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The Official Journal of The Kuwait Medical Association

## EDITORIAL



## REVIEW ARTICLE



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# KUWAIT MEDICAL JOURNAL

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# Kuwait Medical Journal (KMJ)

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## Editorial

# The Status of Organ Transplantation in Kuwait

Mohammad H Jamal
Department of Surgery, Faculty of Medicine, Kuwait University, Kuwait

Kuwait Medical Journal 2014; 46 (3): 194 - 195

Kuwait was a leading country in organ transplantation with kidney transplant starting as early as in the late seventies. Major research was also published in the field of transplantation from the department of organ transplantation at Kuwait University led by Professor George Aboona. The invasion was a major setback as it affected all aspects of life in Kuwait, but the return to the business as usual in kidney transplantation was rapid chaired by Dr.Mustafa Almousawi. The peak was in 2004, when 100 cadaveric and living related kidney transplants were performed at Hamed Al-Essa center. Since 1993, there were 1247 cadaveric and living related kidney transplants performed in Kuwait.

The first successful pancreatic transplantation in Kuwait and the Gulf was performed in 2007 by Dr. Husain Hayati and Dr. Adnan Sadeq, and so far around eight cases were done in Kuwait. The demand for more donors is always there, as the current numbers do not cover the patients on the lists for kidney and pancreatic transplantation. Since 1993, there were 195 cadaveric donations only.

This year saw a major step towards improving the status of organ transplantation in Kuwait, by the formation of the committee for multi-organ transplantation by the Minister of Health, Dr. Ali Al-Obaidi and chaired by Dr. Jamal Alharbi the assistant undersecretary. The committee met on several occasions and passed major recommendations including the need to have cadaveric liver and heart transplants in Kuwait.

The demand for liver transplant in particular is going to increase due to the obesity epidemic. Obesity is a major risk factor for nonalcoholic fatty liver disease (NAFLD), which is simply caused by accumulation of triglycerides in the hepatocyets, and can be divided in severity according to the amount of fat accumulated in the liver. NAFLD in itself is a benign entity, however it can progress to non-alcoholic steatohepatitis (NASH) which is associated with necrosis, inflammation, hepatocellular injury and can lead to fibrosis and cirrhosis resulting in liver failure requiring transplant[1].

The drive for progression of NAFLD to NASH is not known, but risk factors associated with NASH include obesity, hyperlipidemia, type 2 diabetes mellitus and insulin resistance. A major challenge in the management of NASH is that it is asymptomatic until liver failure occurs[2,3]

NAFLD prevalence is estimated to be between 75 - 100% in the morbidly obese, defined as those with a body mass index (BMI) of more than 35. NASH in turns develops in 30% of patients with NAFLD[2]. Obesity prevalence in Kuwait is estimated to be around 39% for adult male and 52% for adult female[4].

If we take all these numbers in context, we should realize that at some point we will be facing a major health problem in Kuwait, and that the time has come to start the liver transplantation program, especially with major European countries and the United States closing their doors for cadaveric organ transplantations for foreigners.

Liver transplantation is now considered a safe procedure that is commonly performed worldwide. It is the standard therapy for patients with end stage liver failure, with a one year survival rate of 85 - 90% and five years' survival rate at 70 - 80%. The first liver transplantation for NASH cirrhosis in the United States was performed in 1996 and constituted only 0.11% of all liver transplantations performed in the US that year. In 2007 there was a 40 fold increase in the number of liver transplantations performed for NASH in the US[5].

***Address correspondence to***
*Mohammad H Jamal, MBChB(Hons), MEd, FRCSC, FAHPBA, Assistant Professor of Surgery, Faculty of Medicine, Kuwait University, Kuwait.*
*E-mail: u22mj@yahoo.com*

Liver transplantation, hence is an essential surgical service that should be provided for the public, and is available in countries with similar capabilities as Kuwait, including Qatar. We are still at the planning level of the multiorgan transplantation initiative in Kuwait, but with the right support from the political and the medical community, we should make it happen.

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Review Article

# Actual Medical Management of Stone Diseases in Pediatric Population

Yigit Akın[1], Murat Ucar[2], Selcuk Yucel[2]
[1]Department of Urology, Erzincan University School of Medicine, Erzincan, Turkey
[2]Department of Urology, Akdeniz University School of Medicine, Antalya, Turkey

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**ABSTRACT**

Although the prevalence of urolithiasis is nearly 2 - 3% in childhood, the risk of recurrence may range between 6.5 - 54%. There has been an increase in stone disease in the pediatric age groups. The stone disease in children has multifactorial etiology. After the diagnosis, detailed metabolic evaluation is required. High recurrence rates, therapeutic irregularities and deficiency in diagnosis may lead to co-morbidities such as loss of kidney. After the exact diagnosis, surgical options such as stone extraction and correction of the anatomical anomalies come into question. Besides these, medical and supportive treatments are needed for preventing recurrence, urinary infection and, preserving renal function. Supportive care includes increased fluid intake and dietary modifications. Medical treatment depends on the cause of urinary stone disease. Morbidities of pediatric urolithiasis can be prevented by early diagnosis, detailed metabolic analysis, regular follow-up and medical treatment protocols.

KEY WORDS: children, hypercalciuria, hypocitraturia, oxaluria, urolithiasis.

## INTRODUCTION

Urinary stone diseases are considered to be occurring rarely in the pediatric age group; however, studies in recent years have shown an increase, especially in the prevalence and incidence of ureteric stones[1]. Although they have a prevalence of about 2 - 3%, pediatric stone diseases hava a recurrence risk that may vary between 6.5 - 54%[2]. Besides, it is an important health problem due to high morbidity and risk of end-stage renal failure[3]. It has a multifactorial etiology such as race, gender, genetics, climate and dietary habits[4]. In developing countries, endemic pediatric stone diseases are often limited to the bladder. This is associated with decreased phosphate intake and may often manifest as ammonium acid, urate or uric acid stones. Again, studies in recent years have shown that incidence of stones has increased with increased animal protein consumption in parallel with the rising standards of living in developed countries[5].

Although urinary stone diseases are common in all pediatric age groups, the average age at diagnosis is between 4.2 - 9.4 years[1]. Hereditary factors should be considered in case of children who are diagnosed earlier than these age groups[6].

In the pediatric group, the objective in the treatment of urinary stone disease covers removing the stone, preventing recurrences, maintaining renal functions, preventing urinary system infections, and correcting the anatomical and underlying metabolic problems.

The medical treatment used in urinary system stone diseases is specific to the type of stone and is effective only in a small group of stones. Alkalinization in uric acid stones may also be effective for cystine stones when used in combination with thiols; besides, urine acidification is another method used in infection stones. Objectives of medical treatment covers preventing the formation of new stones, preventing the growth of existing stones and thus reducing the need for surgery and hence, morbidity. In light of all of these, medical treatment may be considered as a preventive treatment. In order to start medical treatment, exact diagnosis should be made. Therefore, metabolic investigations covering stone analysis, urine and serum analysis gain importance.

***Address correspondence to:***
*Yigit Akin, MD, Department of Urology, Erzincan University School of Medicine, TC Saglik Bakanligi, Erzincan Universitesi Tıp Fakültesi Mengucek Gazi, Egitim ve Arastirma Hastanesi, Erzincan, Turkey, Tel: +90-446-226 18 18, Mobile: +90-506-5334999, Fax: 90-446-2261819*
*E-mail: yigitakin@yahoo.com*

In this compilation, general recommendations in pediatric urinary stone diseases and treatment options specific to the type of stone or metabolic disorder are reviewed.

## GENERAL RECOMMENDATIONS

The first general recommendation in all urinary stone diseases is abundant fluid intake. Urine production increases with abundant fluid intake and insoluble concentration in urine and super saturation may be reduced. In various studies conducted, children with stone diseases have been found as taking less fluid than the ones in the control group[7]. Lande *et al* have reported that calcium oxalate, calcium phophate and uric acid super saturation does not occur when urine amount is more than 1 ml/kg/hr[8]. Fluid intake is a critical component of prevention of stones. This is done by effectively reducing the lithogenic factors including calcium, oxalate, uric acid and cystine; besides, the only treatment for patients with primary xanthinuria is large fluid intake. Curhan *et al* reported that drinks such as coffee and tea reduced stone formation while grapefruit juice increased stone formation in a study conducted in adult females with stone[9]. The reason for this may be that it increases the tendency to form oxalate stones due to its high oxalate content. To the best of our knowledge, there are no such studies conducted in pediatric stone patients in the literature. Milk, other fruit juices and water are fluid sources that may be recommended to the pediatric stone patients to be consumed in excess. Surely, alkaline drinks such as lemonade are more advantageous than acid ones in terms of the risk of stone formation[10].

In studies conducted, increased calcium and sodium in urine have been shown to be associated with the increased dietary sodium intake[11]. Frasetto *et al* emphasized that the chloride in the excess dietary sodium chloride intake may lead to low degree metabolic acidosis[12]. By this means, bone mineralization may deteriorate and may also contribute to stone formation. The fact that excess dietary salt intake increases the risk for stone formation has been associated with excess salt intake in developed countries. The reverse mechanism is seen in the case of excess dietary potassium intake[13]. Potassium salts generally come from alkali salts such as potassium citrate. Potassium citrate reduces urinary calcium excretion[14].. Potassium salts are taken from fruits and vegetables in diet. Sodium and potassium have opposite effects on blood pressure similar to their opposite effects on urinary calcium. Excess dietary sodium increases blood pressure whereas excess dieatry potassium decreases blood pressure.

In stone diseases accompanied by hypercalciuria, reduction of urinary calcium excretion is recommended. This may be ensured by reducing the dietary animal protein load, that is by reducing the acid load[15]. Acids that form when these dietary animal proteins are metabolized lead to bicarbonate secretion from the bones. Therefore, bone resorptions that cause osteopenia and hypercalciuria occur[16]. Nouvenne *et al* reported that limiting animal protein and salt intake increased recurrences compared to calcium intake at a normal level in patients with recurrent calcium oxalate stone and hypercalciuria[17]. Apart from these, low dietary calcium intake leads to decreased oxalate that binds with calcium in the intestines and increased urinary oxalate excretion[18]. Moreover, high amount of dietary vitamin C, sucrose and fructose intake may lead to stone formation. On the other hand, high levels of magnesium intake decreases the risk of stone formation[19].

Dietary recommendations should be explained to families in the treatment of pediatric urinary stone diseases and most importantly, it should be noted that dietary habits do not change overnight.

## MEDICAL TREATMENT

### Hypercalciuria

Calcium oxalate and calcium phosphate stones constitute the majority of urinary system stones in children. About 30 - 50% of children who develop stones have hypercalciuria[20]. Hypercalciuria is the most common cause of pediatric urolithiasis. It means that urinary calcium excretion is above 4 mg/kg/day or that urinary calcium / creatinine ratio is above 0.21 in older children. In many children a 24-hour urine collection is not practical and calcium - creatinine ratio in the urine is used to estimate daily calcium excretion. It should be noted that urinary calcium excretion increases with age. Urinary calcium oxalate and phosphate should also be measured for an optimal evlauation[21].

Hypercalciuria usually occurs as a result of disturbances in one or more of the three systems such as increased gastrointestinal calcium absorption, disturbances in bone formation and resorption and renal loss[21]. Hypercalciuric calcium stones are categorized as normocalcemic and hypercalcemic.

Hypercalciuria is not the only factor, but it is associated with many factors. The most common cause in children and adults is idiopathic hypercalciuria. Idiopathic hypercalciuria is defined as hypercalciuria despite the absence of hypercalcemia and occurs in patients without any apparent cause. The gene(s) responsible for familial idiopathic hypercalciuria have not been defined yet, but it is observed as having autosomal dominant character. Four percent of asymptomatic healthy children have evidence of idiopathic hypercalciuria[22] and 40 - 50% of these children have positive family history for urolithiasis[23].

When hypercalciuria is observed, some issues must be ruled out for the diagnosis of idiopathic

hypercalciuria. By definition, blood calcium level of the patient should be normal. In patients with hypercalcemic hypercalciuria, hyperparathyroidism and Vit D hypervitaminosis should be investigated and when clinically detected, prolonged immobilization, sarcoidosis, malignancy, juvenile idiopathic arthritis, excess corticosteroids, adrenal failure or Williams syndrome should be considered. Children with hypercalcemic hypercalciuria should be evaluated in terms of hypoparathyroidism and autosomal dominant hypocalcemic hypercalciuria (mutation in calcium receptor function). Although patients with normocalcemic hypercalciuria are often diagnosed with idiopathic hypercalciuria, prematurity, history of diuretic use (furosemide and acetezolamide), anticonvulsant use (topiramate and zonisamide), ketogenic diet, Dent disease, Bartter syndrome, familial hypomagnesemia and nephrocalcinosis (AHHNK) with hypercalciuria, distal renal tubular acidosis (dRTA), hereditary hypophosphatemic rachitism with hypercalciuria (HHRH) and potential medullary sponge kidney must be ruled out and kept in mind in the first assessment.

**Genetic conditions associated with normocalcemic hypercalciuria**

Dent disease is a condition based on X and occurs as a result of the mutation in CLCN5 gene. This condition is characterized by molecule weighted proteinuria, nephrocalcinosis, hypercalciuria, nephrolithiasis and chronic kidney disease. Clinical picture is usually insidious and asymptomatic throughout the childhood period; signs and symptoms of nephrocalcinosis and hypercalciuria are not common in children. The damage occurs in proximal tubular function and rarely, it may manifest as a part of glycosuria, aminoaciduria, metabolic acidosis and Fanconi syndrome associated with hypophosphatemia. In a limited number of patients, Dent phenotype occurs with the mutation in the OCRL gene (Dent 2). This condition is also associated with the oculocerebrorenal syndrome of Lowe.

Bartter syndrome is an autosomal recessive condition characterized by loss of salt in kidneys, hypokalemia, metabolic alkalosis, hypercalciuria and normal serum magnesium levels. The disease typically manifests itself as salt deficiency, polyuria, dehydration, emesis, constipation and growth retardation in children below six years of age. Severe polyhydramnios, prematurity and rarely, sensorineural hearing loss are distinctive characteristics of the disease. Mutations in SLC12A, KCNJ1 ve BSND genes (type I, type II and type IV Bartter syndrome, respectively) typically result in serious dysfunction in the thick ascending limb of the loop of Henle in the neonatal period (neonatal Bartter syndrome). Mutations in the C1CKB gene (type III Bartter syndrome) usually lead to medium level dysfunction in the thick ascending limb of the loop of Henle. It is usually seen out of the neonatal period (classic Bartter syndrome).

AHHNK is usually seen in childhood together with seizures or tetany accompanying hypomagnesemia. Other clinical findings are recurrent urinary tract infections (UTI), polyuria, polydipsia, growth retardation, nephrolithiasis and progressive kidney failure[24]. AHHNK is an autosomal recessive condition. It occurs with the mutations of both CLDN-16 and CLDN-19 genes. Homozygous CLDN-16 or CLDN-19 mutations are associated with disturbances in the integrity of the tight junctions in the ascending limb of Henle, magnesium, calcium loss in the urine and the resulting hypomagnesemia. Patients usually develop a classical triad composed of hypomagnesemia, hypercalciuria and nephrocalcinosis. In case of the combination of CLDN-19 mutations, deep visual disturbances characterized by macular coloboma, considerable myopia and horizontal nystagmus may be seen[25].

Primary dRTA is a hereditary disease and is characterized by systemic acidosis that occurs as a result of the loss of the ability of the distal tubule to properly acidify the urine. Growth retardation, polyuria, polydipsia, hypercalciuria, hypocitraturia, nephrocalcinosis, kidney stones and hypokalemia are common findings in infancy. Primary dRTA may be autosomal dominant (SLC4A1 gene) or recessive (ATP6V1B1 or ATP6V0A4 genes).

Failure to release H1 ions from $\alpha$-intercalated cells is caused by vacuoles H1-ATPaz (ATP6V1B1 or ATP6V0A4 genes) or a damaged Cl / HCO3 anion exchanger-1(SLC4A1 gene). Patients with ATP6V1B1 mutations may have hearing loss or neural type hearing loss.

HHRH is a rare autosomal recessive disease that is caused by a mutation in the SLC34A3 gene. This condition results in loss of function in the type IIc sodium phosphate carriers of the proximal tubule. Decreased renal phosphate reabsorption results in deep hypophosphatemia, normokalemia, rickets and bone ache. In addition, hypercalciuria and nephrolithiasis are detected. It may occur as a result of the stimulation of 1, 25-dihydroxyvitamin D synthesis triggered by hypophosphatemia. Increased synthesis causes excess urine calcium losses in the face of increased gastrointestinal reabsorption of calcium and normal calcium levels[26].

When there is hypercalciuria, environmental factors that increase calcium excretion such as high sodium consumption and ketogenic diet should be considered. In treatment, sodium restriction, large fluid intake, and a diet rich in proteins and poor in oxalate should be recommended according to weight and age. Thiazide

diuretics prevent calcium excretion through proximal and distal renal tubules. Another diuretic is amiloride. These diuretics may improve calciuria; however, they may also cause abnormalities such as weakness, nausea, orthostatic hypotension, hypercholesterolemia and electrolyte abnormalities. Potassium citrate may be used in hypercalciuria associated with dRTA since it improves metabolic acidemia and hypokalemia and it brings urinary calcium and citrate excretion to normal levels[27]. In addition to all of these, a combination of thiazide diuretics and potassium citrate may also be used[28].

Patients with idiopathic hypercalciuria may also be treated with potassium citrate[29]. This treatment reduces urinary calcium excretion while increasing urinary citrate excretion. Moreover, mineral density of the bone also increases. Urinary pH of the patients should be monitored. At very high pH levels, formation of calcium phosphate stones may become easier[30]. Penido *et al* reported decreased bone mineral density in one third of hypercalcemic children[31]. Parallel to this study, Freundlich *et al* reported that alendronate may have beneficial effects on bone tissue and calcium excretion in children with osteopenia and urinary stone disease[32].

**Hyperoxaluria**

Oxalate is the last product of the metabolic path of glyoxylate and ascorbic acid. It is secreted primarily by kidneys. A majority of the daily oxalate excretion (80 - 85%) is derived from normal metabolic homeostasis and diet constitutes the rest (10 - 15%). Daily urinary oxalate excretion is usually less than 50 mg/d/1.73m$^2$. Due to the challenge of 24-hour urine collection in little children, urinary oxalate / creatinine ratio is used to estimate the oxalate excretion. Increased urinary oxalate excretion may occur due to a hereditary metabolic condition, (primary hyperoxaluria [PH]), more often due to oxalate reabsorption or increased oxalate precursors.

**Primary hyperoxaluria**

Type I and type II PH are rare; they are autosomal recessive diseases in which endogenous oxalate production is increased. Excess oxalate production by the liver leads to nephrocalsinosis and nephrolithiasis which result in increased oxalate excretion. Calcium oxalate deposits cause progressive kidney damage. Its clinical picture may vary from end stage renal failure in newborns to possible random stone disease in adulthood. The diagnosis often eludes observation and there may even be cases where it is realized after the loss of the transplanted kidney[33].

Type I PH occurs due to the mutations in the AGXT gene which causes functional damage in hepatic peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). Deficiency leads to the accumulation of glyoxylate, glycolate and oxalate in urine. Pyridoxine is the basic cofactor for proper AGT activity and rarely, prolonged vitamin B6 deficiency may mimic type I PH. Type II PH occurs due to the mutation in the GRHPR gene which leads to dysfunction in glyoxylate reductase-hydroxypyruvate reductase enzyme activity. Increased oxalate and L-glyceric acid are excreted through the kidney[34]. Type II PH is a lighter form than type I PH, but it is not benign. Recently, a third form type III PH has been defined in eight families who have hyperoxaluria and mutations in the DHDPSL gene[35]. The exact mechanism of the hyperoxaluria that occurs in Type III PH is not clear yet.

**Secondary hyperoxaluria**

In secondary hyperoxaluria, there are both high amounts of dietary oxalate (or oxalate precursors) intake and the dysfunction that causes increased absorption of the dietary oxalic acid into the intestinal system. Gastrointestinal absorption varies in opposite directions with dietary calcium intake and calcium-dependent diet increases oxalate absorption and hypercalciuria[36]. Oxalate is a side product of ascorbic acid metabolism and high dose of vitamin C is also associated with hyperoxaluria. Increased dietary absorption is usually characterized by disturbance in fat absorption or chronic diarrhea. Among secondary causes of hypercalciuria are inflammatory bowel diseases associated with gastrointestinal disease, celiac disease, exocrine pancreatic insufficiency (cystic fibrosis), biliary tract disease and small intestine resection or short bowel syndrome. Pathogenesis in these cases is caused by the presence of free fatty acids that bind to the calcium in the intestinal lumen. This results in free, absorbable, unbound oxalate formation.

Oxalobacter formigenes not only reduces oxalate, it also changes the oxalate released endogenously in the intestines. Thus it reduces the oxalate in blood and in urine and it may be applied orally in PH treatment[37]. Moreover, pyridoxine is used to decrease oxalate excretion in PH. Pyridoxine is an important cofactor of AGT. About 10 - 30% of children with PH type I are sensitive to pyridoxine (> 30% decrease in urinary oxalate excretion). Particularly, they may ensure protection of renal function in patients who are homozygous for Gly170Arg and Phe152Ile mutations within the appropriate treatment period. Treatment should be started in patients with suspicious PH type I (2 - 5 mg/kg/g) and it should be titrated until a diagnosis is made and a response is received (8 - 10 mg/kg/g). High doses of pyridoxine are known to trigger sensory nephropathy. There is no apparent evidence showing

that pyridoxine additions are beneficial unless there is a real pyridoxine deficiency. In PH, liver and kidney transplant are the best treatment methods in patients who developed chronic renal failure. It is essential to prevent excess dietary intake, increase oral calcium intake and to improve gastrointestinal disorders in the treatment of hypercalciuria.

**Hypocitraturia**

Citrate is an important stone inhibitor that prevents the growth of calcium oxalate and calcium phosphate crystals by binding to calcium in urine. It is adjusted in the proximal tubule both by absorption and by metabolism. Hypocitraturia is defined as a citrate / creatinine ratio of below 180 mg/g in men, and below 300 mg/g in women. Intracellular acidosis of the proximal tubule occurs due to hypocitraturia associated both with metabolic acidosis and increased citrate absorption in the proximal tubule. Consequently, ketogenic diet, medications (topiramate, zonisamide and acetazolamide), dRTA and chronic diarrhea are often associated with hypocitraturia. Incomplete dRTA may occur in the absence of apparent systemic acidosis or in hypokalemia. This may usually be neglected in the face of hypocitraturia in case no provocative acid loading test is conducted. Nevertheless, hypocitraturia is idiopathic although in many cases the diets are rich in animal protein and low amounts of vegetable fiber and potassium that lead to low dietary citrate excretion[38]. Potassium citrate is an ideal medical option in treatment. The treatment is safe except for its minor gastrointestinal effects.

**Hypomagnesuria**

It may occur in dietary magnesium deficiency. Magnesium may form a complex with oxalate and it reduces calcium oxalate supersaturation in urine and it may also prevent oxalate reuptake. It is essential to increase dietary intake in treatment.

**Hyperuricosuria**

Uric acid excretion is greater in children than in adults. The highest fractional excretion (Fe) in newborns is (Fe 30 - 50%). It reaches adult values (Fe 8 - 12%) in adolescence[39]. Hyperuricosuria is defined as uric acid excretion greater than 815 mg/d/1.73m$^2$. When the glomerular filtration rate (GFR) is adjusted, uric acid excretion is relatively stable after two years of age. When GFR is greater than 0.56 mg/dl in children older than two years who do not have toilet training, hyperuricosuria may be detected in spot urine. This value may be calculated by using the formula, "urinary uric acid (mg/dl) x plasma creatinine (mg/dl) / urinary creatinine (mg/dl)".

Hyperuricosuria is the greatest risk for stone formation especially, at low urine pH. Hereditary purine metabolism disorders are lymphoproliferative diseases and diseases associated with polystemia and apparent hyperuricemia hyperuricosuria. Rarely, a condition known as hereditary hyperuricemia characterized by hyperuricosuria, nephrolithiasis and activity induced renal failure is also detected. Mutations in both SLC22A12 gene and SLC2A9 gene that code the urate transport in the proximal tubule are known causes for its formation[40]. Other causes of hyperuricosuria include excess purine intake (animal protein), hemolysis, uricosuric medications (probenecid, salicylates and losartan), cyanotic congenital heart disease, melamine toxicity and idiopathic (familial) causes. Moreover, a phenomenon primarily detected in adults is referred to as hyperuricosuric calcium oxalate stones. In this case, hyperuricosuria forms the fundamental basis for the formation of oxalate stones without or with minimal uric acid content (epitaxy).

**HEREDITARY DISEASES OF PURINE METABOLISM**

Phosphoribosyl pyrophosphate synthethase superactivity (PRPSS) is hereditary disease based on X and is formed by the mutation in the PRPS1 gene. Increased PRPSS activity is associated with excess purine production. The following purine degeneration results in hyperuricemia, gout, hyperuricosuria and uric acid nephrolithiasis. Nerve development abnormalities and neural type hearing loss are seen in some affected individuals[41]. Hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency is a purine metabolism disorder in the neonatal period which occurs due to the mutations in the HPRT1 gene associated with excess uric acid production. Complete deficiency of HPRT activity is associated with Lesh-Nyhan syndrome characterized by mental retardation, spastic cerebral palsy, choreoathetosis, uric acid stones, and self-destructive behavior. Children with partial HPRT deficiency may be phenotypically similar to the patients who have complete phenotypical deficiency or moderate neurological symptoms. Kidney stones, uric acid nephropathy, kidney obstruction or gout may be the first signs of the disease.

First line treatment is urine alkalinization and usually potassium citrate is used. Restricting excess dietary animal protein intake in patients may result in increased purine intake and increased uric acid production, and it may contribute both to uricosuria and acidic urine. Allopurinol (4 - 10 mg/kg/g, adults maximum 300 mg/g) is necessary in both hyperuricemia and hyperuricosuria such as PRPSS or HPRT deficiency. Xanthine dehydrogenase inhibition with allopurinol may lead to xanthine accumulation and its excess excretion in the urine. Rarely, secondary xanthuria with xanthine stones may be detected

in children in long-term treatments. If there are comorbid findings of hypercalciuria, hyperoxaluria or hypocitraturia, allopurinol may also be a treatment option for the treatment of hyperuricemic calcium oxalate stones[42].

**Cystinuria**

Cystinuria is an autosomal recessive disease caused by mutations in both SLC3A1 and SLC7A9 genes which results in irregular amino acid transport in the proximal tubule. Cystinuria is characterized by urinary hypersecretion of cystine and lysine, ornitine and arginine, which are among dibasic amino acids. Normal individuals release cystine at a rate of 50 - 60 mg/g/1.73 $m^2$ (less than 30 mg daily). Patients who are homozygous for cystinuria have a cystinuria excretion of more than 400 mg/g/1.73$m^2$ (varies between 400 mg and 3000 mg)[43]. Patients typically have renal colic and urolithiasis in the second and third decades of their lives. However, they may also have staghorn stones in the neonatal period. Weak solubility of cystine in urine causes precipitation in collecting duct systems. If this is not treated, it usually results in frequently recurring kidney stones and renal failure in the long run. Related UTI is frequent; combined cystine and struvite stones may be detected[44].

Irregular cystine transport in cystinuria primarily results from the dysfunction in heavy (rBAT) and light (b0, 1AT) subunits (rBAT/b0, 1AT) in the heteromeric amino acid transporter. Cystinuria is originally categorized into two classes: type I and non-type I (type II and type III). The distinction is based on urine cystine concentration pattern compulsory heterozygote and estimated mode of inheritance. There is classical autosomal recessive inheritance in type I and normal cystine excretion is seen. On the contrary, non-type I heterozygotes (type II and type III) show moderate and high urinary cystine excretion. Types II and III vary among themselves. There is a quasi-normal increase in plasma levels of cystine after oral cystine administration in type III homozygotes[45].

Homozygous mutations in the SLC3A1 gene which code rBAT are associated with type I cystinuria and homozygous mutations in the SLC7A9 gene which code b0,1AT are associated with type II and III cystinuria. A new classification system has been developed. In this system, patients who are homozygous for SLC3A1 mutations are designated as cystinuria type A, patients who are homozygous for SLC7A9 mutations are designated as cystinuria type B, and mutations in both SLC3A1 and SLC7A9 genes are considered as type AB[46].

There is little evidence concerning restriction of proteins which have high cystine content; however, animal protein intake may help increase urinary pH in patients with cystinuria. Children who have stones are recommended not to take increased amounts of protein; but proper protein intake for growth and nutrition according to age should be recommended. The objective in treatment is to ensure the concentration and amount of urine in which cystine may dissolve. This is ensured by large fluid intake and medical treatment. The two most frequently used agents are D-penicillamine and $\alpha$-mercaptopropionylglycine (tiopronin). Cystine is formed as a dimer of cystine and these agents work by reducing the disulphide bonds that bind the two molecules of cystine. Thiol group combines with cystine and forms a more soluble product which is a combination of excreted cystine and the product. D-penicillamine has a wide range of adverse events including febrile reactions, gastrointestinal complaints, liver dysfunctions, taste disturbances, bone marrow suppression, metal deficiencies, membranous glomerulopathy, myasthenia gravis and skin eruptions (elastosis perforans serpiginosa)[6]. A-mercaptopropionylglycine has a similar incidence of adverse events, but it may be slightly lower. Evaluation of liver enzymes, complete blood count, urine analysis, copper and zinc levels should be regularly studied. Special studies (solid-phase trial and high performance liquid chromatography) may assist in distinguishing between urinary cystine and cysteine-drug complexes and in long-term treatment.

Although captopril containing disulfidryl is a drug that may be used in treatment, its hypotensive effects should be taken into account.

**Infection Stones**

Infection stones are seen in 2 - 24% of children who have been diagnosed with kidney stones[6]. They constitute 75% of the stones diagnosed in European children. They are usually seen in children below six years of age. Eighty percent of the patients are male. Infection stones in the urinary system are seen more commonly in patients with anatomic and functional disorders that cause stasis. Infection stones occur due to infections induced by organisms that ensure hydrolysis of urea with the urease enzyme and which form ammonium and bicarbonate as a result[21]. Proteus, Providencia, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Serratia, Enterobacter* and *Staphylococcus* are bacteria that produce urease. The compound that does not produce urease at high pH but is rich in ammonium is magnesium and the bacterium which help stone formation by facilitating precipitation of phosphate is *Escherichia coli*[27].

Infection stones contain ammonium phosphate, carbonate apatite and monoammonium urate. Ammonium phosphate is the main constituent of many infection stones. Ammoniac damages the urothelial glycosaminoglycan layer which is the defense

mechanism against bacteria. These stones may require intervention following long-term antibiotic therapy as of their structure. The incidence of this kind of stone is gradually decreasing, thanks to the developments in infection diagnosis and treatment[46].

The treatment is composed of extracting the stones and correcting the underlying anatomical and / or functional obstruction. In the long-term treatment and follow-up, antibiotic therapy according to urine culture antibiogram is important. Urinary acidification and a balanced fiber diet that is poor in phosphate helps in the treatment.

**Orotic acid stones**

Hereditary orotic aciduria is a rare genetic disease. It occurs due to orotate-phosphoribosyl-transferase and orotidine-5-phosphate-decarboxylase enzyme deficiency responsible for transformation of orotic acid into uridine-5-phosphate. Consequently, orotic acid excreted in urine increases and it crystallizes forming orotic acid stones. Uridine is used in the treatment[27].

**2, 8-Dihydroxyadenineuria**

It is an autosomal recessive disease and there is adenine –phosphoribosyl transferase defect. As a result, there is excess accumulation of 2, 8 dihydroxyadenine. It is very similar to uric acid stones; however, it may be distinguished by metabolic and stone analysis. It may be treated by allopurinol therapy and regulation of diet[47].

**Xanthuria**

Xanthuria is a rare disease and its inheritance is autosomal recessive. Xanthine, which takes part in the formation of uric acid, the final product of purine

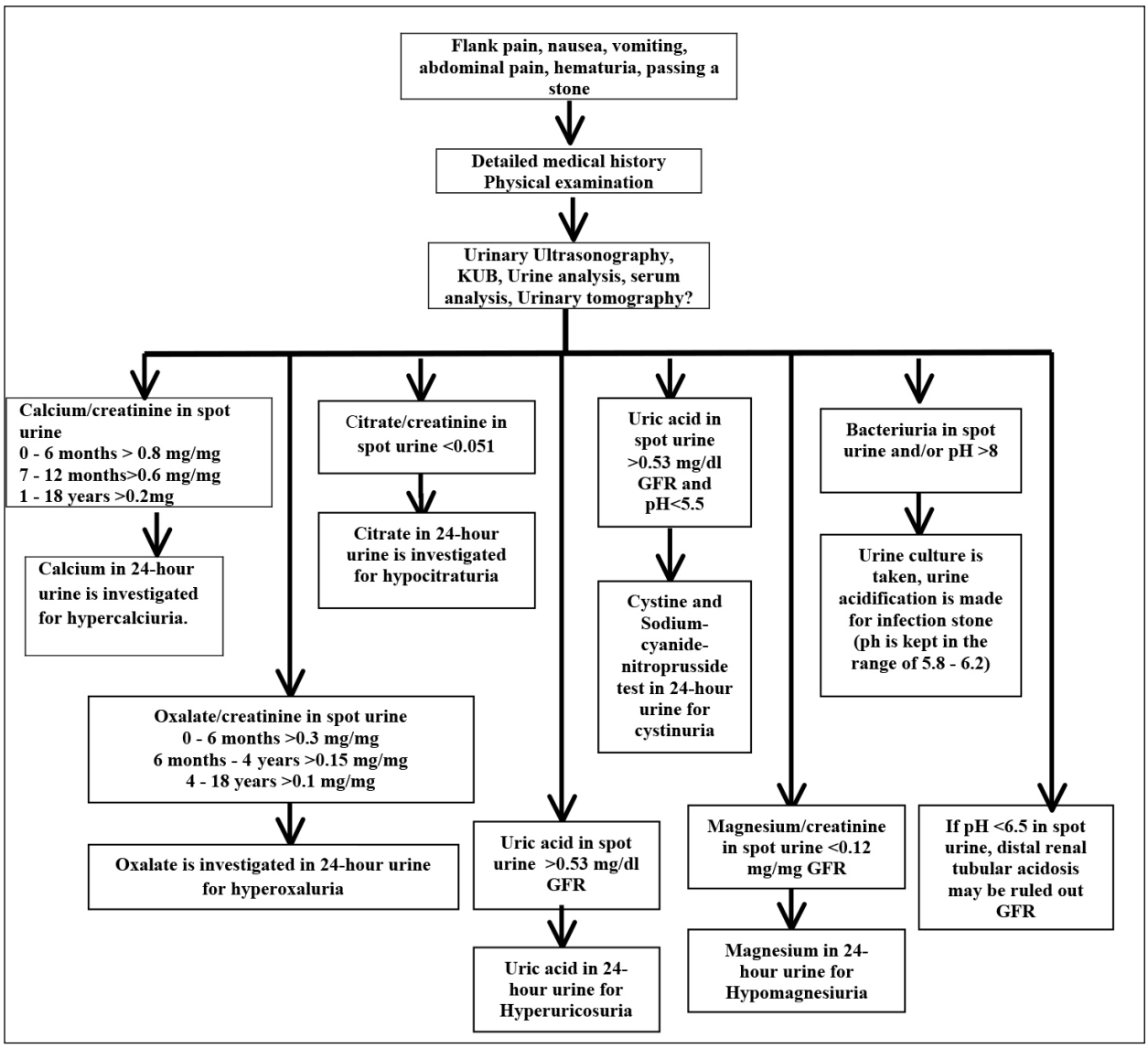


**Fig. 1:** Practical diagnostic algorithm in pediatric urolithiasis

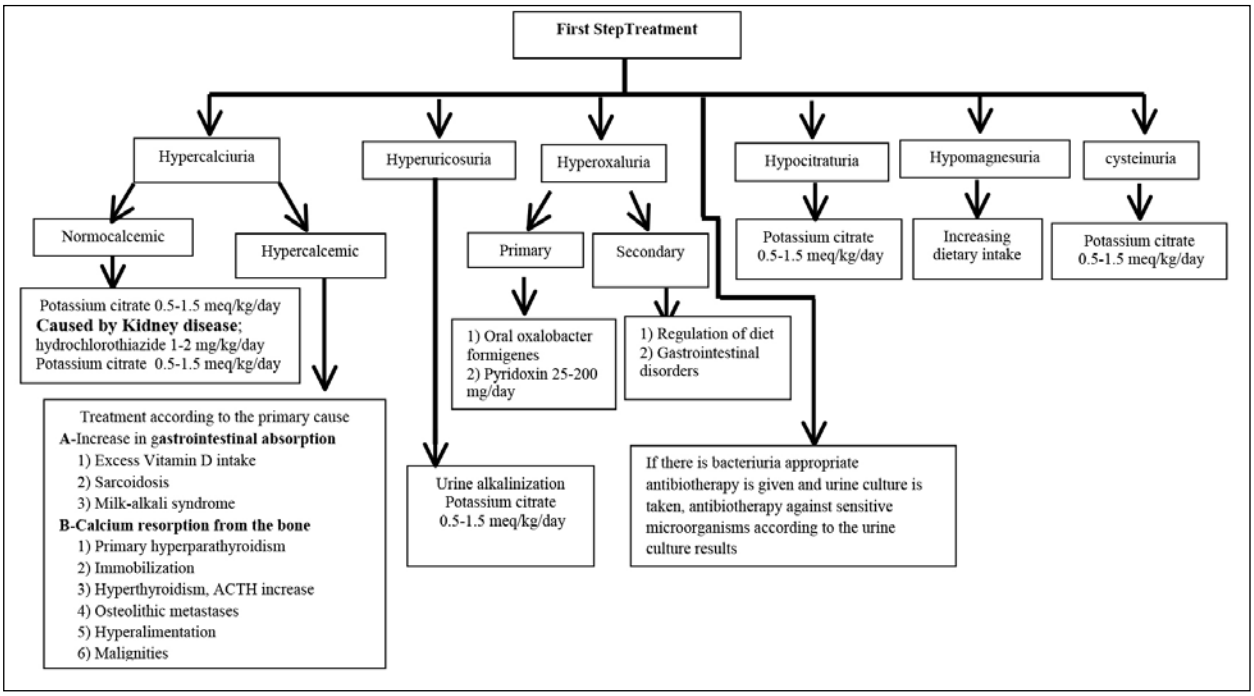


**Fig. 2:** First step treatment in the management for pediatric stone diseases

metabolism, is seen as a result of oxidase enzyme deficiency. Urinary excretion of hypoxanthine and xanthine increases. Urinary solubility of xanthine is minor. Allopurinol may be used in the treatment of this disease. Dietary purine intake should be reduced and a lot of fluids should be taken.

In daily pediatric urology practice, detailed examination is necessary in cases where urolithiasis is seen. Detailed medical history should be recorded first and physical examination should be conducted. Familial history of stones, additional diseases and medications used should be recorded. Metabolic and non-metabolic problems which may be the reason for stone diseases should be kept in mind. In urolithiasis seen in the pediatric age group, the most common non-metabolic disorders may include vesicoureteral reflux disease, urotero-pelvic junction obstructions, neurogenic bladder and other micturition disorders[48]. Then simple clinical assessment may be made. In the simple assessment, first simple urine analysis and

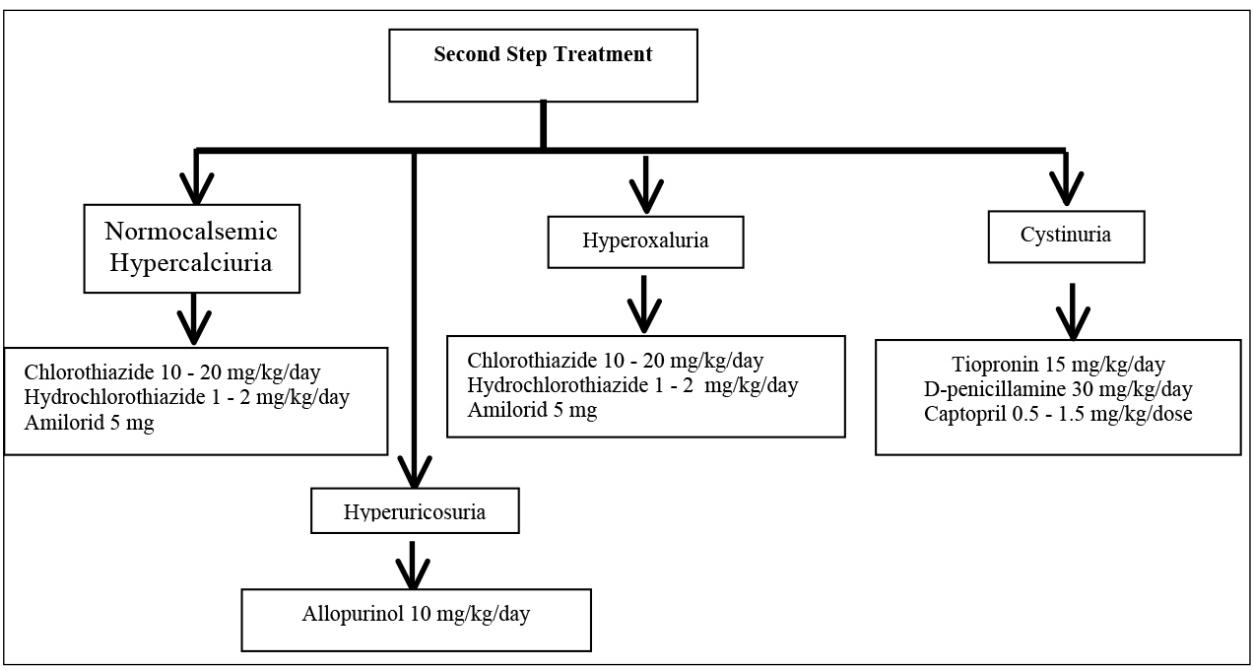


**Fig. 3:** Second step treatment options for pediatric stone diseases

ultrasound are among the tests that may be requested. It may be useful to consider the following algorithm to reach an exact diagnosis after reaching pre-diagnosis with examination of urine and considering other clinical information (Fig. 1).

Following simple clinical examinations, pH, calcium, phosphorus, magnesium, oxalate, sodium, potassium, uric acid, citrate, cystine and creatinine should be investigated in urine collected over 24 hours and the urine amount should be recorded. Moreover, urine culture is recommended[48]. On the other hand, sodium, potassium chloride, calcium, phosphorus, magnesium, creatinine, blood urea nitrogen, alkaline phosphatase, uric acid and intact parathyroid hormone should be investigated in the serum and complete blood count should be done. The probability of stone formation is high, if the calcium / citrate ratio in the 24-hour urine is above 0.326[49]. In pediatric urolithiasis that is commonly seen in daily clinical practices, when it is time to decide on the treatment after diagnostic stages; first, second and third line treatment options are considered according to the cause. It is recommended that the following algorithms are followed for the most commonly seen pathologies and their practical treatments (Fig. 2 - 4). As mentioned above, it is crucial to apply general therapy recommendations in pediatric urolithiasis including large fluid intake and dietary modifications in each stage of these lines of treatment.

If the patient spontaneously passes a stone or a stone was acquired as a result of lithotripsy (ESWL)

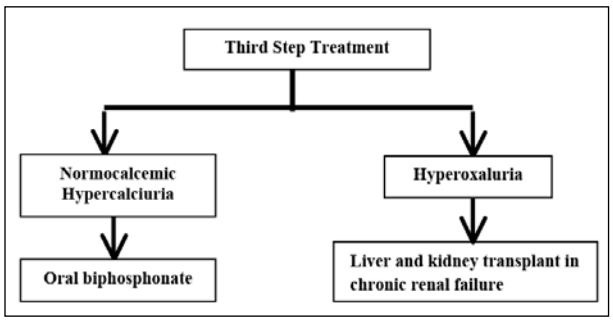


**Fig. 4:** Third step treatment options for pediatric stone diseases

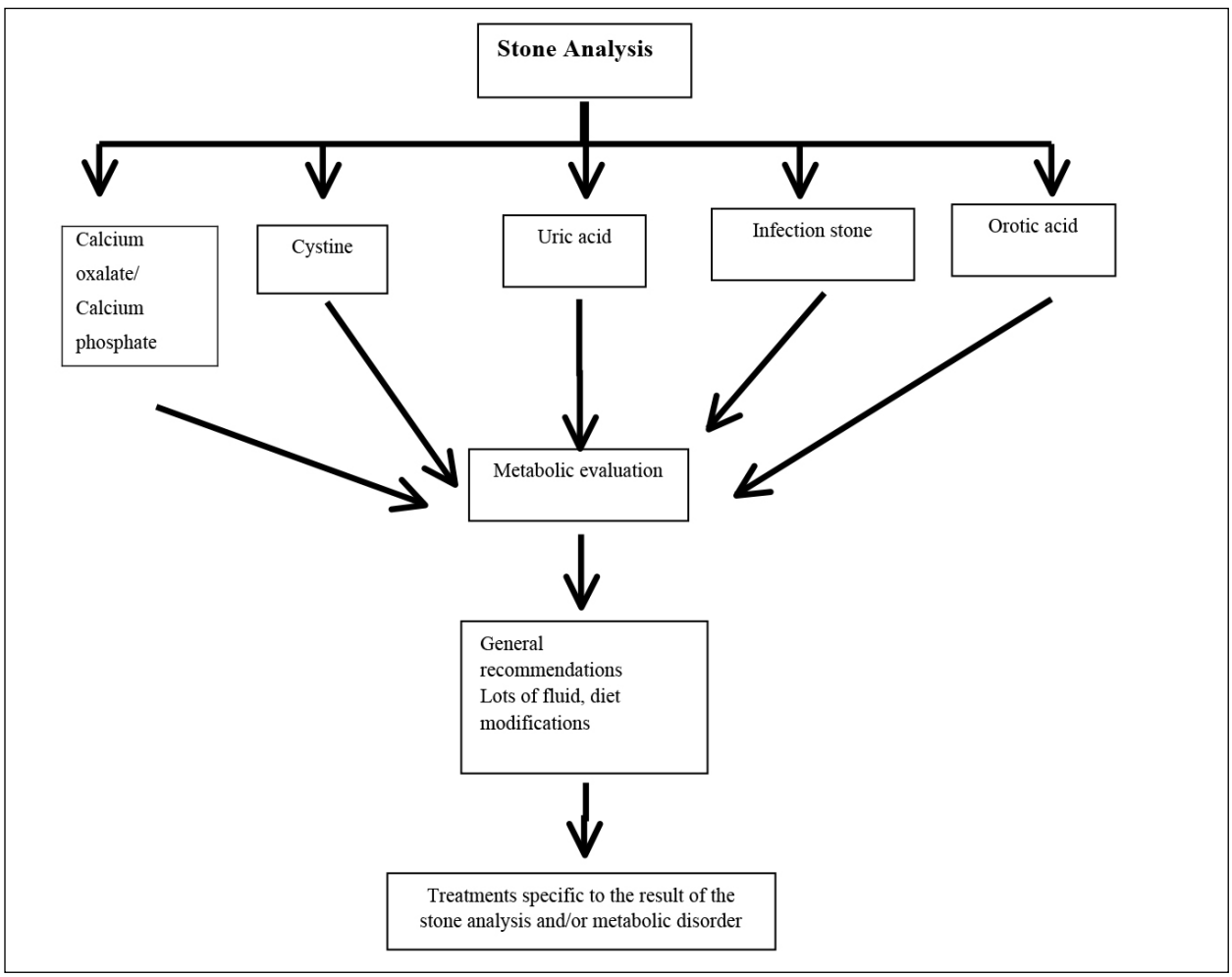


**Fig. 5:** Management, follow-up and impact of metabolic evaluation for pediatric stone diseases

and / or surgical procedures, a stone analysis should definitely be made. After an exact diagnosis is made according to the results of the stone analysis and metabolic analysis, metaphylaxis should be given as mentioned above[50] (Fig. 5).

## CONCLUSION

Urolithiasis, is common in our country in the pediatric age group and requires detailed examination. Delays in diagnosis and treatment may lead to serious consequences that may develop into renal failure. Metabolic abnormalities are common in pediatric urolithiasis and they are also responsible for stone recurrences. Recurrence of stones and renal damage may be prevented with the help of early diagnosis, detailed metabolic examination as well as appropriate follow-up and treatment protocols.

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Original Article

# Factors Indicating the Best Reperfusion Method in Acute Myocardial Infarction: Q Wave Better than Time of Onset

Hesam Mostafavi-Toroghi, Elyas Naghib, Golkoo Hosseini, Mohsen Mouhebati, Alireza Heidari-Bakavoli
Cardiovascular Research Center, Faculty of Medicine, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran

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## ABSTRACT

**Objectives:** To evaluate the admission electrocardiogram (ECG) patterns as prognostic factors and compare the Q wave with other criteria such as time, for choosing the best treatment in acute myocardial infarction (AMI)
**Design:** Prospective case-control study
**Setting:** Cardiac Emergency Departments of Imam Reza and Qaem Hospitals, Mashhad, Iran
**Subjects:** A total of 143 consecutive patients between year 2010 and 2012, diagnosed with AMI who were candidates for reperfusion therapy were enrolled
**Interventions:** The admission and control post-thrombolytic therapy ECGs were taken for all subjects. Then admission ECG patterns, time to therapy and their relation with the reperfusion rate were analyzed.
**Main Outcome Measures:** 60.1% (n = 86) of patients achieved 50% or more ST recovery (good response group) and 39.8% (n = 57) of patients had lower than 50% ST recovery (poor response group).
**Results:** The mean response rate was significantly lower in patients presenting with Q wave (p = 0.023). In patients with initial Q wave, there was no significant difference in response rate whether they were treated within three hours from the onset of symptoms or not (p = 0.75). In contrast, patients without Q wave who received thrombolytic therapy within first three hours had significantly higher reperfusion rates in comparison with those treated after three hours (p = 0.004).
**Conclusion:** It is suggested that, time from the onset of symptoms along with initial Q wave is better for decision making in AMI management, than the time alone.

KEY WORDS: electrocardiography, percutaneous coronary intervention, thrombolytic therapy

## INTRODUCTION

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. It results from an imbalance between myocardial oxygen supply and demand[1,2]. This is due to an occlusive thrombus in most cases[2]. The principal mechanism which could improve the outcome and survival of the myocardial infarction (MI) patients is early achievement of a normal blood flow in the infarct-related coronary artery by early reperfusion strategies (whether by thrombolytic agents such as streptokinase and tissue plasminogen activator (TPA) or by primary per-cutaneous coronary intervention ,(P-PCI)[3, 4]. The successful reperfusion in the infarcted vessel depends on how far the irreversible necrosis has progressed which is traditionally predicted by the time elapsed from the onset of symptoms. That would be an indicator of the extent of the infarction development and the age of the coronary artery thrombus[5]. However, pain perception is not a precise factor, because it is subjective; also, about 20 - 30% of patients especially diabetics and elderly patients diagnosed with AMI have not experienced chest pain on presentation[6,7].

The standard 12-lead electrocardiogram (ECG) is an easily available, non-expensive and simple clinical test that is the most widely used tool for diagnosis and even management of patients suspected of having a coronary artery event (especially AMI). The evolution of coronary occlusion in the process of AMI introduces some changes to ECG such as ST elevation, pathologic Q waves and T-wave inversion to name a few[2,8]. ST segment elevation is an electrocardiographic criterion for administration of thrombolytic therapy[9]. Some researchers have extended the use of ECG to outcome prediction (*e.g.*, lack of ST-segment resolution and development of late pathologic Q wave can be used as predictors of one-year mortality)[10]. Recently, some researchers suggested

*Address correspondence to:*
*Mohsen Mouhebati MD, Cardiovascular Research Center, Faculty of Medicine, Mashhad University of Medical Sciences (MUMS), Mashhad, Iran. P.O. Box: 99199-766-91; Tel: +98-511-8012867; Fax: +98-511-8430492. E-mail: mouhebatim@mums.ac.ir, hesam.mostafavi@gmail.com*

that ECG can provide more objective data about the duration of coronary thrombosis than time from the onset of symptoms. Also, some ECG parameters such as initial pathological Q waves have been thought to be useful for risk stratification and outcome prediction in patients with AMI[11,12]. Although PCI is preferred rather than fibrinolytic therapy in high risk patients and those who present more than three hours after the onset of symptoms, many hospitals currently, especially in developing countries do not have the facilities to perform PCI[13-16]. Therefore, patients should be transferred to a PCI-capable hospital or administered fibrinolytic therapy instead[17]. Previous studies have suggested that ECG parameters could be a better criterion than time alone for decision making in AMI[11, 12].

The aim of this study was to investigate the relationship between the admission ECG changes and the likelihood of successful reperfusion following the administration of streptokinase (STK). We also seek to introduce the admission ECG parameters along with time from the onset of symptoms as a better indicator for administration of thrombolytic therapy for reperfusion.

## SUBJECTS AND METHODS

This was a prospective case-control study conducted between 2010 and 2012 at the Cardiac Emergency Departments in Imam Reza and Qaem Teaching Hospitals, Mashhad, Iran. All patients admitted to the emergency unit and diagnosed with an ST elevation AMI (STEMI) who were candidate for receiving thrombolytic therapy were enrolled to this study. Approval for the study was obtained from the Ethics Committee of Mashhad University of Medical Science (MUMS). One hundred and fifty six consecutive patients were recruited into this study. All demographic and clinical data of the patients were collected by direct examination and history taking. Serial 12-lead ECGs were done on admission and 60 minutes after initiating streptokinase therapy. Reduction of ST-segment elevation has been introduced as a non-invasive marker of reperfusion after thrombolytic therapy[18]. In the present study, summed ST segment resolution has been calculated and considered as an indicator of clot lyses and reperfusion rate. Patients were allocated to two groups based on the success rate of reperfusion following therapy with streptokinase 1.5 mμ over 30 minutes and then ECG parameters have been compared between them. On the other hand, time from the onset of symptoms to thrombolytic therapy has been used for categorizing patient into two groups: a group with three hours or less from the onset and another group with more than three hours passed from the onset of symptoms. ECG parameters were compared between these two groups as well.

### ECG analysis

The ECG analysis was done by two separate cardiologists, blinded to the patients' clinical course; and then results were matched together. The factors measured in the admission ECG were as follow:

- Q wave, duration more than 40 ms and depth more than 25% of R wave considered as pathologic
- QRS duration in a lead with the most amplitude
- ST elevation measured 60 ms after J-point
- Inverted T wave more than 0.5 mv (biphasic T waves were excluded)

ST elevation was measured in the post-streptokinase ECG for evaluation of response to reperfusion treatment, using this formula:

Achieving 50% or more recovery in ST elevation after thrombolytic therapy has been considered as good response and otherwise reflects reduced myocardial reperfusion which is an indicator of lower patency of infarct related artery and poor outcome[18,19].

### Data analysis

All data were entered in a formulated database of Statistical Package for Social Sciences (SPSS 20th release) and analyzed by this software. Parametric and non-parametric variables were analyzed by T-test and Mann-Whitney U test respectively. Discrete variables were analyzed by $\chi^2$ test as well. A two-tailed p-value lower than 0.05 was considered as statistically significant.

## RESULTS

Out of 157 recruited patients, 14 were excluded: six because of non-favorable ECG and questionable indication of STK administration, three because of accelerated idioventricular rhythm, three because of left bundle branch block and two because of left ventricular hypertrophy. Among the remaining 143 cases, 113 were male (79%) and 30 were female (21%). The minimum and maximum age among men was 31 and 89 years and among women was 48 and 86 years respectively. Regarding the past medical history of patients, 31.5% were hypertensive, 17% were diabetic and 38% were dyslipidemic. Opium usage and smoking habit was seen in 21% and 38% of patients respectively. The minimum and maximum duration of time to reperfusion therapy was 30 minutes and 540 minutes respectively. Considering the response to reperfusion treatment, 12 patients have shown 100% response and 13 patients have shown 0% response. Regarding the percentage of ST recovery, 60.1% (n = 86) of patients achieved 50% or more ST recovery which was considered as a good response and 39.8% (n = 57) of patients had lower than 50% ST recovery which was considered as a poor response. Age, sex, height, weight, BMI, pulse rate, diabetes, hyperlipidemia and smoking have shown no significant difference

**Table1:** Comparison of response percentage in different patients

| Variable | Response percentage to fibrinolytic therapy | | p-value |
|---|---|---|---|
| | Positive | Negative | |
| Presence of Q wave in admission ECG | 45.60 ± 33.10 | 58.55 ± 31.76 | 0.023* |
| Diabetes | 42.79 ± 33.79 | 56.29 ± 32.16 | 0.065 |
| Hypertension | 42.84 ± 32.26 | 59.16 ± 31.78 | 0.005* |

Data were expressed as mean ± SD. Analysis were done using T test
*p-value significant

between good response and poor response group. ECG parameters and time from the onset of symptoms were compared between good response and poor response groups (Tables 1 – 4). Patients who had a Q wave in the presenting ECG, as well as hypertensive patients have shown significant lower response after thrombolytic therapy (Table 1). Regarding the time from the onset of symptoms, patients who had received streptokinase in the first three hours from

**Table 2:** Comparison of admission ECG non-parametric parameters and time from onset of symptoms between good response and bad response group of patients

| Parameters of admission ECG | Good response group | Bad response group | p-value |
|---|---|---|---|
| Q wave duration (ms) | 40 (40, 70) | 40 (34.8, 60) | 0.339 |
| Q wave depth (ms) | 3 (2, 7.5) | 3.5 ( 2, 6) | 0.935 |
| QRS duration (ms) | 90 (80, 100) | 90 (80, 100) | 0.827 |
| Total ST elevation (ms) | 9.62 (6.25, 14.31) | 10.25 (6.75, 15.12) | 0.613 |
| Maximum ST elevation (mm) | 3 (2.25, 4.50) | 3.25 (2.12, 4.87) | 0.774 |
| T wave depth (mm) | 2 (0.5, 3) | 1.5 (0.75, 1.81) | 0.767 |

ms = millisecond, mm = millimeter, data expressed as median and interquartile range. Analysis were done using Mann-Whitney test

the onset of symptoms have shown significant higher response rate (Table 4). Regarding time from the onset of symptoms and Q wave simultaneously, time did not make any significant difference in response rate in the patients who had Q wave; However, in patients with no presenting Q wave, those who had received thrombolytic therapy in less than three hours showed significant higher response in comparison with those

**Table 3**: Comparison of admission ECG parametric parameters and HTN between good response and bad response group of patients

| Parameters of admission ECG | Good response group % | Bad response group % | p-value |
|---|---|---|---|
| Inverted T wave | | | 0.995 |
| Present | 3.5 | 3.5 | |
| Absent | 96.5 | 96.5 | |
| HTN | | | 0.026* |
| Present | 24.4 | 42.1 | |
| Absent | 75.6 | 57.9 | |

Analysis were done using $\chi^2$ test, *p-value significant

**Table 4:** Comparison of reperfusion response percentage between groups

| Parameters of admission ECG | Good response group % | Bad response group % | p-value |
|---|---|---|---|
| Time from the onset of symptoms | | | 0.013* |
| ≤ 3 hours | 80.2 | 61.4 | |
| > 3 hours | 19.8 | 38.6 | |
| Time from the onset of symptoms in patients with Q wave | | | 0.758 |
| ≤ 3 hours | 72 | 68 | |
| > 3 hours | 28 | 32 | |
| Time from the onset of symptoms in patients without Q wave | | | 0.004* |
| ≤ 3 hours | 83.6 | 56.2 | |
| > 3 hours | 16.4 | 43.8 | |

Analysis were done using $\chi^2$ test, *p-value significant

who got thrombolytic treatment after three hours from the onset of symptoms (Table 4).

## DISCUSSION

Myocardial infarction (MI) is one of the most common cardiovascular causes of death worldwide. Early intervention by either thrombolytic therapy or primary angioplasty improves the likelihood of reperfusion of an obstructed coronary artery, limits the infarct size, improves left ventricular function and survival[20-22].

Based on the results of the present study, patients who had Q wave in their initial ECG had significant lower response to thrombolytic therapy irrespective of time from the onset of symptoms (p = 0.023). In fact, the presence of Q wave indicates infarct progression. Therefore, patients with Q wave have an older clot with resulting less reperfusion after streptokinase administration in comparison with patients without a Q wave in the admission ECG. This is consistent with the results of Wong *et al*[11, 12]. It has been proven that increasing time to streptokinase therapy is associated with decreasing rate of reperfusion. A number of authors believe that if reperfusion is instituted before three hours of coronary artery occlusion, significant reperfusion and clot lyses will occur whereas, if reperfusion is instituted beyond 3 - 6 hours, less and slower clot salvage will occur[5,22,23]. Based on our results in patients who had received thrombolytic therapy before three hours of coronary artery occlusion, significant higher response occurred as well (p = 0.013). Although it has been demonstrated that P-PCI achieves higher rates of reperfusion in comparison with thrombolytic therapy[24-26], many hospitals do not have the catheterization facilities. On the other hand, it is accepted that the time of clot progression is critical for prompting reperfusion[27].

Regarding the time to therapy and initial Q wave presentation together, the reperfusion rate in patients

who had initial Q wave were similar either before or after three hours from the onset of symptoms (p = 0.75). In contrast, patients without Q wave in their admission ECG showed a significant higher response, if reperfusion treatment has been instituted before three hours versus after three hours from the onset of symptoms (p = 0.004). Thus, it seems that the presence of Q wave in the initial ECG along with time might be more reliable indicator of the progression of the infarction process than the time alone. Therefore, patients who have Q wave in their admission ECG would benefit more from primary PCI than fibrinolytic therapy regardless of time. But for patients without initial Q wave especially those who present earlier, immediate fibrinolytic therapy would be a more beneficial option. Previously, the results of HERO2 study have suggested that presence of initial Q waves in patients with STEMI who have been treated with fibrinolytic therapy is associated with higher 30-day mortality[12]. Moreover, episodes of silent ischemia and prodromal angina and individual pain perception would not affect the Q wave in contrast with time of symptom onset, and this adds another advantage to the utility of Q wave[28-31].

According to the last STEMI guideline for patients presenting to a non-PCI-capable hospital, rapid assessment of 1) the time from onset of symptoms, 2) the risk of complications related to STEMI, 3) the risk of bleeding with fibrinolysis, 4) the presence of shock or severe heart failure, and 5) the time required for transfer to a PCI-capable hospital must be made to make decision about administration of fibrinolytic therapy[32]. The present study suggests that addition of presenting ECG patterns along with time may be more reliable criteria than time alone.

Regarding other parameters of initial ECG, our results demonstrated no significant relationship between QRS duration and response percentage which is in contrast with the results of Kacmaz *et al* who have suggested QRS duration as a predicting factor for response rate[33]. ST segment elevation had no relation with response rate as well; this is consistent with the results of previous studies[12]. There was no significant relation between inverted T wave and response rate. In contrast, Wong *et al* have demonstrated that presence of inverted T wave is associated with lower reperfusion rate[11]. One explanation for this could be that biphasic inverted T has not been mentioned as inverted T in our study.

## CONCLUSION

The presence of Q waves on the admission ECG along with time presents more objective and reliable data for management of AMI patients in comparison with time alone. Moreover, it is an acceptable prognostic factor for lower response rate. The presence of initial Q wave even in early treated patients was associated with less reperfusion rate after fibrinolytic therapy. According to the results of the present study, it seems that patients without Q wave, especially those who are treated earlier would benefit more from fibirinolytic therapy. It is especially helpful in hospitals without catheterization facilities; thus, patients with Q wave in their admission ECG would benefit more from being transferred to a more equipped center regardless of time.

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Original Article

# Human Leukocyte Antigen Class II Genetic Variants are Highly Associated with Rheumatic Heart Disease in Yemeni Patients

Ahmed Lotf Al-Motarreb[1], Riyadh Saif-Ali[2], Arwa Mohammed Othman[3], Haitham Abdullwahab Masood[4], Mojahid Yahyia Nassar[4]

[1]Department of Internal Medicine, Faculty of Medicine, Sana'a University, Sana'a Yemen
[2]Department of Biochemistry, Faculty of Medicine, Sana'a University, Sana'a Yemen
[3]Department of Microbiology, Faculty of Medicine, Sana'a University Sana'a Yemen
[4]HLA Typing Unit, Al-Thawra General Hospital, Sana'a Yemen

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## ABSTRACT

**Objectives:** To investigate the association of rheumatic heart disease (RHD) with human leukocyte antigen (HLA) class II alleles in Yemeni patients
**Design:** Case control study
**Setting:** Al-Thawra Modern General Hospital, Sana'a, Yemen
**Subjects:** One hundred RHD patients (case group) and 50 healthy subjects (control group) were recruited in this study.
**Interventions:** Echocardiography was used to include RHD patients (abnormal echocardiography) and healthy subjects (normal echocardiography).
**Main Outcome Measures:** HLA-DRB1 and HLA-DQB1 polymorphisms were genotyped by sequence-specific oligonucleotide-probe polymerase chain reaction (PCR-SSOP) reverse dot blot hybridization.
**Results:** The results showed that HLA-DRB1*07 and HLA-DQB1*0203 allele as risk factors for RHD (OR = 4.0; 8.7, p = 0.005; 0.02, respectively). In contrast, the HLA-DRB1*11, HLA-DQB1*0305 and HLA-DQB1*0602 alleles showed a protective association against RHD (OR = 0.32; 0.23; 0.24, p = 0.01; 0.03; 0.01, respectively).
**Conclusions:** HLA class II genetic variants were a predisposing factor for development of RHD in Yemeni people. This study also replicated the association of HLA-DRB1*07 with RHD and suggested that HLA-DQB1*0203 allele is a risk factor for RHD.

KEY WORDS: HLA-DRB1, HLA-DQB1, molecular mimicry, rheumatic heart disease

## INTRODUCTION

Rheumatic heart disease (RHD) is still a major public health burden in developing countries due to the morbidity and mortality resulting from the heart lesions that follow a rheumatic fever (RF) episode in 30 - 45% of patients. It was estimated worldwide that at least 15.6 million individuals have RHD, and this disease is leading to 233,000 deaths annually. The highest prevalence of RHD was reported from developing countries than developed countries[1-4]. Prevalence of RHD was reported to be 0.8 / 1000 in Oman[5], 2.4 / 1000 in Saudi Arabia[6], 3 / 1000 in Sudan[7], 6.2 / 1000 in Egypt[8], 5.7 / 1000 in sub-Saharan Africa and in Pakistan[2,9] and 5.8 / 1000 in India[10]. Prevalence of RHD in Northern parts of Yemen was reported to be 3.6 / 1000[11] while in southern parts of Yemen, it was estimated to be 36.5 / 1000[12], which is one of the highest prevalence in the world.

RHD is a consequence of autoimmune reaction triggered by group A streptococcal pharyngitis leading to severe heart valvular damage. The exact reason why only certain individuals exposed to group A streptococci develop RHD is unknown. Molecular mimicry between human cardiac myosin and the M proteins of the group A streptococcal membranes has been proposed as a triggering factor, leading to autoimmunity in individuals with a genetic predisposition factor[13-16]. M protein plays an important role in the bacterial adherence to throat epithelial cells. It shares structural homology with a-helical coiled-coil human proteins like cardiac myosin, tropomyosin, vimentin and several valvular

*Address correspondence to:*
*Arwa Othman, Department of Microbiology, Faculty of Medicine, Sana'a University Sana'a, Yemen. Tel: 00967 777139183, E-mail: arwaothman@hotmail.com*

proteins resulting in cross-reactivity by both T and B lymphocytes[17,18].

Genetic factors have been postulated to be important in determining susceptibility patterns to RHD. RHD is found to be more common in individuals with family history[19-22]. Human leukocyte antigen (HLA) class II polymorphisms were a predisposing factor for RHD. HLA class II molecules are normally expressed on particular immune cells known as professional antigen presenting cells (APCs) such as dendritic cells and macrophages. Professional APCs engulf extracellular protein antigens, degrade them into peptide fragments, couple peptide fragments (epitopes) to the HLA class II molecules for presentation and activation of resting T lymphocytes. The molecular mechanism by which certain MHC class II molecules confer susceptibility to RHD is not clear. However, risk HLA class II alleles may encode HLA molecules that facilitate the presentation of some streptococcal peptides that later will trigger autoimmune responses[23,24]. The predisposing allelic HLA class II variants were different in various populations with HLA-DR7 being predominantly observed in different ethnicities[25-33]. In Yemen, the predisposing HLA class II alleles remain practically unknown. The aim of this study was to investigate the association of HLA class II alleles with RHD in Yemeni patients.

## SUBJECTS AND METHODS

### Study Subjects

Yemeni RHD patients aged 14 to 45 years who attended the outpatient clinic at Al-Thawra Hospital in Sana'a for treatment were invited to participate in this study. One hundred RHD patients (57 females, 43 males) freely participated in the study (case group). The diagnosis of RHD was confirmed using echocardiogram in each patient. For control group, normal subjects aged 18 to 47 years in the same geographical area as the patients were invited to participate in this study. Fifty healthy individuals (28 females, 22 males) freely participated to act as control group. In order to exclude presence of subclinical RHD in this group, echocardiogram was used in each healthy study subject. Venous blood, 3 - 4 ml was collected from each participant. The study was approved by ethical committee at Sana'a University.

### HLA class II genotyping

Genomic DNA was extracted from peripheral blood leukocytes using PureLink Genomic DNA kit (Invitrogen, USA). HLA class II DRB1 and DQB1 genotyping were carried out using sequence-specific oligonucleotide-probe polymerase chain reaction with Dynal RELI SSO HLA-DRB1 and Dynal RELI SSO HLA-DQB1 kits, respectively (Invitrogen, USA).

### Statistical analysis

Statistical Package for Social Science (SPSS) 12 (SPSS Inc, Chicago, IL, USA) was used for comparing the frequency of HLA-DRB1 and HLA-DQB1 alleles between the patients and the controls using the chi-square test or Fisher's exact test, as appropriate. Odds ratio (OR) with their 95% confidence intervals were calculated and alleles showing an association with RHD at 5% or less level of significance were deemed to be significant.

## RESULTS

The echocardiographic data of the patients with RHD are depicted in Table 1. The results showed that

**Table 1:** Echocardiographic data of 100 patients with rheumatic heart disease

| Echocardiographic parameter | Patients with rheumatic heart disease number (%) |
|---|---|
| Site of lesion | |
| Mitral valve | 29 (29) |
| Mitral and aortic | 52 (52) |
| Mitral, aortic and tricuspid | 19 (19) |
| Main Echocardiographic abnormality | |
| Mitral regurgitation | 47 (47) |
| Mitral stenosis | 3 (3) |
| Mitral regurgitation and stenosis | 50 (50) |

**Table 2:** Association of HLA-DRBI alleles with rheumatic heart disease

| HLA-DRB1 alleles | N (frequency) | | OR | 95% CI | p-value |
|---|---|---|---|---|---|
| | Cases (n = 100) | Controls (n = 50) | | | |
| HLA-DRB1*01 | 24 (0.24) | 9 (0.18) | 1.43 | 0.61 - 3.38 | 0.4 |
| HLA-DRB1*03 | 19 (0.19) | 9 (0.18) | 1.1 | 0.44 - 2.57 | 0.88 |
| HLA-DRB1*04 | 40 (0.40) | 18 (0.36) | 1.2 | 0.59 - 2.39 | 0.64 |
| HLA-DRB1*07 | 31(0.31) | 5 (0.10) | 4.0 | 1.5 - 11.2 | 0.005 |
| HLA-DRB1*08 | 9 (0.09) | 5 (0.10) | 0.89 | 0.28 - 2.81 | 0.84 |
| HLA-DRB1*10 | 2 (0.02) | 3 (0.06) | 0.32 | 0.05 - 1.98 | 0.1[a] |
| HLA-DRB1*11 | 10 (0.10) | 13 (0.26) | 0.32 | 0.13 - 0.79 | 0.01 |
| HLA-DRB1*12 | 4 (0.04) | 5 (0.1) | 0.38 | 0.1 - 1.5 | 0.15 |
| HLA-DRB1*13 | 44 (0.44) | 23 (0.46) | 0.92 | 0.47 - 1.82 | 0.82 |
| HLA-DRB1*15 | 5 (0.05) | 4 (0.08) | 0.6 | 0.16 - 2.36 | 0.5 |
| HLA-DRB1*16 | 9 (0.09) | 4(0.08) | 1.14 | 0.33 - 3.89 | 0.84 |

OR = odds ratio, CI = confidence interval, [a] = The p-value was generated using Fisher's exact test.

**Table 3:** Association of HLA-DQBI alleles with rheumatic heart disease

| HLA-DQB1 alleles | N (frequency) | | OR | 95% CI | p-value |
|---|---|---|---|---|---|
| | RHD cases (n = 100) | Controls (n = 50) | | | |
| HLA-DQB1*0201 | 23 (0.23) | 8 (0.16) | 1.6 | 0.65 - 3.81 | 0.32 |
| HLA-DQB1*0202 | 17 (17) | 5 (10) | 1.8 | 0.64 - 5.33 | 0.25 |
| HLA-DQB1*0203 | 15 (0.15) | 1 (0.02) | 8.7 | 1.1 - 67.5 | 0.02 |
| HLA-DQB1*0301 | 21 (0.21) | 8 (0.16) | 1.4 | 0.6 - 3.4 | 0.5 |
| HLA-DQB1*0302 | 25 (0.25) | 9 (0.18) | 1.5 | 0.65 - 3.6 | 0.33 |
| HLA-DQB1*0303 | 8 (0.08) | 6 (0.12) | 0.64 | 0.21 - 2 | 0.43 |
| HLA-DQB1*0304 | 5 (0.05) | 3 (0.06) | 0.83 | 0.19 - 3.6 | 0.8 |
| HLA-DQB1*0305 | 3 (0.03) | 6 (0.12) | 0.23 | 0.1 - 0.95 | 0.03 |
| HLA-DQB1*0401 | 12 (0.12) | 6 (0.12) | 1 | 0.35 - 2.84 | 1 |
| HLA-DQB1*0402 | 10 (0.10) | 3 (0.06) | 1.7 | 0.5 - 6.6 | 0.41 |
| HLA-DQB1*0501 | 15 (0.15) | 6 (0.12) | 1.3 | 0.47 - 3.57 | 0.62 |
| HLA-DQB1*0502 | 11 (0.11) | 9 (0.18) | 0.56 | 0.22 - 1.5 | 0.23 |
| HLA-DQB1*0503 | 7 (0.07) | 6 (0.12) | 0.6 | 0.18 - 1.74 | 0.31 |
| HLA-DQB1*0504 | 4 (0.04) | 1 (0.02) | 2 | 0.22 - 18.7 | 0.5 |
| HLA-DQB1*0601 | 8 (0.08) | 6 (0.12) | 0.64 | 0.21 - 1.95 | 0.43 |
| HLA-DQB1*0602 | 5 (0.05) | 9 (0.18) | 0.24 | 0.1 - 0.8 | 0.01 |
| HLA-DQB1*0603 | 7 (0.07) | 7 (0.14) | 0.5 | 0.15 - 1.4 | 0.2 |

OR = odds ratio, CI = confidence interval, RHD = rheumatic heart disease.

HLA-DRB1*07 was strongly associated with RHD (OR = 4, p = 0.005) (Table 2). Moreover, HLA-DRB1*11 allele showed a protection against RHD (OR = 0.32, p = 0.01). HLA-DRB1*10 and HLA-DRB1*12 alleles showed a protective effect against RHD; however, they were not statistically significant (OR = 0.32; 0.38, p = 0.1; 0.15, respectively). The other alleles of HLA-DRB1*03, *04, *08, *13, *15, and *16 were not associated with RHD (Table 2).

The HLA-DQB1*0203 allele was a risk factor for RHD (OR = 8.7, p = 0.02). However, HLA-DQB1*0305 and –DQB1*0602 alleles were associated with a protection against RHD (OR = 0.23; 0.24, p = 0.03; 0.01, respectively) (Table 3). The HLA-DQB1 *0201, *0202 and *0402 alleles were not statistically significant risk factors for RHD (OR = 1.6; 1.8; 1.7, respectively). On the other hand, HLA-DQB1*0502 and HLA-DQB1*0603 alleles showed a protective effect against RHD, but statistical significance was not reached (OR = 0.56; 0.5, respectively). The other HLA-DQB1 alleles that were included in this study showed no association with RHD (Table 3).

## DISCUSSION

This study aimed to investigate the association of HLA-DRBI and HLA-DQBI with RHD among Yemeni patients. The present study found that the HLA-DRB1*07 were strongly associated with RHD in Yemen, which is in agreement with previous reports from Egypt[34], Pakistan[32], Turkey[29,35], Latvia[30] and Brasilia[33]. In contrast, the association of HLA-DRB1*07 allele with RHD could not be replicated in Taiwan[36] and Mexican Mestizo[37]. Furthermore, a study from north India showed an association between HLA-DR*14 and RHD[31] while another study performed in south India reported an association with HLA-DRB3*01 and HLA-DRB3*02[38]. Gene-gene and gene-environmental interactions may have contributed to many of the reported differences in gene-disease associations between different racial or ethnic groups[39].

Our study revealed that HLA-DQB1*0203 allele was a risk factor for RHD while HLA-DQB1*0201 and HLA-DQB1*0202 alleles were not statistically significant risk factors, which may be due to small sample size, particularly the control group. HLA-DQB1*0201 and HLA-DQB1*0202 alleles have been reported to be risk factors for RHD among Egyptian[34], Latvian[30] and Mexican[40] populations. On the other hand, the HLA-DRB1*11 allele showed a protective effect against RHD in this study which is in concordance with, other studies in Egypt[34], Turkey[29] and Mexico[37]. Moreover, our data suggest that HlA-DQB1*0602 allele may confer a protective effect against RHD, which is consistent with other studies[30, 34]. HLA class II molecules play a central role in T cells activation and mounting an immune response against extracellular microorganisms such as group A β-hemolytic streptococci. Exogenous antigens are engulfed and processed into small peptide fragments by antigen presenting cells. Antigenic peptides are then associated with HLA class II molecules and transported to the cell surface to be recognized by the T cells receptor (TCR), thus, triggering the activation of the adaptive immune response[41].

The molecular mechanism by which HLA class II variants confer susceptibility to autoimmune diseases is not clear[24]. However, the HLA-DRB1 and HLA-DQB1 risk alleles were the most associated alleles with the RHD patients and seems to be associated with the development of valvular lesions in the patients with RHD. Those risk alleles may facilitate the presentation

of some streptococcal peptides that later will trigger autoimmune reactions. Streptococcal epitopes that have similarity to cardiac proteins might activate autoreactive T lymphocytes. These autoreactive T cells may activate B cells to produce antibodies which cross react with the endothelial surface protein of heart valvular and cardiac myosin peptides. The cross-reactive antibodies might up-regulate the expression of vascular cell adhesion molecule 1 (VCAM-1) which facilitates migration of immune cells leading to inflammation of heart valve resulting in damaging the heart valve and formation of valve scar[42,43]. The limitation of this study was the poor response of subjects to participate, which resulted in small sample size, particularly the control group. This limitation will seriously affect the results and conclusions of the present study and a larger population study will be needed to confirm the results suggested by the study.

## CONCLUSION

This study suggests that certain HLA class II genetic variants were a predisposing factor for developing RHD in Yemeni people, in spite of the small sample size. This study replicated the association of HLA-DRB1*07 with RHD seen in other published reports. In addition, this study suggested that HLA-DQB1*0203 is a risk factor for RHD in Yemen which needs to be confirmed with a larger population study.

## ACKNOWLEDGMENT

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Original Article

# No Association between Schizophrenia and Female Hepatocellular carcinoma: A Case-Control Study in Taiwan

Shih-Wei Lai[1,2], Cheng-Li Lin[3,4], Kuan-Fu Liao[5,6]
[1]School of Medicine, China Medical University and [2]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan
[3]Department of Public Health, China Medical University and [4]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[5]Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan
[6]Department of Internal Medicine, Taichung Tzu Chi General Hospital, Taichung, Taiwan

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## ABSTRACT

**Objective:** To investigate the relationship between schizophrenia and hepatocellular carcinoma (HCC) in women in Taiwan
**Design:** Case-control study by analyzing the database from the Taiwan National Health Insurance program
**Subjects:** There were 922 female subjects aged 40 years or older with newly diagnosed HCC as the case group and 3688 female subjects aged 40 years or older without HCC as the control group.
**Main Outcome Measure:** The relationship between schizophrenia and HCC was investigated.
**Results:** After controlling for confounding factors, multivariable logistic regression analysis showed that the odds ratio of HCC was 1.82 (95% CI = 0.64, 5.18) in subjects with schizophrenia, when compared with non-schizophrenia subjects.
**Conclusions:** There is no association between schizophrenia and HCC in women in Taiwan.

KEYWORDS: female, HCC, schizophrenia

## INTRODUCTION

In order to investigate the relationship between schizophrenia and hepatocellular carcinoma (HCC) in women in Taiwan, we designed a case-control study by controlling for the confounding factors of HCC. The database from the Taiwan National Health Insurance program was analyzed. The previous studies have documented the details of this insurance program[1, 2].

## SUBJECTS AND METHODS

There were 922 female subjects aged 40 years or older with newly diagnosed HCC as the case group (mean age 70.98 years and standard deviation 8.43 years) from 2000 to 2010 (based on International Classification of Diseases 9th Revision-Clinical Modification, ICD-9 155, 155.0 and 155.2) and 3688 female subjects without HCC as the control group (mean age 70.41 years and standard deviation 8.84 years). Both groups were matched with age (every five years) and index year. We defined the index date as the date of diagnosing HCC. Schizophrenia (ICD-9 295 and V11.0) and other co-morbidities were diagnosed before the index date. We excluded all subjects with any cancer diagnosed before the index date (ICD-9 140-208).

## RESULTS

There were 10 subjects with schizophrenia among HCC cases (1.08%) and 30 subjects with schizophrenia among control subjects (0.81%) (Chi-square test, p = 0.43). The HCC group had higher proportions of diabetes mellitus (39.48% Vs 27.90%), cirrhosis (63.34% Vs 1.41%), alcoholic liver damage (1.84% Vs 0.43%), other chronic hepatitis (62.26% Vs 16.08%),

*Address correspondence to:*
*Kuan-Fu Liao, Department of Internal Medicine, Taichung Tzu Chi General Hospital, No.66, Sec. 1, Fongsing Road, Tanzi District, Taichung City, 427, Taiwan. Tel: 886-4-2205-2121, Fax: 886-4-2203-3986, E-mail: kuanfuliao@yahoo.com.tw*

**Table 1:** Odds ratio and 95% confidence interval of HCC associated with schizophrenia and other co-morbidities

| Variables | Crude | | Adjusted † | |
|---|---|---|---|---|
| | OR | (95% CI) | OR | (95% CI) |
| Age (per one year) | 1.01 | (0.999,1.02) | | |
| Co-morbidities before index date (yes Vs no) * | | | | |
| Schizophrenia | 1.34 | (0.65, 2.75) | 1.82 | (0.64, 5.18) |
| Diabetes mellitus | 1.69 | (1.45, 1.96) | 1.09 | (0.86, 1.38) |
| Cirrhosis | 120.78 | (89.06, 163.81) | 49.32 | (35.67, 68.20) |
| Alcoholic liver damage | 4.31 | (2.17, 8.57) | 1.00 | (0.32, 3.14) |
| Other chronic hepatitis | 8.61 | (7.34, 10.10) | 2.09 | (1.62, 2.70) |
| Hepatitis B infection | 19.25 | (13.70, 27.04) | 5.63 | (3.50, 9.06) |
| Hepatitis C infection | 35.69 | (27.31, 46.63) | 8.41 | (5.84, 12.11) |

† Adjusted for diabetes mellitus, cirrhosis, alcoholic liver damage, other chronic hepatitis, hepatitis B infection and hepatitis C infection
*The co-morbidities included before index date were as follows: Schizophrenia (ICD-9 295 and V11.0), diabetes mellitus (ICD-9 250), cirrhosis (ICD-9 571.2, 571.5 and 571.6), alcoholic liver damage (ICD-9 571.0, 571.1 and 571.3), other chronic hepatitis (ICD-9 571.40, 571.41, 571.49, 571.8 and 571.9), hepatitis B infection (ICD-9 V02.61, 070.20, 070.22, 070.30 and 070.32) and hepatitis C infection (ICD-9 V02.62, 070.41, 070.44, 070.51 and 070.54); OR = odds artio; CI= confidence interval

hepatitis B infection (18.87% Vs 1.19%) and hepatitis C infection (41.54% Vs 1.95%) than those in the control group, with statistical significance (Chi-square test, $p < 0.0001$). After controlling for confounding factors, multivariable logistic regression analysis showed that the odds ratio of HCC was 1.82 (95% CI = 0.64, 5.18) in subjects with schizophrenia, when compared with non-schizophrenia subjects (Table 1).

## DISCUSSION

To date, no consistent results exist about the relationship between schizophrenia and risk of HCC. Lichtermann *et al* in Finland reported that no significant association is detected between schizophrenia and HCC (standardized incidence ratio = 1.55, 95% CI = 0.67, 3.04)[3]. In contrast, Chou *et al* in Taiwan reported that female schizophrenia patients have lower risk of HCC (hazard ratio = 0.5, 95% CI = 0.35, 0.73)[4]. In the present study, after adjusting for the key confounding factors of HCC, no association was found between schizophrenia and HCC in women. This means that both diseases have their unique pathogenesis beyond existing knowledge. Moreover, only 40 female schizophrenia subjects were included. That is, the number is too small to achieve statistical significance.

Because of the presence of conflicting results, it is recomended that further studies with more cases are conducted to clearly determine the relationship between schizophrenia and HCC in women.

## CONCLUSION

No association is detected between schizophrenia and HCC in women in Taiwan.

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**Conflict of Interest Statement:** The authors disclose no conflicts of interest

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Original Article

# Can We Predict Depression in Patients with Rheumatoid Arthritis?

Suzan M Attar
Department of Internal Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

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## ABSTRACT

**Objectives:** Depression and rheumatoid arthritis (RA) are disabling conditions that, if untreated, are associated with high morbidity and mortality. Depression is common in RA patients. The aims of this study were to evaluate whether depression could be predicted in RA patients at a tertiary-care center and to determine the clinical factors associated with the occurrence of depression in RA patients.
**Design:** Cross-sectional study
**Setting:** King Abdulaziz University Hospital, Jeddah, Saudi Arabia, from January 2008 to December 2010.
**Subjects:** Two hundred patients with RA
**Intervention(s):** None
**Main Outcome Measure(s):** Depression was evaluated using the Beck Depression Inventory, and disease activity was evaluated using the 28-Joint Disease Activity Score index. Risk factors that may predispose to depression have been evaluated.
**Results:** The prevalence of depression in RA patients was 18%. Depression was more common in RA patients with high disease activity (56%) than in those with low disease activity (5%). There was a significant correlation between depression and RA disease activity ($r = 0.366$, $p = 0.001$). Patients with high disease activity had twice the risk of developing depression relative to patients with low disease activity (OR = 2.41 [95% CI 1.09-5.34]). Whenever a physician found a state of high disease activity in a patient, depression could be predicted to occur 73% of the time.
**Conclusion:** Depression could be expected among RA patients with high disease activity. Rheumatologists should consider assessing the psychological status of their patients, especially those with high disease activity, to optimize medical treatment and to ensure adherence to medication.

KEYWORDS: depression, disease activity, rheumatoid arthritis

## INTRODUCTION

The community prevalence of depression worldwide is 6.8 - 21.3%[1]. This prevalence increases three-fold in patients with chronic diseases[2,3]. Rheumatoid arthritis (RA) is a chronic inflammatory disorder that targets the joints and can cause permanent deformity leading to disability or premature mortality if the disease is not treated early and aggressively. Depression is common in individuals with RA, although reported prevalence varies considerably between 13% and 42% due to differences in study design and method used to identify depression[4]. However, regardless of the debate about the best diagnostic criteria to be used, there is general agreement that depressive symptoms are common in RA patients and are associated with decreased health status[5] and that it is one of the factors associated with increased mortality (both suicidal and non-suicidal)[6,7]. Investigators have been searching for factors that predispose to depression in RA patients for early detection and prevention and therefore improving both morbidity and mortality[3-7]. In Saudi Arabia, data on depression in RA patients and its predisposing factors is limited. The objectives of this study were to estimate if depression could be predicted in a well-defined, hospital-based population of patients with RA and to define the clinical factors associated with the occurrence of depression.

## SUBJECTS AND METHODS

A cross-sectional study was conducted from January 2008 to December 2010 at a tertiary-care teaching center in the western region of Saudi Arabia at King Abdulaziz University Hospital (KAUH). The study was approved by the Biomedical Ethical Research Committee of the Faculty of Medicine of King Abdulaziz University (KAU).

*Address correspondence to:*
*Dr Suzan Mansoor Attar, MD, FACR, FACP, FRCP(C), Associate Professor & Rheumatologist, Dept. of Internal Medicine, King Abdulaziz University. PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. Tel: +966-2-6408243, Fax: +966-2-6408315, E-mail: suzan_attar@hotmail.com*

**Patient selection**

Patients with RA who attended regular follow-up appointments at the adult outpatient clinic were included in this study. RA patients were diagnosed according to the 1987 American College of Rheumatology (ACR) classification criteria[8]. If the first criteria were not applicable, the 2010 ACR / European League Against Rheumatism classification criteria for RA were used to diagnose early disease[9]. Patients on a chronic high dose of steroids > 7.5 mg/ day, with thyroid hormone disturbances or with a history of depression or psychiatric illness prior to developing RA were excluded from the study. A formal informed consent was obtained from patients who were willing to participate in the study.

As the prevalence of depression among patients with RA has been reported to be 13 - 42%[4], we hypothesized the expected prevalence in our patients to be 13% and to reach significance at 23%. The sample size, which was calculated using MedCalc statistical software that is available at www.medcalc.be, was initially comprised of 160 patients. The size was increased by 25%, to a total of 200 patients, to account for non-respondents.

The following data were collected: age, gender and disease duration, which was divided into early disease (< 2 years) and established disease (> 2 years),[10] medication use, specifically steroids (dose < 7.5 mg/day), DMARDs (disease-modifying antirheumatic drugs: methotrexate (MTX) and antimalarial agents (hydroxychloroquine [HCQ] or chloroquine)) and Biological treatment; the presence of co-morbid illnesses, including diabetes mellitus, hypertension, cardiovascular disease, respiratory disease, renal disease and malignancy. Diabetes mellitus was defined according to the World Health Organization (WHO) definition as a fasting plasma glucose ≥126 mg/dl (7.0 mmol/l).[11] Hypertension was classified according to the WHO–International Society of Hypertension guidelines as a diastolic blood pressure > 90 mmHg or by the patient being treated with an antihypertensive agent[12]. Cardiovascular disease was documented if any of the following were present: ischemic heart disease, arrhythmia, congestive heart failure or peripheral vascular disease. The presence of respiratory disease included a patient having pneumonia, non-cardiogenic pulmonary edema, chronic obstructive pulmonary disease or pre-existing radiographic interstitial infiltrates indicating lung fibrosis or bronchiectasis. The presence of renal disease included kidney amyloidosis, nephrotic syndrome or chronic renal failure, and malignancy of any type, including lymphoproliferative disorders, was recorded.

**Assessment of depression**

Depression was assessed using the Beck Depression Inventory (BDI) self-report instrument, which measures the severity of recent depressive symptoms[13]. The BDI consists of 21 items related to symptoms of depression, including hopelessness and irritability, cognitive components such as guilt or feelings of being punished and physical symptoms such as fatigue and weight loss. Each item has four possible answers, and the scores on each of the 21 questions range from 0 - 3; the highest possible score for the test is 63 and lowest possible score is zero. A score above 16 was reported as depression. The Arabic version of the BDI has been tested and validated on Arabic-speaking patients using an identical grading system[14].

**Assessment of RA disease activity**

Disease activity was assessed using the 28-Joint Disease Activity Score index (DAS28) and levels of C-reactive protein (CRP). CRP was measured using immunonephelometry (using BN II system by Dade Behring®) . The patients were divided into three groups depending on the DAS28 score: Group I: high disease activity with a DAS28 score > 5.1; Group II: moderate disease activity with a DAS28 score between 5.1 and 3.2; and Group III: low disease activity with a DAS28 score < 3.2[15,16].

**Statistical analysis**

Data analysis was performed using the Statistical Package for Social Sciences (SPSS version 18, SPSS Inc.,

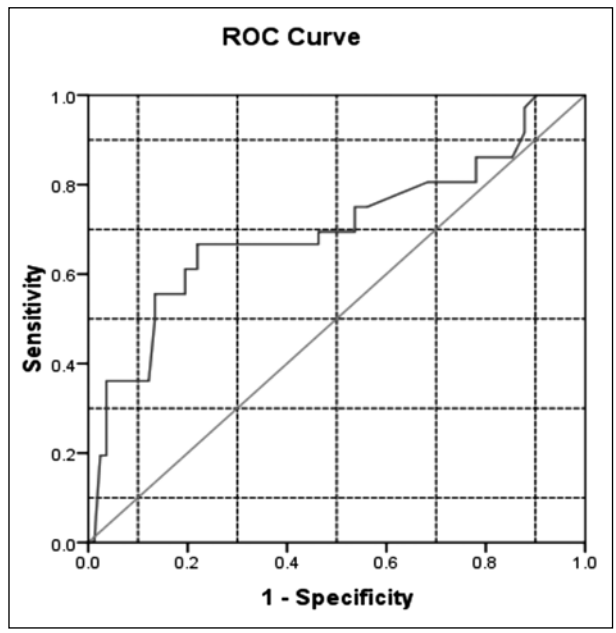


**Fig. 1:** Receiver operating curve to predict the cut-off point for depression on DAS-28

Chicago, Illinois, USA). The mean ± standard deviation (SD) was calculated for the quantitative data and the percentages were calculated for categorical variables. The Student's t-test was used for comparing the means of two continuous variables. The numbers and percentages were compared using the Chi-square test. The odds ratios and 95% confidence intervals were calculated to estimate risk. The Pearson correlation was used to find the correlation between the studied variables. A receiver operating curve (ROC) was plotted to determine a suggested cut-off point of the DAS28 that assisted with predicting depression (Fig. 1). The results were considered significant if p-value was < 0.05.

## RESULTS

The mean (± SD) age of the RA patients was 48.33 (13.2) years. Out of the study subjects, 152 were female (76%). The mean disease duration (± SD) was 4 ± 3.7 years. Ninety-six patients (48%) had a disease duration ≤ 2 years, and 104 patients (52%) had disease duration of > 2 years. The mean DAS-28 score was 4.6 ± 1.3. Out of the RA subjects, high disease activity levels were found in 76 patients (38%), moderate disease activity levels were found in 102 patients (51%) and low disease activity levels were found in 22 patients (11%).The demographic and clinical characteristics of patients with RA are shown in Table 1.

Based on the BDI scale, depression was observed in 36 RA patients (18%). It was more common in patients with high disease activity than in those with moderate disease activity or low disease activity; depression occurred in 20 patients (56%) with high disease activity, in 14 patients (39%) with moderate disease activity and in two patients (5%) with low disease activity.

By Chi-square testing, there is a significant ($p < 0.05$) association between depression in RA patients and disease duration of less than 2 years (OR = 0.64 (95%) CI, 0.29 - 1.41) but not with duration more than 2 years. No significant association was detected between the BDI score and co-morbid illnesses or medication use.

The Pearson correlation showed a significant correlation between disease activity measured by the DAS-28 and the scores on the BDI scale ($r = 0.366$, $p = 0.001$), which indicated that the higher the disease activity measured by the DAS-28 score the higher was the score on the BDI and increased possibility that the patient had depression. There was a significant negative correlation between age and the score on the BDI scale ($r = - 0.143$, $p = 0.044$), which means that the younger a patient is the more likely the patient is to be depressed.

Upon applying the receiver operating curve (ROC) at cut off DAS-28 of 5.1, the sensitivity for predicting depression in an RA patient was 73%, the specificity was 69%, and the area under the curve (AUC) was 70% at the 95% confidence interval (59 - 81%), $p < 0.001$. This finding indicates that when the DAS-28 is above 5, a physician could estimate that the patient has a 73% chance of being depressed.

**Table 1:** Demographic and clinical characteristics in patients with RA

| Characteristics | Depression N = 36 (%) | No Depression N = 164 (%) | p-value | Odds ratio (95% CI) |
|---|---|---|---|---|
| Age (yr): mean ± SD (Range) | 45.6 ± 13.26 (28 - 83) | 48.93 ± 13.1 (18 - 75) | 0.17 | - |
| Gender | | | | |
| Women | 32 (89) | 120 (93) | 0.31 | 1.43 (0.58 - 3.55) |
| Men | 4 (11) | 12 (7) | - | 1.58 (0.48 - 5.27) |
| Co-morbid illness | | | | |
| Absent | 34 (94) | 132 (81) | - | Reference category |
| Present | 2 (6) | 32 (19) | 0.036* | 0.24 (0.04 - 1.12) |
| Duration of disease: mean ± SD | 5.19 ± 4.19 | 3.63 ± 3.49 | | |
| ≤ 2 years (n = 96) | 14 (39) | 82 (50) | 0.035* | 0.64 (0.29 - 1.41) |
| >2 years (n = 104) | 22 (61) | 82 (50) | - | Reference category |
| DAS-28 score: mean ± SD | 5.09 ± 1.36 | 4.54 ± 1.24 | 0.024* | |
| High ( n = 76) | 20 (56) | 56 (34) | 0.014* | 2.41 (1.09 - 5.34) |
| Moderate (n = 102) | 14 (39) | 88 (54) | 0.077 | 0.55 (0.25 - 1.22) |
| Low (n = 22) | 2 (5) | 20 (12) | - | Reference category |
| Medication | | | | |
| Steroids (n = 62) | 10(17.2) | 26 (18.3) | 0.57 | 0.92 (0.46 - 2.07) |
| DMARDs | | | | |
| Antimalarial | 16 (44) | 66 (40) | 0.35 | 1.19 (0.54 - 2.61) |
| Methotrexate | 32 (89) | 136 (83) | 0.27 | 1.65 (0.5 - 5.98) |
| Biologics | 4 (13) | 14 (10) | 0.42 | 1.34 (0.35 - 4.76) |

RA: Rheumatoid arthritis; DAS-28: Disease Activity Score Index, DMARDs: Disease Modifying Antirheumatic Drugs, TNF: Tumour Necrosis Factor, CI: Confidence interval

* Significant p-value < 0.05, obtained by Chi-square testing, except for age where student's t-test was used.

## DISCUSSION

Our study showed that 18% of RA patients suffer from depression. RA patients with high disease activity (56%) are more likely to be depressed than those with low disease activity (5%). There was a significant positive correlation between depression measured by the BDI and RA disease activity measured by the DAS-28. Whenever there is a high disease activity state, the physician could predict that the patient has a 73% chance of being depressed.

Depression is an important co-morbid illness in RA for many reasons. In a large British registry involving 7,818 RA patients, depression ranked second in disease co-morbidity with RA, after ischemic heart disease[3]. It was associated with a high mortality rate, as shown by Ang *et al*., in a large US cohort of 1,290 patients, in which the hazard ratio of clinical depression to mortality was 2.2 (95% CI 1.2 - 3.9, p = 0.01)[6]. Suicide and suicidal ideation were observed in 50% and 11% of the patients, respectively[7,17]. Depression is a known risk factor for poor outcomes due to non-adherence to treatment of other chronic illnesses[18].

Other studies have produced conflicting results regarding levels of depression in RA patients. Some studies have found higher levels of depression in RA patients[2,19], while other studies have not found the same trends[20]. Our study found a prevalence of depression of 18% in individuals with RA, which is comparable to the rate in the UK of 19%, lower than the rate in Egypt of 66%, and higher than the rate in Australia of 6.4%[3,19,21]. This difference may be attributed to many factors, specifically the different instruments used to assess depression and the different ages of the patients in a study. In our study, we used the BDI scoring system, which has an important advantage because it does not rely on the somatic symptoms that occur in both RA and depressed patients. A systematic review involving 16,922 patients[22] showed that depression increases the somatic symptoms of patients with co-morbid illnesses. Regardless of the instrument used for depression assessment, there is general agreement that pain and the functional limitations caused by RA can lead to depression.

Numerous factors have been found to be associated with depression in RA patients, including low income, poor mental health, status as a female, certain ethnic backgrounds[23], the number of tender joints[24], the functional limitations[25], the high rheumatoid factor[26], and high levels of inflammatory markers and pro-inflammatory cytokines. There is agreement that depressive symptoms are correlated with inflammatory markers, specifically with CRP[27-30]. There are conflicting reports regarding the association between depression and RA disease activity measured by the DAS-28; some studies have shown a significant correlation[31], and higher disease activity in the depressed group[32-33]. Other studies have not demonstrated a relationship between depression and disease activity[34-35]. In our study, we observed a significant and positive correlation between depression assessed by the BDI score and disease activity evaluated by the DAS-28-CRP score. We found that higher disease activity existed in the depressed group. Despite this fact, patients often fail to discuss depression with healthcare professionals. It has been observed that patients with RA report depression at only 50% of their appointments[2], and none of our patients reported depression although 38% of the patients had high disease activity. It has been documented that RA patients with high disease activity and depression fail to respond to treatment, including treatment with biologics[31]. Because of this important observed-relationship, we tried to explore whether depression could be predicted in the clinical setting and observed that whenever there is a high disease activity state, a rheumatologist will be able to predict depression in 73% of cases. In our literature search, we found that this relationship had not been previously studied. It is important that physicians inquire about symptoms of depression when they treat RA patients, especially in patients with high disease activity. RA patients with depression should be referred to a psychiatrist to begin antidepressant medication and the medical therapy should be optimized using caution with high doses of steroids.

Steroid treatment is well-known for causing depression as a side effect. We did not report any significant effect of steroids in depressed RA patients. In our study, the patients who were treated with steroids received doses of less than 7.5 mg, a treatment plan that is less likely to cause depression. This effect was evident in a recent study conducted in Germany, which included 1066 patients with RA[36].

One strength of our study was that we used the DAS-28-CRP score, which includes clinical, and laboratory parameters (*i.e.*, global health, the number of tender and swollen joints and the CRP level) and the BDI score to assess depression, which omit the somatic symptoms that could cross-react with RA symptoms.

## CONCLUSION

The results of this study have several implications for research and clinical practice. As the depressed patients have been referred to psychiatrists, we could evaluate their response to disease activity status after starting antidepressant medications.

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## Original Article

# Adherence of Type-2 Diabetic Patients to Treatment

Hana T Al-Majed[1], Ali E Ismael[2], Haya M Al-Khatlan[3], Medhat K El-Shazly[4]
[1]Department of Applied Medical Sciences, College of Health Sciences, Public Authority for Applied Education and Training, Kuwait
[2]Department of Medicine, Farwaniya Hospital, Ministry of Health, Kuwait; Department of Medicine, Faculty of Medicine, Zagazig University, Egypt
[3]Department of Medical Records, College of Health Sciences, Public Authority for Applied Education and Training, Kuwait
[4]Department of Medical Statistics, Medical Research Institute, Alexandria University, Egypt; Department of Health Information and Medical records, MoH, Kuwait

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**ABSTRACT**

**Objectives:** To determine the percentage of non-adherent patients with type 2 diabetes (T2D) attending primary health care (PHC) settings and to assess related factors
**Design:** Cross sectional case-control study
**Setting:** Five primary health care centers (one from each health region in Kuwait)
**Subjects:** Six hundred and ninety-three T2D patients
**Methods:** Comparison between cases and control was conducted using univariate analysis followed by a logistic regression analysis. The collected data included socio-demographic, clinical, and patients' practice data.
**Main Outcome Measures:** Adherence to T2D treatment recommendations
**Results:** Among 693 participants in this study, 181 were diagnosed as non-adherent to treatment recommendations with an overall 26.1% rate. They were compared with 512 adherent patients. Within socio-demographic variables, only education and family income were proved to be significantly associated with adherence to treatment. Among clinical variables, poor glycemic state (OR = 2.1, 95% CI: 1.2 – 4.7), hypertension (OR = 1.9, 95% CI: 1.2 - 3.2), co-morbid conditions (OR = 3.2, 95% CI: 1.3 - 6.2) were significant determinants of the outcome of interest. Regular follow-up visits, compliance with diet recommendations and mild physical activity were significant protective determinants related to patients' practice (OR = 0.4, 95% CI: 0.1 - 0.9), (OR = 0.3, 95% CI: 0.1- 0.6), (OR = 0.3, 95% CI: 0.2 – 0.8),and (OR = 0.5, 95% CI: 0.2 – 0.9) respectively.
**Conclusion:** Many amenable factors were associated with non-adherence. Health education to diabetic patients should be emphasied to improve patients' knowledge, attitude and practice to encourage their adherence. Further studies are needed regarding physicians' practice and their relation with patients.

KEY WORDS: adherence, treatment, type 2 diabetes

## INTRODUCTION

Patient adherence to prescribed therapies in type 2 diabetes (T2D) is an area of enormous importance because of the strong correlations between adherence, patient outcomes, and treatment costs. Since diabetes is a chronic condition, long-term adherence to therapy is a necessity[1].

Given the large number of patients inflicted by T2D and the associated cost burden to payers, employers, and patients themselves, there exists a significant opportunity to improve outcomes and reduce costs. One potential target for improving outcomes is patient adherence to prescribed therapy. Improvements in adherence would improve glycemic control, that would help reduce morbidity and mortality related to uncontrolled T2D[1,2].

Based on data from studies involving patients with diabetes in the US, every percentage point reduction in glycated hemolobin (HbA1C) is associated with a 40% reduction in the risk of microvascular complications such as kidney diseases, eye diseases, and neuropathies[3]. Moreover, a recent report by World Health Organization (WHO) stated that, because the magnitude of non-adherence and the scope of its sequelae are so alarming, more health benefits worldwide would result from improving adherence to existing treatments than by developing new medical treatments[4].

*Address correspondence to:*
*Dr. Hana Thunayan AlMajed, Associate Professor of Physiology, Department of Applied Medical Sciences, College of Health Sciences, Public Authority for Applied Education and Training, Kuwait.Tel: (+965) 99062377, Fax (+965) 22563603, E-mail: almajed777@hotmail.com*

Epidemiological studies have found many factors associated with drug adherence[5,6]. Reviews reported that adherence has been associated with patient factors, social and medical support, and medication related aspects[7,8]. Patient's age (older patients being more adherent), economic status (patients with a higher economic status being more adherent) and health beliefs (patients with beliefs about medicines as being harmful were less adherent) are among patient-related factors[4,9].

Adherence to prescribed therapies should be considered as key dimension of health care quality that should be emphasized by physicians in each follow-up visit[10]. The aim of the present study was to evaluate adherence to prescribed therapies of T2D patients attending primary health care (PHC) settings in Kuwait, and to determine the associtaed risk factors.

## SUBJECTS AND METHODS

### Setting and study design

All inhabitants in Kuwait, Kuwaiti and non-Kuwaiti, are health insured by law. Ministry of health provides health care for diabetic patients through a well-organized system including primary, secondary and tertiary care facilities within five health regions. PHC is provided through 92 centers distributed proportionate to the population size in each health region. Specialized diabetes clinics are located in 42 centers. All diabetic center patients are initially diagnosed by general practitioners (GPs) or family physicians (FPs). Diagnosed patients were then followed by GP, FP or diabetologist, if the center had a diabetic clinic, on the basis of Kuwaiti guidelines. Secondary and tertiary care for diabetic patients are delivered through a group of general and specialized hospitals through outpatients clinics and inpatients services, where patients are referred to by GPs, FPs.

This study was carried out in five PHC centers representing the five health regions in Kuwait. The field duration of the study covered six months starting from the beginning of January till the end of June 2012. All T2D patients attending the selected centers were sequentially recruited. One index day was randomly defined for each of the selected centers for collection of data. Newly discovered cases were excluded from the study. The inclusion criteria were paients with T2D for at least one year, who came with complete reports in their medical records. All eligible subjects were asked to participate in the study. The final study sample size was 693 subjects.

The first study phase was a cross-sectional study to determine the percentage of patients' adherence to treatment recommendations. The second one was a nested case-control study, where all non-adherent patients (case group, n = 181) were compared with all other adherent patients (control group, n = 512) to determine factors that could be associated with non-adherence.

### Study questionnaires

Data were collected by interviewing patients and reviewing their medical records using a specially designed questionnaire that was derived from previous studies dealing with the same topic as well as from our own experience. It included socio-demographic characteristics (age, gender, nationality, education, occupation, marital status, housing and family income) and clinical data (treatment type, glycemic state, presence of hypertension, co-morbid conditions, and long term diabetic complications), in addition to patient' practice (regular follow-up, compliance with diet recommendations, regular check of blood glucose at home, measuring blood pressure at home, self monitoring of blood glucose (SMBG), smoking, and physical activity).

### Measures

Body weight was measured using a scale (Detectoscale, MO USA) to the nearest 0.5 kg, and height was measured in centimeters using the same scale. Body mass index (BMI) was calculated as weight in kg / height in meters squared. It was used as a measure of obesity. Individuals with a BMI between 25 and 29.9 were considered as overweight, while individuals with a BMI of 30 to 34.9 were considered obese. Subjects with BMI ≥ 35 were considered as morbidly obese. The average of three blood pressure measurements was obtained using a standardized sphygmomanometer after a five-minute sitting rest. Hypertension was considered as uncontrolled by treatment on the basis of clinical judgment and confirmed by the presence of systolic blood pressure value ≥ 140 mmHg and / or diastolic pressure ≥ 90 mmHg[11].

Complete blood count (CBC), fasting levels of both glucose and lipid were investigated using the standard laboratory protocols in Ministry of Health-Kuwait. Subjects were asked to fast overnight for at least 12 hours before the day of the examination. According to the hospital biochemical laboratories, the appropriate reference ranges for blood serum analyses were followed. It was estimated as lower and higher limits; Hb: 120 g/l and 150 g/l respectively, fasting glucose: 3.8 - 4.0 mmol/l and 6.1 mmol/l respectively. The glycemic state of patient referred to the last value of HbA1C and it was considered adequate if the level was < 7%. Normal levels for blood lipids were identified as 4.0 mmol/l for total cholesterol, 1.7 mmol/l for triglycerides, 2.5 mmol/l for LDL, and 1.0 mmol/l (in males) and 1.2 mmol/l (in females) for HDL[12].

**Table 1:** Socio-demographic characteristics of adherent and non-adherent type-2 diabetic patients

| Variables | Adherence | | | | Significance p-value |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | n | % | n | % | |
| Gender | | | | | |
| Male | 83 | 45.9 | 263 | 51.4 | $X^2 = 1.62$ |
| Female | 98 | 54.1 | 249 | 48.6 | p = 0.20 |
| Age (years) | | | | | |
| < 50 | 89 | 49.2 | 215 | 42.0 | $X^2 = 3.11$ |
| 50 - 59 | 43 | 23.8 | 149 | 29.1 | p = 0.21 |
| ≥ 60 | 49 | 27.1 | 148 | 28.9 | |
| Nationality | | | | | |
| Non-Kuwaiti | 102 | 56.4 | 293 | 57.2 | $X^2 = 0.04$ |
| Kuwaiti | 79 | 43.6 | 219 | 42.8 | p = 0.84 |
| Education | | | | | |
| Less than primary | 129 | 71.3 | 308 | 60.2 | $X^2 = 9.45$ |
| Primary / Intermediate | 20 | 11.0 | 69 | 13.5 | p = 0.02 |
| Secondary | 17 | 9.4 | 51 | 10.0 | |
| University or higher | 15 | 8.3 | 84 | 16.4 | |
| Occupation | | | | | |
| Not working | 109 | 60.2 | 294 | 57.4 | $X^2 = 0.43$ |
| Working | 72 | 39.8 | 218 | 42.6 | p = 0.51 |
| Marital state | | | | | |
| Unmarried | 11 | 6.1 | 38 | 7.4 | $X^2 = 0.37$ |
| Married | 170 | 93.9 | 474 | 92.6 | p = 0.54 |
| Family income / month (Kuwait Dinar) | | | | | |
| < 500 | 77 | 42.5 | 188 | 36.7 | $X^2 = 7.64$ |
| 500 – 999 | 55 | 30.4 | 154 | 30.1 | p = 0.05 |
| 1000 – 1499 | 41 | 22.7 | 113 | 22.1 | |
| ≥ 1500 | 8 | 4.4 | 57 | 11.1 | |
| Housing | | | | | |
| Villa | 2 | 1.1 | 11 | 2.1 | $X^2 = 3.91$ |
| Middle income | 78 | 43.1 | 202 | 39.5 | p = 0.27 |
| Limited income | 22 | 12.2 | 90 | 17.6 | |
| Flat | 79 | 43.6 | 209 | 40.8 | |
| Total | 181 | 100.0 | 512 | 100.0 | |

**Definitions**

Type 2 diabetes was defined according to the American Diabetes Association criteria when fasting blood glucose ≥ 7 mmol/l, and / or 2-hour postprandial glucose ≥ 11.1 mmol/l, and / or HbA1C ≥ 6.5%.

Patients were classified as having cardiovascular complication on the basis of the presence of clinical symptoms and signs and confirmed by medical reports in their records. Also, patients were diagnosed as having diabetic neuropathy if diffuse or focal (peripheral sensory or motor) defects were reported. Nephropathy was considered if a patient had microalbuminuria, clinical proteinuria, or was subjected to dialysis.

Major limb complications included foot ulcer, claudication, gangrene, persistent ischemic pain or amputation. Co-morbidity included conditions that had been already present prior to the diagnosis of diabetes (angina pectoris, hypertension, renal disease, endocrine dysfunction, dyslipidemia and liver diseases. Physical activity was considered, if it was practiced for 30 minutes at least 3-4 times a week.

Patient's adherence to treatment was determined using six questions. Patients responded "yes or no" to each of the following: "do you sometimes forget to take your medicine", "have you ever run out of your medicine", "do you sometimes take your medicine late", "do you sometimes decide not to take your medicine because someday you feel that your treatment does more harm than good", "do you think that you have too many pills to take", and "when you feel better, do you sometimes stop taking your medicine". Patient was classified as non-adherent to treatment, if he / she answered three or more questions by "yes"[13]. Regular follow up of visits was considered if at least 70% of the predetermined schedule of appointments in the clinic during the last 12 months were fullfilled.

**Statistical analysis**

Analysis was initially carried out based on a series of univariate comparisons. In order to control simultaneously for possible confounding effect of the variables, multiple logistic regression was used for the final analysis. In the univariate analysis Chi-square

**Table 2:** Clinical characteristics of of adherent and non-adherent type-2 diabetic patients

| Variables | Adherence | | | | Significance p-value |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | n | % | n | % | |
| Duration of diabetes (years) | | | | | |
| < 5 | 63 | 34.8 | 165 | 32.2 | $X^2 = 2.76$ |
| 5 - 9.9 | 43 | 23.8 | 119 | 23.2 | p = 0.43 |
| 10 - 14.9 | 45 | 24.9 | 114 | 22.3 | |
| ≥ 15 | 30 | 16.6 | 114 | 22.3 | |
| Treatment | | | | | |
| Oral | 111 | 61.3 | 346 | 67.6 | $X^2 = 2.35$ |
| Insulin | 13 | 7.2 | 32 | 6.3 | p = 0.31 |
| Combined | 57 | 31.5 | 134 | 26.2 | |
| Glycemic state (HbA1C) | | | | | |
| Good control | 24 | 13.3 | 105 | 20.5 | $X^2 = 4.64$ |
| Poor control | 157 | 86.7 | 407 | 79.5 | p = 0.03 |
| Dyslipidemia | | | | | |
| No | 7 | 3.9 | 33 | 6.4 | $X^2 = 1.63$ |
| Yes | 174 | 96.1 | 479 | 93.6 | p = 0.27 |
| Hypertension | | | | | |
| No | 86 | 47.5 | 297 | 58.0 | $X^2 = 5.96$ |
| Yes | 95 | 52.5 | 215 | 42.0 | p = 0.02 |
| Obesity | | | | | |
| No | 31 | 17.1 | 87 | 17.0 | $X^2 = 5.56$ |
| Overweight | 60 | 33.1 | 177 | 34.6 | p = 0.14 |
| Obese | 38 | 21.0 | 140 | 27.3 | |
| Morbidly obese | 52 | 28.7 | 108 | 21.1 | |
| Microalbuminuria | | | | | |
| -ve | 160 | 88.4 | 435 | 85.0 | $X^2 = 1.30$ |
| +ve | 21 | 11.6 | 77 | 15.0 | p = 0.25 |
| Co-morbid conditions | | | | | |
| No | 110 | 60.8 | 372 | 72.7 | $X^2 = 8.92$ |
| Yes | 71 | 39.2 | 140 | 27.3 | p = 0.003 |
| Chronic complications | | | | | |
| No | 98 | 54.1 | 231 | 45.1 | $X^2 = 4.37$ |
| Yes | 83 | 45.9 | 281 | 54.9 | p = 0.04 |
| Total | 181 | 100.0 | 512 | 100.0 | |

test was used to detect the association between non-adherence and explanatory variables. In multiple logistic regression analysis, the association between exposure and outcome was expressed in terms of odds ratio (OR) together with their 95% confidence intervals (95% CI).

All the explanatory variables included in the logistic model were categorized into two or more levels (R = reference category): gender: maleR, female; age (years): < 50R, 50 - 59, > 60; nationality: non-KuwaitiR, Kuwaiti; education: less than primaryR, primary / intermediate, secondary, university or higher; occupation: not workingR, working; marital state: unmarriedR, married; monthly family income (KD): < 500R, 500 - 999, 1000 - 1499, > 1500; housing: villaR, middle income, limited income, flat; duration of diabetes (years): < 5R, 5 - 9.9, 10 - 14.9, > 15; treatment: 5R, oralR, insulin, combined; glycemic state (A1C): good controlR, poor control; dyslipidemia: noR, yes; hypertension: noR, yes: obesity: noR, overweight, obese, severely obese; microalbuminuria: -veR, +ve ; co-morbid conditions: noR, yes; chronic complications: noR, yes; regular follow-up visits: noR, yes; compliance with diet recommendations: noR, yes; regular check of blood glucose at home: noR, yes; measuring of blood pressure at home: noR, yes; SMBG: noR, yes; smoking: yesR, no, ex- smoker; physical activity: sedentaryR, mild, moderate. Analysis was performed using the SPSS package.

## RESULTS

Among 693 T2D patients who participated in the study, 181 were diagnosed as non-adherent to treatment recommendations with an overall rate of 26.1%. Those patients were compared with 512 patients who were considered adherent to treatment recommendations. The socio-demographic, clinical, and personal practice together with the results of unvariate analyses are presented in Tables 1 - 3. The results of the final analysis using multiple logistic regression are summarized in Table 4.

**Table 3:** Patients' practice of adherent and non-adherent type-2 diabetic patients

| Variables | Adherence | | | | Significance p-value |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | n | % | n | % | |
| Regular follow-up visits | | | | | |
| No | 12 | 6.6 | 8 | 1.6 | $X^2 = 12.25$ |
| Yes | 169 | 93.4 | 504 | 98.4 | $p < 0.001$ |
| Compliance with diet recommendations | | | | | |
| No | 125 | 69.1 | 111 | 21.7 | $X^2 = 133.68$ |
| Yes | 56 | 30.9 | 401 | 78.3 | $p < 0.001$ |
| Regular check of blood glucose at home | | | | | |
| No | 151 | 83.4 | 374 | 73.0 | $X^2 = 7.84$ |
| Yes | 30 | 16.6 | 138 | 27.0 | $p = 0.005$ |
| Measuring of blood pressure at home | | | | | |
| No | 173 | 95.6 | 484 | 94.8 | $X^2 = 0.30$ |
| Yes | 8 | 4.4 | 28 | 5.5 | $p = 0.59$ |
| Self monitoring of blood glucose | | | | | |
| No | 172 | 95.0 | 454 | 88.7 | $X^2 = 6.16$ |
| Yes | 9 | 5.0 | 58 | 11.3 | $p = 0.013$ |
| Smoking | | | | | |
| Yes | 35 | 19.3 | 70 | 13.7 | $X^2 = 5.88$ |
| No | 137 | 75.7 | 428 | 81.6 | $p = 0.05$ |
| Ex- smoker | 9 | 5.0 | 14 | 2.7 | |
| Physical activity | | | | | |
| Sedentary | 164 | 90.6 | 337 | 65.8 | $X^2 = 44.53$ |
| Mild | 16 | 8.8 | 102 | 19.9 | $p < 0.001$ |
| Moderate | 1 | 0.6 | 73 | 14.3 | |
| Total | 181 | 100.0 | 512 | 100.0 | |

**Socio-demographic characteristics**

No significant association between adherence to treatment and socio-demographic factors was detected except for educational level and monthly family income. Patients with university level of education had half the risk of being non-adherent than those with less than primary level (OR = 0.5, 95% CI: 0.2 – 0.9). Patients who had monthly family income ≥ 1500 Kuwaiti dinar (KD) were less liable to be non-adherent as compared with patients who had family income < 500 KD (OR = 0.4, 95% CI: 0.1 - 0.9).

**Clinical variables**

Among clinical factors, glycemic control, hypertension, presence of associated co-morbid conditions and presence of long term diabetic complications were significantly associated with outcome of interest. Patients with poor glycemic control, as indicated by the level of HbA1C, had more than double the risk of being non-adherent to treatment as compared to patients with good control (OR = 2.1, 95% CI: 1.2 - 4.7). Hypertension seemed to increase the risk of non-adherence by 90% (OR = 1.9, 95% CI: 1.2 - 3.2). Patients who suffered from associated co-morbidity had more than triple the risk of being non adherent to treatment (OR = 3.2, 95% CI: 1.3 – 6.2). On the other hand, patients with one or more complications due to long term diabetes, were proved to be more adherent to treatment as compared with patients free from these complications (OR = 0.6, 95% CI: 0.4 - 0.4).

**Patients' practice**

Among patients' practice, regular follow-up visits, compliance with diet recommendations, non-smoking and practicing mild physical activities were the only amenable factor that could be proved to be significant protective factors against non-adherence to treatment (OR = 0.4, 95% CI: 0.1 – 0.9), (OR = 0.3, 95% CI: 0.1 – 0.6), (OR = 0.3, 95% CI: 0.2 – 0.8),and (OR = 0.5, 95% CI: 0.2 – 0.9) respectively.

**DISCUSSION**

Adherence to prescribed medications is a key dimension of healthcare quality[14]. Prior researches found that the proportion of patients' adherent to oral hypoglycemic agents (OHA) varies from 50% to 80% across primary care clinics[15]. The present study showed that the rate of non-adherence to medications was 26.1%.This goes in accordance with a similar study that was carried in Mwanza city,Tanzania where 28.3% of participants reported non-adherence[16]. However, the percentage of non-adherence in the present study was higher than that found by Parada *et al*., who reported a figure of 9.9%[17]. On the other hand, in a study conducted in Al-Hasa district of Saudi Arabia, it was reported that the overall prevalence of

**Table 4:** Factors associated with non-adherence to treatment recommendation among type 2 diabetic patients: results of multivariate logistic regression analysis

| Variables | Odds Ratio | 95% CI |
|---|---|---|
| Education | | |
| Less than primary [R] | 1 | |
| Primary / Intermediate | 0.6 | (0.2 – 2.3) |
| Secondary | 0.7 | (0.4 – 1.9) |
| University or higher | 0.5 | (0.2 – 0.9) |
| Family income / month (KD) | | |
| < 500 [R] | 1 | |
| 500 – 999 | 0.9 | (0.5 – 1.1) |
| 1000 – 1499 | 0.9 | (0.4 – 1.2) |
| ≥ 1500 | 0.4 | (0.1 – 0.8) |
| Glycemic state | | |
| Good control [R] | 1 | |
| Poor control | 2.1 | (1.1 – 4.7) |
| Hypertension | | |
| No [R] | 1 | |
| Yes | 1.9 | (1.2 – 3.2) |
| Co-morbid conditions | | |
| No [R] | 1 | |
| Yes | 3.2 | (1.3 – 6.2) |
| Chronic complications | | |
| No [R] | 1 | |
| Yes | 0.6 | (0.4 – 0.9) |
| Regular follow-up visits | | |
| No [R] | 1 | |
| Yes | 0.4 | (0.1 – 0.9) |
| Compliance with diet recommendations | 1 | |
| No [R] | 0.3 | (0.1 – 0.6) |
| Yes | | |
| Smoking | 1 | (1.1 – 2.5) |
| Yes [R] | 0.3 | (0.2 – 0.8) |
| No | 1.5 | (0.5 – 4.9) |
| Ex- smoker | | |
| Physical activity | 1 | |
| Sedentary [R] | 0.5 | (0.2 – 0.9) |
| Moderate | 0.0 | (0.0 – 0.2) |

[R] = Reference category, OR = Odds ratio, CI = Confidence interval

therapeutic non-compliance of the participants was 67.9%[18]. Tiv *et al*., found that 39% of patients reported good medication adherence, 49% medium adherence and 12% poor adherence[19]. However, the lack of standard measurements prevent comparison being made between studies and across populations.

Review of the medical literature suggests that three general considerations are important for individualized therapy: disease pathophysiology, modifiers of treatment response, and risks of non-adherence. The available literature includes evaluation of key non-genetic factors, such as age, race, BMI, patient sex, disease duration, and baseline glycated hemoglobin level[16]. Adherence to medication in patients with T2D varies widely, yet the factors that influence adherence according to patients are not fully known[20].

Tiv *et al*., reported that socio-demographic factors such as age < 45 years and financial difficulties were significant determinants of non-adherence[19]. In the present study, it was found that higher monthly income was protective against non-adherence. However, no association between age and adherence could be detected. Nagrebetsky *et al*., reported that the relationships between older age and better glycemic control are not explained by better adherence, but may partly relate to lower BMI[21]. Another study reported that poverty lowers self-efficacy among adults with diabetes[22].

Parada *et al*., reported that patients with a high school education or greater and those who more positively rated their health were more likely to be classified as adherent compared to those with less than a high school education[17]. Similarly, in the present study, participants with high education were less liable to be non-adherent. In their study, Khan *et al*., proved that lower level of education, irregularity of follow-up visits, non-adherence to exercise regimen and insulin treatment were significantly associated with non-adherence[18].

Among patient factors, in the present study, irregular follow-up visits, non-compliance with diet recommendations, smoking and irregular practicing of excercises proved to be risk factors for non-adherence to treatment. This could be due psychological factors as patients' beliefs and motivation towards the therapy, negative attitude, patient-prescriber relationship, understanding of health issues and patient's knowledge[14]. This goes in accordance with results of Khan *et al*., who found that patients who were regular on follow-up had a significantly higher compliance rate than those who were irregular and that non-compliance was higher among the patients who did not follow the exercise regime than those who followed it[18]. However, this did not hold for instructions on diet where non-compliance was statistically insignificant.

In general, many individuals with diabetes mellitus, hypertension, and hyperlipidemia have difficulty achieving control of all three conditions. Individuals who simultaneously achieve multiple treatment goals may provide insight into self-care strategies for individuals with co-morbid health conditions[23]. In the present study, hypertension and presence of co-morbidity were significantly associated with non-compliance.

Compliance with antidiabetic therapy has the potential to impact on the risk for complications by an effect on glycemic control[24]. However, in the present study, patients with chronic complications were found to be more adherent to therapy. This finding could be an association rather than a cause, indicating

that patients became more adherent to treatment after development of complications and feeling the seriousness of their condition.

In the current study, there was a significant positive association between good glycemic control and patient aherence to treatment. Al-Qazaz *et al*., found that higher knowledge of diabetes, higher medication adherence and using mono-therapy were significant predictors of good glycemic control in the multivariate analysis[25]. Also, in a recent study, it was proved that medication adherence was associated with greater reductions in HbA1C for both SMBG non-users and users[14]. It is interesting that medication-non-adherent SMBG users had similar reductions in HbA1C compared with medication-adherent non-SMBG users. However, the effect of SMBG, in the current study, could not be proved, after standardization of data, as a significant derterminant of adherence due to the small number of patients who practiced it.

A multidisciplinary team approach to diabetes management has been shown to improve outcomes and to have a neutral or beneficial effect on costs. The treatment plan itself plays an additional role in the likelihood of a patient adhering to treatment[20]. Most of interventions that have attempted to improve medication adherence in T2D have been educational; on the assumption that knowledge regarding diabetes might affect patients' adherence to their treatment regimen[18].

We acknowledge some limitations in our study. As we relied upon patient interview and record study, the data obtained might be, to certain extent, affected by the quality of recording. Also, as in any case-control study, the design of the study is by definition retrospective and is subjected to recall bias. Nevertheless, the results are consistent with those coming from cohort studies.

Reconciling the different measures of non-adherence and reported rates can be difficult because self-reported and quantitative adherence measures are not highly correlated[26] and no single gold-standard approach is available. Self-reported measures are more easily implemented in clinical settings[27] but validity may be affected by social desirability bias in some individuals[28].

Also, other important factors that could affect patient adherence to treatment were not included in this study and should be further investigated. They are that related to physicians and their relation with patients and that related to the availability of therapies.

## CONCLUSION

The high economic burden raised by diabetes and its complications challenges the Kuwaiti health care system. Because diabetes is a chronic condition, long-term adherence to therapy is a necessity. The study helped to identify the magnitude of the problem of non-adherence among T2D patients and risk factors that should be avoided, especially those related to patients' practice.

For improving adherence, availability of information to patients that might help them to become and remain adherent should be maintained. Further studies are needed regarding physicians' practice and physician-patient relationship.

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Original Article

# Mortality and Short Term Outcome of Very Low Birth Weight (VLBW) Infants at a Tertiary Care Center in Saudi Arabia: 9 Years' Data

Badr Sobaih, Adnan Hadid, Amull Fariss, Rozina Banoo, Turki AlKharfi, Khalid AlFaleh
Neonatal Intensive Care Unit, Department of Pediatrics, King Saud University, Riyadh, Kingdom of Saudi Arabia

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**ABSTRACT**

**Objectives:** To assess the mortality and major morbidity rates of very low birth weight (VLBW) infants delivered at King Khalid University Hospital (KKUH) over a nine-year period. The secondary objective was to benchmark our data to the National Institute of Child and Health Development (NICHD) neonatal research network published figures.
**Design:** Retrospective analysis of prospectively collected data
**Setting:** Neonatal Intensive Care Unit, KKUH, Riyadh, KSA
**Subjects:** All VLBW infants born alive at KKUH with birth weights less than 1500 g and gestational age of 32 weeks or less during the period from 1999 to 2007.
**Interventions:** Data were collected from NICU database and follow-up clinic database and then analyzed by the use of Microsoft Excel program. Mortality and various morbidities in this group of infants were evaluated and results were compared with international figures.
**Main Outcome Measures:** Mortality and major morbidity rates
**Results:** A total of 468 VLBW infants were included in this study. The infants had a mean gestational age of 27.5 weeks and a mean birth weight of 992 g. Mortality rate was 11.2% (survival rate of 88.8%). Survival varies dramatically per gestational age. The commonest morbidity was respiratory distress syndrome (95.2%), followed by retinopathy of prematurity (34.5%), and bronchopulmonary dysplasia (BPD) (27.4%). Early neonatal sepsis was documented in 11% of infants.
**Conclusion:** The survival of VLBW infants at KKUH is high and comparable to international figures. Although short term outcomes were quite satisfactory, the high rate of sepsis is alarming and requires urgent intervention.

KEY WORDS: gestational age, neonatal morbidity, preterm birth, survival of infants

## INTRODUCTION

Survival of very low birth weight (VLBW) infants continues to improve, particularly of infants less than 1000 g at birth, mainly due to advances in prenatal care including the use of antenatal corticosteroid therapy, and postnatal surfactant replacement therapy[1]. Despite this improvement, there has been minimal change in the boundaries of viability and in the number of infants surviving without significant neonatal morbidity[2]. Poor growth in early childhood is common in extremely preterm children. Improving early growth must be a priority for clinical care[3]. The contribution of preterm birth to population disability rates has often been discussed with the implication that increasing survival at extremely low gestational age simply increases the burden of disability in the population as a whole. Being born prematurely is not a normal event, despite its routine nature today. Although a lot of work had been done to prevent or reduce prematurity, the main duty of neonatologists remains to work on dealing with morbidities of these infants and trying to prevent or minimize long term adverse neurodevelopmental outcome which could be optimally conducted by the use of proper long-term follow-up programs designed to deal with such group of infants and their families[4-6]. Knowledge of local data augment clinicians ability to provide appropriate counseling to parents, plan resources and benchmark local data to international standards.

*Address correspondence to:*
*Dr. Bader Sobaih, Assistant Professor and Consultant, Department of Pediatrics and Neonatology, King Khalid University Hospital and College of Medicine, King Saud University, Riyadh, PO Box 2925, Riyadh, 11461, Kingdom of Saudi Arabia. Tel: 966-505453580, Fax: 966-14672395, E-mail: drbhsobaih_01@hotmail.com (new) bsobaih@ksu.edu.sa ; drbsobaih@yahoo.com*

Few published studies from Saudi Arabia reported the rates of mortality and morbidity outcomes in such tiny newborns[7-14]. However, most of these studies were single centered and did not reflect the magnitude of prematurity and its complications at the national level.

Our main objectives were to assess the mortality and major morbidity rates of VLBW infants delivered at King Khalid University Hospital (KKUH) over a nine-year period. Our secondary objective was to benchmark our data to the National Institute of Child and Health Development (NICHD) neonatal research network published figures.

## SUBJECTS AND METHODS

A retrospective analysis of prospectively collected data at KKUH in Riyadh, Saudi Arabia was conducted. Data were collected from year 1999 to 2007. VLBW infants born alive with a birth weight less than 1500 g and 32 weeks gestation or less were included. Data were collected after careful review of the medical records. The Institutional Ethics ReviewBoard (IERB) at KKUH approved our study.

Baseline demographic data included maternal history, maternal age, parity, use of antenatal steroids, antenatal antibiotics, gestational age, birth weight, sex, mode of delivery, Apgar score, as well as need for mechanical ventilation, and surfactant administration.

Our primary outcome was mortality defined as death prior to hospital discharge. Other neonatal morbidities were also included as secondary outcomes. Intraventricular hemorrhage (IVH) was detected routinely by head ultrasound performed during the first four weeks of life, and IVH was graded according to Papile's classification, from 0 - 4[15]. If multiple ultrasounds were done in the first four weeks, then the worst grade was recorded. Periventricular leucomalacia (PVL) refers to periventricular echogenecity detected on head ultrasound done at any time during the NICU stay. Respiratory distress syndrome (RDS) was diagnosed, if the infant needed supplemental oxygen along with a chest radiograph consistent with RDS. Pneumothorax was considered to be present, if the infant had extra pleural air diagnosed by chest radiograph or needle aspiration. Patent ductus arteriosus (PDA) was diagnosed *via* echocardiography with evidence of left-to-right shunting. Necrotizing enterocolitis (NEC) was diagnosed clinically with abdominal distension and intolerance to feed or bloody stool, in addition to an abdominal radiograph showing pneumatosis intestinalis, pneumoperitoneum, or gas in the biliary tree. Bell's classification was used for staging[16]. Retinopathy of prematurity (ROP) was detected on routine retinal examination and was recorded utilizing the International Classification of ROP[17]. Bronchopulmonary dysplasia (BPD) was defined as oxygen requirement at 36 weeks corrected age[18]. Sepsis was considered, if a blood culture or a cerebrospinal fluid culture was positive with a bacterial pathogen and early sepsis was defined as positive culture in the first 72 hours of life.

We present our descriptive data as median and range for continuous variables and frequency and percentages for categorical data. Our data for mortality was further subcategorized according to mortality by gestational age. To benchmark our data and performance, we performed a direct comparison with NICHD data published in 2007[19].

**Table 1:** Maternal and infants baseline characteristics

| Infant Characteristics | Mean ± (Standard deviation) |
|---|---|
| Birth weight (g) | 992.7 (287) |
| Mother age | 28.9 (6.1) |
| Parity ± | 1 (0-11) |
| Apgar score 1 min | 5 (2.0) |
| Apgar score 5 min | 7.4 (1.5) |
| Admission temperature | 35.7 (1.0) |
| Days on oxygen | 57 (53.9) |
| Length of hospital stay | 71 (53.2) |
| Day feeding started | 1 (1-32) |
| Age full feed ± | 39.4 (51.1) |
| Weight on discharge (g) | 2357.4 (739.5) |

## RESULTS

A total of 468 eligible infants were included for the study period (1999 - 2007). Included infants had a mean birth weight of 992 g. Majority of mothers were Saudis (93%), and around 70% of them were booked at our hospital. There was equal gender distribution. Four hundred and fifteen infants survived to discharge, with survival rate of 88.8%. Maternal and infants demographic data are shown in Table 1. Survival rate per gestational age showed a dramatic improvement of survival beyond 25 weeks gestation. Infants born at 23 and 24 weeks gestation had a survival rate of 61 and 65% respectively. Only one infant at 22 weeks gestation was included and it died (Table 2). Of note, extreme low birth weight infants born at our institution

**Table 2:** Survival rates based on gestational age

| Gestational age in weeks | Survived / Total | Survival rate % |
|---|---|---|
| 22 | 0 / 1 | 0 |
| 23 | 11 / 18 | 61.0 |
| 24 | 26 / 40 | 65.0 |
| 25 | 28 / 33 | 84.8 |
| 26 | 63 / 70 | 90.0 |
| 27 | 44 / 49 | 90.0 |
| 28 | 58 / 62 | 93.6 |
| 29 | 54 / 59 | 91.5 |
| 30 | 77 / 78 | 98.7 |
| 31 | 39 / 43 | 91.0 |
| 32 | 15 / 15 | 100 |
| Total | 415 / 468 | 88.8 |

**Table 3:** Baseline and survival data at King Khalid University Hospital (KKUH) compared with National Institute of Child Health and Human Development (NICHD) 2007

| Characteristics | KKUH (468) | NICHD (18,150) |
|---|---|---|
| Birth weight, g (range) | | |
| Mean (range) | 992 (500 -1483) | 1033 (998 -1066) |
| Standard deviation | 287 | 289 |
| Other parameters (%) | | |
| Antenatal steroids | 77.5 | 79 |
| Antenatal antibiotics | 33.8 | 70 |
| Membrane rupture > 24hrs | 3.5 | 24 |
| Multiple births | 29.6 | 26 |
| Small for gestational age | 12.5 | 21 |
| Mode of delivery (%) | | |
| SVD | 52.2 | 42 |
| Cesarean section | 47.8 | 58 |
| Delivery room resuscitation ( %) | | |
| Endotracheal intubation | 75.4 | 53 |
| Resuscitation drug | 3.4 | 5 |
| Survival rate (%) | 88.8 | 85 |

SVD = spontaneous vaginal delivery

were offered full resuscitation, if they were born with a weight of 500 g or more. Antenatal steroids were administered to 77.5% of mothers (Table 3).

RDS was present in 95.2% of infants. Surfactant treatment was given to 80% of infants, and around 28% of infants received postnatal steroids for evolving BPD, which developed in 27.4% of infants. PDA was diagnosed in 31% of infants; 48.3% out of these received indomethacin therapy and 12.4% underwent surgical ligation. Cranial ultrasound was performed in 90% of infants and showed IVH in 13.9% of infants; of these; 2.7% were grade I IVH, 3.4% grade II IVH, 4.4% grade III IVH, and 3.4% grade IV IVH. Only 1.3% of infants with IVH were diagnosed with PVL. Of note, our institution utilized indomethacin prophylaxis strategy for IVH and PDA for all infants born at less than 1000 g. ROP of all stages was diagnosed in 34.5% of infants (Table 4).

We observed a high rate of early and late onset sepsis at our institution affecting 48% of infants. Around one quarter of all cases of sepsis were labeled as early (within the first 72 hours of life). NEC was diagnosed in 15.6% of infants.

The baseline characteristics of our subjects including mean birth weight, antenatal steroids utilization, rate of cesarean section (CS) deliveries, were quite comparable to NICHD data. As for the short term neonatal morbidities, the rate of RDS and delivery room endotracheal intubation in our unit was double the number reported in the NICHD data possibly due to different definitions and delivery room practices utilized. Our rates of early and late onset sepsis far exceed the rates reported by NICHD. The rates of severe IVH (grade III and IV) were almost half the reported figures in the NICHD data probably due to utilization of indomethacin prophylaxis strategy in our unit.

**Table 4:** Short term outcomes at King Khalid university hospital (KKUH) compared with National Institute of Child Health and Human Development (NICHD) 2007

| Morbidity | KKUH % | NICHD, % |
|---|---|---|
| Respiratory distress syndrome | 95.2 | 44 |
| Surfactant therapy | 80 | 58 |
| Postnatal steroids | 27.9 | 17 |
| Pneumothorax | 5 | 5 |
| Bronchopulmonary dysplasia | 27.4 | 22 |
| Patent ductus arteriosus (PDA) | 31 | 29 |
| Indomethacin for PDA | 48.3 | 79 |
| Surgery for PDA | 12.4 | 19 |
| Sonogram done | 90 | 93 |
| Grade I IVH | 2.7 | 11 |
| Grade II IVH | 3.4 | 4 |
| Grade III IVH | 4.4 | 7 |
| Grade IV IVH | 3.4 | 5 |
| Periventricular leukomalacia | 1.3 | 3 |
| NEC Proven | 15.6 | 7 |
| Early onset sepsis | 11.0 | 2 |
| Late onset sepsis | 37.2 | 22 |
| ROP all stages | 34.5 | 59 |

ROP = Retinopathy of prematurity, IVH = Intraventricular hemorrhage, NEC = Necrotizing enterocolitis

## DISCUSSION

In this study, we report our institutional short-term outcome data of VLBW infants. Our data showed a similar survival rate in addition to major short term outcomes when compared to international figures. Although we had no survivals at 22 weeks (those born above 500 g), the survival rate of infants born at 23 weeks was surprisingly high. A recent report from a high quality tertiary care unit showed no survival at this age[14]. This could partially be explained by accuracy of gestational assessment since 30% of our mothers were un-booked.

The high rate of RDS in our unit is quite puzzling compared to international figures. The retrospective nature of our data makes it difficult to pinpoint a clear explanation to this observation. However, we believe that the high rate of un-booked mothers makes it difficult to anticipate and prepare for such high risk deliveries, to administer full course antenatal steroids, and have the infant born with the presence of an experienced neonatal team. It is also not clear to us why 75% of cases got intubated in the delivery room and what were the criteria utilized for such an aggressive practice.

Despite having a higher rate of RDS and possibly sicker infants compared to NICHD report, we observed almost half the rate of severe IVH in our population. This observation is most likely due to our inherited practice of indomethacin prophylaxis for infants born less 1000 g at birth. Our practice for many reasons did

not decline post the publication of the TIPP trial as observed in the international arena.

It is well known that both early and late onset sepsis decreases the survival of VLBW infants and increases their risk of long-term neurocognitive impairment[20]. We have observed a very high rate of sepsis in our unit compared to international standards. The increased rates of early onset sepsis could be explained by the increased rate of un-booked mothers and lack of proper preparatory action prior to delivery. However, it is not quite difficult to explain the high rate of late onset sepsis. Lack of vigilance in observing proper hand washing, extremely low rates of exclusive breast feeding, over crowding in improper NICU design are all possible contributory factors.

Although our study represents one of the largest cohorts of VLBW infants in the country, the retrospective nature of our data collection, in addition to the heterogeneity in the resource availability and neonatal practices hamper our ability to generalize our data to a national level. Therefore, accurate, representative and prospective data of survival and major morbidities of VLBW infants in Saudi Arabia are still needed.

## CONCLUSION

The survival of VLBW infants at KKUH is high and comparable to international figures. Although short-term outcomes were quite satisfactory, the high rate of sepsis is alarming and requires urgent intervention.

## ACKNOWLEDGMENT

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**Competing interests:** None to declare

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Case Report

# Paraduodenal (Treitz's) Hernia: Unusual Cause for Recurrent Intestinal Obstruction

Khaled H Al-Hammad, Zahraa Ismail, Maher Maurice
Department of Surgery, Mubarak Al-Kabeer Hospital, Kuwait

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**ABSTRACT**

Among congenital internal hernias, the paraduodenal hernia is the most common one and is known as Treitz's hernia (TH). It results from an abnormal rotation of the midgut. Internal hernias overall, are difficult to be evaluated clinically and radiologically and are usually diagnosed on exploratory laparotomy due to intestinal obstruction. We present in this report, a rare case of left paraduodenal hernia presenting as recurrent intestinal obstruction.

KEY WORDS: abdominal pain, bowel obstruction, internal hernia, laprotomy

## INTRODUCTION

An internal hernia, which maybe congenital or acquired, is the protrusion of a viscous through a normal or abnormal opening within the confines of the abdominal cavity[1]. It comprises 2% of all hernias and account for 1% of all cases of intestinal obstruction[1,2]. Paraduodenal hernia, also known as Treitz's hernia (TH) is relatively rare. However, it is considered the most common congenital malformation that leads to internal herniation and accounts for 25 - 53% of all cases[1,3], in which 50% of these patients will have intestinal obstruction[4]. They are difficult to diagnose before laparotomy[5]. In this report, we present a 36-year-old male patient, who developed recurrent intestinal obstruction due to a left paraduodenal hernia (PH). We also hope to increase awareness regarding the clinical and radiological variations in the presentation of such a case.

## CASE REPORT

A 36-year-old Indian male patient presented to the emergency department of the Mubarak Al-Kabeer hospital in December 2011 with progressive abdominal pain. It was colicky in nature and associated with nausea and vomiting. He experienced a similar attack seven months prior to his present admission. A plain abdominal film showed dilated bowel loops. A CT-scan of the abdomen (Fig. 1) showed evidence of bowel obstruction but he discharged himself against medical advice when he was offered exploratory laparotomy and when the pain was relieved spontaneously. However, he was re-admitted when the abdominal pain recurred. On physical examination, there was a diffuse tenderness over the abdomen with exaggerated bowel sounds. All hernia orifices were normal. No signs of peritonitis were detectable. Digital rectal examination showed an empty rectum. Blood tests showed no abnormality except a total leucocytic count of 11.1 x $10^9$/l. Plain abdominal film showed dilated small bowel loops, mainly jejunal loops, with no air under diaphragm. A CT-scan of the abdomen (Fig. 2) performed at the time of admission revealed the presence of a circumscribed cluster of proximal jejunal loops at the left upper quadrant adjacent to the left side of superior mesenteric vessels with a picture of complete small bowel obstruction. The patient was started on intravenous fluids and antibiotics. Emergency exploratory laparotomy was performed through a midline incision. We preferred not to attempt laparoscopy from the start to avoid any iatrogenic bowel injury due to the distention of the abdomen. On exploration, we found that most of the small bowel loops were trapped in a sac lined by peritoneum. This sac extended from the transverse colon superiorly

*Address correspondence to:*
*Khaled H Al-Hammad, Department of Surgery, Mubarak Al-Kabeer Hospital, Al-Jabriya, Kuwait. P O Box 43787, Code: 32052 Kuwait. Tel: (+965)99100191, E-mail: duke_alhammad@hotmail.com*

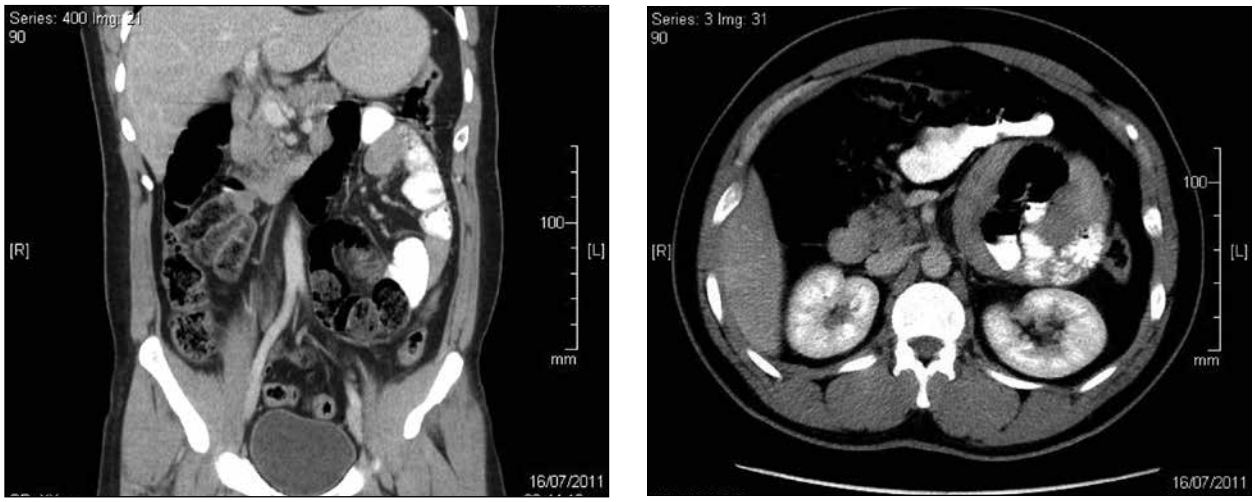


**Fig. 1 (A & B):** CT-scan of the abdomen showing evidence of bowel obstruction

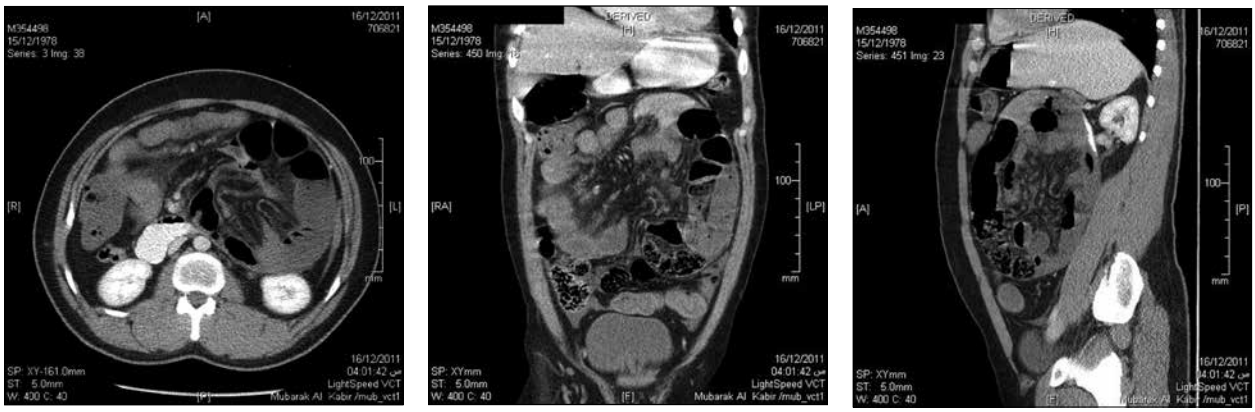


**Fig. 2 (A, B & C ):** CT-scan of the abdomen showing a circumscribed cluster of proximal jejunal loops at the left upper quadrant with picture of complete small bowel obstruction

to the descending colon laterally and inferiorly. The neck of the sac was made of a fibrous band extending from the transverse mesocolon to a point midway of the small bowel mesentery (Fig. 3, 4). The hernia was reduced and the defect was widened. The congested bowel was covered with warm packs and the patient was given 100% oxygenation until the bowel showed normal color and peristalsis. The patient tolerated the procedure well and had an uncomplicated recovery. He was discharged on the 5th postoperative day.

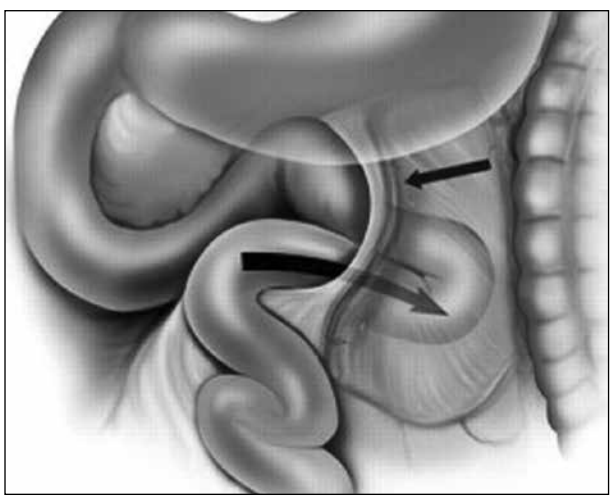

**Fig. 3:** A diagram showing the same operative findings

## DISCUSSION

PH and TH result from abnormal rotation of the midgut during the embryonic development that leads to failure of fusion of the mesocolon with the peritoneum of the body wall which leaves a potential space between the transverse colon, ascending colon, descending colon and small bowel mesentery[1,2]. It can be divided into two spaces. The right space known as the fossa of Waldeyer and the left space known as the fossa of Landzert[1,6]. The PH results from invagination of the small bowel into these unsupported areas[1,2,6]. It is known as Treitz's hernia (TH) due to its relation to the Treitz's ligament[7]. The PH have also been termed mesentericoperitoneal, congenital mesocolic or retroperitoneal hernias[7]. The left PH is more common than the right one with an incidence ratio of 3:1[1,6]. Although the hernia is congenital, most patients become symptomatic in the adult life[8]. The symptoms range between non-specific abdominal pain, recurrent

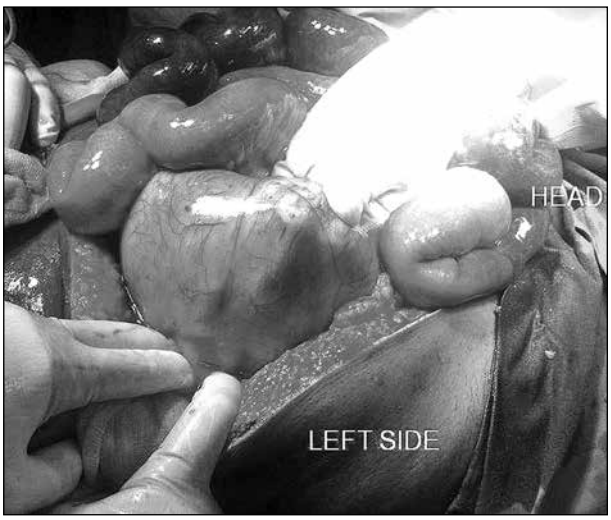


**Fig. 4:** Operative photograph showing the sac after reduction of the contents

picture of intestinal obstruction to acute abdomen with incarceration or strangulation[8]. The diagnosis of such a case is only possible at the time of surgery[5]. A CT-scan may be a helpful initial imaging choice[9,10]. A characteristic finding is a cluster of small bowel loops between the stomach and the pancreas[8-10]. Also, a sac like mass with encapsulation at or above the ligament of Treitz can be seen[11,12]. PH should be surgically repaired, once it is diagnosed, as 50% of them can cause intestinal obstruction[6,7,13]. The procedure consists of manual reduction of the hernia content followed by repair of the defect using non-absorbable sutures or widening of the defect opening taking care to avoid the mesenteric vessels[14]. Laparoscopic surgery for PH has also been reported[9,14], especially in left-sided PH, as it is technically easier and the indications are expected to increase with more accurate preoperative diagnosis and imaging technique[15-17].

## CONCLUSION

Internal herniation should be kept in mind as a differential diagnosis whenever a patient of any age group presents with acute intestinal obstruction, especially when there is no evidence of hernia clinically, or no past history of abdominal surgeries. PH, especially the left-sided one, is the most common cause of internal herniation.

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Case Report

# Laparoscopic Management of Heterotopic Pregnancy after Induction of Ovulation using Clomiphene Citrate

Ashraf Salah El Badry[1], Marium Al Dosary[1], Manish Juneja[2]
[1]Department of Obstetrics and Gynecology, Adan Hospital, Kuwait
[2] Department of Pathology, YIACO, Adan Hospital, Kuwait

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**ABSTRACT**

Heterotopic pregnancy (HP) is a rare condition and occurs with increasing frequency in cases of assisted reproductive technology and infertility treatment. We present a case of HP after induction of ovulation using clomiphene citrate in a 23-year-old lady who had primary infertility for two years. HP was diagnosed early in the pregnancy, at seven weeks of gestation, and managed by laparoscopic salpingostomy. The intrauterine pregnancy continued till term. The obstetrician should have a high index of suspicion in every case presenting with symptoms of lower abdominal pain in a confirmed intrauterine pregnancy. A high resolution ultrasound examination should be performed by an experienced person to confirm the diagnosis. Early diagnosis and management of HP will reduce morbidity and mortality, and improve outcome of the intrauterine pregnancy.

KEYWORDS: abdominal pain, ectopic pregnancy, salpingostomy

## INTRODUCTION

Heterotopic pregnancy (HP) is defined as the presence of an intrauterine pregnancy co-existing with an ectopic pregnancy[1,2]. It was first described by Duverney in 1708[1]. The incidence of HP is 1 / 7000 to 1 / 30,000 in spontaneous pregnancies. It has also been reported to be as high as 1 / 100 after the use of assisted reproductive technology[2-4]. Clomiphene citrate, which increases the rate of twin pregnancy, could be associated with a HP rate of 1 / 900[5]. This is probably due to the combined effect of ovarian hypersimulation and the subsequent simultaneous transfer of several embryos into the uterus with retrograde flow into the fallopian tubes. Indeed, any factor predisposing a patient to an increased risk of ectopic pregnancy and / or multiple gestations may contribute to HP[1,6,7]. Due to the difficulty in the diagnosis, HP carries therapeutic challenges for the gynecologists. Early diagnosis and laparoscopic treatment of HP provide a good outcome[8].

## CASE REPORT

A 23-year-old Kuwaiti housewife, primigravida married for two years, was admitted into our hospital casualty due to mild lower abdominal pain and vaginal bleeding of one-day duration. She had 6 ± 5 weeks of amenorrhea and had had a positive pregnancy test 10 days earlier. She had primary infertility for two years due to anovulatory and irregular cycles. She got pregnant after the induction of ovulation by clomiphene citrate (after the fourth course). On examination, her general condition was good, her blood pressure was 120/70 mmHg, her pulse rate was 85 beats per minute, full and regular, and she was afebrile. The abdomen was found to be soft and lax, with mild tenderness over the left iliac fossa with no rebound tenderness. Vaginal examination revealed very mild bleeding which was dark red in color. The external cervical os was closed and there was mild tenderness on side to side movement of the cervix. Transvaginal ultrasound examination was carried out and showed a slightly enlarged uterus with an intrauterine gestational sac, with fetal echo and clear fetal heart pulsations. In the left adnexa, there was another extrauterine gestational sac with fetal echo and pulsations visualized. Both crown-rump lengths were matched with seven weeks' gestation. A mild fluid collection was seen in the Douglas pouch. Both ovaries were normal and a left corpus luteium, 30 mm in diameter, was seen.

***Address correspondence to:***
*Dr Ashraf Salah El Badry, P O Box 6705, Salmyia 22078, Kuwait. Tel: 50819995, 66052473, E-mail address ashraf_elbadry@hotmail.com*

After the diagnosis of HP was made, the patient was admitted to the hospital and she was kept fasting. Her basic investigations showed the following results: Hb: 11.2 gm/dl, WBCs: 9.15 x $10^9$, platelet count: 329 x $10^9$, blood group: O Rh positive. Urine routine, random blood sugar, liver and renal function tests were within normal range. Cross matching was done and two units of packed RBCs were kept ready for use. The patient was fully counseled about the treatment options between salpingectomy and salpingostomy, including the advantages and disadvantages of each procedure. She preferred laparoscopic salpingostomy and gave a written informed consent.

Diagnostic laparoscopy was carried out under general anesthesia. The patient was placed in supine position. Pneumoperitoneum was created by using a Veress needle through a vertical umbilical incision. The correct needle position was confirmed by the saline drop method. The $CO_2$ tube was connected to the needle and slow insufflation was done until the intra-abdominal pressure reached 15 mmHg. The Veress needle was removed and the skin incision was enlarged using a scalpel No. 11. A 10 mm trocar was inserted through the umbilical wound followed by placement of the telescope (after proper adjustment of the camera). After initial visualization of the abdominal and pelvic cavities, two 5 mm trocars (left and right side lateral to the rectus muscle) were inserted under direct vision.

On visualizing the pelvic cavity, the uterus was found bulky and anteverted in position. Both ovaries looked normal with a left corpus luteium. The right tube looked healthy. The left tube was found distended at its fimbrial segment with a mass of about 3 cm in diameter. About 150 ml of blood was found in the Douglas pouch. A linear salpingostomy incision was made over the tubal bulge on the antimesenteric side with a needletip unipolar electrode using cutting current. Water pressure, through irrigation probe, was used to dissect and dislodge the product of conception and the gestational sac was removed completely. The specimen was sent for histopathological examination. The bleeding points were successfully controlled using bipolar cautery. Irrigation and suction of the pelvic cavity was done. At the end of the procedure, the instruments and telescope were removed leaving a gas valve of umbilical port open to let out all the gas. The three ports of entry were sutured.

The patient had a smooth postoperative period and was discharged well on the fourth postoperative day after ultrasound confirmation of fetal viability of the intrauterine pregnancy. She was given instructions to attend the hospital casualty in case of acute abdominal pain. Histopathological examination confirmed the diagnosis of left tubal pregnancy. (Fig. 1 and 2)

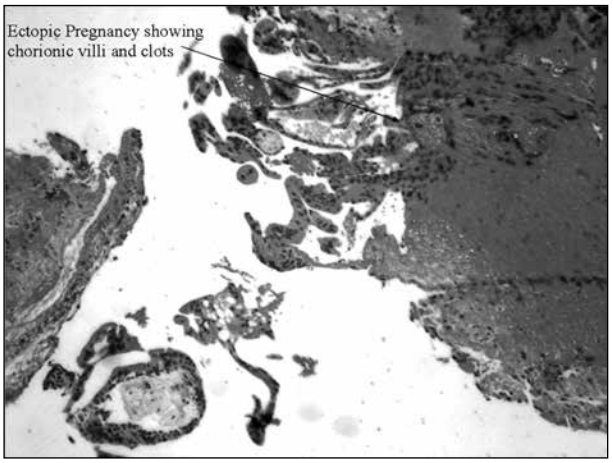


**Fig. 1:** High power magnification revealing hemorrhagic and degenerative, fibrinous tissue with scattered chorionic villi

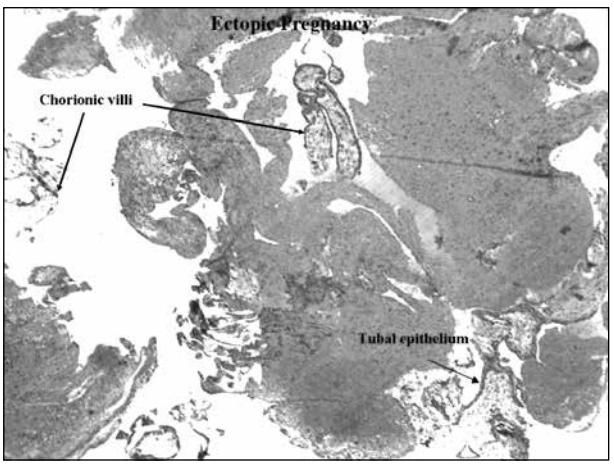


**Fig. 2:** High power magnification of the left fallopian tube showing chorionic villi invading the tubal epithium confirming tubal ectopic pregnancy

The patient was seen in our outpatient clinic one week after discharge. She was in good condition, symptom free and her vital signs were normal. Transvaginal ultrasound examination confirmed fetal viability. The measurement matched the gestational age, and no adnexal masses could be visualized. Subsequently, she was attending the clinic regularly. The pregnancy progressed normally and regular ultrasound examination ensured fetal normality and fetal growth. At 39 weeks of gestation, she had spontaneous vaginal delivery of a live, healthy, normal girl who weighed 3300 gm with a good Apgar score. Both mother and baby were discharged home well on the second day. Six weeks later, she was seen in the clinic and was found to be in good condition. She was breast feeding her baby and was planning to use condoms as a contraceptive method. Possibility of further ectopic pregnancy was fully explained and she was advised to have an early check-up in case of a missed period.

## DISCUSSION

Nowadays, the use of assisted reproductive technology and the use of ovulation inducing medications can increase the risk of HP. Our patient had primary infertility for two years and got pregnant after the induction of ovulation using clomiphene citrate. Both factors increase the risk of ectopic pregnancy.

The majority of HP cases are diagnosed late. Significant morbidity and occasional mortality have been reported as a result of a delay in diagnosis[1]. Often, abdominal and pelvic ultrasound fails to show the ectopic pregnancy because of the awareness of an existing intrauterine pregnancy[1,7]. In our case, the diagnosis of HP was made early in pregnancy (at around 7 weeks gestation) as she had risk factors and presented with symptoms of ectopic pregnancy. HP pregnancy was confirmed by transvaginal ultrasound examination showing the co-existing live intrauterine pregnancy with another extrauterine gestational sac with a pulsating fetal echo inside it. As no single investigation can predict the presence of an HP, it should be suspected in any patient who has lower abdominal pain in the early phase of an obvious intrauterine pregnancy following fertility treatment[6,9]. The positive predictive value of the ultrasound in detecting an ectopic pregnancy has been reported to be between 50 and 95%[10].

The management of HP remains controversial. Surgical removal of the ectopic gestation by salpingectomy or by salpingostomy is the treatment of choice in cases of HP[11]. It is reported that surgical management offers a clear advantage over conservative or medical treatment using methotrexate (either local or systemic administration) or intracardiac potassium chloride injection, especially, in the presence of a live intrauterine pregnancy[6]. Laparoscopic treatment is desirable in a stable patient as it is associated with less blood loss and uterine manipulation, lower analgesia requirement, short postoperative stay and a quicker postoperative recovery. Unilateral salpingectomy is preferred to salpingostomy when the contralateral tube is healthy. This is due to the higher rate of persistent trophoplastic tissue and it requires serial monitoring of serum beta- hCG levels which is not possible in the presence of a live intrauterine pregnancy[12]. Our patient was hemodynamically stable and after comprehensive counseling about the treatment options of laparoscopic salpingectomy versus salpingostomy, she preferred to conserve the tube if possible. As the intrauterine pregnancy was unstable in view of the presence of vaginal bleeding and there was a possibility of miscarriage after the surgery, she preferred salpingostomy and gave a signed informed consent. Complete removal of intact gestational sac from the tube, by using water pressure, minimized the risk of persistent ectopic pregnancy.

## CONCLUSION

The obstetrician should be aware of the possibility of HP especially in women of reproductive age presenting with symptoms suggestive of ectopic pregnancy. High resolution transvaginal ultrasound transducers and meticulous technique should be used by experienced personnel to diagnose HP. Having a high index of suspicion for HP, proper diagnosis and early intervention would decrease the morbidity and mortality, and improve the outcome of the intrauterine pregnancy.

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Case Report

# Milk of Calcium Gallbladder - Limy Bile Syndrome: An Unusual Cause for Acute Cholecystitis

Khaled H Al-Hammad Mohammed Abdel-Hamid, Mervat Al-Saleh
Department of Surgery, Mubarak Al-Kabeer Hospital, Kuwait

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**ABSTRACT**

A rare disorder in which accumulation of calcium salts in the gallbladder leads to the formation of a whitish substance known as the milk of calcium gallbladder or limy bile syndrome. We report such a case which presented as acute cholecystitis. The diagnosis was done by plain X-ray and ultrasonography (USG) of the abdomen and laparoscopic cholecystectomy was performed. The pathogenesis for such a case is also discussed.

KEY WORDS: bile pigment, laparoscopic cholecystectomy, milky bile

## INTRODUCTION

Milk of calcium gallbladder or limy bile syndrome is a rare disorder in which there is accumulation of calcium carbonate (commonest) or oxalate in the gallbladder[1]. The lumen of the gallbladder is filled with a radiopaque material whose consistency varies from fluid to paste-like or even firm to solid. Its color ranges from white, grey, yellow to brown and sometimes black depending on the amount of the bile pigments in the gallbladder[1,2]. The etiology is unknown, although gallbladder stasis is believed to be the main factor[2].

## CASE REPORT

A 36-year-old Filipino female was admitted to Mubarak Al-Kabeer Hospital in August 2009 with a persistent right sided upper abdominal pain of two days duration. It was dull aching in nature with no history of fever or jaundice. This was her second attack within one year. On examination, she had a temperature of 36.8 ºC with abdominal tenderness over the right upper quadrant (positive Murphy's sign) and there was no hepatomegaly. Blood tests showed a total leucocytic count of 11.1 x $10^9$/l and the liver function tests were normal (total bilirubin 5 µmol/l; direct bilirubin 1 µmol/; alkaline phosphatase 54 IU/l; albumin 44 g/l). Plain X-ray (Fig. 1) and ultrasound (Fig. 2) of the abdomen performed at the time of admission confirmed the diagnosis as a case of acute cholecystitis induced by limy bile. The abdominal ultrasound also revealed that the intra-hepatic biliary radicals and the common bile duct were normal. The patient was started on intravenous fluids and antibiotics. Emergency laparoscopic cholecystectomy was performed on the next day and showed a thickened wall gallbladder containing a whitish, semisolid, paste-like substance and wide cystic duct (Fig. 3A, B, C & D). No stones were found. After an uneventful recovery she was discharged on the next day of surgery. On follow-up of the case, the histopathological examination of the gallbladder revealed acute on top of chronic cholecystitis while the biochemical analysis of the substance (bile) showed calcium oxalate with a pH of 8.5 (reference range: 6.5 - 9, mean: 7.25). The serum calcium level was normal 2.33 mmol/l and the corrected calcium was 2.25 mmol/l (reference range: 2.2 - 2.6 mmol/l). The parathormone level was also normal (5.23 pmol/l reference range: 1.3 - 9.3 pmol/l). On her normal diet the urinary calcium excretion was 2.2 mmol/l in 24 hours (reference range: 1.2 - 10 mmol/l in 24 hours) with a urine-creatinine clearance of 106.1 ml/m (reference range: 80 - 120ml/m).

***Address correspondence to:***

*Dr. Khaled H Al-Hammad, Registrar and Resident in Kuwaiti Board of Surgery, Dept. of Surgery, Mubarak Al-Kabeer Hospital, Al-Jabriya, Kuwait. P O Box 43787, Code: 32052 Kuwait. Tel: (+965)99100191, E-mail: duke_alhammad@hotmail.com*

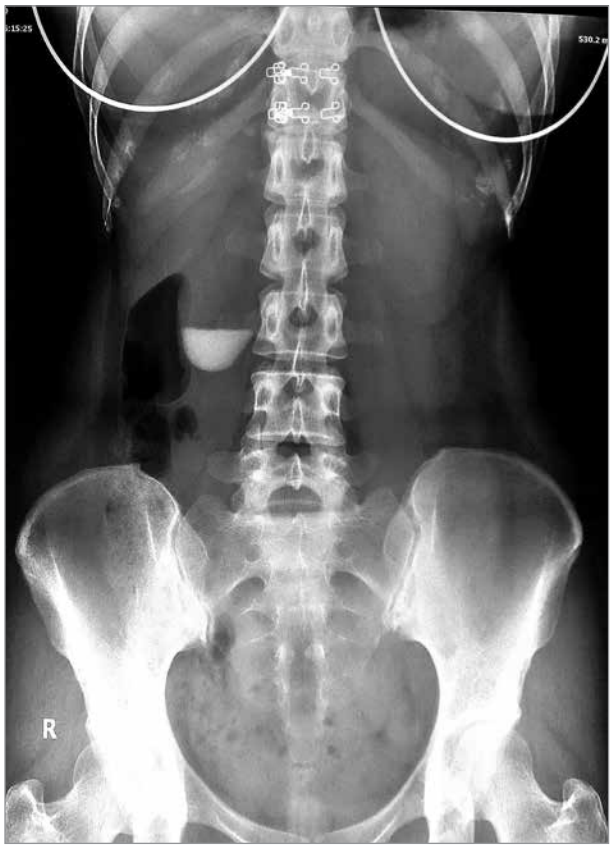


**Fig. 1:** Plain X-ray of the abdomen showing a pear shaped opacity with a fluid level in the right hypochondrium indicating milk of calcium gallbladder.

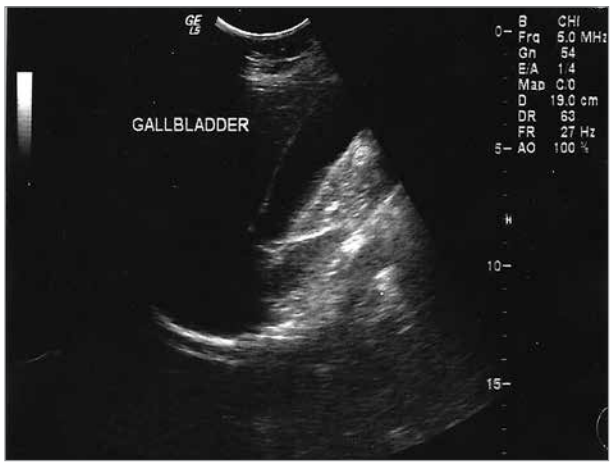


**Fig. 2:** Abdominal ultrasound showing a well distended gallbladder with hyperechoic fluid-posterior acoustic shadow indicating milk of calcium gallbladder

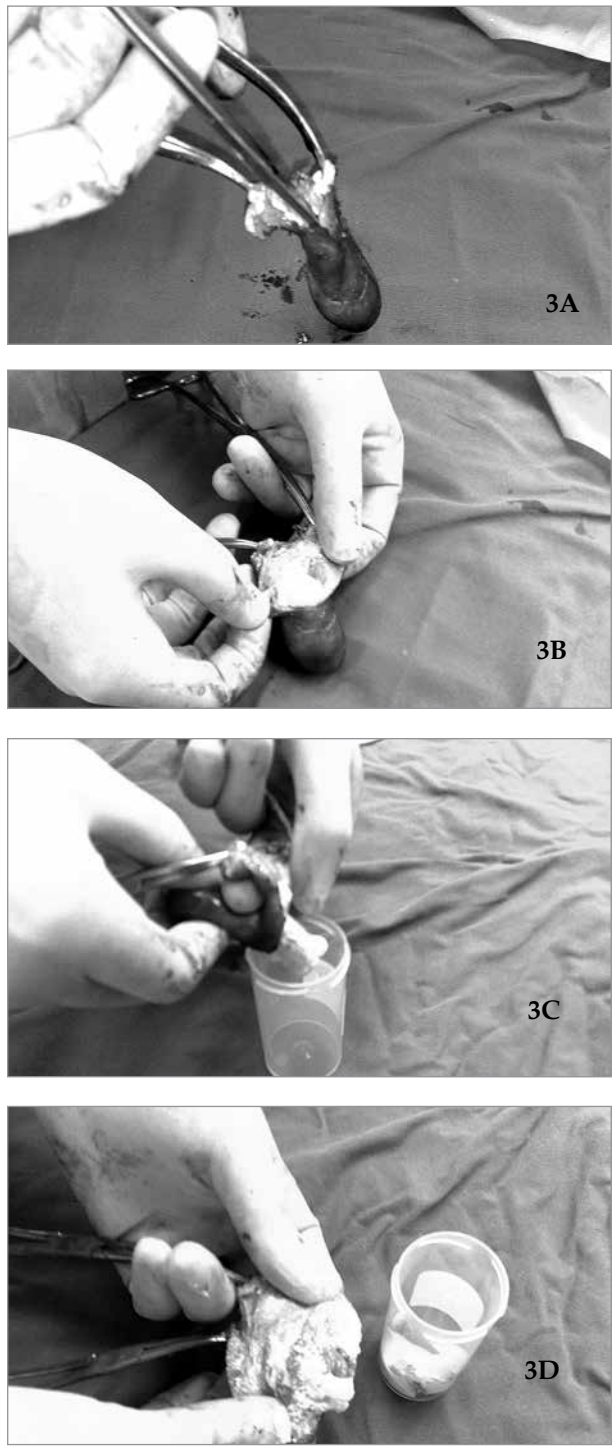


**Fig. 3 (A, B, C & D):** Operative photograph of the excised gallbladder showing a thickened wall containing a whitish, semisolid, paste-like substance (bile)

## DISCUSSION

In 1911, Churchman first described the findings of a white substance in the gallbladder as white "milky" bile[1]. A substance also called "limy bile" was reported by Knutsson in 1933 and only 300 cases had been reported until 1988[1,3]. It is a rare disease predominantly of the adults with male : female ratio is 1:3 with almost the same age and sex distribution as those for gallstones alone[3,4]. Limy bile syndrome accounts for 0.1 - 1.7% of patients operated on for gall stones in western countries[5,6]. Its presentation ranges from abdominal discomfort or pain (biliary colic) to acute or chronic cholecystitis[6]. It can lead to obstructive jaundice or pancreatitis with the passage

of the limy bile into the common bile duct[6] but it also can pass spontaneously without any symptoms or signs depending on the consistency of the bile[7]. The diagnosis of such case can be made depending on the plain X-ray of the abdomen where it appears as a radio-opaque shadow below the liver margin[8]. The different types of gallstones (*e. g.*, cholesterol, mixed and pigmented) are principally formed due to abnormal bile constituents (*e.g.*, cholesterol, phospholipids and bile salts)[9]. There are several factors that favor gallstone formation which can occur due to obesity, hormones (*e. g.*, estrogen, progesterone, use of oral contraceptive pills) marked weight loss, hemolytic anemia, liver cirrhosis and ileal disease[10,11]. Also pro-nucleating factors (including infections, calcium and bacterial biofilms) and gallbladder stasis (which can occur from total parenteral nutrition, octreotide use, pancreatic insufficiency and spinal cord injury) can promote gallstone formation[10]. The pathogenesis of the limy bile formation or the precipitation of calcium salts in the gallbladder has not been clearly defined. Various factors have been suggested to play a role in its formation is due to abnormal calcium metabolism[8,12], a variable pH of the gallbladder[13-15] or gallbladder stasis which is believed to be the main cause[2]. In our case, the presentation was in the form of acute cholecystitis. There was no evidence of abnormal calcium metabolism or malfunction of the liver. The pH was in the higher normal range but some studies revealed that calcium salt formation in the gallbladder occurs when the pH is above 6.6[13-15] as in our case. Also the intra-operative finding of a wide cystic duct could be explained by prolonged or partial cystic duct obstruction which can lead to stasis of the bile with the formation of the limy bile. A close differential diagnosis of milk of calcium gallbladder is the porcelain gallbladder which is characterized histologically by flakes of dystrophic calcium within chronically inflamed and fibrotic wall of gallbladder. On plain radiography it shows calcifications in segment of the wall or the entire wall. Also it is differentiated from limy bile by its inability to contract on gallbladder contractility test with cholecystokinin or in response to a fatty meal. The strategy for managing patients with limy bile is individualized based on symptoms, the clinical conditions and the location of the limy bile. Also any associated biliary stones or lesions causing biliary obstruction can be included. Most of surgeons prefer surgical intervention for early acute cholecystitis to minimize the rate of complications (*e. g.*, infection and obstruction), the rate of conversion to open surgery (due to subsequent adhesions formation) and enable significantly shorter total hospital stay[16-18]. In our case we preferred early intervention with laparoscopic cholecystectomy to avoid any further complications.

## CONCLUSION

Milk of calcium gallbladder is a rare disorder that can be diagnosed with plain X-ray of the abdomen and needs early intervention with cholecystectomy to avoid any complication.

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Case Report

# Delayed Diagnosis of Leprosy in a Kuwaiti Child

Mariam Al-Fadhli[1], Fawzi E Ali[2], Mohammad Saraya[1]
[1]Department of Medicine, Infectious Diseases Hospital, Kuwait
[2]Medical Rehabilitation Center, Kuwait

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**ABSTRACT**

Leprosy is a chronic infectious disease affecting primarily the skin, peripheral nerves, and some visceral tissues. The skin lesions take the form of macules, papules, plaques, nodules and diffuse infiltration. If hypo-pigmented macules are the only manifestation of leprosy in patients living in non-endemic areas, they may be misdiagnosed as other more common skin diseases. We report the case of an 8-year-old Kuwaiti boy who presented with hypo-pigmented macules for the last four years. He was given various diagnoses until neurologic manifestations set in. That was when the diagnosis of leprosy was suspected and confirmed by biopsy. Awareness of leprosy should be raised in non-endemic countries like Kuwait which have a sizeable expatriate work force coming from endemic areas.

KEYWORDS: hypo-pigmented macules, infectious disease , Kuwait, multibacillary, *mycobacterium leprae*

## INTRODUCTION

Leprosy is a chronic, infectious, systemic disease caused by *Mycobacterium leprae*[1]. It is transmitted from person to person and has an insidious onset. It has a long incubation period which averages 3 - 5 years[2]. The disease presents polar clinical forms (the "multibacillary" lepromatous leprosy and the "paucibacillary" tuberculoid leprosy), as well as other intermediate forms with hybrid characteristics, depending on the immunity status of the host[3].

Leprosy primarily affects the skin, peripheral nerves, mucosa of the upper respiratory tract and the eyes[4]. The hallmark clinical findings in leprosy are hypo-pigmented skin lesions with loss of sensation. Other skin lesions seen are papules, nodules and skin infiltration. However, the clinical presentation is often different from the usual pattern, leading to confusion in diagnosis. Sensory loss is a typical feature of leprosy, but is late to appear. Presence of acid-fast bacilli in tissue specimens is regarded as a gold standard for diagnosis[2].

Worldwide, two to three million people are estimated to be permanently disabled by leprosy. India has the largest number of cases, with Brazil second and Myanmar in the third position[5]. The treatment regimen recommended by WHO in 1981 is based on multi-drug therapy (MDT) to avoid bacterial resistance. WHO has supplied MDT free of charge to leprosy patients in all endemic areas since 1995 and targeted to eliminate leprosy as a public health problem from the world by the year 2000. MDT treats leprosy very well, but there is no proof that it concurrently interrupts transmission[6].

Leprosy is rare in more developed countries[7]. These countries are magnets for migration and population migration from countries where leprosy is endemic has lead to an upward trend in prevalence and a change in the epidemiology of the disease. This also created a challenge for health care workers who have little experience in diagnosis and therapy of leprosy, a disease that mimics many common dermatological and neurological entities. The same situation is seen in oil-rich Arab countries which depend heavily on foreign contract workers, most of them coming from endemic countries[8].

## CASE PRESENTATION

An 8-year-old Kuwaiti boy was brought by his family to the hospital with complaints of skin eruption in the form of hypo-pigmented areas all over his body which started four years ago. The boy had been given different diagnoses since the lesions first appeared and had accordingly received different treatments with no improvement. This diagnosis included discoid eczema, pityriasis versicolor, pityriasis alba, naevus achromicus, mycosis fungoides and vitiligo. Recently, the boy started to suffer from loss of sensation in his

***Address correspondence to:***
*Mariam Al-Fadhli, Al-Andalus, Area 6, Street 102, House 275, Kuwait.Tel: +965 99660936, Fax: +965 24899253, E-mail: medicine209@gmail.com*

left hand leading to a painless burn injury.

On clinical examination, multiple, rounded to oval, rather uniform, hypo- pigmented macules were noted on both sides of the body (Fig. 1 and 2). The lesions had raised erythematous edges and their surfaces were dry, rough and anesthetic. Erythema of the face was obvious. Both ulnar nerves were thickened and palpable. No data was available about the progression of the skin lesions over the duration of the disease. There was nothing in the boy's past history to indicate reduced immune status. He had received all routine childhood vaccinations including BCG. He suffered uncomplicated chickenpox at the age of three years.

A skin biopsy was taken from the lower back and

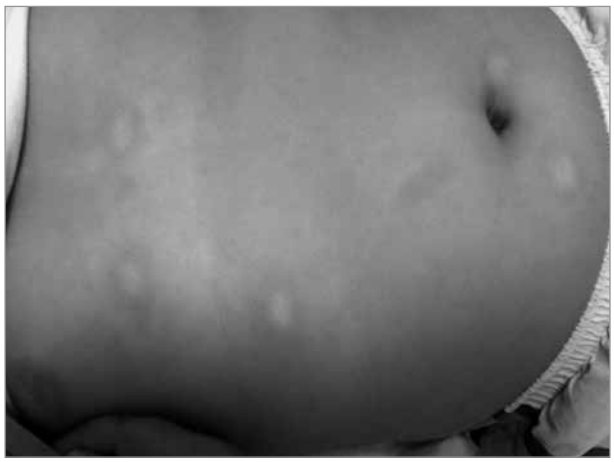

**Fig. 1:** Abdominal wall showing several hypo-pigmented macules with erythematous edges

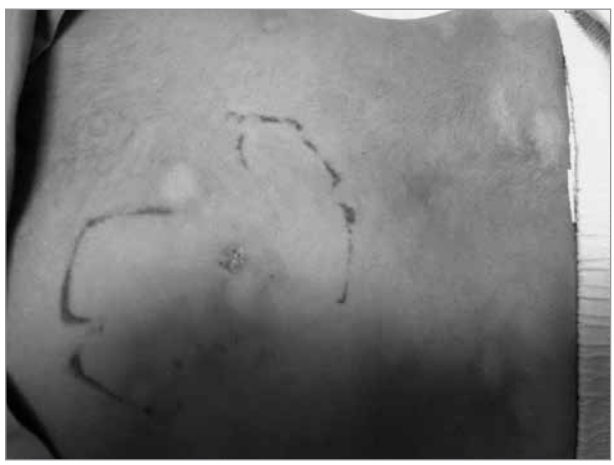

**Fig. 2:** Back showing several hypo-pigmented macules with erythematous edges as well as the site of biopsy

revealed round infiltrates consisting of epitheliod cells and lymphocytes. The infiltrates had a tendency to surround adnexal structures. Many acid-fast bacilli (AFB) were present inside the histiocytes (Fig. 3). This picture was diagnosed as borderline lepromatous leprosy (BLL).

His blood count (CBC) was within normal limits

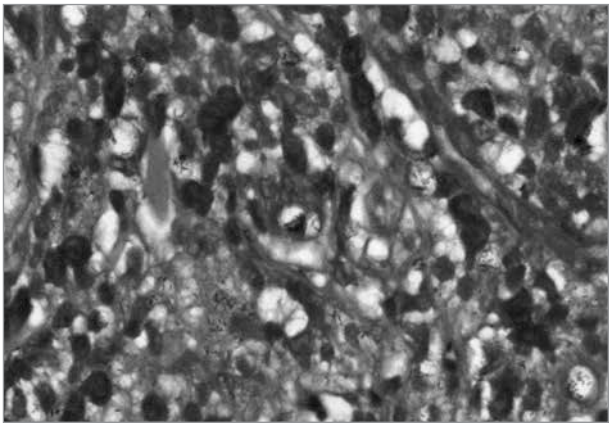

**Fig. 3:** Histopathology of the biopsy showing lympho-histyocytic infiltrate and numerous acid-fast bacilli (AFB)

(WBC $8.6x10^9$/l with normal differential, hemoglobin 134 g/l, RBC $4.8 \times 10^{12}$/l & platelet count of $201 \times 10^9$/l. Other laboratory investigations (liver and kidney function tests, serum electrolytes, urine analysis and chest X-ray) and other systemic examinations were within normal limits. The patient was given treatment in the form of rifampicin, dapsone and clofazimine.

Household contacts were found healthy without suspicious lesions. Careful history taking revealed that the boy may have contracted leprosy from an Indonesian expatriate nanny who took care of him in his early years. The boy's family recalled that the nanny had similar skin lesions to the ones developed by the boy. By the time the boy presented, that nanny had left Kuwait without ascertaining the diagnosis of her skin condition.

## DISCUSSION

Kuwait is a non-endemic country for leprosy. With resident expatriates forming a little more than 2/3rd of Kuwait's population and the majority of them hailing from endemic countries for leprosy, the disease is mainly an imported one in Kuwait. Over 95% of leprosy cases in Kuwait are foreign born[9]. The small number of the indigenous population who get infected, do so through contact with infected expatriates especially domestic servants, or through travel to endemic countries.

Due to the long incubation period of leprosy, most cases are not diagnosed until several years after initial exposure. Leprosy characteristically occurs in adults but children can also be susceptible. In areas of high prevalence, leprosy among children younger than 15 years represents 5 - 10% of new cases[10,11]. A household contact is present in more than third of children, and paucibacillary forms are more frequent. It is rare to find leprosy in children in non-endemic areas. There were no children among 167 new cases with leprosy detected in Kuwait[9,12].

There are several causes for misdiagnosing

dermatological lesions of leprosy in children. White patches represent a frequent occurrence among children and a thorough evaluation is needed, if leprosy is suspected. There is a large differential diagnoses of more common disorders of hypo-pigmentation in children[13,14]. The hallmark anesthetic nature of skin lesions may not be easy to demonstrate, especially in a small child. In any age, leprosy manifestations may be concealed by other co-morbid skin diseases[15]. The dry lesions of leprosy can be complicated by eczema which may confuse the diagnosis, except for the peculiarity that it is non-pruritic[16].

The diagnosis of leprosy in this case was delayed because the initial presentation was solely with skin lesions in a child from a non-endemic area. The morphology of the lesions had a wide differential diagnosis. After sensory loss had made its appearance, the suspicion of leprosy was raised which was confirmed by skin biopsy.

The foreign nanny who is suspected to be the source of infection came from Indonesia which is a known endemic country for leprosy. Foreign workers first entering Kuwait are screened for infectious diseases before they are issued residence permits. These screens include blood work and chest radiography but no physical examination is performed which means that cases of leprosy would escape detection. Still, if screening physical examination was instituted, subjects in the long incubation period of leprosy would not be caught. Nearly 60% of expatriate patients develop their symptoms 2 - 5 years after entry into Kuwait[12]. So, the best way is to keep a high index of suspicion for query skin lesions that fall within the spectrum of leprosy. This applies as well to other Arabian Gulf countries[8] and more developed countries[7] which face the same situation.

As our case shows, delay in diagnosis of leprosy can have serious neurological consequences for the patient[2]. Leprosy can be difficult to diagnose outside endemic areas. Increased awareness among physicians would lead to rapid diagnosis and thus minimizing damage and disability[17]. At the present time, it seems likely that we shall see more cases of leprosy in Kuwait than ever before. It is important to be on alert for such cases at all times and more so, during these times of globalization and increased international travel.

## CONCLUSIONS

We believe that there are cases of leprosy not identified in Kuwait due to lack of awareness among physicians about the disease, which leads to misdiagnosis and wrong treatments for patients who are then left to suffer with the debilitating damage caused by this disease. Screening for leprosy is an important question for health authorities in countries with extensive immigration.

## ACKNOWLEDGEMENT

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Case Report

# Invasive Airway Aspergillosis in an Immunocompetent Host: A Case Report

Hui-zhen Fan, Hua-peng Yu, Huo-jin Deng
Department of Respiratory Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou, China

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**ABSTRACT**

Invasive airway aspergillosis (IAA) is a rarely reported type of invasive pulmonary aspergillosis (IPA). In most patients, IAA is associated with immune dysfunction or other underlying diseases. It is very rare in patients with normal immune function and without pre-existing diseases. We describe here, a previously healthy 58-year-old male farmer who presented to our department with cough and bloody sputum associated with shortness of breath and who was diagnosed with IAA despite having no apparent immunodeficiency.

KEY WORDS: C-reactive protein, immune dysfunction, invasive pulmonary aspergillosis (IPA)

## INTRODUCTION

The incidence of invasive pulmonary aspergillosis (IPA) has increased yearly, due to developments in medical science and technology; the wide use of broad-spectrum antibiotics, corticosteroids, and immunosuppressants; the increased rates of solid organ transplantation, catheterization, and tumor chemotherapy and radiotherapy; and the increased incidence of blood diseases and AIDS. Invasive airway aspergillosis (IAA), also called invasive tracheobronchial aspergillosis (ITBA), is a rarely reported type of IPA. In IAA, the trachea and bronchus are the main or even only organs infected by aspergillus[1], and the disease mainly affects patients with immune dysfunction or other underlying diseases. IAA is very rare in patients with normal immune function and no pre-existing diseases. We describe here, the case of a patient who presented with IAA despite no apparent immunodeficiency.

## CASE REPORT

A 58-year-old man was admitted to our department with cough, bloody sputum for one year, and shortness of breath for six months, which became aggravated over the previous four days. One year earlier, this patient had been diagnosed with tuberculosis at a local hospital due to cough and bloody sputum without obvious causes. Antituberculosis treatment with isoniazid and rifampin for six months eased his symptoms of cough, but the patient still had blood stained sputum. Six months prior to admission to our department, his symptoms of cough and bloody sputum increased, and he began to experience chills, fever (maximum body temperature, 40 °C), and shortness of breath. The patient was again seen at his local hospital, where he was diagnosed with pneumonia. After antibiotic treatment with cefuroxime for two months, his body temperature returned to normal, but his symptoms of cough, bloody sputum and shortness of breath did not improve significantly.

Four days prior to admission to our department, his shortness of breath suddenly worsened, and he began to experience breathing difficulties and hoarseness. He was again admitted to his local hospital. A chest X-ray revealed atelectasis of his left lung, a leftward shift of his mediastinal trachea, and an upward shift of the left copola of the diaphragm. The patient was diagnosed with lung cancer, but treatment with anti-inflammatory, antispasmodic and antiasthma agents (names of specific drugs were not available) did not improve his symptoms. He was, therefore, admitted to our hospital. Since the onset of his disorder, the patient

***Address correspondence to:***
*Huo-jin Deng, Department of Respiratory Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou 510280, China. Tel: +86-13640286518. E-mail: denghj51889@126.com, 110851512@qq.com*

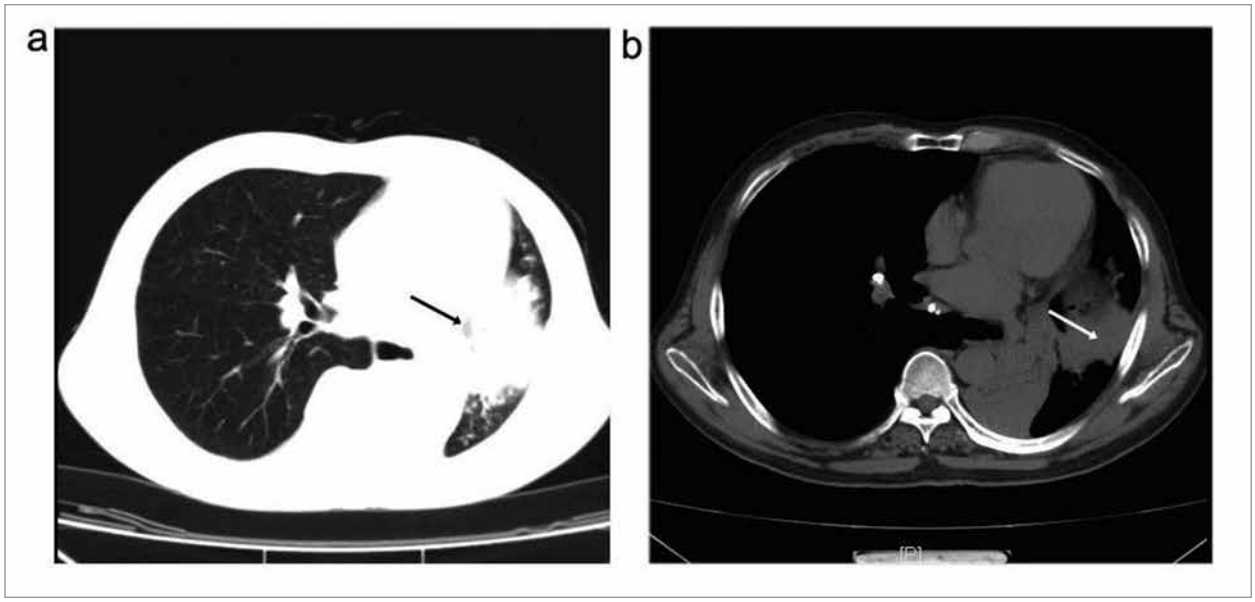


**Fig. 1a, b:** Chest CT scan, showing atelectasis in the left lower lobe, occlusion of the left main bronchus, multiplicity of the mediastinum, and swollen and partially calcified lymph nodes

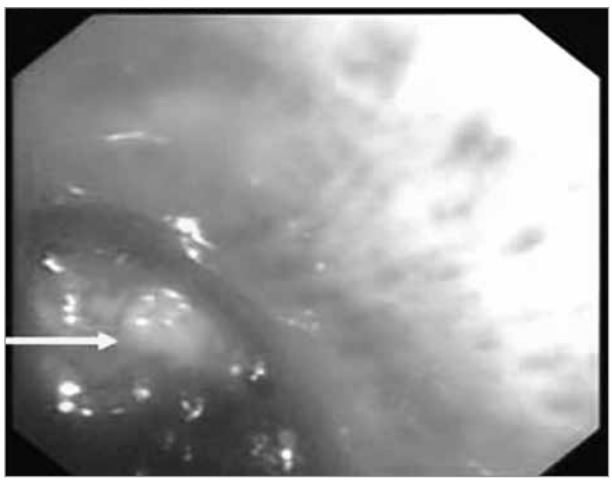

**Fig. 2**: Fiberoptic bronchoscopy, showing a visible round mass with smooth surfaces at the opening of the left main bronchus

had lost 3 kg in weight. Physical examination showed that his vital signs were stable. Soft, swollen lymph nodes, measuring about 0.5 × 0.5 cm, were palpable in the right submandibular area, but there was no tenderness or adhesion to surrounding tissue. His throat was congested, his trachea slightly shifted to the left, and his left respiratory movements and fremitus were significantly weakened. Percussion of the left lung yielded a dull sound, whereas percussion of his right lung was silent. The breath sounds of his left lung were weaker than those of his right lung, but no wet or dry rales were heard. His heart and abdomen were normal.

Routine blood counts, blood glucose, electrolyte, and liver and kidney function tests, lung cancer markers, and prothrombin time were normal. He was negative for anti-HIV antibodies and for a spectrum of

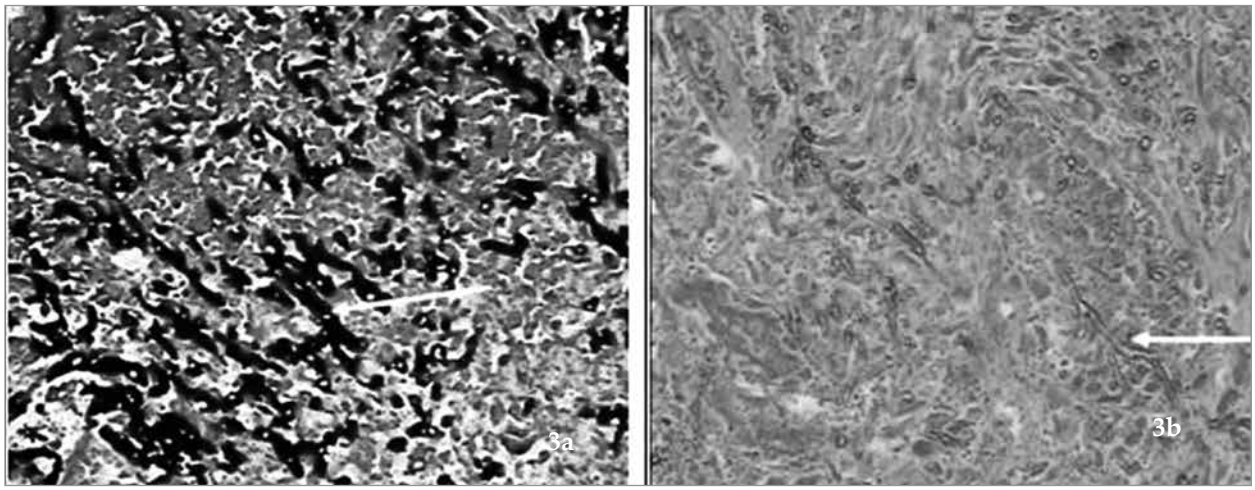


**Fig. 3:** Pathological examination, showing **(a)** a large number of fungal hyphae in the tissue, which had acute angle branch and separation and **(b)** Methenamine silver staining (positive)

auto-antibodies. His serum concentration of C-reactive protein (CRP) was 6.84 mg/l. Gram-positive cocci were visible in sputum smears, but a sputum culture was negative. A chest CT scan showed atelectasis in the left lower lobe, an occlusive left main bronchus, and swelling and partial calcification of multiple lymph nodes in the mediastinum (Fig. 1). Fiberoptic bronchoscopy revealed a visible round mass with smooth surfaces completely blocking the lumen at the opening of his left main bronchus (Fig. 2). This mass was considered a neoformation of the left main bronchus. To determine whether it was a bronchial lung tumor, a tissue sample was biopsied. The bronchial sample was negative on smears and culture. Pathological examination showed a large number of fungal hyphae in the tissue, which had an acute angle branch and separation (Fig. 3). Methenamine silver staining and PAS staining of the tissue were positive. The patient was diagnosed with aspergillosis and treated with intravenous amphotericin B and argon plasma coagulation on bronchoscopy. After treatment, the patient's status was stable. The size of the mass in the left main bronchus was slightly reduced, his symptoms of cough were eased, and the bloody sputum disappeared. The patient requested to be discharged for financial reasons, but died of massive hemoptysis two and a half months later.

## DISCUSSION

Recent increase in the use of bronchoscopy and improvements in respiratory system interventional techniques have been associated with the increased diagnosis of IAA. Aspergillus species are widely distributed in nature, with more than 250 species currently known, although only a few species are pathogenic in humans[2]. The most common of these species is *Aspergillus fumigatus*, which accounts for 50 - 60% of Aspergillus infections, followed by *A. flavus, A. niger and A. terreus*, each of which accounts for 10 - 15% of infections in humans[3]. Spores of Aspergillus, about 2 - 3 μm in diameter, are suspended in the air and are easy to inhale into the lower respiratory tract[4]. The ability of these spores to cause disease is dependent on the immune status of the patient and on any damage to target organs. Depending on the site of infection, Aspergillus infections can be characterized as upper airway infections, tracheal and bronchial aspergillosis and diseases of the lung parenchyma. Although not precisely known, the incidence of airway Aspergillosis is very low[1]. The incidence of airway aspergillosis has been reported to be 3 - 22% after lung transplantation[5], with 5 - 10% of the latter patients showing involvement of the airways only and not the lungs. Most patients with IAA had IPA[6]. The pathogenesis of IAA is not yet clear, although airway invasion by Aspergillus may be due to a decline in airway defense functions resulting from structural damage and impaired mucociliary clearance[7]. Most patients with IAA also have an immune dysfunction[8] or other underlying diseases, such as congenital defects in the lung and trachea, severe asthma, bronchiectasis, and chronic obstructive pulmonary disease[9]. Indeed, 74% of patients with airway Aspergillus were reported to have an immune dysfunction, with about 68% having received a lung transplant or undergoing surgery for lung cancer[10]. Our patient was a previously healthy farmer without impaired immune function, underlying disease, history of glucocorticoid use, or other clear causes of IAA. We, therefore, speculate that the disease was caused by inhalation of mouldy rice.

The clinical signs and symptoms of IAA are non-specific, but may frequently include cough, sputum, hemoptysis, fever, chest tightness, chest pain, shortness of breath, difficulty breathing or respiratory failure. Chest radiographic changes are not specific, but may include thickening of the tracheal wall and bronchiectasis at a nearby site. Patients with airway obstruction that causes pulmonary consolidation are diagnosed primarily by microscopy and culture of sputum and bronchoalveolar lavage fluid (BALF)[11]. The confirmation of this diagnosis depends on a biopsy of the lesion under bronchoscopic guidance. Mucus plugs, inflammation of the mucosa, necrotic tissue or neoformation may be visible on bronchoscopy. IAA must be clearly distinguished from a pulmonary tumor. Our patient presented with cough, bloody sputum, fever, and shortness of breath. Chest CT showed consolidation of the left lung and partial atelectasis. He had been previously misdiagnosed at another hospital with tuberculosis, pneumonia, and lung cancer, delaying appropriate treatment. He was ultimately diagnosed by bronchoscopic biopsy in our hospital, but he died of massive hemoptysis because he did not receive further treatment for financial reasons. IAA can be treated with voriconazole, itraconazole, posaconazole, amphotericin B, or caspofungin, for a minimum of 6 - 12 weeks. Patients also receiving immunosuppressive therapy should be treated with antifungal therapy throughout the entire process until cured. Simultaneously, these patients should receive endotracheal interventional treatment, such as laser, high-frequency electrocautery, microwave, or argon plasma coagulation under bronchoscopic guidance. In addition to hormone therapy, Aspergillus-induced asthma and airway hyper-responsiveness have been reported, with omalizumab showing optimal results[12]. Voriconazole and endotracheal interventional treatment such as argon plasma coagulation may have been optimal for this patient. Endotracheal interventional treatment *via*

a bronchoscope is suitable for patients with central airway obstructive mass. This patient was not eligible for surgery because the mass was located in his left main bronchus. In addition to timely diagnosis and treatment, the prognosis of IAA depends on a patient's immune status and underlying diseases. Prognosis is usually good in patient with normal immune function and without malignant or other underlying diseases, but remains poor in patients with serious underlying diseases. The mortality rate in patients with aspergillosis in the airway after hematological malignancies or stem cell transplantation was as high as 70%[13], but was only 20% in patients with benign primary disease[14]. Therefore, treatment of airway aspergillosis also involves the active treatment of the primary disease.

## CONCLUSION

In conclusion, our findings suggest that patients with unexplained cough and shortness of breath should be assessed by fiberoptic bronchoscopy for an accurate diagnosis, thus reducing the likelihood of misdiagnoses and missed diagnoses.

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Case Report

# Agnogenic Myeloid Metaplasia: A Rare Cause of Ascites

Yasin Sahinturk, Arda Gokay, Ayhan Hilmi Cekin
Gastroenterology and Internal Medicine Clinic, Antalya Training and Research Hospital, Antalya, Turkey

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**ABSTRACT**

A 65-year-old woman diagnosed with agnogenic myeloid metaplasia (AMM) was referred to our hospital due to complaints of ascites that developed two months after a splenectomy. The patient had massive ascites with a serum-ascites albumin gradient of 1.5. The ascites was transudative, assumed to have developed from peritoneal hematopoiesis during the course of portal hypertension that itself developed after splenectomy. To the best of our knowledge, no report in the literature has described a case diagnosed as AMM with ascites after splenectomy. Thus this report is the first case of AMM with ascites that developed two months after splenectomy.

KEY WORDS: clonal disorder, peritoneal hematopoiesis, ascites, splenectomy

## INTRODUCTION

Agnogenic myeloid metaplasia (AMM), first described by Heuck in 1879, is a clonal disorder arising from the neoplastic transformation of early hematopoietic stem cells[1]. Splenomegaly, anemia, leukocytosis and thrombocytosis (60%), osteosclerosis, and leukoerythroblastosis seen in peripheral blood smears (extramedullary hematopoesis) are the diagnostic criteria for AMM[1]. AMM presents clinically as dizziness and fatigue related to anemia, bone pain in the course of osteosclerosis, and a hypermetabolic state resulting in weight loss, night sweats, fever, and bone, muscle and joint pain.

Laboratory findings are anemia with leukoerythroblastosis due to a shortening of erythrocyte life span and decreased production[2]. Leukocytosis with immature myeloid cells is generally present. In the course of AMM, thrombocytosis is present during the early period, but when disease progresses, thrombocytes may be normal or decreased[2]. Also, huge and abnormal thrombocytes are seen in peripheral blood smears[3].

Differentiating AMM from chronic myeloid leukemia is important. Philadelphia chromosome negativity and absence of ABL/BCR gene replacement are important in the differentiating AMM from chronic myeloid leukemia.[2]

Portal hypertension occurs in approximately 7% of patients with AMM and may be related to increased portal flow resulting from marked splenomegaly and to intrahepatic obstruction resulting from thrombotic obliteration of small portal veins. This may result in variceal bleeding or ascites[4].

Chemotherapeutics have mainly been used as cytoreductive therapy to control leukocytosis, thrombocytosis, or organomegaly. Hydroxyurea is the preferred agent, but other drugs (*e.g.*, interferon, cladribine) have also been used. Busulfan has been used, but it is not a preferred agent in view of the lesser toxicity of hydroxyurea. Ruxolitinib is indicated for myelofibrosis and is an effective agent to reduce splenomegaly[4].

We hereby report a case of AMM that developed ascites two months after splenectomy.

## CASE REPORT

A 65-year-old woman presented to our clinic with symptoms of general fatigue and dizziness. She had anemia and splenomegaly. She had been diagnosed as myelofibrosis after a bone marrow biopsy and started on interferon alpha-2 therapy 3,000.000 IU, three times per week. After six months, she quit interferon therapy due to the worsening of fatigue and was started on hydroxyurea treatment 500 mg, twice per

***Address correspondence to:***
*Yasin Sahinturk. Antalya Eğitim ve Araştırma Hastanesi Gastroenteroloji Servisi, Antalya, Turkey. Tel: +905322465194, Fax: +902428248580, E-mail: drsahinturk@yahoo.com*

day. Hydroxyurea treatment was managed according to her white blood cell and platelet counts. In the course of the treatment, splenomegaly became huge and she needed multiple transfusions. Therefore, she underwent a splenectomy, after which she suffered from leakage of ascites from the drains. Two months after splenectomy, massive ascites became evident and she was directed to our department. Physical examination showed massive ascites and abdominal hernia; other physical findings were normal. Her laboratory data are shown in Table 1.

**Table 1:** Laboratory (hematology and blood chemistry) results of the patient

| Parameter | Result |
|---|---|
| Hematocrit | 30.9% |
| Hemoglobin | 9.2 g/dl |
| White cell count | 43.67 x $10^3$/$mm^3$ |
| Platelet count | 736,000 x $10^3$/$mm^3$ |
| Mean corpuscular volume | 85.1 $\mu m^3$ |
| Erythrocyte sedimentation rate | 92 mm / hour |
| Partial thromboplastin time | 38.5 sec |
| Prothrombin time | 15.1 sec |
| International normalized ratio (INR) | 1.19 |
| Sodium | 140 mmol/l |
| Carbon dioxide | 22 mmol/l |
| Chloride | 101 mmol/l |
| Potassium | 5.2 mmol/l |
| Glucose | 74 mg/dl |
| Protein total | 6.5 mg/dl |
| Albumin | 3.6 g/dl |
| Alkaline phosphotase | 173 IU/l |
| Aspartate aminotransferase | 19 IU/l |
| Alanin aminotransferase | 54 IU/l |
| Lactate dehidrogenase | 1125 IU/l |
| Ferritin | 397.1 ng/ml |

Biopsy specimens from the spleen showed immunohistochemically MPO (+) CD61(+) CD15(+) (Fig. 1), and she was diagnosed histologically as AMM.

She was evaluated for ascites etiology, and her serum ascites albumin gradient was calculated to be 1.5 as transudation. Peritoneal fluid laboratory results were as follows: albumin 2.1 g/dl, glucose 105 mg/dl, lactate dehydrogenase 485 IU/l, and protein 3.6 g/dl.

Her autoimmune markers were negative, hepatic markers were non-reactive, and tumor markers were in the normal range. An ultrasonography showed an enlarged liver 19 cm in diameter, with a portal vein diameter of 15 mm and portal thrombosis. Upper abdomen magnetic resonance imaging (MRI) and portal vein magnetic resonance angiography showed a portal vein diameter of 15 mm without a thrombus. An esophago-gastro-duodenoscopy performed one month after splenectomy showed no esophageal varices. In addition, a second esophago-gastro-duodenoscopy eight months after splenectomy showed three grade 1 lower esophageal varices. She had no gynecological problems. An echocardiography, showed her ejection fraction to be 60% and no pericardial effusion or valve problems. Ascites cytology revealed non-specific reactive changes and was negative for malignant cells. Liver biopsy showed extramedullary hematopoesis. The t (9 - 22) and Jak2 mutations were negative. Finally, an abdominal hernia operation was performed, and specimens taken from the peripheral part of the adipose tissue showed blastic cells related to extramedullary hematopoesis. Her hydroxyurea treatment was increased to 3 x 1, and ascitic fluid drainage was performed. She was started on diuretic treatment for her ascites.

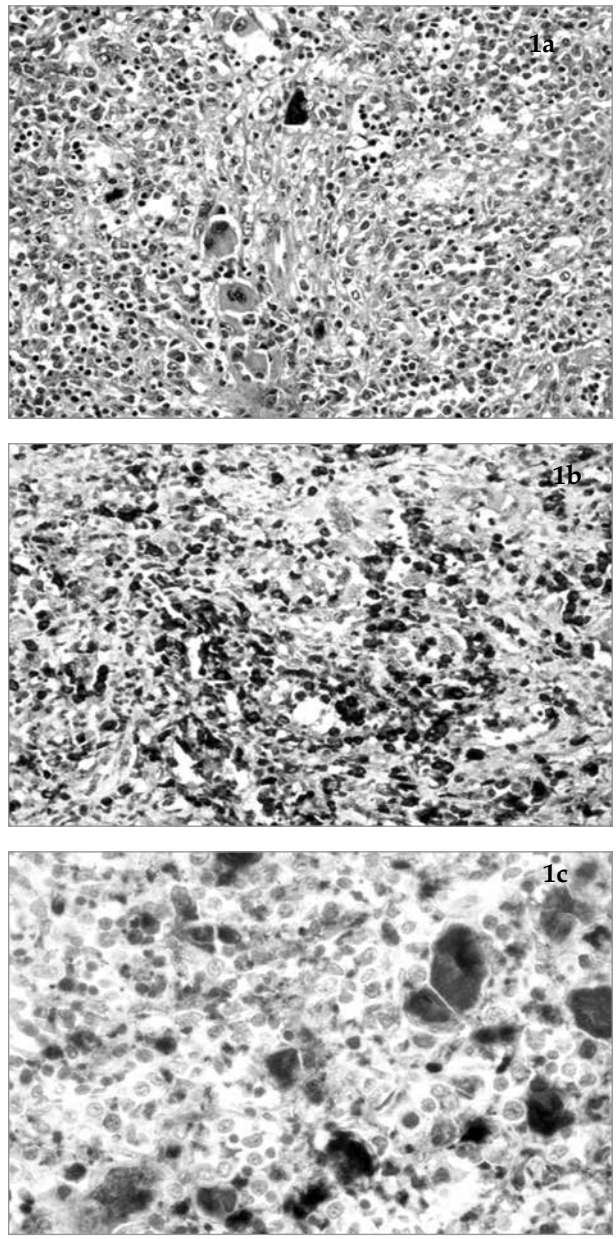


**Fig: 1 (a):** Histological image of spleen tissue showing megakaryocytes and myeloid cells (Hematoxylin & Eosin, X 200) **(b)** Immunohistochemically, myeloid cells are myeloperoxidase (MPO +); **(c)** megakaryocytes show CD61(+) expression.

## DISCUSSION

The exact mechanisms leading to ascites in AMM remain controversial; three theories have been proposed. The first theory states that portal hypertension (PH) develops in patients with myelofibrosis due to sinusoidal narrowing. Intrahepatic obstruction caused by extramedullary hematopoesis and infiltration of the liver by myeloid cells leads to increased hepatic portal pressure and ascites[2,5]. The second theory states that an increased spleen volume causes increased portal blood flow and ascites[2,5,6]. The final hypothesis is related to the hypercoagulable state and stasis caused by sinusoidal narrowing, which contributes to portal vein thrombosis and ascites[2,6]. In our patient, we did not find portal vein thrombosis. She exhibited sinusoidal narrowing in the liver, causing resistance to portal blood flow. Blood flow from the sinusoidal part per unit time decreases and blood accumulates in the portal vein and spleen. Jacobs reported a prevalence of 10% for portal hypertension in patients with AMM[7]. Massive splenomegaly occurs and adsorbs the blood in the portal vein. This is an important mechanism for stabilizing portal tension. After splenectomy, this compensation disappears, and resistance to portal blood flow caused by the liver in the sinusoidal area directly affects the portal vein. As expected, this sudden portal pressure increase causes development of ascites. Pitcock *et al* found no ascites at presentation among 70 patients[8]. On the other hand, Nakov *et al* reported three out of 29 cases with ascites[9]. Also, a case of massive hepatomegaly but no ascites after splenectomy was reported by Towell and Levine[5]. In the course of the disease, sinusoidal narrowing increases due to continuing extramedullary hematopoiesis in this region. Therefore, resistance to portal blood flow increases to a damaging degree. Oren and Goldman reported the case of a patient with esophageal variceal bleeding, and ascites was found in ectopic hematopoietic areas in the peritoneal cavity; megakaryocytes and erythroblasts were evident upon investigation of ascites cytology[10]. Peritoneal extramedullary hematopoiesis also contributes to ascitic fluid development in patients with AMM. Also, Kumar and Naylor reported five cases of peritoneal extramedullary hematopoesis in patients with AMM[11].

In summary, peritoneal extramedullary hematopoesis and intrahepatic sinusoidal obstruction were found in the etiology of ascites. Spleen functions as an absorber of the portal tension that results from hepatic sinusoidal resistance. After splenectomy, this function disappears and sudden portal hypertension and ascites occur.

## CONCLUSION

Cases with extramedullary hematopoiesis (as in AMM) must be evaluated in the differential diagnosis of ascites, and clinicians must be aware that splenectomy may worsen the course of diseases with a post-splenic ascites etiology.

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Case Report

# Herpes Zoster Infection in an Infant

Mariam Al-Fadhli, Mohammad Saraya
Department of Medicine, Infectious Diseases Hospital, Kuwait

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**ABSTRACT**

Herpes zoster in infancy is rare but can develop following intrauterine or postnatal exposure to Varicella zoster virus. We report a case of herpes zoster in a 5-month-old male baby, whose mother had varicella infection at 5-months of gestation. He was treated with acyclovir and first generation cephalosporin for herpes zoster with staphylococcal skin infection.

KEY WORDS: baby, grouped vesicles, intrauterine, varicella

## INTRODUCTION

Herpes zoster is caused by reactivation of *Varicella zoster virus* (VZV) from the dorsal sensory ganglia or the cranial nerve ganglia after a previous primary infection with chicken pox. Herpes zoster (HZ) is characterized by painful, vesicular dermatomal eruptions in groups[1,2]. HZ occurs sporadically without demographic, seasonal, gender, racial or occupational differences. Reactivation of the virus occurs following a decrease in virus-specific cell-mediated immunity. Factors that decrease immune function, such as human immunodeficiency virus infection, chemotherapy, malignancies and chronic corticosteroid use, may also increase the risk of developing HZ. HZ in infancy is rare but can develop following intrauterine or postnatal exposure to HZV[3,4].

## CASE REPORT

A 5-month-old male baby presented to the pediatric outpatient department of the Infectious Diseases Hospital (IDH), Kuwait with history of grouped, fluid filled lesions over right buttock, posterior aspects of right thigh and leg for three days. There was no history of fever, ear discharge or cough and cold. He did not have loose motions. The baby was being exclusively breast fed. The mother had a history of varicella infection when she was five months pregnant, which resolved spontaneously. The baby was born at full-term. There were no visible cutaneous abnormalities noticed. The rest of the growth and development was normal.

On examination, the baby was irritable but afebrile. There were grouped vesicles on an erythematous base over the right side of buttock, posterior aspects of the right leg and thigh corresponding to the dermatomes S2, S3 and S4. There was a yellowish discharge from the lesion. No other abnormalities were noted. He was admitted for treatment of possible bacterial superadded infection complicating HZ. The findings from a Tzanck smear were positive for multinucleated giant cell supporting HZ diagnosis.

Complete blood cell count, serum electrolytes, liver and kidney function tests were within normal limit. Methicillin-sensitive *Staphylococcus aureus* was isolated from the skin lesions. Serologic tests obtained on admission were positive for anti-VZV IgG, but negative for anti-VZV IgM. HIV serology was negative in both mother and the baby.

The patient received intravenous therapy, including acyclovir and first generation cephalosporin. He showed improvement in the eruption and exudates, and was discharged after five days. He recovered completely without sequelae.

## DISCUSSION

Primary varicella tends to occur in childhood, whereas HZ is disease of adults, with most patients being older than 45 years[3]. Childhood as well as

***Address correspondence to:***
*Dr Mariam Al-Fadhli, Al-Andalous, Area 6, Street 102, House 275, Kuwait. Tel: +965 99660936, Fax: +965 24899253, E-mail:medicine209@gmail.com*

infantile HZ has two recognized risk factors: exposure to VZV infection *in utero* and exposure to VZV infection during the first months of life[1]. Infantile HZ is more commonly associated with intrauterine VZV infection than postnatal infection with VZV. However, it can occur after unrecognized subclinical varicella in infants born to varicella zoster immune mothers[5]. HZ has also been described in newborns infants whose mother had been exposed to VZV infection during pregnancy[6,7]. VZV infection occurring throughout pregnancy can lead to childhood or infantile HZ[8,9]. In the present case, the mother had varicella infection during 2nd trimester of pregnancy and baby manifested HZ at five months of age. Infantile HZ is slightly more common in male babies and all the dermatomes are involved[2]. The baby in the present case was not immunodeficient. Even in immunocompetent children, decrease in specific cellular immunity may play an important role in the mechanism of virus reactivations[10].

The diagnosis can usually be made on clinical grounds; distinguishing it from zosteriform herpes simplex virus infection may however be difficult[11]. Tzanck smear may support the clinical diagnosis. Prodromal symptoms are usually not seen in childhood shingles as in the present case.

Oral or intravenous acyclovir has been used for five to eight days or for two days after new lesions stops developing for VZV in children[12]. The goals of antiviral therapy in HZ are to decrease pain, inhibit viral replication and shedding, promote healing of skin lesions, and prevent or reduce the severity of postherpetic neuralgia[12]. It is well known that children with HZ have a better prognosis than adults, with milder symptoms and lesser complications.

## CONCLUSION

HZ can occur at any age regardless of immune status of the individual. Childhood or infantile HZ, as in the present case, usually occurs as a result of reactivation of primary infection by VZV acquired *in utero* or less commonly acquired during early infancy. Diagnosis is usually clinical. However, it should be differentiated from zosteriform herpes simplex virus infection. Patient is usually managed by acyclovir.

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# Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2014; 46 (3): 258 -260

## Real-World Use of Fingolimod in Patients with Relapsing Remitting Multiple Sclerosis: A Retrospective Study Using the National Multiple Sclerosis Registry in Kuwait

Al-Hashel J[1], Ahmed SF, Behbehani R, Alroughani R
[1]Department of Neurology, Ibn Sina Hospital, P.O. Box 25427, 13115, Safat, Kuwait

**CNS Drugs 2014 Jul 11 [Epub ahead of print]**

**Background:** Fingolimod is an oral sphingosine-1-phosphate-receptor modulator, which has demonstrated efficacy in clinical trials and has recently been approved for multiple sclerosis (MS) treatment in Kuwait. Post-marketing studies are important to demonstrate real-life efficacy and safety.
**Objective:** The objective of this study was to examine the efficacy and safety of fingolimod treatment in a clinical setting.
**Methods:** Using the national Kuwait MS registry, relapsing remitting MS patients who had been prescribed fingolimod for ≥6 months were retrospectively identified. Three-monthly clinical evaluations and 6-monthly magnetic resonance imagings (MRIs) were performed. Patient status pre- and post-treatment was compared using chi-square and Student t-tests.
**Results:** A total of 175 patients were included: 75.4 % female (n = 132); mean age 33.3 ± 9.2 years; mean disease duration 7.2 ± 5.2 years; mean fingolimod use 21.7 ± 9.1 months. Most had used previous disease-modifying therapy (78.9 %; n = 138), mainly interferons (66.9 %; n = 117). Twenty-three patients (11.4 %) discontinued/withdrew fingolimod; of whom eight had relapses. The proportion of relapse-free patients improved significantly (86.3 % vs. 32.6 %; $p < 0.001$), while the proportion of patients with MRI activity decreased (18.3.6 % vs. 77.7 %; $p < 0.001$). Mean expanded disability status scale (EDSS) score at the last visit improved when compared with pre-treatment (2.26 ± 1.49 vs. 2.60 ± 1.44; $p = 0.03$). Forty-three (24.6 %) patients experienced adverse events; headaches and lymphopenia were the most commonly reported adverse events.
**Conclusion:** Fingolimod treatment was associated with reduced relapse and MRI activity, and an improved EDSS score. Discontinuation/withdrawal rates and adverse events were low. Fingolimod presents a promising treatment for MS in Kuwait.

## The Efficacy of Laparoscopic Sleeve Gastrectomy in Treating Adolescent Obesity

Al-Sabah SK[1], Almazeedi SM, Dashti SA, Al-Mulla AY, Ali DA, Jumaa TH
[1]Department of Surgery, Amiri Hospital, Kuwait Ministry of Health, Kuwait, Kuwait.

**Obes Surg 2014 Jun 27 [Epub ahead of print]**

**Background:** Laparoscopic sleeve gastrectomy (SG) is becoming a popular and preferred primary bariatric intervention; however, its applicability in the adolescent age group remains controversial. The aim of this study is to evaluate the efficacy of SG in treating obesity and its co-morbidities among adolescents.
**Methods:** A retrospective study was conducted of patients aged 12 - 21 who underwent SG from 2008 to 2012 at Amiri Hospital, Kuwait. The major outcome measures were percent excess weight loss (%EWL) over a 2-year follow-up period, resolution of co-morbidities, and occurrence of complications.

**Results:** A total of 135 adolescent patients underwent the procedure, of which, 97 (71.9 %) were females. The patients had a median age of 19 years (range 12-21), mean body mass index of 48.5 kg/m2, and mean follow-up period of 20 ± 11.4 months. The %EWL at 2 years for males and females was 84 and 77 %, respectively. All of the patients with type 2 diabetes mellitus and 75 % of those with hypertension showed complete resolution of the disease at 2 years.
**Conclusion:** SG seems to be an effective and safe bariatric procedure in obese adolescents, as it can significantly decrease excess body weight and reduce co-morbidities in a relatively short period of time.

## Conversional Surgery: Single-Step Conversion of Laparoscopic Adjustable Gastric Band to Laparoscopic Sleeve Gastrectomy

Al Sharqawi N[1], Al Sabah S, Al Mulla A, Al Anezi K, Jumaa T
[1]Department of Surgery, Al Amiri Hospital, Kuwait City, Kuwait

**Obes Surg 2014 Jul 10 [Epub ahead of print]**

**Background:** Although some patients attain good outcomes after adjustable gastric band (LAGB), a certain quantity have experienced complications and insufficient weight loss. The objective of this study is to assess the safety and outcome of laparoscopic sleeve gastrectomy (LSG) as a conversion surgery after a failed LAGB.
**Methods:** This is a retrospective analysis of 40 patients who received LSG as conversional surgery from 2009 to 2012 in Al Amiri Hospital, Kuwait. Data analyzed included percentage of excessive weight loss (EWL%), body mass index (BMI), and postoperative complications. Paired t test was utilized to evaluate total weight loss after both procedures.
**Results:** Among the 40 patients that underwent conversion surgery, the mean age was 36 years old, 34 (85 %) of which were females. Follow-up for LAGB was 1 to 11 years (median, 4.5 years) and 6 months to 3 years (median, 1 year) for LSG. Mean BMI before LAGB was 44 kg/m2 (SD = 7.2) and mean weight was 117.2 kg (SD = 25.1). A percentage of 20 % achieved good outcomes and 7.5 % experienced complications and 60 % insufficient weight loss. Median EWL% achieved with LAGB was 11.5 %, and after LSG, a median EWL% of 56.9 % was recorded. After conversional surgery, a significant drop in BMI was noted with p value < 0.002.
**Conclusions:** Laparoscopic conversion from LAGB to LSG may be considered as an alternative for patients with a failed LAGB procedure. However, a longer follow-up study is required to validate the results.

## Treating Sleeve Gastrectomy Leak with Endoscopic Stenting: The Kuwaiti Experience and Review of Recent Literature

Alazmi W[1], Al-Sabah S, Ali DA, Almazeedi S
[1]Department of Gastroenterology, Amiri Hospital, Kuwait University, Kuwait, Kuwait

**Surg Endosc. 2014 Jun 20 [Epub ahead of print]**

**Background:** Obesity today is a leading cause of global morbidity and mortality, and bariatric surgeries such as laparoscopic sleeve gastrectomy (LSG) are increasingly playing a key role in its management. Such operations, however, carry many difficult and sometimes fatal complications, including leaks. This study aims at evaluating the effectiveness of endoscopic stenting in treating gastric leaks post-LSG.
**Methods:** A retrospective study was conducted to the patients who were admitted with post-LSG gastric leak at Al-Amiri Hospital Kuwait from October 2008 to December 2012 and were subsequently treated with stenting. The patients were stented endoscopically with self-expandable metal stent (SEMS), and a self-expandable plastic stent (SEPS) was used to facilitate stent removal.

**Results:** A total of 17 patients with post-LSG leaks underwent endoscopic stenting. The median age was 34 years (range 19-56), 53 % of the patients were male, and mean body mass index (BMI) was 43 kg/m$^2$. The median duration of SEMS placement per patient was 42 days (range 28-84). The SEPS-assisted retrieval process took a median duration of 11 days (range 14-35). Successful treatment of gastric leak was evident in 13 (76 %) patients, as evident by gastrografin swallow 1 week after stent removal. In addition, a shorter duration between the LSG and the time of stent placement was associated with a higher success rate of leak seal.
**Conclusions:** The use of SEMS appears to be a safe and effective method in the treatment of post-LSG leaks, with a success rate of 76 %. The time frame of intervention after surgery is critical, as earlier stent placement is associated with favorable outcomes. Finally, SEPS is often required to facilitate SEMS removal, and further modification of stents and its delivery system may improve results.

# Rationale, Design, Methodology and Hospital Characteristics of the First Gulf Acute Heart Failure Registry (Gulf CARE)

Sulaiman KJ[1], Panduranga P[1], Al-Zakwani I[2], Alsheikh-Ali A[3], Al-Habib K[4], Al-Suwaidi J[5], Al-Mahmeed W[3], Al-Faleh H[6], El-Asfar A[7], Al-Motarreb A[8], Ridha M[9], Bulbanat B[10], Al-Jarallah M[10], Bazargani N[11], Asaad N[5], Amin H[12]
[1]Department of Cardiology, Royal Hospital, Muscat, Oman
[2]Department of Pharmacology and Clinical Pharmacy, Sultan Qaboos University and Gulf Health Research, Muscat, Oman
[3]Department of Cardiology, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates.
[4]Department of Cardiology, King Fahad Cardiac Centre, King Khalid University Hospital, College of Medicine, Riyadh, Saudi Arabia
[5]Department of Cardiology, Hamad General Hospital, Doha, Qatar
[6]Department of Cardiology and Cardiovascular Surgery, Security Forces Hospital, Riyadh, Saudi Arabia
[7]Department of Cardiology, Prince Salman Cardiac Center, Saudi Arabia.
[8]Department of Medicine, Sana'a University, Sana'a, Yemen
[9]Department of Cardiology, Adan Hospital, Kuwait
[10]Department of Cardiology, Al-Amiri Hospital, Saudi Arabia
[11]Department of Cardiology, Dubai Hospital, Dubai, United Arab Emirates
[12]Department of Cardiology, Mohammed Bin Khalifa Cardiac Centre, Bahrain

**Heart Views 2014; 15:6-12 doi: 10.4103/1995-705X.132137**

**Background:** There is paucity of data on heart failure (HF) in the Gulf Middle East. The present paper describes the rationale, design, methodology and hospital characteristics of the first Gulf acute heart failure registry (Gulf CARE).
**Materials And Methods:** Gulf CARE is a prospective, multicenter, multinational registry of patients >18 year of age admitted with diagnosis of acute HF (AHF). The data collected included demographics, clinical characteristics, etiology, precipitating factors, management and outcomes of patients admitted with AHF. In addition, data about hospital readmission rates, procedures and mortality at 3 months and 1-year follow-up were recorded. Hospital characteristics and care provider details were collected. Data were entered in a dedicated website using an electronic case record form.
**Results:** A total of 5005 consecutive patients were enrolled from February 14, 2012 to November 13, 2012. Forty-seven hospitals in 7 Gulf States (Oman, Saudi Arabia, Yemen, Kuwait, United Gulf Emirates, Qatar and Bahrain) participated in the project. The majority of hospitals were community hospitals (46%; 22/47) followed by non-University teaching (32%; 15/47) and University hospitals (17%). Most of the hospitals had intensive or coronary care unit facilities (93%; 44/47) with 59% (28/47) having catheterization laboratory facilities. However, only 29% (14/47) had a dedicated HF clinic facility. Most patients (71%) were cared for by a cardiologist.
**Conclusions:** Gulf CARE is the first prospective registry of AHF in the Middle East, intending to provide a unique insight into the demographics, etiology, management and outcomes of AHF in the Middle East. HF management in the Middle East is predominantly provided by cardiologists. The data obtained from this registry will help the local clinicians to identify the deficiencies in HF management as well as provide a platform to implement evidence based preventive and treatment strategies to reduce the burden of HF in this region.

# Forthcoming Conferences and Meetings

Compiled and edited by
**Babichan K Chandy**

Kuwait Medical Journal 2014; 46 (3): 261 -272

2014 European Association for **Vision and Eye Research** (EVER) Congress
Oct 1 - 4, 2014
*France* / Nice
Contact: EVER
Phone: 011-32-16-233-849; Fax: 011-32-16-234-097
Email: ever@ever.be

Core Skills in **Laparoscopic Surgery**
Oct 1 - 3, 2014
*United Kingdom* / Colchester
Contact: Colchester General Hospital
Phone: 011-44-12-4568-6791
Email: daisy.martlew@anglia.ac.uk

Emergency Skills in **Oral & Maxillofacial Surgery**
Oct 1 - 2, 2014
*United Kingdom* / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

10th Congress of the Asia Pacific Federation of Societies for **Surgery of the Hand**
Oct 2 - 4, 2014
*Malaysia* / Kuala Lumpur
Contact: Marcus, Console Communications
Email: apfssh2014@console.com.my

2014 World Congress of International Society of **Addiction Medicine** (ISAM)
Oct 2 - 6, 2014
*Japan* / Yokohama
Contact: Marilyn Dorozio, Office Administration, ISAM
Phone: 403-813-7217
Email: ISAM.mdorozio@gmail.com

**Anesthesia** Spectrum
Musculoskeletal Navigator Canary Islands Cme Cruise
Oct 2 - 13, 2014
*United Kingdom* / Southampton
Contact: Dr. Martin Gerretsen, Director of CME, Sea Courses Cruises
Phone: 888-647-7327; Fax: 888-547-7337
Email: cruises@seacourses.com

Society for **Cardiovascular Angiography & Interventions** (SCAI)-Fortis Fellows Course
Oct 2 - 4, 2014
*India* / New Delhi
Contact: SCAI
Phone: 202-741-9854; Fax: 800-863-5202
Email: info@scai.org

7th Annual **Breast Cancer** Meeting: Hot Topics in Breast Cancer
Oct 3, 2014
*United Kingdom* / London
Contact: Education and Conference Centre, The Royal Marsden
Phone: 011-44-20-7808-2921
Email: conferencecentre@rmh.nhs.uk

**Neurology**
Oct 3, 2014
*United Kingdom* / Edinburgh
Contact: Christine Berwick, Education Co-ordinator, Royal College of Physicians of Edinburgh
Phone: 011-44-13-1247-3634; Fax: 011-44-13-1220-4393
Email: c.berwick@rcpe.ac.uk

Eso-Esso Masterclass in **Breast Cancer Surgery**
Oct 4 - 7, 2014
*Switzerland* / Ermatingen (Lake Constance)
Contact: European School of Oncology
Phone: 011-39-2-854-6451
Fax: 011-39-2-8546-4545
Email: eso@eso.net

**Oral Dermatology and Oral Pathology** Canada and New England Cruise
Oct 4 - 11, 2014
*Canada* /Quebec / Montreal
Contact: Continuing Education, Inc., Meeting Planner, Continuing Education, Inc.
Phone: 800-422-0711 or 727-526-1571; Fax: 727-522-8304
Email: contactus@continuingeducation.net

13th World Congress of the **Human Proteome**
Oct 5 - 8, 2014
*Spain* / Madrid
Contact: Scientific Secretariat, Tilesa Kenes Spain
Phone: 011-34-91-361-2600
Email: hupo2014@kenes.com

Short Course on **Systems Genetics**
Oct 5 - 11, 2014
*Germany* /Maine / Bar Harbor
Contact: The Jackson Laboratory
Phone: 207-288-6000
Email: coursesandconferences@jax.org

4th World Congress on **Virology**
Oct 6 - 8, 2014
*United States* / Texas / San Antonio
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: virology2014@omicsonline.net

9th International Conference of **Anticancer Research**
Oct 6 - 10, 2014
*Greece* / Sithonia
Contact: John G. Delinasios, Dr., Int. Inst. of Anticancer Research
Phone: 011-30-22950-53389
Fax: 011-30-22950-52945
Email: conference@iiar-anticancer.org

2nd Annual Single Cell **Genomics & Transcriptomics** Asia Congress
Oct 7 - 8, 2014
*Singapore* / Singapore
Contact: Freda Shi, Marketing Exec, 2014 Oxford Global Asia Conferences
Phone: 011-65-6-570-2208
Email: f.shi@oxfordglobalasia.com

4th Annual Next **Generation Sequencing** Asia Congress
Oct 7 - 8, 2014
*Singapore* / Singapore
Contact: Freda Shi, Marketing Exec, Oxford Global Asia Conferences
Phone: 011-65-6570-2208
Email: f.shi@oxfordglobalasia.com

**Limb Reconstruction**: Series 3, Course 3
Oct 8 - 9, 2014
*United Kingdom* / Manchester
Contact: British Association of Plastic, Reconstructive and Aesthetic Surgeons
Phone: 011-44-20-7831-5161, Fax: 011-44-20-7831-4041

2014 **Health & Wellbeing in Children**, Youth & Adults with Developmental Disabilities
Oct 8 - 10, 2014
*Canada* / British Columbia / Vancouver
Contact: Interprofessional Continuing Professional Education, University of British Columbia
Phone: 604-827-3112; Fax: 604-822-4835
Email: katia.ipce@ubc.ca

**Family Medicine** Mediterranean Cruise
Oct 8 - 19, 2014
*Italy* / Rome
Contact: Continuing Education, Inc., Meeting Planner, Continuing Education, Inc.
Phone: 800-422-0711 or 727-526-1571; Fax: 727-522-8304
Email: contactus@continuingeducation.net

21st Hands-on Workshop on **CT Colonography** Advanced
Oct 9 - 10, 2014
*United Kingdom* / Leeds
Contact: European Society of Gastrointestinal & Abdominal Radiology
Phone: 011-43-1-535-8927
Fax: 011-43-1-535-7037, Email: office@esgar.org

2014 International Congress of **Endoscopic & Laparoscopic** Surgeons of Asia
Oct 9 - 11, 2014
*Indonesia* / Bali
Contact: Paulina Lo, Managing Partner, PT. Pharma-Pro International
Phone: 011-62-6-386-9502, Fax: 011-62-6-386-9503
Email: elsa2014@pharma-pro.com

2014 **Viral Hepatitis** Congress
Oct 9 - 11, 2014
*Germany* / Frankfurt
Contact: David Bennett, Congress Manager,KnowledgePoint360 Group
Phone: 011-44-16-2566-4392, Fax: 011-44-16-2566-4391
Email: hep@kp360group.com

2014 **Diabetic Limb Salvage** (DLS) Conference
Oct 9 - 11, 2014
*United States* / District of Columbia / Washington
Contact: DLS
Phone: 337-235-6606 ; Fax: 337-235-7300
Email: info@dlsconference.com

9th World Congress on **Immunopathology, Respiratory Allergy & Asthma**
Oct 9 - 12, 2014
*Russia* / Sochi
Contact: Congress Secretariat,World Immunopathology Organization
Phone: 011-7-495-735-1414; Fax: 011-7-495-735-1441
Email: info@wipocis.org

Challenges & Management of **Liver Cirrhosis**
Oct 10 - 11, 2014
*Germany* / Freiburg
Contact: Prof. Dr. Alexander L. Gerbes,Leber Centrum München®,Klinikum der Universität München
Phone: 011-49-89-7095-2292, Fax: 011-49-89-7095-2392
Email: sekretariat.gerbes@med.uni-muenchen.de

Current Practice of **Vascular Ultrasound**
Oct 10 - 12, 2014
*United States* / District of Columbia / Washington
Contact: Institute for Advanced Medical Education
Phone: 802-824-4433

**Laparoscopic TME Cadaveric** Course
Oct 10, 2014
*United Kingdom* / Newcastle Upon Tyne Surgery
Contact: Ethicon Professional Education Department
Email: profed@its.jnj.com

Royal Marsden **Bladder & Testicular Cancer** Conference
Oct 10, 2014
*United Kingdom* / London
Contact: Education and Conference Centre, the Royal Marsden
Phone: 011-44-20-7808-2921
Email: conferencecentre@rmh.nhs.uk

Novel Strategies in the Treatment of CKD Complications – CKD-MBD, PEW, **Renal Anaemia, Arterial Hypertension**
Oct 11, 2014
*Bulgaria* / Hissarya
Contact: Emil Paskalev, M.D. D.sc., Local Coordinator, University hospital "Alexandrovska"
Phone: 011-35-92-923-0539
Email: emilpaskalev@abv.bg

**Genes, Neurons & Behavior**: The Neurobiology of Endophenotypes
Oct 11-18, 2014
*Italy* / Tuscany Genetics
Contact:,Neuroscience School of Advanced Studies
Phone: 011-39-577-173-0037
Email: info@nsas.it

17th Congress of the International Society for **Burn Injuries**
Oct 12 - 16, 2014
*Australia* / Sydney
Contact: Congress Manager,arinex pty limited
Phone: 011-61-2-9265-0700; Fax: 011-61-2-9267-5443
Email: isbi2014@arinex.com.au

Masters Course in **Medical Rhinoplasty**
Oct 13, 2014
*Thailand* / Bangkok
Contact: Ezyhealth Conferences & Events International Pte Ltd
Phone: 011-65-6395-9357
Fax: 011-65-6395-9394
Email: asiaaesthetic@ezyhealth.com

Medical and Surgical **Retina**
Oct 13 - 17, 2014
*Turkey* / Ankara
Contact: European School for Advanced Studies in Ophthalmology
Phone: 011-41-91-921-1154

Management of the **Term Breech**
Oct 14, 2014
*United Kingdom* / London
Contact: Barbara Mettle-Olympio, Royal College of Obstetricians and Gynaecologists
Phone: 011-44-20-7772-6279
Email: bmettle-olympio@rcog.org.uk

Chromatin & Epigenetics: From Omics to Single Cells
Oct 14-15, 2014
*France* / Strasbourg
Contact: ABCAM Plc
Phone: 647-799-3007, Fax: 647-799-3014

Operative Skills in **Orthopaedic Surgery**
Oct 14 - 16, 2014
*United Kingdom* / Liverpool Orthopedics
Contact: Royal Liverpool University Hospital
Phone: 011-44-15-1706-3580
Email: rlb-tr.MASTERUnit@nhs.net

7th International Congress of the **Growth Hormone** Research Society & International Society for Insulin-like Growth Factors Research
Oct 15 - 18, 2014
*Singapore* / Singapore
Contact: GRS-IGF 2014 Secretariat, The Meeting Lab Pte Ltd
Phone: 011-65-6346-4402
Fax: 011-65-6346-4403
Email: secretariat@grs-igf2014.org

8th International Symposium on Objective Measures in **Auditory Implants**
Oct 15 - 18, 2014
*Canada* / Ontario / Toronto
Contact: Continuing Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info-ENT1409@cepdtoronto.ca

**Anaesthesia** for Major Surgery
Oct 16 - 17, 2014
*United Kingdom* / London
Contact: Education and Conference Centre, The Royal Marsden
Phone: 011-44-20-7808-2921
Email: conferencecentre@rmh.nhs.uk

**Pan GHQ** Medical Conference
Oct 16 - 18, 2014
*United Arab Emirates* / Abu Dhabi
Contact: DiaEdu Management Consultancy, DiaEdu Management Consultancy
Phone: 011-971-50-929-9239
Email: bkadara@diaedu.com

2014 **Diabetes** Asia Conference
Oct 16 - 19, 2014
*Malaysia* / Kuala Lumpur
Contact: Rosmawati, Ms, National Diabetes Institute
Phone: 603-7876 1676
Fax: 603-7876 1679
Email: enquiry@nadidiabetes.com.my

1st Middle East North Africa Committee for Research & Treatment in **Multiple Sclerosis** (MENACTRIMS) Congress
Oct 17 - 18, 2014
*United Arab Emirates* / Dubai
Contact: Basil Kadara, Events Coordinator,DiaEdu Management Consultancy
Phone: 011-97-1-4453-2975
Email: bkadara@diaedu.com

International School of **Thyroid Ultrasonography**
Oct 17 - 18, 2014
*Italy* / Pisa
Contact: Denise Rizzitelli, Congress Coordinator, Meridiano Congress International
Phone: 011-39-6-8859-5210; Fax: 011-39-6-8859-5234
Email: d.rizzitelli@meridiano.it

New Trend in Management of **Genitourinary Malignancy**
Oct 17 - 18, 2014
*Romania* / Brasov
Contact: American Society of Clinical Oncology
Phone: 571-483-1300
Email: meetings@asco.org

Advanced Catheter Ablation: New Tips, Techniques & Technologies for **Complex Arrhythmias**
Oct 18 - 21, 2014
*United States* / California / San Francisco
Contact: Charlene Tri,CME Specialist,Mayo Clinic
Phone: 800-283-6296, Fax: 507-538--0146
Email: cvcme@mayo.edu

2014 Update and Review of **Internal Medicine**
Oct 19 - 24, 2014
*United States* / New Mexico / Albuquerque
Contact: Office of Continuing Medical Education, University of New Mexico School of Medicine
Phone: 505-272-3942, Fax: 505-272-8604
Email: CMEWeb@salud.unm.edu

**Family Medicine**: **Palliative Care** Tahiti and Society Islands Cruise
Oct 18 - 25, 2014
*Tahiti* / Papeete
Contact: Continuing Education, Inc., Meeting Planner, Continuing Education, Inc.
Phone: 800-422-0711 or 727-526-1571; Fax: 727-522-8304
Email: contactus@continuingeducation.net

3rd International Summit on **Toxicology & Applied Pharmacology**
Oct 20 - 22, 2014
*United States* / Illinois / Chicago
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: toxicology2014@omicsonline.net

4th World Congress on **Cancer Science & Therapy**
Oct 20 - 22, 2014
*United States* / Illinois
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: cancerscience2014@omicsonline.net

Basic Practical Skills in **Obstetrics & Gynaecology**
Oct 20 - 21, 2014
*United Kingdom* / London
Contact: *Royal* College of Obstetricians and Gynaecologists
Phone: 011-44-20-7772-6245
Email: events@rcog.org.uk

Up-To-Date Management of **Venous Thromboembolism**
Oct 21, 2014
*United Kingdom* / London
Contact: Conferences Team, Royal College of Physicians of London
Phone: 011-44-20-3075-2389
Email: conferences@rcplondon.ac.uk

2014 **Cardiovascular** Interventions
Oct 22 - 24, 2014
*United States* / California / La Jolla
Contact: Andrew Johnson,Conference & CME Planner, Scripps Health
Phone: 858-652-5400
Email: med.edu@scrippshealth.org

30th Annual Fall Conference on **Pediatric Emergencies**
Oct 22 - 25, 2014
*United States* / Hawaii / Big Island
Contact: Symposia Medicus
Phone: 800-327-3161 or 925-969-1789
Fax: 925-969-1795

46th Congress of the International Society of **Paediatric Oncology**
Oct 22 - 25, 2014
*Canada* / Ontario / Toronto
Contact: Linda Friedman, APM, Kenes International
Phone: 011-41-22-908-0488
Fax: 011-41-22-906-9140
Email: siop@kenes.com

9th World **Stroke** Congress
Oct 22 - 25, 2014
*Turkey* / Istanbul
Contact: Vanessa Fisher, APM, Kenes International
Phone: 011-41-22-908-0488
Fax: 011-41-22-906-9140
Email: stroke@kenes.com

9th International Conference on **Frontotemporal Dementias**
Oct 23- 25, 2014
*Canada* / British Columbia
Contact: Conference Secretariat,Continuing Professional Development,University of British Columbia
Phone: 604-875-5101
Email: ftd.vancouver2014@ubc.ca

**Head & Neck IM/IGRT** Education Course
Oct 23 - 25, 2014
*Canada* / Ontario / Toronto
Contact:,Accelerated Education Program, Radiation Medicine Program,Princess Margaret Hospital
Email: aep@rmp.uhn.on.ca

**Pulmonary** Rehabilitation
Oct 23 - 25, 2014
*Netherlands* / Horn
Contact:,European Respiratory Society
Fax: 011-41-21-213-0100
Email: school@ersnet.org

2014 International Meeting of **International Psychogeriatric Association** (IPA)
Oct 23 - 26, 2014
*China* / Beijing
Contact: IPA
Phone: 847-501-3310
Fax: 847-501-3317
Email: membership@ipa-online.org

**Head & Neck IM/IGRT** Education Course
Oct 23 - 25, 2014
*Canada* / Ontario / Toronto
Contact: Accelerated Education Program, Radiation Medicine Program, Princess Margaret Hospital
Email: aep@rmp.uhn.on.ca

**Pulmonary Rehabilitation**
Oct 23 - 25, 2014
*Netherlands* / Horn
Contact: European Respiratory Society
Fax: 011-41-21-213-0100
Email: school@ersnet.org

2014 International **Heart + Brain** Summit
Oct 24 - 26, 2014
*United States* / Ohio / Columbus
Contact:etouches
Phone: 800-580-4129; Fax: 800-580-4129
Email: osuhbsummit@cbc-us.com

2014 International **Kidney Cancer** Symposium
Oct 24 - 25, 2014
*United States* / Illinois / Chicago
Contact: NIU Outreach
Fax: 815-753-6900
Email: outreachregistration@niu.edu

2014 World Congress of **Internal Medicine** (WCIM 2014)
Oct 24 - 28, 2014
*South Korea* / Seoul
Contact: Secretariat, WCIM 2014
Phone: 011-82-2-566-2229; Fax: 011-82-2-6254-8049
Email: wcim2014@intercom.co.kr

20th Annual Advances in **Physiology & Pharmacology** in Anesthesia & Critical Care
Oct 25 - 28, 2014
*United States* / West Virginia / White Sulphur Springs
Contact: Sherri Stockner,Office of Continuing Medical Education,Wake Forest School of Medicine
Phone: 336-716-2712
Email: sstockne@wakehealth.edu

Future of **Deep Brain Stimulation**
Oct 25 - Nov 1st
*Italy* / Tuscany
Contact:,Neuroscience School of Advanced Studies
Phone: 011-39-577-173-0037
Email: info@nsas.it

2014 Masters Experience **Foot/Ankle**
Oct 25 - 26, 2014
*United States* / Illinois / Rosemont
Contact: Arthroscopy Association of North America
Phone: 847-292-2262; Fax: 847-292-2268
Email: info@aana.org

International **Resident Leadership** Summit
Oct 25 - 26, 2014
*Canada* / Ontario / Toronto
Contact: Royal College of Physicians & Surgeons of Canada Services Centre
Phone: 800-461-9598 and/or 613-730-6243
Fax: 613-730-2410
Email: cpd@royalcollege.ca

2nd Annual International Conference on **Pharmacology** & Pharmaceutical Sciences
Oct 27 - 28, 2014
*Singapore* / Singapore
Contact: PHARMA Conference Secretariat,Conference Secretariat,Global Science and Technology Forum (GSTF)
Phone: 011-65-6327-0166, Fax: 011-65-6327-0162
Email: imee@globalstf.org

2nd International Conference on **HIV/AIDS**, Stds, & Stis
Oct 27 - 29, 2014
*United States* / Nevada / Las Vegas
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: std-aids2014@omicsonline.net

3rd International Conference & Exhibition on **Cell & Gene Therapy**
Oct 27 - 29, 2014
*United States* / Nevada / Las Vegas
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: celltherapy2014@omicsonline.net

**Advanced Cadaveric Trauma** Emergency Surgery Course
Oct 27 - 28, 2014
*United Kingdom* / Newcastle
Contact: Lorraine Waugh, Newcastle Surgical Training Centre
Phone: 011-44-19-1223-1264; Fax: 011-44-19-1223-7248
Email: Lorraine.waugh@nuth.nhs.uk

2014 International Conference on **Healthcare**
Oct 28 - 29, 2014
*Singapore* / Singapore
Contact: Tan Lee Ming,Mr,Aventis School of Management
Phone: 011-65-6720-3333, Fax: 011-65-6720-2222
Email: leeming@aventisglobal.edu.sg

7th Asia-Pacific **Heart Rhythm Scientific Session** (APHRS)
Oct 29 - Nov 1, 2014
*India* / New Delhi
Contact: Secretariat, APHRS
Email: secretariat@aphrsindia.com

**Diabetes and Endocrinology**
Oct 29, 2014
*United Kingdom* / Edinburgh
Contact: Felicity Garvie, Education Co-ordinator, Royal College of Physicians of Edinburgh
Phone: 011-44-13-1247-3607; Fax: 011-44-13-1220-4393
Email: f.garvie@rcpe.ac.uk

Preceptorship on MRI in **Multiple Sclerosis**
Oct 30 - 3, 2014
*Italy* / Milan
Contact: David H. Slangen, Congress Coordinator, Meridiano Congress International
Phone: 011-39-6-8859-5211
Fax: 011-39-6-8859-5234
Email: d.slangen@meridiano.it

World Congress on Controversies in **Thrombosis and Hemostasis**
Oct 30 - Nov 2, 2014
*Germany* / Berlin
Contact: Secretariat, CongressMed
Phone: 011-972-73-706-6950; Fax: 011-972-73-706-6959
Email: cith@congressmed.com

6th International Conference on the **Epididymis**
Oct 31 - Nov 3, 2014
*China* / Shanghai
Contact: Shanghai Institute of Biochemistry & Cell Biology
Phone: 011-86-21-5492-0000
Fax: 011-86-21-5492-1011
Email: sibcb@sibs.ac.cn

**Autism, ADHD & Developmental Disabilities** through the Lifespan-Biological & Environmental Perspectives
Nov 1 - 8, 2014
*Italy* / Venice
Contact: Continuing Education, Inc,Continuing Education, Inc.
Phone: 800-422-0711
Email: contactus@continuingeducation.net

2014 **HIV Glasgow**
Nov 2 - 6, 2014
*United Kingdom* / Glasgow
Contact: Georgina Palmer, Congress Assistant, KP360 Group
Phone: 011-44-16-2566-4127
Email: hivglasgow@kp360group.com

3 Day Course on **Obstetric Anaesthesia & Analgesia**
Nov 3 - 5, 2014
*United Kingdom* / London
Contact: Obstetric Anaesthetists' Association
Phone: 011-44-20-7631-8883
Fax: 011-44-20-7631-4352

3rd International Conference on **Translational Medicine**
Nov 3 - 5, 2014
*United States* / Nevada / Las Vegas
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744
Fax: 650-618-1414
Email: translationalmedicine2014@conferenceseries.net

5th World Congress on **Diabetes & Metabolism**
Nov 3 - 5, 2014
*United States* / Nevada / Las Vegas
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: diabetes2014@omicsonline.net

**Medicine** and Society in Ethiopia
Nov 3 - 16, 2014
*Ethiopia* / Addis Ababa
Contact: Jon Baines Tours
Phone: 011-44-20-7223-5618; Fax: 011-44-20-7228-7290
Email: info@jonbainestours.co.uk

Writing a **Journal Article**
Nov 3, 2014
*United Kingdom* / Edinburgh
Contact: Royal College of Physicians of Edinburgh
Phone: 011-44-13-1225-7324

**Obstetrics & Gynaecology** in South Africa
Nov 4 - 15, 2014
*South Africa* / Johannesburg
Contact: Jon Baines Tours
Phone: 011-44-20-7223-5618; Fax: 011-44-20-7228-7290
Email: info@jonbainestours.co.uk

**Gynaecological Cancers**
Nov 5, 2014
*United Kingdom* / London
Contact: Education and Conference Centre, The Royal Marsden
Phone: 011-44-20-7808-2921
Email: conferencecentre@rmh.nhs.uk

**Cardiology**
Nov 6, 2014
*United Kingdom* / Edinburgh
Contact: Eileen Strawn, Symposium Co-ordinator, Royal College of Physicians of Edinburgh
Phone: 011-44-13-1247-3619; Fax: 011-44-13-1220-4393
Email: e.strawn@rcpe.ac.uk

10th International Congress of the Asia Pacific **Hernia** Society
Nov 6-8, 2014
*India* / Jaipur
Contact:,Congress Secretariat,Max Institute of Minimal Access, Metabolic & Bariatric Surgery
Phone: 011-91-98-1169-0841, Fax: 011-91-11-6611-5585
Email: aphs2014@ayils.com

2014 **Infectious Diseases** Update
Nov 7 - 8, 2014
*Canada* / British Columbia / Victoria
Contact: Nova Clinical Services
Phone: 250-658-6056; Fax: 250-658-6109
Email: info@novaclinical.com

7th **Medication Safety** Conference
Nov 7 - 9, 2014
*United Arab Emirates* / Abu Dhabi
Contact: Synovetics
Phone: 011-971-2-443-4331; Fax: 011-971-2-491-8626
Email: info@synovetics.com

12th International Congress of **Neuroimmunology**
Nov 9 - 13, 2014
*Germany* / Mainz
Contact: ISNI Secretariat, International Society of Neuroimmunology
Phone: 011-39-6-519-3499
Fax: 011-39-6-519-4009
Email: secretariat@isniweb.org

9th International **Respiratory Syncytial virus** Symposium (RSV 2014)
Nov 9 - 13, 2014
*South Africa* / Cape Town
Contact: Carolyn Ackermann,Project Manager,Scatterlings Conference & Events
Phone: 011-27-11-463-5085
Fax: 011-27-11-463-3265
Email: caro@soafrica.com

Advances in **Cell Based Assays**
Nov 11 - 12, 2014
*United Kingdom* / London
Contact: Fateja Begum,Delegate Co-ordinator,SMi Group
Phone: 011-44-20-7827-6000
Email: fbegum@smi-online.co.uk

22nd Annual Scientific Meeting of International Society of **Hair Restoration Surgery** (ISHRS)
Nov 12 - 16, 2014
*Thailand* / Bangkok
Contact: ISHRS
Phone: 630-262-5399; Fax: 630-262-1520
Email: info@ishrs.org

2014 Meeting of International Federation for **Adipose Therapeutics & Science** (IFATS)
Nov 13 - 16, 2014
*Netherlands* / Amsterdam
Contact: IFATS
Phone: 603-643-2325
Fax: 603-643-1444

5th Bit World **Gene Convention**
Nov 13 - 16, 2014
*China* / Hai Kou
Contact: Teresa Xiao
Phone: 011-86-411-8457-5669 ext. 872
Email: teresa@gene-congress.com

Advanced **Head & Neck MR** Imaging
Nov 13 - 15, 2014
*Croatia* / Zagreb
Contact: Ms. Elena Skocek, Coordinator of Educational Activities, European Society for Magnetic Resonance in Medicine and Biology
Phone: 011-43-1-535-1306; Fax: 011-43-1-535-7041
Email: eskocek@esmrmb.org

**Gastroenterology**
Nov 13, 2014
*United Kingdom* / Edinburgh
Contact: Felicity Garvie, Education Co-ordinator, Royal College of Physicians of Edinburgh
Phone: 011-44-13-1247-3607; Fax: 011-44-13-1220-4393
Email: f.garvie@rcpe.ac.uk

**Emirates Oncology** Conference
Nov 14 - 16, 2014
*United Arab Emirates* / Abu Dhabi
Contact: American Society of Clinical Oncology
Phone: 571-483-1300
Email: meetings@asco.org

2014 Hands-On **Carotid & Vertebral Duplex Imaging & Doppler**
Nov 15 - 16, 2014
*United States* / Texas / Dallas
Contact: Amy Donaldson, Registrar
Phone: 972-353-3200 (USA, CDT, UTC-6), 800-845-3484 (North America, Caribbean)
Fax: 817-577-4250
Email: info@kmaultrasound.com

**Ophthalmic Block Hands-On Workshop**
Nov 15 - 16, 2014
*United States* / Florida / Orlando
Contact: Northwest Anesthesia Seminars
Phone: 800-222-6927; Fax: 509-547-1265

Twins 2014: Joint 3rd World Congress on **Twin Pregnancy** & 15th International Congress of International Society of Twin Studies
Nov 16 - 19, 2014
*Hungary* / Budapest
Contact: MCA Scientific Events
Phone: 011-39-2-3493-4404; Fax: 011-39-2-3493-4397
Email: info@twin2014.eu

2nd International Congress on **Bacteriology & Infectious** Diseases
Nov 17 - 19, 2014
*United States* / Illinois / Chicago
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: bacteriology2014@omicsgroup.us

3rd International Conference on **Surgery & Anesthesia**
Nov 17 - 19, 2014
*United States* / Illinois / Chicago
Contact: Conference Secretariat, Omics Publishing Group
Phone: 650-268-9744; Fax: 650-618-1414
Email: surgery-anesthesia2014@omicsonline.net

**Virtual Colonography** Course
Nov 17 - 19, 2014
*United States* / Ontario / Toronto
Contact: Theresa A. Findlay, Hons B.A., M.Ed., Office of Continuing Education & Professional Development, University of Toronto
Phone: 416-340-4800 ext. 5108
Email: Theresa.Findlay@uhn.ca

43rd Global Congress on Minimally Invasive **Gynecology**
Nov 17 - 21, 2014
*Canada* / British Columbia / Vancouver
Contact:,American Association of Gynecologic Laparoscopists
Phone: 714-503-6200

**Molecular Pathology & Targeted** Treatments for Non-Small Cell Lung Cancer
Nov 18, 2014
*United Kingdom* / Manchester
Contact: Education Events, The School of Oncology, The Christie NHS Foundation Trust
Phone: 011-44-16-1446-3403
Email: education.events@christie.nhs.uk

2014 Acquired **Brain Injury** Conference
Nov 20 - 21, 2014
*Canada* / Ontario / Toronto
Contact: Toronto ABI Network
Phone: 416-597-3057; Fax: 416-597-7021
Email: info@abinetwork.ca

2014 Association for **Behavioral and Cognitive Therapies** (ABCT) Convention
Nov 20 - 23, 2014
*United States* / Pennsylvania / Philadelphia
Contact: ABCT
Phone: 212-647-1890; Fax: 212-647-1865

Baha **Hearing Implant** Course
Nov 20 – 21, 2014
*United Kingdom*
Contact: Carol Anne Cockayne, Cochlear
Email: CCockayne@cochlear.com

6th International **Hip Arthroscopy** Meeting
Nov 21 - 22, 2014
*Germany* / Munich
Contact: Juliane Fricke, Assistant Conventions, Intercongress GmbH
Phone: 011-49-761-6969-9240
Email: juliane.fricke@intercongress.de

2014 Masters Experience **Knee: Cartilage**
Nov 21- 23, 2014
**United States** / Illinois / Rosemont
Contact:,Arthroscopy Association of North America
Phone: 847-292-2262
Fax: 847-292-2268
Email: info@aana.org

4th World Congress of Regional **Anaesthesia and Pain Therapy**
Nov 24 - 28, 2014
*South Africa* / Cape Town
Contact: Robert Nesbitt, APM, Kenes International
Phone: 011-41-22-908-0488
Fax: 011-41-22-908-9140
Email: wcrapt2014@kenes.com

Basic Practical Skills in **Obstetrics & Gynaecology**
Nov 24 - 25, 2014
*United Kingdom* / London
Contact: Royal College of Obstetricians and Gynaecologists
Phone: 011-44-20-7772-6245
Email: events@rcog.org.uk

27th World Congress of International College for **Maxillofacial Surgeons**
Nov 25 - 28, 2014
*Mexico* / Cancun
Contact:,ACADEMIA MEXICANA DE CIRUGÍA, A.C.
Phone: 52-55-5669-0530, 52-55-5682-7589
Email: kimura_takao@yahoo.com.mx

15th Asia-Pacific Congress of Clinical **Microbiology & Infection**
Nov 26 - 29, 2014
*Malaysia* / Kuala Lumpur
Contact: Ms. Shikha, Reliance Conventions and Events
Phone: 011-60-3-2170-2000
Fax: 011-60-3-2730-9972 / 73
Email: apccmi@relianceconventions.com

**Tropical Medicine** Excursion to Ghana
Nov 26 - December 6, 2014
*Ghana* / Accra
Contact: Kay Schaefer, MD, Tropical Medicine Excursions
Phone: 011-49-221-340-4905
Fax: 011-49-321-2147-5305
Email: contact@tropmedex.com

Laparoscopic Incisional & **Groin Hernia** Training (LIGHT) Cadaver Course
Nov 28, 2014
*United Kingdom* / Newcastle
Contact: Ethicon Professional Education Department
Email: profed@its.jnj.com

Update on **Living Kidney Donation**
Nov 28 - 29, 2014
*Germany* / Munich
Contact: Prof. Dr. Dr. h.c. Uwe Heemann, Local Coordinator, Klinikum rechts der Isar
Phone: 011-49-89-4140-2231; Fax: 011-49-89-4140-7734
Email: uwe.heemann@lrz.tum.de

Diagnostic and Operative **Hysteroscopy**
Dec 2 - 4, 2014
*United Kingdom* / London
Contact: Sarah Monro, Royal College of Obstetricians and Gynaecologists
Phone: 011-44-20-7772-6437
Email: smonro@rcog.org.uk

2014 World **Cancer** Conference
Dec 3 - 6, 2014
*Australia* / Melbourne
Contact: American Society of Clinical Oncology
Phone: 571-483-1300
Email: meetings@asco.org

2014 Advances & Controversies in **Clinical Nutrition**
Dec 4 - 6, 2014
*United States* / Maryland / National Harbor
Contact:,American Society for Nutrition
Phone: 301-634-7050, Fax: 301-634-7894

10th International Congress on **Non-Motor Dysfunctions in Parkinson's Disease** & Related Disorders
Dec 4 - 7, 2014
*France* / Nice
Contact: Ronit Eisenbach, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140

20th World Congress on Controversies in **Obstetrics, Gynecology & Infertility**
Dec 4 - 7, 2014
*France* / Paris
Contact: Secretariat, CongressMed
Phone: 011-972-73-706-6950
Email: cogi@congressmed.com

2nd Workshop of **Chronic Kidney Disease** - Mineral Bone Disorders Era-Edta Working Group
Dec 5, 2014
*Italy* / Milan
Contact: Mario Cozzolino, Local Coordinator
Phone: 011-39-2-8184-4381
Email: Mario.cozzolino@unimi.it

2nd World Congress on **Clinical Lipidology**
Dec 5 - 7, 2014
*Austria* / Vienna
Contact: Cheryl Marsh, Project Manager, Paragon Group
Phone: 011-27-21-409-7878; Fax: 011-27-21-409-7050
Email: secretariat@clinical-lipidology.com

Level 1 Certificate Course in **Aesthetic Medicine**
Dec 5 - 7, 2014
*United States* / Delaware / Newark
Contact: Ellen Dahlin,Business Manager,AAAM
Phone: 310-944-1790
Email: ellen@aaamed.org

2014 Interpretation & Reporting of **Peripheral Vascular Ultrasound**
Dec 6, 2014
*United States* / Texas / Dallas
Contact: Amy Donaldson, Administrative Director
Phone: 972-353-3200 (USA, CDT; UTC -06:00) | 800-845-3484 (North America, Caribbean)
Fax: 817-577-4250
Email: info@kmaultrasound.com

10th Annual Liver Transplant Symposium
Dec 6, 2014
*United States* / Pennsylvania / Hershey
Contact: Continuing Education, Penn State Hershey College of Medicine
Phone: 717-531-6483; Fax: 717-531-5604
Email: ContinuingEd@hmc.psu.edu

Update in Current Management of **Sexually Transmitted Infections & HIV Infection**
Dec 8, 2014
*United Kingdom* / London
Contact: Conferences Team, Royal College of Physicians of London
Phone: 011-44-20-3075-2389
Email: conferences@rcplondon.ac.uk

International School of **Musculoskeletal Ultrasound**: Elbow to Fingers
Dec 9 - 11, 2014
*Italy* / Genoa
Contact: Denise Rizzitelli, Meridiano Congress International
Phone: 011-39-6-8859-5210; Fax: 011-39-6-8859-5234
Email: d.rizzitelli@meridiano.it

2014 Experts in **Stone Disease**
Dec 11 - 13, 2014
*South Africa* / Cape Town
Contact: Erasmus S.A.
Phone: 011-30-210-741-4700
Fax: 011-30-210-725-7532
Email: info@esdconference.com

**Psoriasis**: From Gene to Clinic
Dec 11 - 13, 2014
*United Kingdom* / London
Contact: Conference and Event Services, British Association of Dermatologists
Email: conference@bad.org.uk

2014 **Brain & Behavior**
Dec 12 - 13, 2014
*United States* / Louisiana / New Orleans
Contact: Center for Continuing Education, Tulane University Health Sciences Center
Phone: 504-988-5466; Fax: 504-988-1779
Email: cme@tulane.edu

2014 Hands-On **Transvaginal Pelvic Ultrasound Imaging & Doppler**
Dec 12, 2014
*United States* / Texas / Dallas
Contact: Amy Donaldson, Registrar, Keith Mauney & Associates ultrasound Training Institutes Est. 1981
Phone: 972-353-3200 (USA, CDT, UTC-6)
Fax: 817-577-4250
Email: info@kmaultrasound.com

2014 World Psychiatric Association Regional Congress: Yin and Yang of **Mental Health** in Asia-Balancing Polarities
Dec 12 - 14, 2014
*China* / Hong Kong
Contact:,Congress Secretariat,Hong Kong Academy of Medicine
Phone: 852-2871-8787, Fax: 852-2871-8898
Email: wpa2014@hkam.org.hk

16th Egyptian Workshop on **Therapeutic Endoscopy**
Dec 13 - 14, 2014
*Egypt* / Cairo
Contact: Prof. Ibrahim Mostafa,Course Director,Egypt Gastro Hep
Phone: 011-20-122-211-3466, Fax: 011-20-2-2395-3822
Email: ibrahimmostafa@egyptgastrohep.com

2014 Hands-On **Carotid & Vertebral Duplex Imaging & Doppler**
Dec 13-14, 2014
*United States* / Texas / Dallas
Contact: Amy Donaldson, Registrar
Phone: 972-353-3200 (USA, CDT, UTC-6)
Fax: 817-577-4250
Email: info@kmaultrasound.com

Advanced **Cardiac Life Support Recertification**
Dec 13, 2014
*Canada* / Ontario / Toronto
Contact: Terry G. Smith, ALS Program Manager,Sunnybrook Health Sciences Centre
Phone: 416-480-4943, Fax: 416-480-5325
Email: terryg.smith@sunnybrook.ca

2014 Amsterdam Live **Endoscopy**
Dec 15 - 16, 2014
*Netherlands* / Amsterdam
Contact: Mrs. Jacqueline van der Woude, European Postgraduate Gastro-surgical School
Phone: 011-31-20-566-3926 or 566-6468
Fax: 011-31-20-697-5594
Email: info@amsterdamendoscopy.com

Targeted Treatments for **Cancers of the Digestive System**
Dec 16, 2014
*United Kingdom* / Manchester
Contact: Education Events, the School of Oncology, the Christie NHS Foundation Trust
Phone: 011-44-16-1446-3403
Email: education.events@christie.nhs.uk

**Hair Transplant** Course
Dec 18 - 20, 2014
*United Arab Emirates* / Dubai
Contact: Ashok Chaturvedi, President & CEO
Email: ashok@ibcme.com

6th Annual Conference on Emergencies & Challenges in **Pediatrics**
Dec 19 - 20, 2014
*United States* / New York / New York
Contact:,Symposia Medicus
Phone: 800-327-3161 or 925-969-1789
Fax: 925-969-1795

7th International **Hemodialysis** Course
Dec 22 - 26, 2014
*Egypt* / Mansoura
Contact: Hussein Sheashaa, Local Coordinator, Mansoura University, Egypt
Email: sheashaa@mans.edu.eg

Topics in **Internal Medicine & Mental Health** Eastern Caribbean Cruise
Dec 22-29, 2014
*United States* / Florida / Fort Lauderdale
Contact: Continuing Education,Continuing Education, Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

Comprehensive **Colposcopy**
Jan 7 - 10, 2015
*United States* / Florida / Tampa
Contact:,American Society for Colposcopy & Cervical Pathology
Phone: 301-733-3640
Fax: 240-575-9880

5th Course on **Epilepsy Surgery** Basic Course
Jan 12 - 16, 2015
*Czech Republic* / Brno
Contact: Ivana Tarabová,Congress Agency,TA-SERVICE s.r.o.
Phone: 011-420-543-211-134
Email: tarabova@ta-service.cz

6th International Course on **Ophthalmic & Oculoplastic Reconstruction & Trauma** Surgery
Jan 14 - 16, 2015
*Austria* / Vienna
Contact: Helmut Weissmann, MD, Advanced Ophthalmic Trainings
Phone: 011-43-22-432-0898
Fax: 011-43-22-432-0898 ext. 15
Email: office@ophthalmictrainings.com

9th Annual **Human Amyloid Imaging** Conference
Jan 14 - 16, 2015
*United States* / Florida / Miami Beach
Contact:,Conference Secretariat,World Events Forum
Phone: 224-938-9523
Email: meetings@worldeventsforum.com

1st Annual Utah **Pediatric Otolaryngology** Update
Jan 17, 2015
*United States* / Utah / Salt Lake City
Contact: Halley Langford,University of Utah
Phone: 801-581-7515
Fax: 801-585-5744
Email: halley.langford@hsc.utah.edu

**Cardiovascular** Summit: Solutions for Thriving in a Time of Change
Jan 22 - 24, 2015
*United States* / Florida / Orlando
Contact:,American College of Cardiology
Phone: 202-375-6000 ext. 5603
Fax: 202-375-7000
Email: resource@acc.org

2015 Advances in **Fetal & Neonatal Imaging** Course
Jan 23 - 25, 2015
*United States* / Florida / Orlando
Contact: Barbara Quattrone, Membership Services
Phone: 703-648-0680 ext. 4907
Email: bquattrone@acr.org

2015 American Society for Peripheral Nerve (ASPN) Annual Meeting
Jan 23 - 25, 2015
*Bahamas* / Paradise Island
Contact:, ASPN
Phone: 978-927-8330

**Rheumatology and Musculoskeletal Medicine** for Primary Care
Jan 23 - 25, 2015
*United States* / Nevada / Las Vegas
Contact:,Medical Education Resources, Inc.
Phone: 800-421-3756 or 303-798-9682
Fax: 303-798-5731
Email: info@mer.org

9th Asia Pacific Conference on **Clinical Nutrition** (APCCN 2015)
Jan 26 - 29, 2015
*Malaysia* / Kuala Lumpur Nutrition
Contact: Shu Shan, Conference Secretariat, Console Communications Sdn Bhd
Phone: 011-60-3-2162-0566; Fax: 011-60-3-2161-6560
Email: apccn2015@console.com.my

**7th Immunotherapeutics & Immunomonitoring** Conference
Jan 29 - 30, 2015
*United States* / Paradise Point Resort & Spa | San Diego, CA
Contact: Amber Kempf
Phone: 626-256-6405 x110
Email: spex@gtcbio.com

11th International Kawasaki Disease Symposium
Feb 3 - 6, 2015
*United States* / Hawaii / Honolulu
Contact:,American Heart Association
Phone: 888-242-2453 (US) or 214-570-5935
Email: scientificconferences@heart.org

33rd Annual **Infectious Diseases** Conference
Feb 6 - 7, 2015
*United States* / California / Sacramento
Contact: Vickie Hidalgo,Marketing,UC Davis CME
Phone: 916-734-5390, Fax: 916-734-0776
Email: vickie.hidalgo@ucdmc.ucdavis.edu

Translation of the **Cancer** Genome
Feb 7 - 9, 2014
*United States* / California / San Francisco
Contact:,American Association for Cancer Research
Phone: 215-440-9300, Fax: 215-440-9313
Email: aacr@aacr.org

2015 Strandness Symposium & **Vascular Care**
Feb 15 - 19, 2015
*United States* / Hawaii / Oahu
Contact: Vickie Hidalgo,Marketing,UC Davis Office of Continuing Medical Education and UC Davis Vascular Center
Phone: 916-734-5390, Fax: 916-734-0776
Email: vickie.hidalgo@ucdmc.ucdavis.edu

Relevant Topics in **Anesthesia**
Feb 15 - 20, 2015, 2015
*Dominican Republic* / Punta Cana
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065
Fax: 509-547-1265
Email: info@nwas.com

Reviews in **Anesthesia** Practice
Feb 15-20, 2015
*Jamaica* / Port Maria
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065, Fax: 509-547-1265
Email: coleen@nwas.com

2015 **Perinatal Medicine**
Feb 16 - 19, 2015
*United States* / Hawaii / Maui
Contact:,Office of Continuing Medical Education,Keck School of Medicine of University of Southern California
Phone: 323-442-2555, Fax: 888-665-8650
Email: usccme@usc.edu

8th International Conference on Advanced Technologies & Treatments for **Diabetes**
Feb 18 - 21, 2015
*France* / Paris
Contact: Audrey Alloul,APM,Kenes International
Phone: 011-41-22-908-0488, Fax: 011-41-22-906-9140
Email: attd@kenes.com

Facelifts, Submental & Facial Contouring: Advanced **Esthetic Surgery** Techniques
Feb 21 - 22, 2015
*United States* / Louisiana / New Orleans
Contact:,American College of Oral & Maxillofacial Surgeons
Phone: 202-367-1182, Fax: 202-367-2182
Email: info@acoms.org

2015 **State-of-the-Art Echocardiography**
Feb 22 - 24, 2015
*United States* / Arizona / Scottsdale
Contact:,American Society of Echocardiography
Phone: 919-861-5574
Email: sota@asecho.org

Emerging **Healthcare Issues** Mystical Malaysia & Myanmar
Feb 24 – Mar 9, 2015
*Singapore* / Singapore
Contact:,Professional Education Society
Phone: 877-737-7005
Email: info@pestravel.com

12th Annual Gulf Heart Assocation & 4th Kuwait **Cardiac** Society Conference
Mar 4 - 7, 2015
*Kuwait* / The Regency Hotel
Contact: Organizer
E-mail: kuwaitcardiac@gmail.com

# WHO-Facts Sheet

1. Physical Activity
2. Maternal Mortality
3. Mercury and Health
4. Violence Against Women
5. Preventing Unsafe Abortion
6. Mental Health and Older Adults

Compiled and edited by
**Babichan K Chandy**

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## 1. PHYSICAL ACTIVITY

**What is physical activity?**

WHO defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits.

The term "physical activity" should not be confused with "exercise", which is a subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness. Both, moderate and vigorous intensity physical activity brings health benefits.

The intensity of different forms of physical activity varies between people. In order to be beneficial for cardiorespiratory health, all activity should be performed in bouts of at least 10 minutes duration. WHO recommends:

- for children and adolescents: 60 minutes of moderate to vigorous intensity activity per day;
- for adults (18+): 150 minutes of moderate-intensity activity per week.

**KEY FACTS**

- Physical inactivity is the fourth leading risk factor for death worldwide.
- Approximately 3.2 million people die each year due to physical inactivity.
- Physical inactivity is a key risk factor for noncommunicable diseases (NCDs) such as cardiovascular diseases, cancer and diabetes.
- Physical activity has significant health benefits and contributes to prevent NCDs.
- Globally, one in three adults is not active enough.
- Policies to address physical inactivity are operational in 56% of WHO Member States.
- WHO Member States have agreed to reduce physical inactivity by 10% by 2025.

**Benefits of physical activity**

Regular physical activity of moderate intensity – such as walking, cycling, or doing sports – has significant benefits for health. At all ages, the benefits of being physically active outweigh potential harm, for example through accidents. Some physical activity is better than doing none. By becoming more active throughout the day in relatively simple ways, people can quite easily achieve the recommended activity levels.

Regular and adequate levels of physical activity:

- improve muscular and cardiorespiratory fitness;
- improve bone and functional health;
- reduce the risk of hypertension, coronary heart disease, stroke, diabetes, breast and colon cancer and depression;
- reduce the risk of falls as well as hip or vertebral fractures; and
- are fundamental to energy balance and weight control.

**Risks of physical inactivity**

Physical inactivity is the fourth leading risk factor for global mortality and causes 6% of all deaths. It is only outstripped by high blood pressure (13%) and tobacco use (9%) and carries the same level of risk as high blood glucose (6%). Approximately 3.2 million people die each year because they are not active enough.

***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/*

Physical inactivity is on the rise in many countries, adding to the burden of noncommunicable diseases and affecting general health worldwide. People who are insufficiently active have a 20% to 30% increased risk of death compared to people who engage in at least 30 minutes of moderate intensity physical activity on most days of the week.

Physical inactivity is the main cause for approximately:

- 21–25% of breast and colon cancers
- 27% of diabetes
- 30% of ischaemic heart disease.

**Reasons for physical inactivity**

The levels of physical inactivity increased across the globe. Globally, around 31% of adults aged 15 and over were not active enough in 2008 (men 28% and women 34%). In high-income countries, 41% of men and 48% of women were insufficiently physically active, as compared to 18% of men and 21% of women in low-income countries. Low or decreasing physical activity levels often correspond with a high or rising gross national product. The drop in physical activity is partly due to inaction during leisure time and sedentary behaviour on the job and at home. Likewise, an increase in the use of "passive" modes of transportation also contributes to physical inactivity.

Several environmental factors which are linked to urbanization can discourage people from becoming more active, such as:

- fear of violence and crime in outdoor areas
- high-density traffic
- low air quality, pollution
- lack of parks, sidewalks and sports/recreation facilities.

**How to increase physical activity?**

Both, society in general and individuals can take action to increase physical activity. In 2013, WHO Member States agreed to reduce physical inactivity by 10% in the framework of the "Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020".

Policies and plans to address physical inactivity have been developed in about 80% of WHO Member States, though these are operational in only 56% of the countries. National and local authorities are also adopting policies in a range of sectors to promote and facilitate physical activity.

Policies to increase physical activity aim to ensure that:

- walking, cycling and other forms of active transportation are accessible and safe for all;
- labour and workplace policies encourage physical activity;
- schools have safe spaces and facilities for students to spend their free time actively;
- Quality Physical Education (QPE) supports children to develop behaviour patterns that will keep them physically active throughout their lives; and
- sports and recreation facilities provide opportunities for everyone to do sports.

**WHO response**

The "Global Strategy on Diet, Physical Activity and Health", adopted by the World Health Assembly in 2004, describes the actions needed to increase physical activity worldwide. The "Global Recommendations on Physical Activity for Health", published by WHO in 2010, focus on primary prevention of NCDs through physical activity. It proposes different policy options to reach the recommended levels of physical activity globally, such as:-

- the development and implementation of national guidelines for health-enhancing physical activity;
- the integration of physical activity within other related policy sectors, in order to secure that policies and action plans are coherent and complementary;
- the use of mass media to raise awareness of the benefits of being physically active;
- the surveillance and monitoring of actions to promote physical activity.

## 2. MATERNAL MORTALITY

**Overview**

Globally, maternal mortality is unacceptably high. About 800 women die from pregnancy- or childbirth-related complications around the world every day. In 2013, 289,000 women died during and following pregnancy and childbirth. Almost all of these deaths occurred in low-resource settings, and most could have been prevented.

**KEY FACTS**

- Every day, approximately 800 women die from preventable causes related to pregnancy and childbirth.
- 99% of all maternal deaths occur in developing countries.
- Maternal mortality is higher in women living in rural areas and among poorer communities.
- Young adolescents face a higher risk of complications and death as a result of pregnancy than older women.
- Skilled care before, during and after childbirth can save the lives of women and newborn babies.

- Between 1990 and 2013, maternal mortality worldwide dropped by almost 50%.

**Progress towards achieving the fifth Millennium Development Goal**

Improving maternal health is first of the eight Millennium Development Goals (MDGs) adopted by the international community in 2000. Under MDG5, countries committed to reducing maternal mortality by three quarters between 1990 and 2015. Since 1990, maternal deaths worldwide have dropped by 45%.

In sub-Saharan Africa, a number of countries have halved their levels of maternal mortality since 1990. In other regions, including Asia and North Africa, even greater headway has been made. However, between 1990 and 2013, the global maternal mortality ratio (i.e. the number of maternal deaths per 100,000 live births) declined by only 2.6% per year. This is far from the annual decline of 5.5% required to achieve MDG5.

**Where do maternal deaths occur?**

The high number of maternal deaths in some areas of the world reflects inequities in access to health services, and highlights the gap between rich and poor. Almost all maternal deaths (99%) occur in developing countries. More than half of these deaths occur in sub-Saharan Africa and almost one third occur in South Asia.

The maternal mortality ratio in developing countries in 2013 is 230 per 100,000 live births versus 16 per 100,000 live births in developed countries. There are large disparities between countries, with few countries having extremely high maternal mortality ratios around 1000 per 100,000 live births. There are also large disparities within countries, between women with high and low income and between women living in rural and urban areas.

The risk of maternal mortality is highest for adolescent girls under 15 years old and complications in pregnancy and childbirth are the leading cause of death among adolescent girls in developing countries.

Women in developing countries have on average many more pregnancies than women in developed countries, and their lifetime risk of death due to pregnancy is higher. A woman's lifetime risk of maternal death – the probability that a 15 year old woman will eventually die from a maternal cause – is one in 3700 in developed countries, versus one in 160 in developing countries.

**Why do women die?**

Women die as a result of complications during and following pregnancy and childbirth. Most of these complications develop during pregnancy. Other complications may exist before pregnancy but are worsened during pregnancy. The major complications that account for nearly 75% of all maternal deaths are:

- severe bleeding (mostly bleeding after childbirth)
- infections (usually after childbirth)
- high blood pressure during pregnancy (pre-eclampsia and eclampsia)
- complications from delivery
- unsafe abortion.

The remainder are caused by or associated with diseases such as malaria, and AIDS during pregnancy.

Maternal health and newborn health are closely linked. It is estimated that almost three million newborn babies die every year, and an additional 2.6 million babies are stillborn.

**How can women's lives be saved?**

Most maternal deaths are preventable, as the health-care solutions to prevent or manage complications are well known. All women need access to antenatal care in pregnancy, skilled care during childbirth, and care and support in the weeks after childbirth. It is particularly important that all births are attended by skilled health professionals, as timely management and treatment can make the difference between life and death.

Severe bleeding after birth can kill a healthy woman within hours, if she is unattended. Injecting oxytocin immediately after childbirth effectively reduces the risk of bleeding.

Infection after childbirth can be eliminated, if good hygiene is practiced and, if early signs of infection are recognized and treated in a timely manner.

Pre-eclampsia should be detected and appropriately managed before the onset of convulsions (eclampsia) and other life-threatening complications. Administering drugs such as magnesium sulfate for pre-eclampsia can lower a woman's risk of developing eclampsia.

To avoid maternal deaths, it is also vital to prevent unwanted and too-early pregnancies. All women, including adolescents, need access to contraception, safe abortion services to the full extent of the law, and quality post-abortion care.

**Why do women not get the care they need?**

Poor women in remote areas are the least likely to receive adequate health care. This is especially true for regions with low numbers of skilled health workers, such as sub-Saharan Africa and South Asia. While levels of antenatal care have increased in many parts of the world during the past decade, only 46% of women in low-income countries benefit from skilled care during childbirth. This means that millions of births are not assisted by a midwife, a doctor or a trained nurse.

In high-income countries, virtually all women have at least four antenatal care visits, are attended by a skilled health worker during childbirth and receive postpartum care. In low-income countries, just over a third of all pregnant women have the recommended four antenatal care visits.

Other factors that prevent women from receiving or seeking care during pregnancy and childbirth are:

- poverty
- distance
- lack of information
- inadequate services, and
- cultural practices.

To improve maternal health, barriers that limit access to quality maternal health services must be identified and addressed at all levels of the health system.

*For more information contact:*
*WHO Media centre; Telephone: +41 22 791 2222;*
*E-mail: mediainquiries@who.int*

## 3. MERCURY AND HEALTH

**Overview**

Mercury exists in various forms: elemental (or metallic) and inorganic (to which people may be exposed through their occupation); and organic (e.g., methylmercury, to which people may be exposed through their diet). These forms of mercury differ in their degree of toxicity and in their effects on the nervous, digestive and immune systems, and on lungs, kidneys, skin and eyes.

Mercury occurs naturally in the earth's crust. It is released into the environment from volcanic activity, weathering of rocks and as a result of human activity. Human activity is the main cause of mercury releases, particularly coal-fired power stations, residential coal burning for heating and cooking, industrial processes, waste incinerators and as a result of mining for mercury, gold and other metals.

**KEY FACTS**

- Mercury is a naturally occurring element that is found in air, water and soil.
- Exposure to mercury – even small amounts – may cause serious health problems, and is a threat to the development of the child in utero and early in life.
- Mercury may have toxic effects on the nervous, digestive and immune systems, and on lungs, kidneys, skin and eyes.
- Mercury is considered by WHO as one of the top ten chemicals or groups of chemicals of major public health concern.
- People are mainly exposed to methylmercury, an organic compound, when they eat fish and shellfish that contain the compound.

Once in the environment, mercury can be transformed by bacteria into methylmercury. Methylmercury then bioaccumulates (bioaccumulation occurs when an organism contains higher concentrations of the substance than do the surroundings) in fish and shellfish. Methylmercury also biomagnifies. For example, large predatory fish are more likely to have high levels of mercury as a result of eating many smaller fish that have acquired mercury through ingestion of plankton.

People may be exposed to mercury in any of its forms under different circumstances. However, exposure mainly occurs through consumption of fish and shellfish contaminated with methylmercury and through worker inhalation of elemental mercury vapours during industrial processes. Cooking does not eliminate mercury.

**Exposure to mercury**

All humans are exposed to some level of mercury. Most people are exposed to low levels of mercury, often through chronic exposure (continuous or intermittent long term contact). However, some people are exposed to high levels of mercury, including acute exposure (exposure occurring over a short period of time, often less than a day). An example of acute exposure would be mercury exposure due to an industrial accident.

Factors that determine whether health effects occur and their severity include:

- the type of mercury concerned
- the dose
- the age or developmental stage of the person exposed (the foetus is most susceptible)
- the duration of exposure, and
- the route of exposure (inhalation, ingestion or dermal contact).

Generally, two groups are more sensitive to the effects of mercury. Foetuses are most susceptible to developmental effects due to mercury. Methylmercury exposure in the womb can result from a mother's consumption of fish and shellfish. It can adversely affect a baby's growing brain and nervous system. The primary health effect of methylmercury is impaired neurological development. Therefore, cognitive thinking, memory, attention, language, and fine motor and visual spatial skills may be affected in children who were exposed to methylmercury as foetuses.

The second group is people who are regularly exposed (chronic exposure) to high levels of mercury (such as populations that rely on subsistence fishing or people who are occupationally exposed). Among

selected subsistence fishing populations, between 1.5/1000 and 17/1000 children showed cognitive impairment (mild mental retardation) caused by the consumption of fish containing mercury. These included populations in Brazil, Canada, China, Columbia and Greenland.

A significant example of mercury exposure affecting public health occurred in Minamata, Japan, between 1932 and 1968, where a factory producing acetic acid discharged waste liquid into Minamata Bay. The discharge included high concentrations of methylmercury. The bay was rich in fish and shellfish, providing the main livelihood for local residents and fishermen from other areas.

For many years, no one realised that the fish were contaminated with mercury, and that it was causing a strange disease in the local community and in other districts. At least 50,000 people were affected to some extent and more than 2000 cases of Minamata disease were certified. Minamata disease peaked in the 1950s, with severe cases suffering brain damage, paralysis, incoherent speech and delirium.

**Health effects of mercury exposure**

Elemental and methylmercury are toxic to the central and peripheral nervous systems. The inhalation of mercury vapour can produce harmful effects on the nervous, digestive and immune systems, lungs and kidneys, and may be fatal. The inorganic salts of mercury are corrosive to the skin, eyes and gastrointestinal tract, and may induce kidney toxicity, if ingested.

Neurological and behavioural disorders may be observed after inhalation, ingestion or dermal exposure of different mercury compounds. Symptoms include tremors, insomnia, memory loss, neuromuscular effects, headaches and cognitive and motor dysfunction. Mild, subclinical signs of central nervous system toxicity can be seen in workers exposed to an elemental mercury level in the air of 20 $\mu g/m^3$ or more for several years. Kidney effects have been reported, ranging from increased protein in the urine to kidney failure.

**How to reduce human exposure from mercury sources**

There are several ways to prevent adverse health effects, including promoting clean energy, stopping the use of mercury in gold mining, eliminating the mining of mercury and phasing out non-essential mercury-containing products.

**Promote the use of clean energy sources that do not burn coal**

Burning coal for power and heat a major source of mercury. Coal contains mercury and other hazardous air pollutants that are emitted when the coal is burned incoal-fired power plants, industrial boilers and household stoves.

**Eliminate mercury mining, and use of mercury in gold extraction and other industrial processes.**

Mercury is an element that cannot be destroyed; therefore, mercury already in use can be recycled for other essential uses, with no further need for mercury mining. Mercury use in artisanal and small-scale gold mining is particularly hazardous, and health effects on vulnerable populations are significant. Non-mercury (non-cyanide) gold-extraction techniques need to be promoted and implemented, and where mercury is still used, safer work practices need to be employed to prevent exposure.

Phase out use of non-essential mercury-containing products and implement safe handling, use and disposal of remaining mercury-containing products.

Mercury is contained in many products, including:

- batteries
- measuring devices, such as thermometers and barometers
- electric switches and relays in equipment
- lamps (including some types of light bulbs)
- dental amalgam (for dental fillings)
- skin-lightening products and other cosmetics, and
- pharmaceuticals.

A range of actions are being taken to reduce mercury levels in products, or to phase out mercury-containing products. In health care, dental amalgam is used in almost all countries. A 2009 WHO expert consultation concluded that a global near-term ban on amalgam would be problematic for public health and the dental health sector, but a phase down should be pursued by promoting disease prevention and alternatives to amalgam; research and development of cost-effective alternatives; education of dental professionals and the raising of public awareness.

Mercury use in some pharmaceuticals, such as thiomersal (ethyl mercury), which is used as a preservative in some vaccines, is very small by comparison with other mercury sources. There is no evidence that suggests a possible health hazard resulting from the amounts of thiomersal currently used in human vaccines.

Inorganic mercury is added to some skin-lightening products in significant amounts. Many countries have banned mercury-containing skin-lightening products because they are hazardous to human health.

**Political agreement**

The continued release of mercury into the environment from human activity, the presence of

mercury in the food chain, and the demonstrated adverse effects on humans are of such concern that in 2013 governments agreed to the Minamata Convention on Mercury. The Convention obliges government Parties to take a range of actions, including to address mercury emissions to air and to phase-out certain mercury-containing products.

**WHO response**

The World Health Organization publishes evidence about the health impacts of the different forms of mercury, guidance on identifying populations at risk from mercury exposure, tools to reduce mercury exposure, and guidance on the replacement of mercury-containing thermometers and blood pressure measuring devices in health care.

## 4. VIOLENCE AGAINST WOMEN

**Introduction**

The United Nations defines violence against women as "any act of gender-based violence that results in, or is likely to result in, physical, sexual or mental harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life."

**KEY FACTS**

- Violence against women - particularly intimate partner violence and sexual violence against women - are major public health problems and violations of women's human rights.
- Recent global prevalence figures indicate that 35% of women worldwide have experienced either intimate partner violence or non-partner sexual violence in their lifetime.
- On average, 30% of women who have been in a relationship report that they have experienced some form of physical or sexual violence by their partner.
- Globally, as many as 38% of murders of women are committed by an intimate partner.
- Violence can result in physical, mental, sexual, reproductive health and other health problems, and may increase vulnerability to HIV.
- Risk factors for being a perpetrator include low education, exposure to child maltreatment or witnessing violence in the family, harmful use of alcohol, attitudes accepting of violence and gender inequality.
- Risk factors for being a victim of intimate partner and sexual violence include low education, witnessing violence between parents, exposure to abuse during childhood and attitudes accepting violence and gender inequality.
- In high-income settings, school-based programmes to prevent relationship violence among young people (or dating violence) are supported by some evidence of effectiveness.
- In low-income settings, other primary prevention strategies, such as microfinance combined with gender equality training and community-based initiatives that address gender inequality and communication and relationship skills, hold promise.
- Situations of conflict, post conflict and displacement may exacerbate existing violence and present new forms of violence against women.

Intimate partner violence refers to behaviour by an intimate partner or ex-partner that causes physical, sexual or psychological harm, including physical aggression, sexual coercion, psychological abuse and controlling behaviours.

Sexual violence is any sexual act, attempt to obtain a sexual act, or other act directed against a person's sexuality using coercion, by any person regardless of their relationship to the victim, in any setting. It includes rape, defined as the physically forced or otherwise coerced penetration of the vulva or anus with a penis, other body part or object.

**Scope of the problem**

- Population-level surveys based on reports from victims provide the most accurate estimates of the prevalence of intimate partner violence and sexual violence in non-conflict settings. The first report of the "WHO Multi-country study on women's health and domestic violence against women" (2005) in 10 mainly developing countries found that, among women aged 15 - 49:
- between 15% of women in Japan and 71% of women in Ethiopia reported physical and/or sexual violence by an intimate partner in their lifetime;
- between 0.3 - 11.5% of women reported experiencing sexual violence by a non-partner since the age of 15 years;
- the first sexual experience for many women was reported as forced – 17% in rural Tanzania, 24% in rural Peru, and 30% in rural Bangladesh.

A more recent analysis of WHO with the London School of Hygiene and Tropical Medicine and the Medical Research Council, based on existing data from over 80 countries found that globally, 35% of women have experienced either physical and/or sexual intimate partner violence or non-partner sexual violence. Most of this violence is intimate partner violence. Worldwide, almost one third (30%) of all women who have been in a relationship have experienced physical and/or sexual violence by their intimate partner, in some regions this is much higher.

Globally as many as 38% of all murders of women are committed by intimate partners.

Intimate partner and sexual violence are mostly perpetrated by men against women and child sexual abuse affects both boys and girls. International studies reveal that approximately 20% of women and 5 -10% of men report being victims of sexual violence as children. Violence among young people, including dating violence, is also a major problem.

**Risk factors**

Factors found to be associated with intimate partner and sexual violence occurs within individuals, families and communities and wider society. Some factors are associated with being a perpetrator of violence, some are associated with experiencing violence and some are associated with both.

Risk factors for both intimate partner and sexual violence include:

- lower levels of education (perpetration of sexual violence and experience of sexual violence)
- exposure to child maltreatment (perpetration and experience)
- witnessing family violence (perpetration and experience)
- antisocial personality disorder (perpetration)
- harmful use of alcohol (perpetration and experience)
- having multiple partners or suspected by their partners of infidelity (perpetration); and
- attitudes that are accepting of violence and gender inequality (perpetration and experience).

Factors specifically associated with intimate partner violence include:

- past history of violence
- marital discord and dissatisfaction, and
- difficulties in communicating between partners.

Factors specifically associated with sexual violence perpetration include:

- beliefs in family honour and sexual purity
- ideologies of male sexual entitlement, and
- weak legal sanctions for sexual violence.

The unequal position of women relative to men and the normative use of violence to resolve conflict are strongly associated with both intimate partner violence and non-partner sexual violence.

**Health consequences**

Intimate partner and sexual violence have serious short- and long-term physical, mental, sexual and reproductive health problems for survivors and for their children, and lead to high social and economic costs.

- Violence against women can have fatal results like homicide or suicide.
- It can lead to injuries, with 42% of women who experience intimate partner reporting an injury as a consequence of this violence.
- Intimate partner violence and sexual violence can lead to unintended pregnancies, induced abortions, gynaecological problems, and sexually transmitted infections, including HIV. The 2013 analysis found that women who had been physically or sexually abused were 1.5 times more likely to have a sexually transmitted infection and, in some regions, HIV, compared to women who have not experienced partner violence. They are also twice as likely to have an abortion.
- Intimate partner violence in pregnancy also increases the likelihood of miscarriage, stillbirth, pre-term delivery and low birth weight babies.
- These forms of violence can lead to depression, post-traumatic stress disorder, sleep difficulties, eating disorders, emotional distress and suicide attempts. The same study found that women who have experienced intimate partner violence were almost twice as likely to experience depression and problem drinking. The rate was even higher for women who had experienced non partner sexual violence.
- Health effects can also include headaches, back pain, abdominal pain, fibromyalgia, gastrointestinal disorders, limited mobility and poor overall health.
- Sexual violence, particularly during childhood, can lead to increased smoking, drug and alcohol misuse, and risky sexual behaviours in later life. It is also associated with perpetration of violence (for males) and being a victim of violence (for females).

**Impact on children**

- Children who grow up in families where there is violence may suffer a range of behavioural and emotional disturbances. These can also be associated with perpetrating or experiencing violence later in life.
- Intimate partner violence has also been associated with higher rates of infant and child mortality and morbidity (e.g. diarrhoeal disease, malnutrition).

**Social and economic costs**

The social and economic costs of intimate partner and sexual violence are enormous and have ripple effects throughout society. Women may suffer isolation, inability to work, loss of wages, lack of participation in regular activities and limited ability to care for themselves and their children.

**Prevention and response**

Currently, there are few interventions whose effectiveness have been proven through well designed studies. More resources are needed to strengthen the prevention of intimate partner and sexual violence, including primary prevention, i.e. stopping it from happening in the first place.

Regarding primary prevention, there is some evidence from high-income countries that school-based programmes to prevent violence within dating relationships have shown effectiveness. However, these have yet to be assessed for use in resource-poor settings. Several other primary prevention strategies: those that combine microfinance with gender equality training; that promote communication and relationship skills within couples and communities; that reduce access to, and harmful use of alcohol; and that change cultural gender norms, have shown some promise but need to be evaluated further.

To achieve lasting change, it is important to enact legislation and develop policies that:

- address discrimination against women;
- promote gender equality;
- support women; and
- help to move towards more peaceful cultural norms.

An appropriate response from the health sector can play an important role in the prevention of violence. Sensitization and education of health and other service providers is therefore, another important strategy. To address fully the consequences of violence and the needs of victims/survivors requires a multi-sectoral response.

## 5. PREVENTING UNSAFE ABORTION

**Overview**

An abortion happens when a pregnancy is terminated so that it does not result in the birth of a child. Unsafe abortion occurs when a pregnancy is ended either by persons lacking the necessary skills, or in an environment that does not conform to minimal medical standards, or both.

The persons' skills and medical standards considered safe in the provision of abortion are different for medical abortion (which is performed with drugs alone), and surgical abortion (which is performed with a manual or electric aspirator). Skills and medical standards required for safe abortion also vary depending upon the duration of the pregnancy and evolving scientific and technical advances.

**KEY FACTS**

- Around 22 million unsafe abortions are estimated to take place worldwide each year, almost all in developing countries.
- Deaths due to unsafe abortion account for 13% of all maternal deaths. Africa is disproportionately affected, with nearly two-thirds of all abortion-related deaths.
- Around five million women are admitted to hospital as a result of unsafe abortion every year.
- More than three million women who have complications following unsafe abortion do not receive care.
- The annual cost of treating major complications from unsafe abortion is estimated at $680 million.
- Almost every abortion death and disability could be prevented through sexuality education, use of effective contraception, provision of safe, legal induced abortion, and timely care for complications.

Women, including adolescents, with unwanted pregnancies often resort to unsafe abortion when they cannot access safe abortion. Barriers to accessing safe abortion include:

- restrictive laws
- poor availability of services
- high cost
- stigma
- conscientious objection of health-care providers, and
- unnecessary requirements such as mandatory waiting periods, mandatory counselling, provision of misleading information, third-party authorization, and medically unnecessary tests, that delay care.

**Scope of the problem**

Based on 2008 data, WHO estimates that there are approximately 22 million unsafe abortions annually, resulting in 47,000 deaths, and more than five million complications such as:

- incomplete abortion (failure to remove or expel all of the pregnancy tissue from the uterus)
- haemorrhage (heavy bleeding);
- infection
- uterine perforation (caused when the uterus is pierced by a sharp object), and
- damage to the genital tract and internal organs by inserting dangerous objects such as sticks, knitting needles, or broken glass into the vagina or anus.

Globally, unsafe abortion accounts for an estimated 13% of all pregnancy-related deaths.

In developed regions, it is estimated that 30 women die for every 100,000 unsafe abortions. That number rises to 220 deaths per 100,000 unsafe abortions in developing regions and 520 in sub-Saharan Africa.

Mortality from unsafe abortion disproportionately affects women in Africa. While the continent accounts for 29% of all unsafe abortions, it sees 62% of all abortion-related deaths.

**Who is at risk?**

Any woman with an unwanted pregnancy who cannot access safe abortion is at risk of unsafe abortion. Poor women are more likely to have an unsafe abortion than more affluent women. Deaths and injuries are higher when unsafe abortion is performed later in pregnancy. The rate of unsafe abortions is higher where access to effective contraception and safe abortion is limited or unavailable.

**Complications of unsafe abortion requiring emergency care**

The major life-threatening complications resulting from unsafe abortion are hemorrhage, infection, and injury to the genital tract and internal organs.

**Signs and symptoms**

An accurate initial assessment is essential to ensure appropriate treatment and prompt referral for complications of unsafe abortion. The critical signs and symptoms of complications that require immediate attention include:

- abnormal vaginal bleeding
- abdominal pain
- infection, and
- shock (collapse of the circulatory system).

Complications of unsafe abortion can be difficult to diagnose. For example, a woman with an extra-uterine or ectopic pregnancy (abnormal development of a fertilized egg outside of the uterus) may have symptoms similar to those of incomplete abortion. It is essential, therefore, for health-care personnel to be prepared to make referrals and arrange transport to a facility where a definitive diagnosis can be made and appropriate care can be delivered quickly.

**Treatment and care**

- Hemorrhage: timely treatment of heavy blood loss is critical, as delays can be fatal.
- Infection: treatment with antibiotics along with evacuation of any remaining pregnancy tissue from the uterus, as soon as possible.
- Injury to the genital tract and/or internal organs: if this is suspected, early referral to an appropriate level of health care is essential.

**Access to treatment for abortion complications**

Health-care providers are obligated to provide life-saving medical care to any woman who suffers abortion-related complications, including treatment of complications from unsafe abortion, regardless of the legal grounds for abortion. However, in some cases, treatment of abortion complications is administered only on condition that the woman provides information about the person(s) who performed the illegal abortion.

The practice of extracting confessions from women seeking emergency medical care as a result of illegal abortion, and the legal requirement for doctors and other health-care personnel to report cases of women who have undergone abortion, delays care and increases the risks to women's health and lives.

**Prevention and control**

Unsafe abortion can be prevented through:

- good sexuality education;
- prevention of unintended pregnancy through use of effective contraception, including emergency contraception; and
- provision of safe, legal abortion.
- In addition, deaths and disability from unsafe abortion can be reduced through the timely provision of emergency treatment of complications.

**Economic impact**

In addition to the deaths and disabilities caused by unsafe abortion, there are major social and financial costs to women, families, communities, and health systems.

WHO provides global technical and policy guidance on the use of contraception to prevent unintended pregnancy, safe abortion, and treatment of complications from unsafe abortion.

## 6. MENTAL HEALTH AND OLDER ADULTS

**Overview**

Older adults, those aged 60 or above, make important contributions to society as family members, volunteers and as active participants in the workforce. While most have good mental health, many older adults are at risk of developing mental disorders, neurological disorders or substance use problems as well as physical illness or disability.

**KEY FACTS**

- Globally, the population is ageing rapidly. It is projected that the number of persons aged 60 or over is expected to more than triple by 2100.
- Mental health and emotional well-being are as important in older age as at any other time of life.
- Neuropsychiatric disorders among the older adults account for 6.6% of the total disability (DALYs) for this age group.
- Approximately 15% of adults aged 60 and over suffer from a mental disorder.

**The problem**

The world's population is ageing rapidly. Between 2000 and 2050, the proportion of the world's older adults is estimated to double from about 11% to 22%.

In absolute terms, this is an expected increase from 605 million to two billion people over the age of 60. Older people face special physical and mental health challenges which need to be recognized.

Over 20% of adults aged 60 and over suffer from a mental or neurological disorder (excluding headache disorders) and 6.6% of all disability (disability adjusted life years-DALYs) among over 60s is attributed to neurological and mental disorders. The most common neuropsychiatric disorders in this age group are dementia and depression. Anxiety disorders affect 3.8% of the elderly population, substance use problems affect almost 1% and around a quarter of deaths from self-harm are among those aged 60 or above. Substance abuse problems among the elderly are often overlooked or misdiagnosed.

Mental health problems are under-identified by health-care professionals and older people themselves, and the stigma surrounding mental illness makes people reluctant to seek help.

**Risk factors for mental health problems among the older adults**

Multiple social, psychological, and biological factors determine the level of mental health of a person at any point of time. As well as the typical life stressors common to all people, many older adults lose their ability to live independently because of limited mobility, chronic pain, frailty or other mental or physical problems, and require some form of long-term care. In addition, older people are more likely to experience events such as bereavement, a drop in socioeconomic status with retirement, or a disability. All of these factors can result in isolation, loss of independence, loneliness and psychological distress in older people.

Mental health has an impact on physical health and vice versa. For example, older adults with physical health conditions such as heart disease have higher rates of depression than those who are medically well. Conversely, untreated depression in an older person with heart disease can negatively affect the outcome of the physical disease.

Older adults are also vulnerable to physical neglect and maltreatment. Elder maltreatment can lead not only to physical injuries; but also to serious, sometimes long-lasting psychological consequences, including depression and anxiety.

**Dementia and depression among the elderly as public health issues**

Dementia: Dementia is a syndrome in which there is deterioration in memory, thinking, behaviour and the ability to perform everyday activities. It mainly affects older people, although it is not a normal part of ageing.

It is estimated that 35.6 million people worldwide are living with dementia. The total number of people with dementia is projected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050, with majority of sufferers living in low- and middle-income countries.

There are significant social and economic issues in terms of the direct costs of medical, social and informal care associated with dementia. Moreover, physical, emotional and economic pressures can cause great stress to families. Support is needed from the health, social, financial and legal systems for both people with dementia and their caregivers.

Depression: Depression can cause great suffering and leads to impaired functioning in daily life. Unipolar depression occurs in 7% of the general elderly population and it accounts for 1.6% of total disability (DALYs) among over 60 year olds. Depression is both under diagnosed and undertreated in primary care settings. Symptoms of depression in older adults are often overlooked and untreated because they coincide with other late life problems.

Older adults with depressive symptoms have poorer functioning compared to those with chronic medical conditions such as lung disease, hypertension or diabetes. Depression also increases the perception of poor health, the utilization of medical services and health care costs.

**Treatment and care strategies**

It is important to prepare health providers and societies to meet the specific needs of older populations, including:

- training for health professionals in old-age care;
- preventing and managing age-associated chronic diseases including mental, neurological and substance use disorders;
- designing sustainable policies on long-term and palliative care; and
- developing age-friendly services and settings.

**Health promotion**

Mental health of older adults can be improved through promoting active and healthy ageing. Mental health-specific health promotion for the older adults involves creating living conditions and environments that support wellbeing and allow people to lead healthy and integrated lifestyles. Promoting mental health depends largely on strategies which ensure the elderly have the necessary resources to meet their basic needs, such as:

- providing security and freedom;
- adequate housing through supportive housing policy;
- social support for elderly populations and their caregivers;

- health and social programs targeted at vulnerable groups such as those who live alone, rural populations or who suffer from a chronic or relapsing mental or physical illness;
- violence or older adults maltreatment prevention programs; and
- community development programs.

**Interventions**

Prompt recognition and treatment of mental, neurological and substance use disorders in older adults is essential. Both psychosocial interventions and medicines are recommended.

There is no medication currently available to cure dementia but much can be done to support and improve the lives of people with dementia and their caregivers and families, such as:

- early diagnosis, in order to promote early and optimal management
- optimizing physical and psychological health, including identifying and treating; accompanying physical illness, increasing physical and cognitive activity and optimizing well-being
- detecting and managing challenging behavioural and psychological symptoms, and
- providing information and long-term support to caregivers.

**Mental health care in the community**

Good general health and social care is important for promoting older people's health, preventing disease and managing chronic illnesses. Training all health providers in working with issues and disorders related to ageing is therefore important. Effective, community-level primary mental health care for older people is crucial. It is equally important to focus on the long-term care of older adults suffering from mental disorders, as well as to provide caregivers with education, training and support.

An appropriate and supportive legislative environment based on internationally accepted human rights standards is required to ensure the highest quality of services to people with mental illness and their caregivers.

Dementia, along with depression and other priority mental disorders are included in the WHO Mental Health Gap Action Programme (mhGAP). This program aims to improve care for mental, neurological and substance use disorders through providing guidance and tools to develop health services in resource poor areas.