosed. Her BP dropped to 90/50 mmHg. She desaturated rapidly; oxygen saturation was 70% and soon progressed to hypoventilation and hypoxia on room air. Subsequently, she was intubated, sedated, connected to mechanical ventilation and shifted to the Intensive Care Unit (ICU). Routine laboratory tests including serum electrolytes, glucose, blood count, urine routine, amylase and D' dimers ordered at this time were normal. Chest X-ray did not show any abnormality and the electrocardiogram (ECG) revealed only sinus tachycardia. The arterial blood gas before and after the intubation revealed a pH

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of 7.34; PO_2 76 mmHg; PCO_2 40; HCO_3 3 mmol/l, and pH, 7.41; PO_2 85 mmHg; PCO_2 34.1; HCO_3 22.1, respectively. Urgent computed tomographic scan (CT Scan) performed on the brain was unremarkable. Also, CT angiography of the chest was done to exclude the diagnosis of the pulmonary emboli because of the history of difficulty in breathing, tachycardia and desaturation shortly after initial presentation was normal.

Past medical history was unremarkable but family history revealed that the patient had eaten canned salted fish three days prior to the development of the symptoms. At this point botulism was suspected based on this history and clinical presentation. Serum and stool samples were collected and sent to the Anerobe Reference Laboratory, Department of Microbiology, Faculty of Medicine, for *C. botulinum* culture and toxin detection. By this time, antitoxin was not available in Kuwait. On day 2, sedation was stopped and she was able to obey commands. Neurological examination revealed impaired gag and cough reflex and unequal pupil with sluggish reaction to light. There was no ophthalmoplegia but a prominent muscle weakness in the upper and the lower limbs in proximal muscle group than in the distal group (2/5 in proximal, 3/5 in distal muscle group), generalized areflexia with mute planter reflex with sensation intact. Full neurological assessment was done repeatedly which revealed subsequent development of progressive flaccid quadriparesis along with bulbar muscles involvement.

C. botulinum anti-toxin (trivalent-equine/ botulinum antitoxin; Behring, Germany) was given within 48 hours of the presentation in two divided doses in 250 ml normal saline infused slowly after a negative sensitivity test; vital signs were closely monitored for evidence of hypersensitivity reaction or anaphylaxis during the infusion. The diagnosis of botulism was confirmed by the isolation of *C. botulinum* from stool specimen by anerobic culture and API 20 A (system for identification of anerobes). Nerve conduction study and electromyelogram (NCS / EMG) study showed low amplitude motor response from the examined nerves, the initial amplitude of M-wave was very low in the median nerve. Latencies were normal, nerve conduction velocities were normal and sensory responses were also normal. These electrical findings, with a negative tensilon test, are in keeping with the diagnosis of botulism.

On day 5, 3 days after the anti-toxin therapy, there was a gradual clinical improvement in terms of ventilation parameters and muscle power strength in the limbs. A full recovery was achieved after 14 days in the ICU with the active physiotherapy programs. Patient was discharged home in stable and good condition and was seen later in the outpatient with no complications except for mild weakness 4/5 in proximal part of the lower limbs. Repeat electromyographic study was completely normal during this visit.

DISCUSSION

Botulism is a rare and serious disease, one of the most frightening disease in the last two centuries. The potent neurotoxin produced by *C. botulinum* causes paralytic illness. Seven immunologically distinct toxins have been identified[3,4] and designated A-G. These toxins are amongst the most potent toxins known[5]; as little as 100 ng can be lethal. Most human cases are caused by the type A, B or E. The types A and B are the most common cause of food-borne botulism while type E is usually associated with ingestion of contaminated sea food which made us speculate that our patient suffered from type E botulism. The fact that our patient's illness was moderately severe supports this assertion as infection with A, B, and C is more severe and longer lasting than those poisoned by type E toxin[6].

Food-borne botulism is caused by ingestion of preformed toxin in processed food as was likely the case with our patient whose illness was suspected to be associated with salted fish which is known to cause outbreaks of botulism in Egypt[7]. Another form is wound botulism caused by growth of the bacterium and production of toxin in a traumatic wound which was certainly not the case in our patient as there was no sign of trauma or history of previous injuries. Increasing number of wound botulism cases have recently been linked to the use of black tar heroin in the United States of America[8]. In food-borne botulism, particularly those involving toxin types B and E, the gastro-intestinal (GI) symptoms such as nausea and vomiting may precede neurological symptoms, as was the case in our patient. In our patient, the GI symptoms which started after consumption of canned home preserved salted fish appear to have triggered the illness 24 h before the presentation in the hospital.

The classical description of botulism clinical presentation in most of the reported cases in the literature is comparable to our case with fulminant progression of a descending, symmetrical flaccid paralysis of the motor system accompanied by bulbar involvement necessitating requirement for ventilatory support. This is a well-recognized and known complication of botulism with history suggestive of food intoxication, thus, strongly raising the index of suspicion for botulism, provided that in this case the sensory system is unaffected and the intellectual function is spared in afebrile illness throughout. The differential diagnosis of botulism encompasses other neuromuscular disorders including,

polyradioculopathies (Guillian-Barre syndrome: GB), Miller-Fisher syndrome (MF), myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), tick-paralysis, diphtheritic neuropathy and stroke syndrome. The differential diagnosis of botulism generally involves consideration of rare conditions or unusual presentation of common problems such as stroke. It is often best to pursue a diagnosis of botulism, perhaps in parallel with others until the diagnosis is clear and a thorough history and meticulous physical examination can effectively eliminate most competing diagnoses.

The only specific treatment for botulism is administration of botulism antitoxin and it has been used since the 1960's. It can arrest the progression of paralysis and decrease the duration of paralysis and dependence on mechanical ventilation. The paralysis resolves in weeks to months[9], like in our case a marked improvement in muscle power strength was achieved in a three-week period including respiratory and bulbar muscles. Antitoxin should be given early in the course of illness, ideally within 24 h after the onset of symptoms because antitoxin neutralizes only toxin molecules that are yet unbound to nerve endings and animal experiments have confirmed this relationship[10]. Three preparations are currently used: a trivalent botulinum antitoxin that provides coverage against C. botulinum types A, B and E, investigational pentavalent botulism toxoid which provides coverage against types A-E and an investigational heptavalent preparation which covers types A-G. The trivalent antitoxin provides coverage against the three most common causes of human botulism and it is the only antitoxin approved for use in United States and has been administered to both children and pregnant women during the second and third trimester without complications[11]. Hence, this antitoxin was administered to our patient with remarkable response.

CONCLUSION

A single incident of food-borne botulism should be considered a public health emergency because of the potential severity of the illness. This report should serve as a reminder to the front-line medical professional about botulism so that urgent action can be taken once a suspected case is identified.

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Case Report

A Young Male with Behcet's Disease and Right Ventricular Thrombi

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ABSTRACT

Behcet's disease is a multisystem inflammatory disease that can rarely affect the cardiovascular system leading to bad prognosis. We report the case of a 23-year-old male who presented with hemoptysis and recurrent oral and genital ulcers. He was found to have multiple right ventricular thrombi and left lower lobe pulmonary artery pseudoaneurysm and was diagnosed as Behcet's disease. He was successfully treated with warfarin, cyclophosphamide, and corticosteroids in addition to left lower lobe posterior segmentectomy and resection of the pulmonary artery pseudoaneurysm.

KEY WORDS: Behcet's disease, hemoptysis, pulmonary artery pseudoaneurysm

INTRODUCTION

Behcet's disease is a chronic relapsing vasculitis of unknown etiology that can involve any organ. Diagnosis can be made mainly by clinical criteria and cardiovascular involvement is not among them[1]. Cardiac and pulmonary artery involvement are rare, but carry a bad prognosis[2]. Cardiac involvement is unusual, but cardiac thrombosis is very rare. We report the case of a patient with Behcet's disease presenting with hemoptysis, right ventricular thrombus and pulmonary artery aneurysm.

CASE REPORT

A 23-year-old middle-eastern healthy male was admitted to our hospital with recurrent hemoptysis. Detailed history revealed that the patient had recurrent genital and oral ulcers. Routine blood investigations were normal. Chest X-ray showed bilateral lower lobe infiltrates. Bronchoscopy did not identify the source of hemoptysis. Computed tomography of the chest revealed bilateral lower lobe ground glass appearance, left lower lobe posterior segment pulmonary artery pseudoaneurysm with *in-situ* thrombosis and a right ventricular (RV) mass. Trans-thoracic and trans-esophageal echocardiography were done and showed multiple RV masses (Fig. 1). Three masses were attached to the interventricular septum and two attached to the free RV wall. Cardiac MRI confirmed the presence of pulmonary artery pseudoaneurysm and RV masses with density consistent with RV thrombi. Lung ventilation / perfusion scan showed bilateral segmental mismatched defects. Computed tomography of abdomen and pelvis was normal. Selective bronchial artery angiogram showed presence of arterial collaterals to both lower lobes with the collaterals on the left side draining into a lower branch of the left pulmonary artery. Selective embolization of these collaterals was done (Fig. 2). No deep vein thrombosis was detected in the legs and the pelvis. Connective tissue disease workup was unremarkable. The patient was diagnosed with Behcet's disease and treated with cyclophosphamide and prednisone and then switched to imuran and prednisone and was anticoagulated with warfarin. After a month he had another episode of hemoptysis. Repeated echocardiography showed a complete resolution of the RV masses. Left lower lobe posterior segmentectomy was successfully done. This patient is currently on imuran and prednisone and is regularly followed up in the cardiology clinic with no recurrence of hemoptysis. His follow up echocardiograms at two, three and six months showed freedom from RV thrombi (Fig. 3).

DISCUSSION

Behcet's disease is a rare multisystemic inflammatory disease found mostly among the Japanese and Mediterranean basin populations. Behcet's disease was described initially by Hulushi Behcet in 1937 as a triad of oral ulcers, genital ulcers and uveitis, but the spectrum of this disease has expanded

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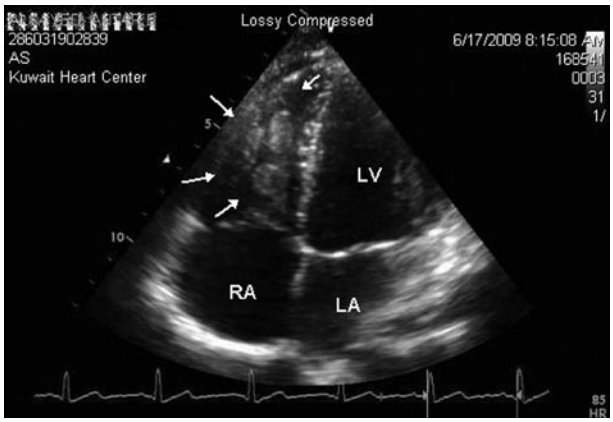

Fig. 1A: Transthoracic echocardiography showing right ventricular masses (4 chambers views)

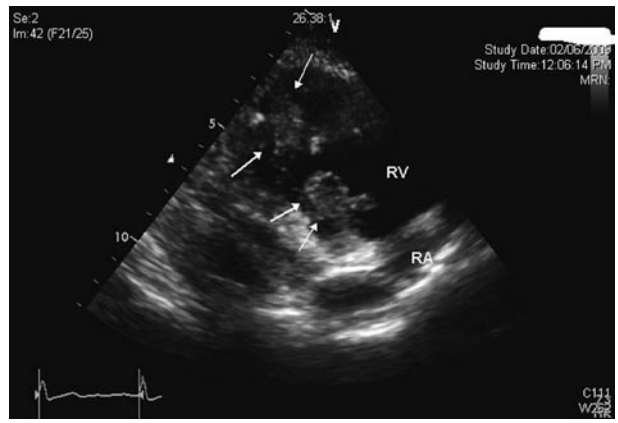

Fig. 1B: Parasternal view showing right ventricular masses (RV inflow)

RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium

to involve most organ systems[3,4]. Cardiovascular involvement in Behcet's disease is not frequent and ranges between 7 - 29% of all reported cases[5].

Most clinical manifestations of Behcet's disease result from vasculitis predominantly of the venous system. Superficial thrombophlebitis and deep vein thrombosis are the commonest presentations among the cardiovascular involvement although thrombosis of the superior and inferior vena cavae, Budd–Chiari syndrome and dural sinus thrombosis might be encountered[6].

Arterial involvement is seen in 12% of patients with Behcet's disease, predisposing to arterial obstruction or aneurysmal formation. It commonly affects pulmonary, femoral, popliteal, subclavian and carotid arteries[7]. This report describes pulmonary artery involvement.

Detection of a pulmonary artery aneurysm in the setting of a vasculitic illness is highly suggestive of Behcet's disease, and is found rarely in other forms of vasculitis. Pulmonary artery involvement is an important cause of mortality secondary to massive hemoptysis, with 30% of patients dying in two years[8]. The most probable mechanism that causes hemoptysis is erosion of the pulmonary artery aneurysm into the bronchus which was the case in this report[7].

Cardiac pathology was reported relatively infrequently in Behcet's disease with male to female ratio of 23:2. Intracardiac thrombi were found in 1.78% of all patients, and were mostly right sided. They are commonly found in the right atrium, extending into the superior or inferior venae cavae or protruding through the tricuspid valve into the right ventricle.

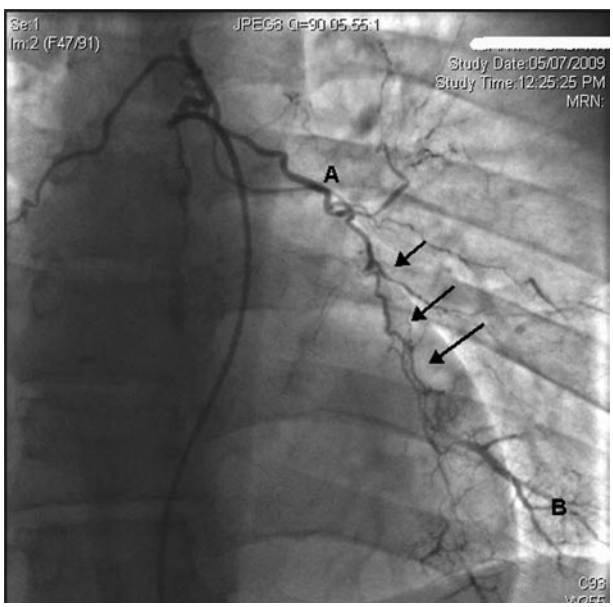

Fig. 2A: Bronchial artery angiogram showing collateral draining into inferior branch of left pulmonary artery (arrows). **A:** bronchial artery, **B:** inferior branch of left pulmonary artery

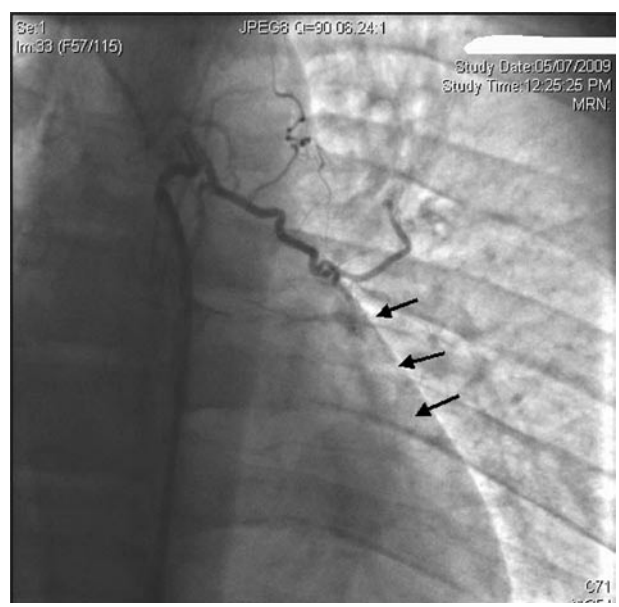

Fig. 2B: Bronchial collaterals disappeared after embolization

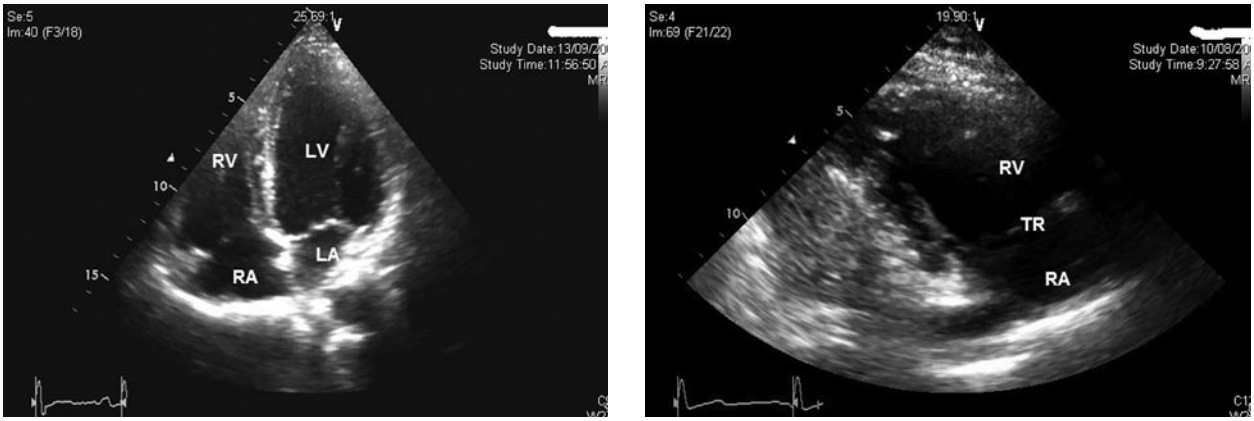

Fig. 3A and B: The right ventricular masses disappeared **A:** 4 chambers view. **B:** left parasternal view (RV inflow)
RV: right ventricle, LV: left ventricle, RA: right atrium, LA: left atrium, TR: tricuspid valve.

Involvement of the left ventricle and atrium is a rare occurrence. Intra-cardiac thrombi can be multiple in one or multiple chambers[9].

In the Mogulkoc review, patients who had only anticoagulation for cardiac thrombi did better than those who had surgery. The reasons for death in this group were infection, massive hemoptysis, and pulmonary thromboembolism[9].

Other cardiac manifestations in Behcet's disease include dilatation of proximal aorta, interatrial septal aneurysms and mitral valve prolapse. QT dispersion is also significantly higher in patients with Behcet's disease[10].

CONCLUSION

In patients with Behcet disease who present with pulmonary artery aneurysm and cardiac thrombosis, the first-line of treatment is immunosuppressive therapy and cautious anticoagulation. Surgery is reserved for patients who continue to have hemoptysis.

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Case Report

Diagnostic Computerized Tomography Sign in Petersen's Space Hernia after Laparoscopic Roux-en-Y Gastric Bypass

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ABSTRACT

Petersen's space hernia (PSH) is a well-known complication of laparoscopic roux-en-Y gastric bypass (LRYGB) in up to 7% of cases. This led the surgeons to close this defect during surgery. We report the case of a young lady, 25 years old with a body mass index (BMI) of 55 kg/m^2 who had LRYGB in October 2004 with antecolic roux limb, without closing the Petersen's space (PS). Two years later she presented with vague abdominal complaints, which drew our attention to the occurrence of this type of internal bowel herniation through the PS. Routine laboratory investigation and upper endoscopy failed to reveal the problem. However, computerized tomography (CT) scan of the abdomen showed one of the major signs of internal herniation, namely, rotation by 180 degrees of the superior mesenteric vein (SMV) counter-clockwise upon the superior mesenteric artery (SMA). This hernia was reduced surgically through small laparotomy wound after a failed trial to do it laparoscopically. The PS defect was repaired and closed.

KEY WORDS: internal hernia, obesity, radiology

INTRODUCTION

Petersen's space hernia (PSH) is a well known complication of laparoscopic roux-en-Y gastric bypass (LRYGB). Most surgeons in their early experience did not close the Petersen's space (PS), but later, it became apparent that small bowel herniation can happen through this defect in up to 7% of operated cases with serious consequences. Nowadays, we believe that surgeons should close the defect. PSH can be difficult to diagnose postoperatively and in this case report we present unusual CT findings that helped us in diagnosing this problem[1].

CASE REPORT

A 25-year-old female with morbid obesity (BMI = 55 kg/m^2) underwent LRYGB in October 2004. She had an ante-colic roux-limb without closing the PS. According to our earlier practice at that time, we were not closing the PS. The patient did well post-operatively and her BMI was reduced to 28 kg/m^2 in the first year. However, the patient presented to the hospital on three occasions with frequent mild colicky abdominal pain and vomiting. Her last attack was in October 2006, when the pain increased in frequency and intensity over the next few days. Clinical examination showed no abdominal distension and no tenderness. Complete blood count and full chemical profile were normal. Upper endoscopy and gastrointestinal series were normal; however CT scan showed twisting in the small bowel mesentery with the superior mesenteric vein (SMV) rotating about 180 degree anti-clockwise to lie to the left side of the superior mesenteric artery (SMA). The patient had a laparoscopic exploration. A big defect was found at the PS which could not be closed laparoscopically. A mini-laparotomy was done, the hernia was repaired and the defect was closed surgically. The patient recovered well after surgery and was sent home four days later when she was relieved from pain and could tolerate oral intake.

DISCUSSION

LRYGB has been shown to be safe and effective alternative to the traditional open technique. Although lack of postoperative adhesions is one advantage of minimally invasive surgery, and open bariatric surgery has a postoperative obstruction rate of 1 - 3% yet, laparoscopic bypass procedure demonstrates a similar rate of obstruction (0.6 - 3.5%)[2] including a potentially devastating complication, namely, internal small bowel herniation. Internal hernias are potentially fatal and often seen with vague intermittent abdominal pain or acute small bowel obstruction with sometimes

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completely normal contrast radiographic study. In this study, we focused on PSH which occurs through the defect created between the jejunal roux limb mesentery and the transverse mesocolon. Although this type of internal hernia is well-documented, yet failure of initial full work-up including CT scan to diagnose it, has not been previously widely reported. Maintaining a high index of suspicion and expert interpretation of CT images by a radiologist and a surgeon are required when evaluating patients with vague abdominal complaint after LRYGB. Several studies showed that CT scan is the most effective tool in diagnosing PSH with cardinal and specific signs, namely:

1. Dr. Antonio Lannelli in France noted mesenteric vessels engorgement and displacement of mesenteric trunk to be the most common CT sign[3]
2. While Ernesto Garza in Dallas reported other CT signs, like small bowel loops in the left upper quadrant, evidence of small bowel mesentry traversing the transverse colon mesentry, and location of the jejuno-jejunostomy superior to the transverse colon[4]. In addition, crowdings, stretching and engorgement of the main mesentery trunk to the right and signs of small bowel obstruction may be seen[3,4].
3. Lockhart *et al*, from the University of Alabama described seven CT signs of internal hernia[5].
   a. Swirled appearance of mesenteric fat or vessels
   b. Mushroom shape of a hernia
   c. Tubular distal mesenteric fat surrounded by bowel loops
   d. Small bowel obstruction
   e. Clustered loops of small bowel
   f. Small bowel other than duodenum posterior to the SMA
   g. Right-sided location of the distal jejunal anastomosis

   They mentioned that mesenteric swirl was the best single predictor of hernia with high sensitivity and specificity, and the combination of swirled mesentry and mushroom shape of mesentry were better than swirled mesentry alone[4].
4. Suraj A Reddy *et al*, from the University Medical Center, Dallas estimated five CT signs of internal hernia[6]:
   a. Multiple loops of small bowel cephalad to the transverse mesocolon between the stomach and the spleen in the left upper quadrant
   b. Distal jejunal anastomosis at or above the level of the defect or proximal anastomosis (high position of the distal anastomosis)
   c. Ascending course of tightly clustered blood vessels in the small bowel mesentery
   d. Dilatation of the afferent jejunal limb (diameter > 3 mm).
   e. Pinch sign: pinching mass effect on herniated small bowel loops or jejunal afferent limb where they pass through a fatty defect in the transverse mesocolon
5. Alexander Onopchenko from Atlantic City Medical Center in USA found that hernia sign in CT is limited to only distention of both roux limb and the bypassed stomach with whirling of the mesentery at the jejuno-jejunostomy[7]

In our case, whirling of the superior mesenteric vessels was considered the diagnostic radiological sign.

CONCLUSION

PSH after antecolic laparoscopic LRYGB can be associated with mild intermittent pain or severe acute abdomen. A high index of clinical suspicion should be raised in the morbidly obese population. CT scan is the most helpful study to diagnose this problem.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Clinical Characteristics of Multiple Sclerosis in Kuwait: Data from the New MS Registry of Amiri Hospital

Alroughani R, Ashkanani A, Lamdhade S
Department of Medicine, Division of Neurology, Amiri Hospital , Kuwait , Kuwait

Int J Neurosci 2012; 122:82-87

Objectives: To study clinical characteristics of multiple sclerosis (MS) patients in Kuwait and to collect data on annual relapse rates and disability measures.
Method: An MS Registry was created in Amiri Hospital. Demographic, clinical characteristics, and disability measures using Expanded Disability Status Scale (EDSS) score at last visit were collected.
Results: Data from 218 patients formed the basis of the study cohort. Female to male ratio was 1.95. Mean age of onset of MS was 26.8 years. Seventy-eight percent had a relapsing-remitting course, 9.2% had secondary progressive course, and 2.8% had primary progressive course. The clinically isolated syndrome (CIS) group constituted 10.1%. The mean disease duration was 8 ± 7.2 years. Forty-five percent of patients had ≤5 years of disease duration, followed by 24.3% and 25.2% in the 5 - 10 and 10 - 20 years durations. Only 5.5% had MS for > 20 years; 77.1% of patients had < 1 relapse per year, while 22% had 1 - 2 relapses per year; 67.89% of patients had EDSS score < 4, whereas 17.89% were found to have EDSS of ≥ 6.
Summary: MS in Kuwait predominantly affects female. The mean age of onset and frequency of MS types are comparable to worldwide figures. The annual relapse rates and the EDSS scores were relatively low in our cohort.

Knowledge, Misconceptions, and Future Intentions towards Breastfeeding among Female University Students in Kuwait

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Department of Community Medicine and Behavioural Sciences, Faculty of Medicine, Kuwait University

J Hum Lact 2011; 27:358-66

A cross-sectional study using a self-administered questionnaire was conducted on female university students (N = 1106) to explore their knowledge and misconceptions on breastfeeding. Most participants recognized the benefits of breastfeeding, but only a few were aware of the recommendation for exclusive breastfeeding in the first 6 months of life. Misconceptions were common; 66%, 60%, and 55% of participants thought mothers should temporarily stop breastfeeding if they had a fever, skin rash, or sore throat, respectively. Approximately 20% thought mothers should stop breastfeeding if the child had diarrhea, vomiting, or skin rash. Support of breastfeeding in public places was low, but 38% supported breastfeeding in female prayer rooms in public places. Efforts should be made to correct common misconceptions on breastfeeding and increase the support of breastfeeding in public places among university students. Female prayer rooms that exist in all public places in Kuwait can be used to promote breastfeeding in public places in Kuwait.

Prevalence of Chlamydia Trachomatis, Mycoplasma Hominis, Mycoplasma Genitalium and Ureaplasma Urealyticum Infections and Seminal Quality in Infertile and Fertile Men in Kuwait

Al Sweih NA, Al Fadli AH, Omu AE, Rotimi VO

J Androl 2011 Nov 3 [Epub ahead of print]

Objective: This study was undertaken to determine the prevalence of Chlamydia trachomatis, mycoplasmas and ureaplasmas in semen samples of infertile compared with fertile men, and to evaluate the seminological variables of semen from infected and non-infected men.
Materials and Methods: A total of 127 infertile and 188 fertile men seen in Maternity hospital clinic were recruited into the study over a period of 14 months. Specimens were obtained by masturbation and examined for the presence of Ureaplasma urealyticum, Mycoplasma hominis, M. genitalium and C. trachomatis by PCR. Semen analysis was performed according to the World Health Organization (WHO) guidelines.
Results: U. urealyticum, M. hominis, M. genitalium and C. trachomatis were demonstrated in the semen samples of 31 (24.4%) versus 49 (26.1%), 22 (17.1%) versus 61 (32.4%), 6 (4.7%) versus 6 (3.2%), and 5 (3.9%) versus 7 (3.7%), respectively of infertile and control men. Mixed infections were detected in 14 (11%) of infertile and 29 (15.4%) of fertile men. The infertile men positive for M. hominis, had semen samples that showed statistically significant difference in the mean of sperm pH and leukocyte count between infected and uninfected men ($P < 0.03$ and $P < 0.001$, respectively). Similarly, there was statistically significant difference in the leukocyte counts of M. genitalium and C. trachomatis in the infected versus uninfected men. A similar trend was noted in infected fertile versus uninfected men.
Conclusion: There was no statistically significant difference between the prevalence of these urogenital pathogens among infertile versus fertile men. However, genital mycoplasmas and chlamydial infections appeared to negatively influence semen quality.

Premenstrual Dysphoric Disorder: Prevalence and Effects on Nursing Students' Academic Performance and Clinical Training in Kuwait

Omu FE, Al-Marzouk R, Delles H, Oranye NO, Omu AE
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Clin Nurs 2011; 20:2915-2923

Aims: This study investigated the prevalence of Premenstrual Dysphoric Disorder among non-treatment seeking female students at the College of Nursing Kuwait. It also explored the effects of the disorder on their academic performance as shown by their grade point average and rate of absenteeism at clinical training.
Background: Many women worldwide are unaware of this distressing menstrual disorder which affects about 3 - 8% of women of childbearing age. The cyclical mood symptoms often appear during the last week prior to the onset of menstruation. These symptoms interfere with sufferers activities of daily living including occupational, biopsychosocial and sexual activities.
Design: A prospective observational study
Methods: The study used an adapted Arabic version of Daily Record of Severity of Problem for two menstrual cycles to collect data from 110 nursing students.
Result: Data analysis showed Cronbach's alpha coefficient for the adapted tool was 0·95. The rate of premenstrual dysphoric disorder was 5·6%. Hypotheses tested showed no significant effect on students' academic performance but a significant association with absenteeism at clinical training.

Conclusion: The rate obtained in this study was similar to those from recent studies. Participants with high luteal scores believe that the condition have lowered their quality of life by making them choose to be in isolation during the period.
Relevance to Clinical Practice: Nursing students' absenteeism rate at clinical training is a predictor of their work absence pattern after qualification. Absenteeism due to premenstrual dysphoric disorder, a cyclic monthly disorder will be of monthly occurrences if sufferers do not sought medical treatment. Registered nurses absenteeism will not only result in shortage of trained nursing personnel, but also lowered standard of client care. It also has cost implications as temporary substitute staff may have to be employed during their period of absence or sick leave. This has implications for nursing management.

Prevalence of Candida Dubliniensis among Cancer Patients in Kuwait: a 5-year Retrospective Study

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Mycoses 2011; 54:e29-34

Despite close genetic and phenotypic relationship of Candida dubliniensis with Candida albicans, its role in human disease is mostly restricted to oral colonisation, particularly among HIV-infected patients. The prevalence of C. dubliniensis in association with other disease conditions has been infrequently reported. In this study, we present data on the prevalence of C. dubliniensis among yeast species isolated from cancer patients over a 5-year period. A total of 1445 yeast isolates recovered from respiratory specimens, blood, urine and oral swabs were analysed. Candida dubliniensis isolates were provisionally identified by phenotypic methods and their identity was further confirmed by species-specific amplification and/or sequencing of internally transcribed spacer region of rDNA. Antifungal susceptibility for fluconazole was determined by Etest. The number of isolates identified as C. dubliniensis, C. albicans and other yeast species were 71 (4.9%), 862 (59.6%) and 512 (35%) respectively. All the C. dubliniensis isolates originated from respiratory (5.9%) or oral (3.2%) specimens with an overall prevalence of 4.9%, and were found to be susceptible to fluconazole. The isolation of C. dubliniensis from respiratory or oral specimens and not from blood or urine specimens suggests that this species has preference to colonise these sites of human body.

Serotypes and Antibiotic Resistance in Group B Streptococcus Isolated from Patients at the Maternity Hospital, Kuwait

Boswihi SS, Udo EE, Al-Sweih N
Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

J Med Microbiol 2012; 61(Pt 1):126-31

A total of 143 group B streptococcus (GBS) isolates collected from mothers at the Maternity Hospital in Kuwait were investigated for their serotypes and antibiotic resistance, and screened by PCR for the carriage of genes for resistance to tetracycline (tetk, tetM, tetL, tetO), erythromycin (ermA, ermB, ermC, ermTR, ermM, mefA, mefE, msrA) and aminoglycosides (aph3, ant4, ant6). All isolates were serotyped using a latex agglutination test. Most of the isolates belonged to serotypes V (38.5 %), III (20.9 %), Ia (7.7 %) and II (11.2 %). Sixteen isolates (11.2 %) were nontypable. All isolates were susceptible to penicillin, ampicillin and cefotaxime (MICs 0.016-0.094 μg ml(-1)) but were resistant to trimethoprim (92.3 %), tetracycline (89.5 %),

minocycline (89.5 %), high-level kanamycin (76.9 %), chloramphenicol (30.0 %), erythromycin (12.6 %), clindamycin (7.0 %), high-level streptomycin (3.5 %) and ciprofloxacin (0.7 %). The tetracycline-resistant isolates contained tetM (94.5 %), tetO (3.9 %), tetL (1.6 %) and tetK (0.8 %). The erythromycin-resistant isolates contained ermB (61.1 %), ermTR (38.9 %), ermA (5.5 %), mefA (5.5 %) and mefE (11 %). All high-level kanamycin-resistant isolates contained aph3. One of the high-level streptomycin-resistant isolates contained ant6. Partial DNA sequencing of aph3 revealed sequences with 99 % similarity to aph3 found in *Enterococcus faecium, Enterococcus faecalis, Staphylococcus aureus* and *Staphylococcus epidermidis*, suggesting that the GBS isolates could have acquired aph3 from other Gram-positive cocci. The high proportion of isolates with resistance to tetracycline, high-level kanamycin and trimethoprim, and the increase in the prevalence of erythromycin resistance, represents an emerging public health concern that needs further surveillance.

Evaluation of the Primerdesign™ Genesig Real-Time Reverse Transcription-Polymerase Chain Reaction Assay and the INFINITI® Respiratory Viral Panel Plus Assay for the Detection of Human Metapneumovirus in Kuwait

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Department of Microbiology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait

Diagn Microbiol Infect Dis 2012 Jan 31 [Epub ahead of print]

Human metapneumovirus (hMPV) is a respiratory pathogen that was discovered in 2001 and is considered a major cause of both upper and lower respiratory tract infections. A sensitive, fast, and high-throughput diagnostic test is needed for the detection of hMPV that may assist in the clinical management as well as in the reduction of inappropriate therapy. Therefore, a comparison assessment was performed in this study between the PrimerDesign™ genesig real-time reverse transcription-polymerase chain reaction (RT-PCR) Assay and the INFINITI(®) Respiratory Viral Panel Plus Assay (RVP-Plus) for the detection of hMPV infection in patients with respiratory tract infections. A total of 200 respiratory samples were collected from 185 hospitalized patients, during the winter season in Kuwait. Of 185 patients, 10 (5.4%) were positive for hMPV RNA by the in-house RT-PCR assay, while 7 (4%) were positive for hMPV RNA by the real-time RT-PCR assay and 9 (5%) were positive for hMPV RNA by the INFINITI(®) RVP-Plus assay. The high incidence rate (60%) of hMPV infection was in January 2011. The sensitivity of the real-time RT-PCR and INFINITI(®) RVP-Plus assays was 70% and 90%, respectively, with specificity of 100% for both assays. hMPV types A and B could be identified in this study; however, discordant genotyping results were found between the direct sequencing method and the INFINITI(®) RVP-Plus assay in 33% of hMPV-positive patients.

Dispersion Model on PM (2.5) Fugitive Dust and Trace Metals Levels in Kuwait Governorates

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Environ Monit Assess 2012; 184:1731-1737

Frequent dust storms and recent environmental changes were found to affect the human health especially in residents of arid countries. Investigations on the PM(2.5) fugitive dust in six Kuwait Governorate

areas using dispersion Gaussian plume modeling revealed significant relationship between low rate of pollutant emission, low wind velocity, and stable weather conditions' matrix causing high rate of dust deposition in summer than in winter. The rate of dust deposition and trace metals levels in PM(2.5) were in the sequence of G-VI > G-I > G-II > G-V > G-III > G-IV. Trace metals were observed in the sequence of Al > Fe > Zn > Ni > Pb > Cd irrespective of the Governorate areas and the two seasons. The high rate of dust deposition and trace metals in PM(2.5) was reflected by the vast open area, wind velocity, and rapid industrialization besides natural and anthropogenic sources. A combination of air dispersion modeling and nephalometric and gravimetric studies of this kind not only determines the seasonal qualitative and quantitative analyses on the PM(2.5) dust deposition besides trace metals apportionment in six Kuwait Governorate areas, but also characterizes air pollution factors that could be used by environmentalist to deduce preventive measures.

The Palliative Prognostic Index for the Prediction of Survival and In-Hospital Mortality of Patients with Advanced Cancer in Kuwait

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J Palliat Med 2012 Jan 27 [Epub ahead of print]

Introduction: Prognostic scoring systems are increasingly used in cancer care. One of these systems is the Palliative Prognostic Index (PPI) which is based on clinical findings. Few studies validated the PPI in different settings. Our aim was to test the predictive value of the PPI in an acute cancer care setting.
Methods: Prospective study that included patients with advanced cancer admitted to a tertiary cancer center in Kuwait. Patients were divided according to the PPI score into three groups: A (PPI ≤ 3), B (PPI > 3 - ≤ 6), and C (> 6).
Results: The study included 91 hospitalized patients. At the time of PPI assessment, the plan of treatment was best supportive care only in 70 (77%) patients. The majority (80%) of included patients died in-hospital. The in-hospital mortality rate for patients with a PP I > 6 was significantly higher than those with ≤ 6 (93% versus 56%, $p < 0.001$). Using a cutoff point of PPI > 6, in-hospital mortality was predicted with a 73% sensitivity, 78% specificity, 93% positive predictive value, and 41% negative predictive value. The median survival was 61 days (95% confidence interval [CI]: 25.8 - 96.2) for group A, 20 days (95% CI: 4.5 - 35.5) for group B, and 6 days (95% CI: 4 - 8) for group C. The difference in survival was highly significant ($p < 0.001$).
Conclusion: The results suggest that the PPI may be helpful for oncologists in predicting survival and in-hospital mortality of patients with advanced cancer in the acute care setting.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2012; 44 (1): 76 - 84

Pediatric Emergency Medicine: An Evidence-Based Approach
Apr 2 - 6, 2012
Hyatt Regency, Sarasota, FL, *United States*
Contact: D. Reece Pierce, PA-C, P.O. Box 49947
Tel: 866-267-4263; Fax: 941-365-7073
Email: mail@ams4cme.com

Aseptic Surgery Forum 2012
Apr 3 - 4, 2012
Espace Champerret, Paris, *France*
Contact: sylviane ROBINET, 25 Rue André Joineau - 93310 Le Pré Saint Gervais
Tel: +33 1 48 91 89 89; Fax: 0033148434994
Email: s.robinet@simpleway.fr

Neurology Updates for Primary Care
Apr 9 - 13, 2012
Hyatt Regency, Sarasota, FL, *United States*
Contact: D. Reece Pierce, PA-C, P.O. Box 49947
Tel: 866-267-4263; Fax: 941-365-7073
Email: mail@ams4cme.com

A Multidisciplinary Update in **Pulmonary & Critical Care Medicine**
Apr 12 - 15, 2012
The Westin Kierland Resort & Spa, Scottsdale, AZ, *United States*
Contact: Lora Jacobson, 13400 E. Shea Boulevard
Tel: (480) 301-4580; Fax: (480) 301-8323
Email: mca.cme@mayo.edu

Pain Management
Apr 14 - 21, 2012
Celebrity Cruises' Eclipse, m, FL, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

The 5th International Congress of **Prediabetes and Metabolic** Syndrome 2013
Apr 18 - 20, 2013
Austria Center Vienna, Vienna, *Austria*
Contact: Kenes International, 1-3 Rue de Chantepoulet P.O. Box 1726 CH-1211, Geneva 1 Switzerland
Tel: +41 22 908 0488
Email: prediabetes@kenes.com

World Congress of **Cardiology** Scientific Sessions 2012
Apr 18 - 21, 2012
Dubai International Convention and Exhibition Centre, Dubai, *United Arab Emirates*
Contact: Registration, MCI Suisse SA, Rue de Lyon 75, 1211 Geneva 13, Switzerland
Tel: +41 22 33 99 585
Email: congress@worldheart.org

32nd American Society for **Laser Medicine and Surgery** (ASLMS) Annual Conference
Apr 18 - 22, 2012
Gaylord Palms Resort and Covnention Center, Kissimmee, FL, *United States*
Contact: Corri Marschall, 2100 Stewart Avenue, Ste. 240, Wausau, WI 54401
Tel: 715-845-9283; Fax: 715-848-2493
Email: corri@aslms.org

EASL ILC 2012, International **Liver Congress**
Apr 18 - 22, 2012
Centre Convencions Internacional, Barcelona, *Spain*
Contact: Kenes International, 1-3 rue de Chantepoulet, CH-1211 Geneva, Switzerland
Tel: +41 22 908 0488 Fax: +41 22 906 9140
Email: reg_easl2012@easl.eu

Internal Medicine 2012
Apr 19 - 21, 2012
Ernest N. Morial Convention Center, New Orleans, LA, *United States*
Contact: American College of Physicians, 190 Independence Mall West, Philadelphia, PA, 19106
Tel: 800-523-1546, ext 2600; Fax: 215-351-2799
Email: custserv@acponline.org

Nephrology - 2012
Apr 22 - 27, 2012
Fairmont Copley Plaza, Boston, MA, *United States*
Contact: Jennifer Agri, 21 Robin Hill Road, Boston, MA
Tel: 978-304-0935; Fax: 978-304-0936
Email: jennifer@agrimeetings.com

Primary Care Update: **Cardiac Health, Metabolic Syndrome, Obesity and Related Disorders**
Apr 22 - 29, 2012
Royal Caribbean's Allure of the Seas, Ft. Lauderdale, FL, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

NWAC World **Anesthesia** Convention 2012
Apr 24 - 28, 2012
Hilton Hotel Istanbul, Istanbul, *Turkey*
Contact: Kenes International, 1-3 Rue de Chantepoulet PO Box 1726 CH-1211, Geneva 1 Switzerland
Tel: +41 22 908 0488; Fax: +41 22 906 9140
Email: nwac@kenes.com

Pediatrics Review
Apr 27 - May 4, 2012
Holland America's ms Eurodam, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Bone Densitometry Course: Primary Care Provider
Apr 28, 2012
The Peabody Orlando, Orlando, FL, *United States*
Contact: Amy Scrivens, 306 Industrial Park Road Suite 206, Middletown, CT 06457
Tel: 860-259-1000; Fax: 860-259-1030
Email: ascrivens@iscd.org

American Association for **Thoracic Surgery** (AATS) 92nd Annual Meeting 2012
Apr 28 - May 02, 2012
San Francisco, CA, *United States*
Contact: Meeting Organiser: American Association for Thoracic Surgery (AATS)
Telephone: 978-927-8330; Fax: 978-524-8890

Family Medicine: Improving Your Outcomes through Diagnosis and Treatment
Apr 30 - May 4, 2012
Hyatt Regency, Sarasota, FL, *United States*
Contact: D. Reece Pierce, PA-C, P.O. Box 49947
Tel: 866-267-4263; Fax: 941-365-7073
Email: mail@ams4cme.com

23rd European Society for **Pediatric Neurosurgery** (ESPN) Congress
May 1 - 4, 2012
VU University, Amsterdam, *Netherlands*
Contact: Nikolas Dargonakis, 1 KOLOFONTOS & EVRIDIKIS STR
Tel: +30 210 7414730: Fax: +30 210 7257532
Email: n.dargonakis@erasmus.gr

19th International **Surgical Pathology** Sympsium
May 1 - 4, 2012
The Westin, Zagreb, *Croatia*
Contact: Connie Levell, 3050 Superior Drive NW, Rochester, MN 55901
Tel: 507-538-6253; Fax: 507-284-8016
Email: levell.connie@mayo.edu

14th Annual **Echocardiography** Conference: State-of-the-Art 2012
May 2 - 4, 2012
The Roosevelt Hotel, New York, NY, *United States*
Contact: Columbia CME, 630 West 168th Street, Unit 39 New York, NY 10032
Tel: 212-305-3334; Fax: 212-781-6047
Email: cme@columbia.edu

8th International Congress on **Mental Dysfunction** & Other Non-Motor Features in **Parkinson's Disease** and Related Disorders
May 3 - 6, 2012
Intercontinental Berlin Hotel, Berlin, *Germany*
Contact: The Seventh International Congress on Vascular Dementia, 1-3 Rue de Chantepoulet, CH-1211 Geneva 1 Switzerland
Tel: +41 22 908 0488
Email: mdpd@kenes.com

12th International Conference on **Cochlear Implants** and other Implantable Auditory Technologies
May 3 - 5, 2012
Baltimore, MD, *United States*
Sponsoring Organization: Johns Hopkins University (JHU)
Contact: Corinne Aderhold, 1101 North Delaware, Suite 200, Indianapolis, IN 46202
Tel: 1-317-635-4755; Fax: 1-317-635-4757
Email: corinnea@cmcglobal.com

20th European Congress of **Psychiatry**
May 3 - 6, 2012
Prague Congress Centre, Prague, *Czech Republic*
Contact: Kenes International, 1-3 Rue de Chantepoulet
Tel: 41 22 908 0488; Fax: 41 22 906 9140
Email: epa@kenes.com

Immunology 2012: 99th Annual Meeting of the American Association of Immunologists
May 04 - 08, 2012
Boston, MA, *United States*
Contact: Meeting Organiser: The American Association of Immunologists
Tel: 301-634-7178; Fax: 301-634-7887
E-mail: meetings@aai.org

Teaching Quality Improvement and **Patient Safety** in Health Professions Education
May 7 - 8, 2012
Phillips Hall, Rochester, MN, *United States*
Contact: MSCPD, 200 1st Street/Rochester, MN
Tel: 800-323-2688; Fax: 507-284-0532
Email: cme@mayo.edu

The 12th International Symposium on **Myelodysplastic** Syndrome
May 8 - 11, 2013
Hotel Berlin Stauffenbergstraße 26 10785 Berlin, Germany, Berlin, *Germany*
Contact: Kenes International, 1-3 Rue de Chantepoulet P.O. Box 1726 CH-1211, Geneva 1 Switzerland
Tel: +41 22 908 0488
Email: mds@kenes.com

30th Annual Meeting of the European Society for **Paediatric Infectious Diseases**
May 8 - 11, 2012
HELEXPO, Thessaloniki, *Greece*
Contact: Kenes International, 1-3 Rue de Chantepoulet
Tel: 41 22 908 0488; Fax: 41 22 732 2850
Email: espid@kenes.com

12th International Stockholm/Springfield Symposium on **Advances in Alzheimer Therapy**
May 9 - 12, 2012
City Conference Centre, Stockholm, *Sweden*
Contact: Ann Hamilton, SIU, Office of CME, PO Box 19602, Springfield, IL 62794-9602, USA
Tel: +1-217-545-7711; Fax: +1-217-545-4413
Email: ahamilton@siumed.edu

HIV Management 2012: The New York Course
May 10 - 11, 2012
The Hudson Theater, New York, NY, *United States*
Contact: Julie Krantz, 1000 Franklin Village Dr # 103 Franklin, MA 02038
Tel: 888-391-3996; Fax: (508) 528-7880
Email: info@newyorkcourse.com

State of the Art Techniques: **IMRT, IGRT, and SBRT**
May 11 - 13, 2012
Encore at Wynn Las Vegas, Las Vegas, NV, *United States*
Contact: Sara Mansoor, 8280 Willow Oaks Corporate Drive, Suite 500, Fairfax, VA 22031
Tel: 703-502-1550
Email: education@astro.org

Rheumatology and Orthopaedics
May 11 - 21, 2012
Holland America's ms Eurodam, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Pain Management/Neurology/Compliance
May 12 - 21, 2012
Royal Caribbean's Vision of the Seas, Oslo, *Norway*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Women's Health
May 13 - 20, 2012
Holland America's ms Veendam, New York, NY, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

International Research Congress for **Integrative Medicine & Health**
May 15 - 18, 2012
Mariott Hotel Downtown Waterfront, Portland, OR, *United States*
Contact: Karly Kopra, 2545 SW Spring Garden Street, Suite 150, Portland, OR 97219
Tel: 503-244-4294; Fax: 503-244-2401
Email: ircimh@conferencesolutionsinc.com

6th International Congress of the World Federation of **Skull Base** Societies
May 16 - 19, 2012
Hilton Brighton Metropole, Brighton, *United Kingdom*
Contact: Kenes UK, 1st Floor, Chesterfield House, Brighton, UK
Tel: +44 (0) 20 7383 8030
Email: skullbase@kenes.com

Advances in Health Care for Women Over 40
May 17 - 19, 2012
Paris Las Vegas Hotel, Las Vegas, NV, *United States*
Contact: Registration Dept. @ CFORUMS, 6377 Clark Ave., Suite 200, Dublin, CA 94568
Tel: 800-377-7707; Fax: 800-329-9923
Email: info@cforums.com

The 2nd Global Congress for Consensus in **Pediatrics & Child Health**
May 17 - 20, 2012
Radisson SAS Slavyanskaya, Moscow, *Russia*
Contact: Meital Fridenzon, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland
Tel: 41 22 5330 948; Fax: 41 22 5330 948
Email: cip@cipediatrics.org

2nd International Meeting on **Cardiac Problems in Pregnancy**
May 17 - 20, 2012
Leonardo Royal Hotel, Berlin, *Germany*
Contact: Shirley Dinenson, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland
Tel: +41 22 5330 948; Fax: +41 22 5802 953
Email: secretariat@cppcongress.com

Digestive Disease Week® (DDW)
May 19 - 22, 2012
San Diego Convention Center, San Diego, CA, *United States*
Contact: DDW Administration, 4930 Del Ray Avenue Bethesda, MD 20814
Tel: 301-272-0022; Fax: 301-654-3978
Email: ddwadmin@gastro.org

11th International Congress of the European Society of **Pediatric Otorhinolaryngology**
May 20 - 23, 2012
Grand Hotel Krasnapolsky, Dam Square, Amsterdam, *Netherlands*
Contact: J. van Dulmen, Po Box 18, 5298 ZG Liempde, the Netherlands
Tel: +31 411 611199; Fax: +31 411 633805
Email: info@congresservice.nl

NYU's **Sports Medicine Imaging** State of the Art 2012
May 21 - 24, 2012
NYU Langone Medical Center, New York, NY, *United States*
Contact: Michelle Koplik, 462 First Ave, New York, NY
Tel: 212-263-3936
Email:michelle.koplik@nyumc.org

Medical Ethics & Legal Medicine
May 28 - Jun 7, 2012
Holland America's ms Noordam, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Laryngology 2012
Jun 1 - 3, 2012
The Westin, Kuala Lumpur, *Malaysia*
Contact: Kenes UK, 1st Floor, Chesterfield House 385 Euston Road London, NW1 3AU United Kingdom
Tel: +44 (0) 20 7383 8030
Email: Laryngology@kenes.com

40th Annual Workshops in **Clinical Hypnosis** - Introductory and Advanced
Radisson Hotel and Conference Center, Minneapolis, MN, *United States*
Jun 2 - 4, 2011
Contact: Office of Continuing Medical Education, University Park Plaza, Ste 601; 2829 University Ave SE; Minneapolis, MN 55414
Tel: 612-626-7600 or 800-776-8636; Fax: 612-626-7766
Email: cme@umn.edu

2011 Pittsburgh **Liver Update** Symposium (2011 Plus)
William Pitt Union, Pittsburgh, PA, *United States*
Jun 3 - 4, 2011
Contact: Jill March, UPMC Montefiore, 3459 Fifth Avenue Room E-736, Pittsburgh, PA 15213
Tel: 412-647-9509; Fax: 412-802-8799
Email: marchjk@upmc.edu

CINP 2012 - Congress of the Internation College **Neuropsychopharmacology**
Jun 3-7, 2012
Stockholm, *Sweden*
Contact: Vivien Kitzing, Paulsborner Str. 44, Glasgow G74 3XH, Scotland UK
Tel: +49 30 300 669 0
Email: vkitzing@cpo-hanser.de\

4th International Congress on **ADHD**
June 6-9, 2013
Milan, *Italy*
Contact: Verein zur Durchführung Neurowissenschaftlicher Tagungen e. V., Paulsborner Straße 44,14193 Berlin Germany
Tel: +49-30 300 669 0; Fax: +49-30 305 739 1
Email: adhd2011@cpo-hanser.de

The 18th Annual Clinical Reviews and **Primary Care Update**
The Ritz-Carlton, Amelia Island, FL, *United States*
Jun 6 -10, 2011
Contact: Denise Klarich, 4550 San Pablo Rd
Tele: 800-462-9633; Fax: 904-953-2954
Email: cme-jax@mayo.edu

Advances in **Trauma and Acute Care Surgery** (76th Annual Surgery Course)
Jun 7 - 8, 2012
University Hotel Minneapolis, Minneapolis, MN, *United States*
Contact: Bonnie Boucher, 420 Delaware St Se, MMC 195, Minneapolis, MN
Tel: 612-626-1999; Fax: 612-626-0654
Email: boucher@umn.edu Website: http://www.cme.umn.edu

Teaching Course with International Faculty on: **Retinal And Vitreous Surgery**
Jun 7 - 8, 2012
Ufa, Russia, *Russia*
Contact: Prof. Dr. med. Ingrid Kreissig, Dept. of Ophthalmology, Univ. of Mannheim - Heidelberg, 69167 Mannheim, Germany
Tel: +49 - (0) 621 - 383 25 97
Email: Ingrid.kreissig@medma.uni-heidelberg.de

Hot Topics in **Neurology and Neurosurgery** for the Primary Clinician
Jun 7 - 8, 2012
Marriott Hotel, Rochester, MN, *United States*
Contact: MSCPD, 200 1st St. SW; Plummer 2-60 Rochester, MN 55905
Tel: 1-800-323-2688; Fax: 507-284-2509
Email: cme@mayo.edu

Bone Densitometry Course
June 9 - 10, 2012
Hilton Norfolk Airport, Norfolk, VA, *United States*
Contact: Amy Scrivens, 306 Industrial Park Road Suite 206, Middletown, CT 06457
Tel: 860-259-1000; Fax: 860-259-1030
Email: ascrivens@iscd.org

Primary Care: **Neurology** Update 2012
Jun 9 - 16, 2012
Holland America's ms Westerdam, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.n

Primary Care Update: **Cardiac Health, Metabolic Syndrome, Obesity** and Related Disorders
Jun 14 - 24, 2012
Holland America's ms Eurodam, Copenhagen, *Denmark*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.n

Family Medicine: **Dermatology** Review
Jun 16 - 23, 2012
Holland America's ms Westerdam, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Dermatology for Primary Care
Jun 18 - 22, 2012
Hyatt Regency, Sarasota, FL, *United States*
Contact: D. Reece Pierce, P.O. Box 49947
Tel: 866-267-4263; Fax: 941-365-7073
Email: mail@ams4cme.com

Cardiomyocyte Regeneration and Protection
Hilton Torrey Pines, La Jolla, CA, *United States*
Jun 20 - 21, 2011
Contact: Katie, Abcam, 1 Kendall Sq., Suite 341, Cambridge, MA 02139
Tel: 6175774263
Email: ks@abcam.com

12th Congress of the European Society of **Contraception and Reproductive** Health
June 20 - 23, 2012
Athens, *Greece*
Contact: Nancy Habils, Opalfeneweg 3, 1740 Ternat, Belgium
Tel: +32 2 582 08 52; Fax: +32 2 582 55 15
Email: congress@contraception-esc.com

13th National Conference: **Parkinson's 2011**: recent advances in clinical managament
CBI Conference Centre, London, *United Kingdom*
Jun 21, 2011
Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB
Telephone: +44 (0) 207 501 6762; Fax: +44 (0) 207 978 8319
Email: flo.doel@markallengroup.com

12th Congress of the European Society of **Contraception and Reproductive Health**
Jun 20 - 23, 2012
Athens, *Greece*
Contact: Nancy Habils
Tel: 32-2-582- 0852; Fax: 32-2-582-5515
E-Mail:congress@contraception-esc.com

1st **Gynecological Surgery** Conference 2011
Kellogg Conference Hotel at Gallaudet University, Washington D.C, *United States*
Jun 23 - 25, 2011
Contact: Romy Meuter, 953 National Road, PMB#110, Wheeling, VW, 26003, USA
Tel: 1-800-662-0183; Fax: 1-800-662-0183
Email: romy@medineo.org

Family Medicine: A Review and Update of Common Clinical Problems
Jun 25 - 29, 2012
Hyatt Regency, Sarasota, FL, *United States*
Contact: D. Reece Pierce, PA-C, P.O. Box 49947
Tel: 866-267-4263; Fax: 941-365-7073
Email: mail@ams4cme.com

19th Annual Clinical Reviews and **Primary Care** Update
Jun 25 - 29, 2012
The Ritz-Carlton, Amelia Island, FL, *United States*
Contact: Denise Klarich, 4500 San Pablo Road
Tel: 800-462-9633; Fax: 904-953-2954
Email: cme-jax@mayo.edu

15th World Congress of **Pain** Clinicians
Jun 27 - 30, 2012
Granada Convention Center, Granada, *Spain*
Contact: Kenes International, 1-3 Rue de Chantepoulet, CH-1211 Geneva 1 Switzerland
Tel:+41 22 908 0488
Email: wspc2012@kenes.com

Family Medicine
Jun 30 - Jul 7, 2012
Royal Caribbean's Oasis of the Seas, Ft. Lauderdale, FL, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.ne

Novel Treatments for **Schizophrenia**: Prevention and Cognitive Remediation
Jul 4, 2012
New York, NY, *United States*
Contact: Columbia University CME, 601 West 168th Street, Suite 51, New York, NY
Tele: 212-305-3334; Fax: 212-781-6047
Email: cme@columbia.edu

British **Gynaecological Cancer** Society Annual Meeting
Jul 5 - 6, 2012
The QEII Conference Centre, London, *United Kingdom*
Contact: Kenes UK, 1st Floor, Chesterfield House 385 Euston Road London, NW1 3AU United Kingdom
Tel: +44 (0) 20 7383 8030
Email: bgcs@kenes.com

Pediatrics
July 7 - 14, 2012
Royal Caribbean's Mariner of the Seas, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Infectious Disease Review
Jul 7 - 14, 2012
Holland America's ms Westerdam, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Primary Care Update: **Type 2 Diabetes, Metabolic Syndrome and Obesity**
Jul 7 - 17, 2012
Holland America's ms Noordam, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

ICAO 2012, 3rd International Congress on **Abdominal Obesity**
Jul 9 - 12, 2012
Québec Congress Center, Quebec City, *Canada*
Contact: Kenes International, 1-3 Rue de Chantepoulet, PO Box 1726, CH-1211, Geneva 1, Switzerland
Tel: + 41 22 908 0488; Fax: + 41 22 906 9140
Email: icao@kenes.com

Emergency Medicine Review
Jul 10 - 22, 2012
Celebrity's Solstice, Barcelona, *Spain*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

British Society for **Allergy and Clinical Immunology**
Jul 11 - 13, 2012
East Midlands Conference Centre University Park Nottingham NG7 2RJ, Nottingham, *United Kingdom*
Contact: Kenes UK, 1st Floor, Chesterfield House 385 Euston Road London, NW1 3AU United Kingdom
Tel: +44 (0) 20 7383 8030
Email: bsaci@kenes.com

19th ASEAN Federation of **Cardiology** Congress 2012
Jul 13 - 15, 2012
Raffles City Convention Centre, Singapore, *Singapore*
Contact: Kelly Chan, 695E East Coast Road, Singapore 459059
Tel: 6346 4402; Fax: 6346 4403
Email: kellychan@themeetinglab.com

8th FENS Forum of **Neuroscience**
Jul 14 - 18, 2012
Barcelona, *Switzerland*
Contact: Kenes International, 1-3, Rue de Chantepoulet, *France*
Tel: 4122908048; Fax: 4122906914
Email: fens@kenes.com

Dermatology for the PCP
Jul 14 - 24, 2012
Holland America's ms Eurodam, Copenhagen, *Denmark*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

8th International Conference on **Head and Neck Cancer**
Jul 21 - 25, 2012
Metro Toronto Convention Center (South Building), Toronto, *Canada*
Contact: Jennifer Clark, 11300 W. Olympic Blvd, Suite 600, Toronto, CA
Tel: 310-437-0559
Email: jennifer@ahns.info

Geriatric Medicine Review
Jul 21 - 28, 2012
Holland America's ms Westerdam, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Cancer In Women
Jul 21 - 28, 2012
Norwegian Cruise Line's Pride of America, Honolulu, HI, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Primary Care: **Mental Health** Issues with a Focus on Drugs and Behavior
Jul 21 - 28, 2012
Royal Caribbean Splendour of the Seas, Venice, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Medical Ethics & Legal Medicine
Jul 21 - 28, 2012
Royal Caribbean Splendour of the Seas, Venice, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

30th International Congress of **Psychology** - ICP 2012
Jul 22 - 27, 2012
Cape Town International Convention Centre, Cape Town, *South Africa*
Contact: Fatima Seedat, PO Box 989, Houghton 2041, South Africa
Tel: 011 486 3322; Fax: 011 486 3266
Email: info@icp2012.com

A Comprehensive Review of **Movement Disorders** for the Clinical Practitioner
Jul 30 - Aug 2, 2012
St. Regis Hotel, Aspen, CO, *United States*
Contact: Columbia CME, 630 West 168th Street, Unit 39 New York, NY 10032
Tel: 212-305-3334; Fax: 212-781-6047
Email: cme@columbia.edu

Summer **Radiology Symposium** in Whistler
Jul 30 - Aug 3, 2012
Four Seasons Resort, Whistler, British Columbia, Canada, Whistler, *Canada*
Contact: Michelle Koplik, 462 First Ave, *New York*
Tel: 212-263-3936
Email: michelle.koplik@nyumc.org

Topics in **Acute Care**, Women's Health, Emergency Medicine and Family Medicine
Aug 3 - 10, 2012
Royal Caribbean's Rhapsody of the Seas, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Bone Densitometry Course
Aug 8 - 9, 2012
Crowne Plaza Albuquerque, Albuquerque, NM, *United States*
Contact: Amy Scrivens, 306 Industrial Park Road Suite 206, Middletown, CT 06457
Tel: 860-259-1000; Fax: 860-259-1030
Email: ascrivens@iscd.org
Family Medicine

Royal Caribbean's **Rhapsody** of the Seas
Aug 10 - 17, 2012
Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Oral Dermatology and Oral Pathology
Aug 10 - 17, 2012
Celebrity Cruises' Millennium, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Bone Densitometry Course
Aug 18 - 19, 2012
Boston Marriott Newton, Newton, MA, *United States*
Contact: Amy Scrivens, 306 Industrial Park Road Suite 206, Middletown, CT 06457
Tel: 860-259-1000; Fax: 860-259-1030
Email: ascrivens@iscd.org

The 30th World Congress of **Biomedical Laboratory Science**
Aug 18 - 22, 2012
Maritim proArte Hotel, Berlin, *Germany*
Contact: Ilana Berkowitz, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland
Tel: 41 22 5330 948; Fax: 41 22 5802 953
Email: secretariat@ifbls-dvta2012.com

Pediatrics Review
Aug 25 - Sep 1, 2012
Holland America's ms Westerdam, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Psychiatry in Medical Settings
Aug 26 - 28, 2012
JW Marriott Desert Ridge Resort, Phoenix, AZ, *United States*
Contact: MSCPD, 200 1st Street /Rochester, MN 55905
Tel: 800-323-2688; Fax: 507-284-0532
Email: hovey.sierra@mayo.edu

14th European Symposium of **Suiside & Suicidal Behaviour**
Sep 3 - 6, 2012
Tel Aviv - Jaffa, *Switzerland*
Contact: Kenes, 1-3, Rue de Chantepoulet,
Tel: 4122908048; Fax: 4122906914
Email: esssb@kenes.com

The 8th International Conference on **Frontotemporal Dementias**
Sep 5 - 7, 2012
Manchester, *United Kingdom*
Contact: Kenes UK, 385 Euston Road
Tel: 44 (0) 20 7383 8030; Fax: 44 (0) 20 7383 8040
Email: ftd@kenes.com

The **Viral Hepatitis** Congress
Sep 7 - 9, 2012
Johann Wolfgang Goethe-Universität, Frankfurt, *Germany*
Contact: Michele Upton, Victoria Mill, Windmill Street, Macclesfield, Cheshire, SK11 7HQ, UK
Tel: +44 (0) 1625 664195
Email: hep@kp360group.com

Bone Densitometry Course
Sep 8 - 9, 2012
St. Louis Airport Marriott, St. Louis, MO, *United States*
Contact: Amy Scrivens, 306 Industrial Park Road Suite 206, Middletown, CT 06457
Tel: 860-259-1000; Fax: 860-259-1030
Email: ascrivens@iscd.org

24th European Congress of **Pathology**
Sep 8-12, 2012
Prague Congress Centre, Prague, *Czech Republic*
Contact: Juliane Heinicke, Paulsborner Str. 44
Tel:+49 – 30 – 300 669-0 Fax: +49 – 30 – 305 73 91
Email: ecp-prague@cpo-hanser.de

The American Society of Emergency Radiology 2012 Annual Meeting and Postgraduate Course in **Trauma and Emergency Radiology**
September 12 - 15, 2012
New Orleans Marriott, New Orleans, LA, *United States*
Contact: Savanna Lott, 4550 Post Oak Place, Suite 342
Tel: 713-965-0566
Email: aser@meetingmanagers.com

Wound Care
Sep 15 - 22, 2012
Royal Caribbean's Oasis of the Seas, Ft. Lauderdale, FL, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Primary Care: **Arrhythmia Management** and EKG Interpretation with Clinical Examples for Primary Care
Sep 16 - 23, 2012
Norwegian Cruise Line's Epic, Barcelona, *Spain*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Preventive Medicine
Sep 20 - Oct 2, 2012
Celebrity Cruises' Solstice, Barcelona, *Spain*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

15th Biennial Meeting European Society for **Immunodeficiency**
Oct 3 - 6, 2012
Firenze Fiera Piazza Adua, 1, Bordeaux, *France*
Contact: Kenes International, 1-3 Rue de Chantepoulet P.O. Box 1726 CH-1211, Geneva 1 Switzerland
Tel: +41 229080488; Fax: +41 229069140
Email: esid@kenes.com

Women's Health
Oct 5 - 15, 2012
Holland America's ms Noordam, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

The 4th Congress of the European Academy of **Paediatric** Societies
Oct 6 - 9, 2012
Istanbul Congress Center ('ICC'), Istanbul, *Turkey*
Contact: Kenes International, 1-3 Rue de Chantepoulet
Tel: 41 22 908 0488; Fax: 41 22 906 9140
Email: paediatrics@kenes.com

2012 **Cardiometabolic** Health Congress
Oct 10 - 13, 2012
Westin Boston Waterfront Hotel, Boston, MA, *United States*
Contact: Brittany Henry, 788 Shrewsbury Ave.
Tel: 877-571-4700; Fax: 866-218-9168
Email: info@cardiometabolichealth.org

14th Biennial Meeting of the International **Gynecologic Cancer** Society (IGCS)
Oct 13 - 16, 2012
The Vancouver Convention and Exhibition Centre, Vancouver, *Canada*
Contact: Kenes International, 1-3, rue de Chantepoulet, CH-1211 Geneva 1 Switzerland
Tel: +41 22 908 0488
Email: igcs@kenes.com

Medical Ethics & Legal Medicine
Oct 14 - 24, 2012
Norwegian Cruise Line's Sun, Miami, FL, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Pan American **Heart Failure** Congress (PAHF 2012)
Oct 18 - 21, 2012
RIU PLAZA HOTEL, Panama City, *Panama*
Contact: Mrs. Tali Ogorek, 18 Avenue Louis-Casai | 1209 Geneva | Switzerland
Tel: 41 22 5330 948; Fax: 41 22 5802 953
Email: secretariat@pahfcongress.com

Bone Densitometry Course
Oct 20 - 21, 2012
Des Moines Marriott Downtown, Des Moines, IA, *United States*
Contact: Amy Scrivens, 306 Industrial Park Road Suite 206, Middletown, CT 06457
Tel: 860-259-1000; Fax: 860-259-1030
Email: ascrivens@iscd.org

European Association of **Neurosurgical Societies** Congress 2012
Oct 24 - 27, 2012
TBC, Bratislava, *Slovakia*
Contact: Kenes International, 1-3 Rue de Chantepoulet P.O. Box 1726 CH-1211, Geneva 1 Switzerland
Tel: +41 22 908 0488
Email: eans@kenes.com

6th Asian Congress of **Paediatric Infectious Diseases**
Oct 24 - 27, 2012
Bandaranaike Memorial International Conference Hall, Bauddhaloka Mawatha, *Sri Lanka*
Contact: Kenes Asia, ACPID 2012 Conference Secretariat Kenes Asia 5th Floor, PICO Creative Centre 20 Kallang Avenue, Singapore 339411
Tel: +65 6292 0723; Fax: +65 6292 4721
Email: acpid2012@kenes.com

Infectious Disease Review
November 10 - 17, 2012
Norwegian Cruise Line's Pride of America, Honolulu, HI, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Eleventh International Congress on **Drug Therapy in HIV Infection**
Nov 11 - 15, 2012
SECC, Glasgow, *United Kingdom*
Contact: Mandy Shore, Victoria Mill, Windmill Street, Macclesfield, Cheshire SK11 7HQ, UK
Tel: +44 (0)1625 664390; Fax +44 (0)1625 664391
Email: HIV11@kp360group.com

XXXI World Congress of **Internal Medicine**
Nov 11 - 15, 2012
Espacio Riesco, Santiago, *Switzerland*
Contact: Kenes, La Concepción 266 Office 501, Santiago, Chile
Tel: 56-2-9462633; Fax: 56-2-946 2643
Email: wcim2012@kenes.com

The 2nd International Multidisciplinary Forum on **Palliative Care**
Nov 24 - 25, 2012
Hilton Florence Metropole, Hilton Florence Metropole, *Italy*
Contact: Meital Fridenzon, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland
Tel: 41 22 5330 948; Fax: 41 22 5802 953
Email: mfridenzon@paragon-conventions.com

Bone Densitometry Course
Dec 1 - 2, 2012
Hilton Garden Inn Chicago O'Hare, Chicago, IL, *United States*
Contact: Amy Scrivens, 306 Industrial Park Road Suite 206, Middletown, CT 06457
Tel: 860-259-1000; Fax: 860-259-1030
Email: ascrivens@iscd.org

WHO-Facts Sheet

1. Tackling the Global Clean Air Challenge
2. 12,000 Fewer Children Perish Daily in 2010 than in 1990
3. Malaria Deaths a Down but Progress Remains Fragile
4. Key Interventions to Reduce Maternal, Newborn and Child Deaths

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2012, 44 (1): 85-89

1. TACKLING THE GLOBAL CLEAN AIR CHALLENGE

In many cities, air pollution is reaching levels that threaten people's health according to an unprecedented compilation of air quality data released by WHO in September 2011. The information includes data from nearly 1100 cities across 91 countries, including capital cities and cities with more than 100,000 residents.

Key facts

- Air pollution is a major environmental risk to health. By reducing air pollution levels, we can help countries reduce the global burden of disease from respiratory infections, heart disease, and lung cancer.
- The lower the levels of air pollution in a city, the better respiratory (both long- and short-term), and cardiovascular health of the population will be.
- Indoor air pollution is estimated to cause approximately 2 million premature deaths mostly in developing countries. Almost half of these deaths are due to pneumonia in children under five years of age.
- Urban outdoor air pollution is estimated to cause 1.3 million deaths worldwide per year. Those living in middle-income countries disproportionately experience this burden.
- Exposure to air pollutants is largely beyond the control of individuals and requires action by public authorities at the national, regional and even international levels
- The WHO Air quality guidelines represent the most widely agreed and up-to-date assessment of health effects of air pollution, recommending targets for air quality at which the health risks are significantly reduced. The Guidelines indicate that by reducing particulate matter (PM10) pollution from 70 to 20 micrograms per cubic metre, we can cut air quality related deaths by around 15%.

Over 2 million people die from indoor and outdoor air pollution

WHO estimates more than 2 million people die every year from breathing in tiny particles present in indoor and outdoor air pollution. PM10 particles, which are particles of 10 micrometers or less, which can penetrate into the lungs and may enter the bloodstream, can cause heart disease, lung cancer, asthma, and acute lower respiratory infections. The WHO air quality guidelines for PM10 is 20 micrograms per cubic metre ($\mu g/m^3$) as an annual average, but the data released today shows that average PM10 in some cities has reached up to 300 $\mu g/m^3$.

Main findings

The main findings contained in the new compilation are:

- Persistently elevated levels of fine particle pollution are common across many urban areas. Fine particle pollution often originates from combustion sources such as power plants and motor vehicles.
- The great majority of urban populations have an average annual exposure to PM10 particles in excess of the WHO Air Quality guideline recommended maximum level of 20 $\mu g/m^3$. On average, only a few cities currently meet the WHO guideline values.
- For 2008, the estimated mortality attributable to outdoor air pollution in cities amounts to 1.34 million premature deaths. If the WHO guidelines had been universally met, an estimated 1.09 million deaths could have been prevented in 2008. The number of deaths attributable to air pollution in cities has increased from the previous estimation of 1.15 million deaths in 2004. The increase in the mortality estimated to be attributable to urban air pollution is linked to recent increases in air pollution concentrations and in urban population size, as well as improved data availability and methods employed. "Air pollution is a major

Address correspondence to:
Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/

environmental health issue and it is vital that we increase efforts to reduce the health burden it creates," said Dr Maria Neira, WHO Director for Public Health and Environment. "If we monitor and manage the environment properly, we can significantly reduce the number of people suffering from respiratory and heart disease, and lung cancer. Across the world, city air is often thick with exhaust fumes, factory smoke or soot from coal burning power plants. In many countries there are no air quality regulations and, where they do exist, national standards and their enforcement vary markedly. "

Greater awareness of health risks

WHO is calling for greater awareness of health risks caused by urban air pollution, implementation of effective policies and close monitoring of the situation in cities. A reduction from an average of 70 $\mu g/m^3$ of PM10 to an annual average of 20 $\mu g/m^3$ of PM10 is expected to yield a 15% reduction in mortality - considered a major public health gain. At higher levels of pollution, similar reductions would have less impact on reducing mortality, but will nevertheless still bring important health benefits.

Largest contributors to urban outdoor air pollution

In both developed and developing countries, the largest contributors to urban outdoor air pollution include motor transport, small-scale manufacturers and other industries, burning of biomass and coal for cooking and heating, as well as coal-fired power plants. Residential wood and coal burning for space heating is an important contributor to air pollution, especially in rural areas during colder months.

Technical Notes

Air quality data have been compiled from publicly available national or city-specific sources, which are based on results of air quality monitoring conducted by individual cities. The measurements used in the database are taken from monitoring sites in cities, including roadside, but excluding industrial and other recognized 'hot spots' that are not representative of the exposure of many people (e.g. crossings at highways) in order to avoid overestimates.

Measurements as applied in the database, including reported PM10 levels, represent annual averages. PM10 is an important indicator of urban air pollution, and the health risks associated with the complex mixtures of pollutants typically found in cities. The smaller PM10 particles are able to penetrate deep into the lungs, and also to cross into the blood, causing damage in many organ systems. In some cities, measurements of even smaller particles such PM2.5 are available, and these are also included in the database.

The data are based on measurements from 2003 to 2010, with the great majority being reported for the period 2008-2009. Data are presented for individual cities, urban populations of countries (as available), and for WHO regions.

For more information contact: Ms Nada Osseiran, Communications Officer, WHO. Telephone: +41 22 7914475, Mobile: +41 79 445 1624
E-mail: osseirann@who.int
Gregory Hartl, Communications Advisor, WHO. Telephone: +4122 791 4458, E-mail: hartlg@who.int

2. 12,000 FEWER CHILDREN PERISH DAILY IN 2010 THAN IN 1990

The number of children under five years of age dying each year declined from more than 12 million in 1990 to 7.6 million in 2010, according to a UNICEF and WHO report releasing the latest estimates on worldwide child mortality. These new figures show that compared to 1990, around 12,000 more children's lives are saved each day.

Declining child mortality rate in sub-Saharan Africa

An annual report on child mortality found that in sub-Saharan Africa, the region with the highest number of under-five deaths in the world, the speed at which the under-five mortality rate is declining doubled from 1.2 per cent a year during 1990 - 2000 to 2.4 per cent a year during 2000 - 2010.

Rate of progress

Between 1990 and 2010, the under-five mortality rate dropped by more than one-third, from 88 deaths per 1,000 live births to 57.

Unfortunately, this rate of progress is still insufficient to meet Millennium Development Goal 4 (MDG4), which calls for a two-thirds reduction in the under-five mortality rate by 2015.

"Reductions in child mortality are linked to many factors, particularly increased access to health care services around the newborn period. As well as prevention and treatment of childhood illnesses, and improved nutrition, immunization coverage, and water and sanitation," said Dr Margaret Chan, WHO Director General.

Greatest improvements seen in countries where children are most vulnerable

Some of the greatest improvements are in countries where children are most vulnerable. One example is Niger, where the 1990 under-five mortality rate was 311 per 1,000 live births. To address the often large distances between people and health centres, a strategy

of deploying trained community health workers to deliver high-impact interventions at thousands of new health posts across the country was used. In 2010, Niger was one of the five countries with the greatest absolute reductions in overall under-five mortality rates, together with Malawi, Liberia, Timor-Leste and Sierra Leone.

The report shows that newborns and infants are the most at risk of dying, and there has been less progress for them than within the under-five age category as a whole. More than 40 per cent of under-five deaths occur within the first month of life and over 70 per cent in the first year of life.

Disparities persist

The improvements and progress are encouraging – but stark disparities persist. Sub-Saharan Africa is still home to the highest rates of child mortality, with one in eight children dying before reaching five – more than 17 times the average for developed regions (1 in 143). Southern Asia has the second highest rates with 1 in 15 children dying before age five.

Under-five deaths are increasingly concentrated in sub-Saharan Africa and Southern Asia. In 1990, 69 per cent of under-five deaths occurred in these two regions – in 2010, that proportion increased to 82 per cent. About half of all under five deaths in the world took place in just five countries in 2010: India, Nigeria, Democratic Republic of Congo, Pakistan and China.

About UN Inter-agency Group for Child Mortality Estimation (IGME)

IGME was formed in 2004 to share data on child mortality, harmonize estimates within the UN system, improve methods for child mortality estimation report on progress towards the Millennium Development Goals and enhance country capacity to produce timely and properly assessed estimates of child mortality. The IGME, led by the United Nations Children's Fund and the World Health Organization, also includes the World Bank and the United Nations Population Division of the Department of Economic and Social Affairs as full members.

The IGME's independent Technical Advisory Group, comprising leading scholars and independent experts in demography, provides technical guidance on estimation methods, technical issues and strategies for data analysis and data quality assessment.

The IGME updates its child mortality estimates annually after reviewing newly available data and assessing data quality. The 2011 child mortality report contains the latest IGME estimates of child mortality at the country, regional and global levels. Country-specific estimates and the data used to derive them are available from the child mortality database of the IGME.

About UNICEF

UNICEF is on the ground in over 150 countries and territories to help children survive and thrive, from early childhood through adolescence. The world's largest provider of vaccines for developing countries, UNICEF supports child health and nutrition, good water and sanitation, quality basic education for all boys and girls, and the protection of children from violence, exploitation, and AIDS. UNICEF is funded entirely by the voluntary contributions of individuals, businesses, foundations and governments.

About WHO

WHO is the directing and coordinating authority for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

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3. MALARIA DEATHS ARE DOWN BUT PROGRESS REMAINS FRAGILE

Malaria mortality rates have fallen by more than 25% globally since 2000, and by 33% in the WHO African Region, according to the World malaria report 2011, issued in December by WHO. This is the result of a significant scaling-up of malaria prevention and control measures in the last decade, including the widespread use of bed nets, better diagnostics and a wider availability of effective medicines to treat malaria.

However, WHO warns that a projected shortfall in funding threatens the fragile gains and that the double challenge of emerging drug and insecticide resistance needs to be proactively addressed.

Malaria incidence and mortality rates fall

During the past decade, malaria incidence and mortality rates have been cut in all regions of the world, according to the report. In 2010, there were an estimated 216 million cases of malaria in 106 endemic countries and territories in the world. An estimated 81% of these cases and 91% of deaths occurred in the WHO African Region. Globally, 86% of the victims were children under 5 years of age.

There were an estimated 655,000 malaria deaths in 2010, which is 36,000 lower than the year before. While this 5% year-on-year decline represents significant progress, the mortality figures are still disconcertingly

high for a disease that is entirely preventable and treatable. "With malaria deaths in Africa having fallen significantly since 2000, the return on our investment to end malaria deaths has been greater than any I have experienced in the business world. But one child still dies every minute from malaria - and that is one child and one minute too many," says Raymond G. Chambers, the UN Secretary General's Special Envoy for Malaria.

Steady progress in malaria control measures

Long-lasting insecticidal nets have been one of the least expensive and most effective weapons in the fight against malaria. According to the new report, the number of bed nets delivered to malaria-endemic countries in sub-Saharan Africa increased from 88.5 million in 2009 to 145 million in 2010. An estimated 50% of households in sub-Saharan Africa now have at least one bed net, and 96% of persons with access to a net use it.

There has also been further progress in rolling out diagnostic testing, which is crucially important to separate malaria from other febrile illnesses. The number of rapid diagnostic tests delivered by manufacturers climbed from 45 million in 2008 to 88 million in 2010, and the testing rate in the public sector in the WHO African Region rose from 20% in 2005 to 45% in 2010.

Worldwide, the volume of antimalarial medication delivered to the public sector has also increased. In 2010, 181 million courses of artemisinin-based combination therapies (ACTs) were procured, up from 158 million in 2009, and just 11 million in 2005. ACTs are recommended as the first-line treatment for malaria caused by the most deadly malaria parasite, Plasmodium falciparum.

Emerging threats

Plasmodium falciparum resistance to artemisinins, which was confirmed on the Cambodia-Thailand border in 2009, has now also been identified at additional sites in Myanmar and Viet Nam. WHO has recommended that all countries ban the marketing of oral artemisinin-based monotherapies, which have been one of the major factors fostering the emergence and spread of resistance. Despite continued international pressure, 25 countries still allow the marketing of oral artemisinin-based monotherapies and 28 pharmaceutical companies continue to market these products (down from 39 in 2010).

The problem of mosquito resistance to insecticides also appears to be growing, although to date has not been linked to widespread failure of malaria vector control efforts. According to the World malaria report 2011, which includes data on insecticide resistance for the first time - 45 countries around the world have identified resistance to at least one of the four classes of insecticides used for malaria vector control; 27 of these are in sub-Saharan Africa. Resistance has been reported from all WHO Regions except the WHO European Region. India and malaria-endemic countries in sub-Saharan Africa are of greatest concern due to widespread reports of resistance - in some areas to all classes of insecticides - combined with a high malaria burden.

Current malaria control efforts are heavily reliant on a single class of insecticides, the pyrethroids, which are the most commonly used compounds for indoor residual spraying, and the only insecticide class recommended - and currently used - on long-lasting insecticidal nets.

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4. KEY INTERVENTIONS TO REDUCE MATERNAL, NEWBORN AND CHILD DEATHS

A new global consensus has been agreed on the key evidence-based interventions that will sharply reduce the 358,000 women who still die each year during pregnancy and childbirth and the 7.6 million children who die before the age of 5, according to a massive, three-year global study. The study, Essential interventions, commodities and guidelines for reproductive, maternal, newborn and child health, is designed to facilitate decision-making in low- and middle-income countries about how to allocate limited resources for maximum impact on the health of women and children.

The study reviewed more than 50,000 scientific papers to determine the proven effectiveness of interventions and impact on survival, identifying 56 essential interventions that when implemented in "packages" relevant to local settings, are most likely to save lives. The study is released on 15 December 2011 by the World Health Organization (WHO), the Aga Khan University and the Partnership for Maternal, Newborn & Child Health (PMNCH).

Some of the interventions include:

- managing maternal anaemia with iron
- preventing and managing post-partum haemorrhage
- immediate thermal care for newborns
- extra support for feeding small and preterm babies
- antibiotics for the treatment of pneumonia in children.

"What is new," says Dr. Elizabeth Mason, Director of WHO's Department of Maternal, Newborn, Child and Adolescent Health, and an author of the study, "is putting together information in a different way and building consensus among physicians, scientists and professional organizations to lay out an evidence-based path to help women before, during and after birth and their children. Everyone now agrees on the 56 essential interventions."

Suitability for low- and middle-income countries

The first step was a global landscape analysis of what countries and the 440 PMNCH partners were doing to reduce maternal and newborn deaths.

In all, 142 interventions were assessed for their effectiveness and impact on survival by addressing the main causes of maternal, newborn, and child mortality. Drs. Bhutta and Mason and their team also studied the intervention suitability for use in low- and middle-income countries.

They asked what health and outreach workers with limited training could handle at the community level where specialized care is not available. They identified what could be handled in community settings by nurses, midwives and workers with more training. They also identified which patients need to be referred to hospitals where physicians and emergency care are available.

After very extensive consultation and review by a wide group of experts, the list was honed down to 56 essential interventions, accompanied by brief guidelines and reference materials.

"We now have a clear consensus, critical for the survival of women, their infants and children," says Dr. Carole Presern, Director, of PMNCH. "This was a meticulous effort involving many partners. It is truly a landmark moment in advancing the health of women and children."

Maternal and child deaths still a problem

Though considerable progress has been made toward reducing maternal, infant and child deaths, many countries in Africa and India will fall short of the United Nation's Millennium Development Goals 4 and 5, which aim to reduce child deaths and improve maternal health.

Sub-Saharan Africa and south Asia, which have the highest maternal and child death rates, have made some progress, but not enough to meet the Millennium Development Goals by 2015.

More than half of maternal deaths are caused by excessive bleeding (35%) and hypertension (18%).

A child's greatest risk of dying is during the first 28 days of life, accounting for 40% of all deaths among children under the age of 5. Half of newborn deaths occur during the first 24 hours and 75% during the first week of life, with preterm birth, severe infections and asphyxia being the main causes.

A guidance document

The underlying thrust of "Essential Interventions" is to support low- and middle- income countries to meet the Millennium Development Goals 4 and 5. It gives policy makers a way to make informed choices on how to set priorities and where to put their funds and resources, guided by a list of absolutely critical interventions.

The interventions are classified according to three levels:

1. care that can be provided at the community level by community health workers, outreach workers, and volunteers with limited training;
2. primary care, also delivered in the community at a clinic by professionals – nurses, midwives, community health workers – with more training;
3. referral care provided by physicians and skilled nurses and midwives in a hospital able to do Caesarean sections and provide emergency care.

The interventions are also classified according to six target groups:

1. adolescent and pre-pregnancy
2. pregnancy (before birth)
3. childbirth
4. postnatal (mother)
5. postnatal (newborn)
6. infancy and childhood.

In addition to identifying the interventions, the document provides clear guidance on what is needed in terms of training and equipment. For example, if newborns are not breathing, resuscitation equipment is needed.

PMNCH, which has 440 partners, including countries, UN and multilateral agencies, nongovernmental organizations, health groups, foundations, academic and research institutions, and the private sector, will distribute this essential list through its global network and actively advocate for its use. A condensed version on a simple, hand-held slide ruler for instant reference is currently under development.

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