Kidney transplant recipients and the incidence of adverse reactions to cyclosporin

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Cyclosporin monitoring of blood concentration measurements is recognized as an important part of a transplant patient receiving the drug. The quantitation of cyclosporin in biological fluids is essential for several reasons, 1) wide inter and intra-individual variability in pharmacokinetic standard; 2) low blood concentrations due to poor drug absorption or rapid elimination; 3) high blood concentrations; 4. patient compliance with the medication regimen.[1]

Among the most important side effects of the immunosuppressant cyclosporin are nephrotoxicity, neurotoxicity and hypertension.[2-4] Neurological adverse effects associated with post-transplant immunosuppression most commonly develop during the high levels of cyclosporin and can be categorized as a major (expressive aphasia, seizures, confusion, psychosis, encephalopathy, persistent coma) or a minor (tremors, headache, sleep disturbances, nightmares, dysesthesias, photophobia) neurotoxicity.[2,4] It has been consistently documented that cyclosporin causes a reversible, dose-related renal vasoconstriction and a reduction in the glomerular filtration rate and may precipitate systemic hypertension.[2] Hypertension is often observed in allograft recipients. In those who were previously normotensive, this may be due to excessive water volume, intrinsic renal damage or increased vasomotor tone. Use of corticosteroids may also lead to retention of excess water.[3] There are drug interactions that may affect the levels of cyclosporin. Drugs that induce or interfere with the hepatic CYP3A4 enzyme pathway may cause significant change in cyclosporin levels leading to either toxicity or sub-therapeutic levels. Rifampicin, phenytoin and phenobarbitone are potent CYP3A4 inducers, which may reduce blood levels progressively within a few days of commencing therapy. Less potent enzyme inducers include carbamazepine, isoniazid and possibly low-dose glucocorticoids used for supplemental immunosuppression. High doses of cyclosporin have been associated with toxic reactions.[5,6] These are believed to be due to the occurrence of extremely high blood levels, which to date have not been adequately explained. These toxic reactions considerably complicate clinical management. Adverse reaction to cyclosporin seems to be dependent on the individual susceptibility of the recipient. The purpose of the present study was to retrospectively evaluate the incidence of adverse reaction to cyclosporin after kidney transplantation in Isfahan, Iran.

Four hundred and thirty (341 males and 89 females), renal transplant patients (mean age 40 years, range 25-69) who were given cyclosporin approximately 8.5 mg/kg/day (range 3.2-10.7) were included in this study. Cyclosporin pre-dose blood samples were assayed using a radioimmunoassay technique. All patients received cyclosporin and prednisone as immunosuppressive maintenance treatment. The study was conducted one month to 5 years after transplantation. For combination therapy, other drugs that were used for clinical management after kidney transplantation such as; Lovastatin, Cyclovir, Prednisolone, Mycophenolic mofetile, Bactrim, Ciprofloxacin, Insuline, Ranitidine, Adalat, Folic Acid, Imuran, Captopril, Digoxin and Gentamicin were also noted. Information were gathered from the clinical record of the patients. Neurological or renal complication (fits or delirium, increase in serum creatinine, serum urea and reduced urine output) was accepted as signs of cyclosporin toxicity. Patients with or without toxicity were compared by means of the Mann-Whitney U-test, *p* value of less than 0.05 was considered statistically significant.

After kidney transplantation the administered dosage of cyclosporin, produced widely variable whole blood through concentrations (C_0) in different studied patients. It seems that the upper therapeutic concentration incidences of life threatening opportunistic adverse reaction when whole blood trough concentrations as measured by radioimmunoassay exceed 400 µg/L. Toxicity occurred in 234 patients after kidney transplantation. Neurological problems were encountered in approximately 35% of patients mainly fits and confusional states. Of these patients 130 had high cyclosporin blood levels (more than 400 µg/L) on the day complications occurred, and 16 patients had normal therapeutic levels (150-250 µg/L). The 4 patients exhibited delirium 2 days after withdrawal of cyclosporin. All neurological complications disappeared when cyclosporin dosage was reduced or stopped. Twenty-five percent of patients had evidence of renal toxicity. Nephrotoxicity, which associated from therapy, occurred in patients when cyclosporin was administered at dosage of 4.3-10.9 mg/kg. All patients exhibited high serum creatinine levels, which resolved with a reduction in cyclosporin dosage. Mild nephrotoxicity responding to dose reduction occurred in 10-15 kidney transplant recipients. In some patients with renal impairment, cyclosporin trough whole blood concentration was less than 100µg/L. These findings indicate that renal toxicity may occur with cyclosporin even if such concentrations are maintained at low levels. Infection complications occurred in some patients

after kidney transplantation, the majority of cases were bacterial. Fungal infection was less common but included candidiasis and aspergillosis infections. Glucose metabolic disorders occurred in 18 patients and required insulin therapy. Hypertension was occurred in 23% after kidney transplantation, this may be due to excessive water volume, intrinsic renal damage or increased vasomotor tone. As cyclosporin is a substrate of hepatic cytochrome P450, its metabolism might be inhibited or induced by calcium channel blockers, corticosteroids, macrolide antibiotics and other drugs. A decrease in cyclosporin C_0 was observed in 5 patients receiving a combined regimen of cyclosporin and carbamazepine. Cholesterol-lowering agent such as Lovastatin and Clofibrate in 7 kidney transplant recipients reduced cyclosporin trough levels. All these patients rejected kidney grafts within one month after transplant which they were managed with intravenous boluses of steroids. Co-administration of cyclosporin with Bactrim, Ciprofloxacin and Gentamicin in 6 patients resulted in an increase in cyclosporin trough level (caused toxicity side effects) on day 90 and reached statistical significance (p=0.001). Co-administration of cyclosporin with mycophenolic acid in 4 patients also resulted in an increase in cyclosporin blood trough levels.

The administration of cyclosporin is associated with marked variability.[1] There is consensus that trough level monitoring throughout the whole post-transplantation period is indispensable, in order to determine dosage requirements. A cyclosporin dose of 3-5 mg/kg/day orally, seems to be a reasonable starting dose aiming for levels of around 200 µg/L (monoclonal radioimmunoassay on whole blood). However, it is common practice for patients who are several years beyond kidney transplantation to let the levels of cyclosporin drift down to around 150 µg/L. That seems particularly appropriate for those patients who have stable graft function.[5,6] As pharmacokinetic profile is difficult to predict and its nephrotoxic side effects, cyclosporin is not an easy drug to use.[1] The result of this prospective study suggest that increase in cyclosporin level could cause toxicity especially nephrotoxicity that is identified by functional changes caused by a reversible, dose-related renal vasoconstriction.[5,6] Toxic levels of cyclosporin may also cause chronic renal damage. Therefore, one potential approach to prevent cyclosporin nephrotoxicity is cyclosporin dose reduction.[5] One of the most important and relevant issues on the dose of baseline immunosuppression with cyclosporin is what other drugs are being administered.[6] As the dose of cyclosporin could be largely affected by whether it is used alone or as part of dual, triple or even quadruple therapy, therefore, the relevance of manipulating the dose of cyclosporin in response to drug levels and clinical events were investigated. Drug interactions were seen in some patients as the results of inhibition or induction of cyclosporin metabolism by CYP450 enzymes. Ketoconazole, erythromycin and calcium channel blockers inhibit the P450 system and thus they will increase the blood level of cyclosporin. Patients need careful instruction to not stop their antihypertensive medication and should their blood pressure medication be changed, frequent drug levels should be monitored with appropriate adjustment of the dose as necessary. Phenytoin, rifampin and barbiturates have the opposite effect and they may be expected to decrease the levels of cyclosporin. High cyclosporin blood level had a profound effect on the occurrence of toxic side effects (p<0.001). Therefore, the authors stressed the need for organized immunosuppressive monitoring program, the importance of biopsies confirming an absence of rejection, the continued follow-up of recipients for better achievement after organ transplantation. It is recommended that the management of kidney transplant recipients should have the following goals: 1. Minimize the incidence of adverse reaction; 2. Minimize the incidence of acute and chronic rejection; 3. Maintain drug levels within therapeutic range. Therefore, for routine clinical monitoring of cyclosporin, targeting at therapeutic mean levels within an organized immunosuppressive monitoring program may improve outcome after kidney transplantation in Isfahan, Iran.

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A simplified bedside method for estimating glomerular filtration rate in term neonates

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An accurate estimation of renal function in neonates is very essential as many management decisions including fluid and electrolyte administration and the use of therapeutic agents are based on it. An overall estimate of renal function can be made by measuring the glomerular filtration rate (GFR). The classic technique used for GFR requires the use of substances as inulin, Cr-EDTA ^{99}mTc-DTPA, ^{125}I-iothalamate and polyfructosan with multiple timed collections of urine.[1] These methods are expensive, labor intensive and require administration of chemical substances and therefore, are inappropriate in a sick baby. Another novel method described recently for monitoring GFR is the measurement of plasma cystatin C, which requires immunoassay technique and may not be readily available.[2] Schwartz and Brion,[3] in a series of studies described a much more simpler and rapid way of estimating the GFR in neonates by a formula using plasma creatinine.[3] This formula has been adopted by clinicians and has already been used in research.[4] The formula by Schwartz for calculating GFR is kL/Pcr, where k is a constant, L is the length of the infant in centimeters and Pcr is the plasma creatinine value expressed in mg/dl. The value of 'k' was calculated by regression analysis and was found to be 0.45 for term neonates.

We propose further modification in this formula. The reason behind this proposal is that in term infants, variation in length is not much. We have shown in a previous study that the length of the term infants does not deviate much from a mean of 50 centimeters.[5] Thus, we rounded off the length parameter in the Schwartz's formula to 50 cm. We also altered the unit of expression of plasma creatinine from mg/dl to mmol/L, the International System of units or System Internationalé (SI), which is followed extensively and also used in the literature. To convert plasma creatine (Pcr) from mg/dl to mmol/L conversion factor of 88.4 was used. The mathematical derivation for the modified formula is as under Schwartz formula: GFR = 0.45L/Pcr; 0.45 x length (cm) / Pcr (mg/dl); 0.45 x 50 x 88.4/Pcr (mmol/L), where, 50 cm is the rounded off length, and 88.4 is the conversion factor for creatinine from mg/dl to mmol/L. After simplifying, the equation becomes 1989/Pcr (mmol/L). Modified formula (Manzar formula): GFR = 1989/Pcr. To test this formula against the Schwartz formula we conducted this study.

The study was conducted over a 6-month period between January and June 2003 at the Royal Hospital, Muscat, Sultanate of Oman, which is a tertiary referral center for neonates with a birth rate of approximately 5,000 infants annually. Details of all admission and discharge or death are both kept as case files in the Medical Records Department and on the computer database using Visual Dbase Program. Term infants, defined as infants born after 37 completed weeks of gestation, were selected for the study and the data were extracted from the computer database. Each baby's identification number and length in centimeters that was taken by the nurses at the time of admission was retrieved from Visual Basic Database. Each baby's first Pcr value was recovered from the online hospital data storage system (Medicom), which as a protocol, is estimated within 24 hours of admission.

A total of 83 term neonates, out of 311 admission during the specified 6-month period had complete information needed for the study. The Pcr values were reported in SI units as mmol/L by our laboratory using auto-analyser technique (ALEX 20, USA). The GFR was then calculated from the creatinine value using both the methods, the Schwartz formula and modified formula. To convert mmol/L to mg/dl the conversion factor of 88.4 was used, as described. As the nature of the study was retrospective and laboratory based, and no intervention was carried out on the infants, formal approval by the Institution Review Committee and informed parental consent were not considered. This being a pilot study, no sample size calculation was performed. The mean values of GFR were calculated using statistical package for social sciences (SPSS) version 7.5 for windows. Correlation between the variables was performed using Pearson correlation test. A p value of < 0.05 was considered statistically significant. A total of 83 samples from 83 term infants were analyzed. The mean value of GFR was noted to be 32.5 ± 16.9 and 31.8 ± 15.4 ml/min/1.73m^2 by Schwartz and modified method. A statistically significant correlation ($r=0.99$, $p=0.0001$) was obtained between the 2 methods for estimating GFR.

In the present study, we were able to demonstrate that the simplified formula for estimating GFR in term neonates (GFR = 1989/Pcr) is comparable with the Schwartz method (GFR = 0.45L/Pcr). Our finding indicated that rounding off and standardizing length to 50 cm for estimating GFR had no significant effect on GFR calculations. The possible reasons for no significant difference could

be in 2 folds. First, there is usually no wide variation in the length of term babies.[5] Secondly, the muscle mass for term babies does not differ much. It was reported to be 24% of body weight.[1] Thus, including some of the body measurement parameter in the formula for estimating GFR, as carried out for older children, may not be applicable to neonates. The simple reason is that the variation in length and muscle mass in older children is likely to be higher. These facts and that growth, development, size and age profoundly affect GFR estimation is shown recently in a meta-analysis of previous published reports.[6] In our group of term infants the mean value of GFR was noted to be 31.8 ± 15.4 ml/min/1.73m^2 (modified method) which was not different from the normal ranges reported earlier.[3] However, a wide variation was observed ranging from 8.5 to 79 ml/min/1.73m^2. One known reason for the wide variation is the variability of Pcr in the first 72 hours of life.[7] The other reason for the observed variation is in view of the fact that we selected term neonates who were in the intensive care unit with different disease pathology. They were not in a steady state. The ideal study group for that purpose should be the term healthy stable neonates in the postnatal ward. However, to draw extra blood merely for Pcr estimation without indication may not be justified or ethical. Thus, for the study purpose we had to rely on the available creatinine values from the relatively unstable term babies.

It is obvious from the above discussion that GFR is inversely proportional to Pcr. The lower the Pcr the higher will be the GFR or vice versa. Thus, one could argue regarding the fact that instead of GFR one could use Pcr alone for assessing renal function. Schwartz provided the answer to this possible argument in his review on GFR estimation.[3] He suggested that the creatinine value is critically dependent on the percentage of muscle mass, in addition to renal function. In addition, it is easier to grasp a change in GFR as compared to Pcr (for example: a change of 40 ml/min/1.73m^2 in GFR corresponds to 0.2 mg/dl of creatinine). However, with expression of creatinine in SI unit this point loses its strength (0.2 mg/dl means 17.2 mmol/L). However, the advantage of using GFR instead of Pcr in acute renal failure is proven beyond doubt. It has been stated that in cases of acute renal failure when GFR falls abruptly it takes several days for Pcr to reach new constant level and similarly as the failure improves there may be several days before a stable Pcr value is attained. The clinical implication of GFR has been gaining interest. Recently, it has been shown to be an effective prognostic factor in the outcome of infants with posterior urethral valve.[8] Previously, the troublesome and time-consuming methods of GFR estimation could be one of the reasons for under utilization of GFR in clinical settings. Now with the availability of much simpler way of GFR estimation, as described in the study, more could be known regarding the GFR in relation to common neonatal problems. We have already embarked on a prospective study relating GFR to the outcome of asphyxiated neonates with different stages of hypoxic-ischemic-encephalopathy.

In conclusion, the modified formula for GFR estimation, as described in the present study, is a simple, reliable, rapid and a bedside method. To look at the other potential clinical benefits of our modified formula further studies are warranted.

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Anuric unless catheterized

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We present a premature baby with critical illness and subsequent rent in the bladder. A 28-weeks, 1500g male neonate was born in poor general condition to a 19-year-old gravida 2 para 1 whose pregnancy was uneventful. The baby was transferred to this hospital intubated with the diagnosis of acute perinatal asphyxia, respiratory distress syndrome, presumed sepsis and shock. The clinical condition improved after general resuscitative measures, including administration of surfactant, inotropes, broad-spectrum antimicrobials and analgesia (morphine). Placement of umbilical arterial and venous catheter was uneventful. However from day 3, the abdomen became markedly distended, tender and shiny with omphalitis complicated by a spreading cellulitis. Central lines were removed. The baby became anasarcous and anuric, non-responsive to fluid challenge and frusemide. Passed urine freely after catheter was in position. Serum urea rose to 9mmol/L and creatinine, 194mmol/L. Ultrasound (US) showed fullness of the pelvicaliceal systems, ascites and 15-25cc of urine in the bladder. There was no gross or microscopic hematuria. Cultures remained sterile. After 7 days of maximum support, the baby was extubated and catheter was removed. Serum urea and creatinine, and abdominal US became normal. General condition remained good except that twice unless catheterized, the baby became anuric with ascites and elevated serum urea and creatinine. The possibility of a bladder rupture was then entertained. Micturating cystourethrogram (MCUG) demonstrated a leak of contrast from the right posterior bladder wall (**Figure 1**). The urethra was normal. Observational MCUG 5 days later was normal. No recurrence of the problem was noted on follow up to 15 months of age.

Bladder rupture in the absence of demonstrable obstruction is a distinct rarity.[1] It may not be readily identifiable in a septically ill neonate unless there is a high index of suspicion. Peritoneal and urine electrolytes (not requested in our baby) compared with serum values, will prove the presence of urinary ascites and autodialysis.[2,3] The clue which lead to our diagnosis was the episodes of anuria, ascites, rising serum urea and creatinine abating after indwelling catheterization. Micturating cystourethrogram confirmed our diagnosis. It is probable that septic embolization arising from the infected umbilicus could have extended to the bladder resulting in necrosis and weakening of the wall. The umbilical arteries originates from the internal iliac arteries and its branches are the

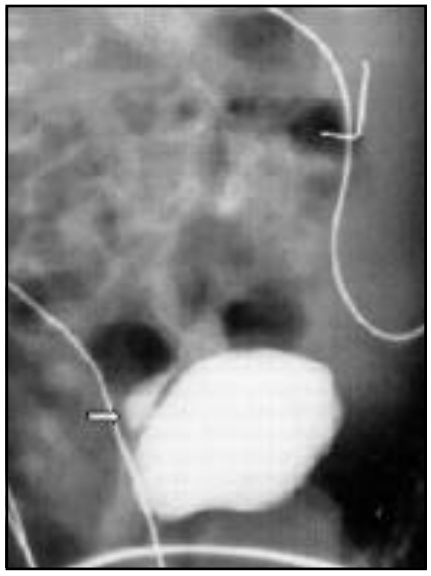

Figure 1 - Micturating cystourethrogram (lateral view) leak of contrast from the right posterior bladder wall.

superior and inferior vesical arteries supplying the bladder.[4] Detrusor areflexia as a result of asphyxia,[5] and hypotonic thin-walled nature of an immature bladder, and morphine infusion can cause bladder overdistension. Whether these trigger factors precipitated the bladder disruption remained speculative. We felt that the bladder drainage allowed time for the point of rupture to spontaneously heal.

Diagnosis of this unusual event should be considered in sick newborns presenting with anuria, and ascites resolving after catheterization. Prompt recognition should result to a satisfactory outcome.

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A surviving baby born 24 weeks of gestational age and 490g weight without mechanic ventilation and surfactant replacement

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The infant weighing <500g at birth is still considered previable.[1] Recently, with the improvements in neonatology, extremely low birth weight neonates are capable of surviving. The survival rate of infants born from 22-25 weeks of gestation increases with each additional week of gestation. Babies born before 22 weeks of gestation have a survival rate of 0%. In advanced centers, babies born at 24 weeks of gestation have a survival rate of 33%. In these infants, the most striking complication, being the highest incidence is retinopathy of prematurity (ROP).[2] Approximately 30-50% of surviving children who weighed less than 750g at birth, or whose gestational age was less than 25 weeks had a moderate to severe disability, including blindness, deafness and cerebral palsy (CP). Many infants had more than one disability.[3] Among surviving infants born at 23-24 completed weeks, 20-30% had disabilities such as cerebral palsy, hydrocephalus, severe cognitive deficit, blindness, deafness or a combination.[2,5]

In this report, we present an extremely low birth weight infant, born at 24 weeks of gestational age and weighed 490g, survived without any disability except blindness in the right eye despite not being admitted in neonatal intensive care unit (NICU). The baby was born at 24 weeks of gestation via spontaneous vaginal delivery as the second of a twin to a 27-year-old healthy mother. The first of the twin, a male weighed 550g, died shortly after delivery. From her history, it was learned that the mother had been admitted to the hospital due to the premature rupture of membrane and uterine contractions at the end of the twenty-third week, she had regular checkup and ultrasound in the maternity hospital and was asked to be referred to a hospital having an NICU. However, the parents refused to be referred to another hospital, as they believed that the baby would not survive and due to financial problems. On the initial physical examination, her weight was 490g and length 28 cm. She was hypoactive, hypothermic, and acrocyanotic. The skin was slightly edematous, thin and gelatinous. Sucking reflex was weakly positive. The breathing was 72, and heart rate was 140 per minute. The rest of the physical examination was unremarkable. According to the New Ballard scores', it was appropriate to the one born at 24 weeks, and it was small for gestational age (SGA). She was put in the incubator and started to receive oxygen with hood, as a ventilator did not exist in the hospital. Peripheral oxygen saturation varied between 80-95%. Her skin was scrubbed with olive oil and an appropriate parenteral fluid and electrolyte therapy was provided. Breast milk feeding in drops was started on day 4, which was increased gradually. As she improved, an anemia was noted, for which fresh whole blood was transfused on day 11, 20, 33 and 37. On the 20th day she lost 20% of her body weight and was reduced to 420g. After 40 days her weight was 500g and started to be fed orally, she gained weight faster. On the 50th day she reached 620g and on the 90th, 1500g. Grade 5 ROP was defined in the right eye at the fourth week and was kept under control. At the end of the third month, the baby was discharged from the hospital. Her controls, physical and neuromotor developments were appropriate for her corrected age. On the last examination in the 14th month (corrected age 10th month), her length was 70cm, weight 7000g and head circumference was 41.5 cm. The physical examination finding was normal except blindness in the right eye. She was considered appropriate for her corrected age with Denver's developmental screening test.

Today, even in the most developed NICUs, extremely premature babies hardly survive. Even though, a baby born weighing between 500-600g and at 24-25 weeks manages to survive, disabilities will is unavoidable.[2] The birth of infants weighing 500g or less can be even more of a dilemma, as these infants are considered previable, yet some will respond to even the modest resuscitation efforts.[6,7] In addition, when faced with an infant weighing < 500g, some physicians may feel an obligation to proceed with maximal resuscitation and initiation of neonatal intensive care as such infants occasionally survive, even though they are below what is considered the stage of viability, which has been defined as either the point of ability to survive or the point of ability to grow and develop normally.[1] The baby was considered at 24 weeks of gestational age according to the last menstrual date, ultrasonographic scanning and New Ballard score, and she was SGA. The baby was put in an incubator in an appropriate level of humidity and warmness, and started to receive oxygen with hood. The body was scrubbed with olive oil every day. Eye and umbilicus care was carried out. She was given appropriate liquid, electrolytes, vitamins, calorie and begun prophylactic antibiotic, and the most importantly, fed with her mother's breast milk as soon as possible. With all these efforts, the baby improved and at the end of the third month, she was discharged healthy except for the blindness in one eye.

In a study, only 18 out of 382 babies born less than 500g (4.7%) were discharged alive from the hospital. Most of the babies were treated in NICU for weeks, and spent much money. Only one of the 18 infants discharged alive was considered to have appropriate weight for gestational age, the other 17 were SGA. Of the 18 infants discharged from the hospital alive, there were 13 survivors, to live beyond 3 years of age; the other 5 died during the first year of life from disabilities. Four infants had no disabilities, 4 had one disability (one CP and 3 mental retardation [MR]), and 5 had multiple disabilities (3 CP and MR; one with CP, MR and blindness, and one with CP, MR, blindness and deafness).[1] As the possibility of survival is low and the possibility of having disability is high and the high rate of costs, the decision of active resuscitation and carrying on intensive care is difficult in case of these babies.[6,7] It is pleasing that the neuromotor development of our patient is normal up to the 14th month; there is only one eye blindness. In the situation of chronic placental insufficiency and intrauterine stress, fetal maturation can be better and glucocorticoids, thyroid hormones, epidermal growth factors and cyclic AMP have positive effects on the lung maturation and production of surfactant. As the hyaline membrane disease (HMD) is commonly seen in male newborns, it is thought that androgens have negative effects on HMD's.[8]

In our patient, there was no explanation of having good maturity other than, stress factor as twins, and female born infant.

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Neonatal systemic candidiasis. *A 14-year review*

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The case records of all neonates admitted to the Special Care Baby Unit (SCBU), Al-Wasl Hospital, Dubai, United Arab Emirates (UAE) in a period of 14 years from May 1987 to April 2001 were analyzed, a total of 9060 admissions, 102 were diagnosed to have systemic candidiasis (1.1%). The mean gestational age was 29.3 weeks and birth weight 1131g. Fifty-two percent were premature, less than 1000g and only 2% were full term infants. All had undergone either umbilical, or peripheral vein catheterization and had received broad spectrum antibiotics except 2 with congenital candidiasis. Lethargy persistent pulmonary infiltrates, recurrent apnea, gastric intolerance and abdominal distension were the common clinical features. Persistent thrombocytopenia sustained more than 3 days was the most common finding in the peripheral smear. Two patients with congenital candidiasis presented with severe leukocytosis [white blood cells (WBC) count >25000/mm^3] without thrombocytopenia. Urine and blood were the most common site for isolation of candida. Twelve percent of death were attributed to candida. Amphotericin B was used in all babies and in 7 cases, 5 flucytosine was added. Five infants had transient rise of blood urea nitrogen >30mg/dL or serum creatinine level >1mg/dL or both.

This study is a retrospective analysis of culture-verified cases of neonates systemic candidiasis. The records were evaluated for gestational age, sex, birth weight, indwelling catheters, days on antibiotics at the onset of symptoms, treatment details and outcome. The clinical data were collected on

standardized form and entered in to the database for analysis. Systemic candidiasis was defined as growth of candida species isolated from one or more normally sterile body fluids (blood, cerebro-spinal fluid, urine, peritoneal fluid) in the presence of clinical signs of infection. Systemic candidiasis was considered contributory to mortality if death occurred within 3 days of a positive culture from sterile body fluids. Specimen were collected and processed according to standard microbiologic techniques. Presumptive identification of *candida albicans* was carried out on germ tube test. Germ tube negative isolates were grouped as c*andida spp*. All babies receiving amphotericin B or 5 flucytosine or both were monitored for renal and hematological toxicity. **Table 1** shows characteristics of neonates with systemic candidiasis. No significant difference was found in infants infected with *candida albicans* and *candida spp* regarding birth weight, gestational age and age at diagnosis and risk factors. Before diagnosis there was no difference between groups in their need for ventilatory support, parenteral nutrition and broad spectrum antibiotic treatment There was a significant drop of platelet counts (<50000/mm^3) despite broad spectrum antibiotic coverage before the diagnosis of all acquired cases of systemic candidiasis. Most common clinical presentation were lethargy, and involvement of respiratory symptoms.

Ninety-eight percent were premature or had low birth weight or both. The highest number of cases were seen in infants weighing less than 1000gm (52%). Seventeen cases received dexamethasone (5-day course) as a treatment for chronic lung disease. All patients had peripheral or umbilical catheterization (venous or arterial) or central line insertion and 33 (22%) were on total parenteral nutrition. Abdominal or renal ultrasonography was performed for all infants with confirmed systemic candidiasis; 2 had increased renal medullary echogenicity detected. Brain ultrasonography was normal in all infants. Echocardiography was performed for 53 infants with cardiac murmur or positive blood culture; only one infant had intracardiac vegetation on the atrial septum. Ophthalmoscopic evaluation was normal in all except one with endophthalmitis. All patients were treated with amphotericin B intravenously with initial dose of 0.25-0.5mg/kg and increased to 1mg/kg/day. The cumulative dose of amphotericin B ranged from 20-30mg/kg (median 26mg/kg). Seven infants with candida meningitis also received oral 5 flucytosine in dosage ranging from 75-100mg/kg/day. Five infants had transient nephrotoxicity manifested by blood urea nitrogen levels >30mg/dL or a serum creatinine level >1mg/dl or both, which fell to the normal range when daily dose of amphotericin was decreased to 0.75mg/kg. Thirteen (12.7%) of 102 infants died; 7 of these patients had definite meningitis and one had endophthalmitis. No difference was observed in mortality pattern for *candida albicans* and *candida spp*.

Table 1 - Characteristics of neonates with systemic candidiasis.

Characteristic	n
Live birth	96612
SCBU admissions	9060
Total number of cases with candidiasis	102
Male to female	61:41
Inborn	80
Transported	22
Incidence/1000 live birth	1
Gestational age (weeks)	29.3 (24- 37)
Birth weight (gms)	1131 (580-3200)
Age of onset of candidiasis (days)	22 (1-30)
Mortality (inborn) (%)	8/80 (10)
Overall mortality (%)	13/102 (12.7)

SCBU - special care baby unit

Systemic candidiasis is a serious problem particularly in very low birth infants and mortality up to 54% has been reported.[1] Incidence of disseminated candidal infections in neonates correlates with improved survival of very low birth weight infants. Possible reasons for this association include the compromised host defenses, colonization of gastro-intestinal tracts, frequent broad spectrum antibiotics and corticosteroid therapy and multiple invasive procedures. It was of interest to perform this study in a SCBU. To our knowledge, it has not been previously undertaken. In our study, the incidence was one per 1000 live births. Consistent with many reports blood and urine was the most common sites of candidal growth. Meningitis was diagnosed only in 7 cases, although Marisol et al[2] reported frequent occurrence of meningitis (25%). Possible reason could be early suspicion of candida infection and initiation of antifungal therapy. The mean age of onset of candidiasis was 22.4 days (ranged from 1-30 days) which is consistent with most of the previous reports from different parts of the world. Although

Narang et al[3] report much earlier onset of candidiasis. The ratio of mean duration of antibiotics to mean age at onset was 0.55 while studies by Faix[1] 0.58 and Narang et al[3] 0.82. The mean birth weight and gestational age was comparable with several studies.[1,5] Most of our babies had non-specific clinical manifestation. Therefore, high index of suspicion for candidiasis in such ill neonates especially when clinical sepsis with thrombocytopenia sustained more than 3 days, fail to respond to broad spectrum antibiotics. Similar findings were reported by Benjamin et al.[4] Adverse effects, such as nephrotoxicity and electrolyte imbalance can be diminished or reversed by decreasing the dose of amphotericin B to 0.75mg/kg/day and careful fluid management. Present study confirms the relative rarity of toxicity of amphotericin B in neonatal period.

It is concluded that systemic candidiasis is relatively common in this part of the world and empiric use of third generation cephalosporins and other board spectrum antibiotics are associated with candidiasis in very low birth infants. This study also suggests that amphotericin B is a reasonably safe choice for empiric therapy in a newborn with birth weight of <1500g, and who is deteriorating despite usual empiric antibacterial treatment.

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Neutropenia

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There is an increasing observation of clinical neutropenia in healthy Omani individual. According to the international range for neutrophil counts (2.5 - 7.5 x 10^9/L), more than 60% of Omani are neutropenic. In Oman, a different range for the neutrophil count is being used. Although this range is lower than the international range, 36% of individuals still have a lower neutrophil counts. In this study it appears that a lower range (0.5 - 4.4 10^9/L) is required to cover 95% of the normal Omani individual. Neutrophils are important in providing immunity against bacterial and fungal infections. They are also important in the removal of exogenous and endogenous debris. The neutrophil count ranges between 2.5 and 7.5 x 10^9/L. A circulating neutrophils count below 1.5 x 10^9/L is usually abnormal, although lower counts may be normal for certain non-white genetic groups, in particular Blacks and Arabs. In these healthy individuals, there are relatively more cells in the marginating pool, and they are able to mount a normal response to infection. Patients with neutrophil counts less than 0.5 x 10^9/L for whatever reason are at increased risk of infection.[1-5] In Oman, the range for neutrophil is 2.0 - 7.5 x 10^9/L, which is lower than the international level. Despite this lower value, some Omani still have even a lower values. According to these ranges, considerable numbers of healthy Omani individuals are considered as neutropenic.

The aims of this study are to find out the percentage of Omani healthy individuals considered as having neutropenia using the international reference range; to find out percentage of Omani healthy individuals considered as having neutropenia using the Oman reference range and to recalculate the reference range that will cover 95% of Omani population.

The study sample was selected from healthy blood donors. The following donors were excluded: individual with history of recent infection or on antibiotics course, individual with allergy or on anti-allergic medications, had a recent immunization, any bleeding tendency, any individual who had surgery or delivered over the last 6 months and those who received recent blood or blood product transfusion. In addition to these, any donors found to have abnormality in hemoglobin level, platelet, or total white blood cell

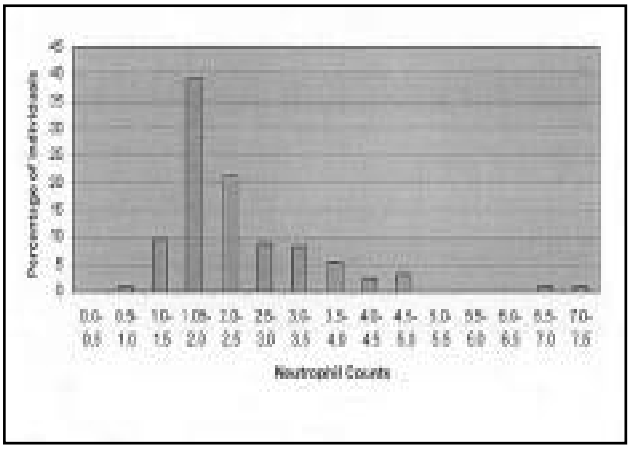

Figure 1 - Different levels of neutrophil counts.

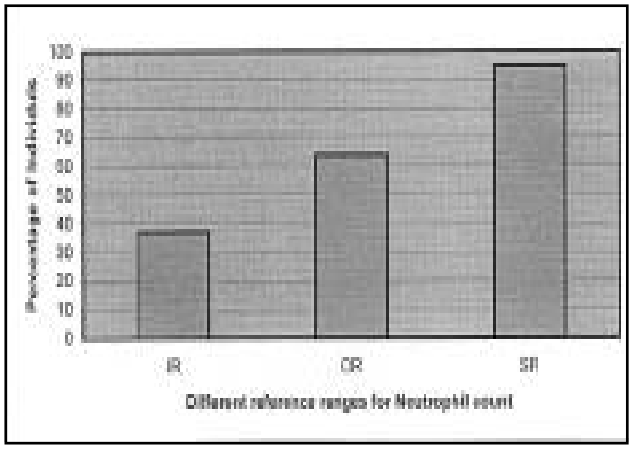

Figure 2 - Comparisson between international (IR), Oman (OR) and this study reference ranges (SR).

counts are excluded. The blood analysis was carried out using Cell - Dyn 3500R automated analyzer.

Total of 126 donors was included in this study. Blood samples were analyzed and found that a) 37% of Omani population are within the international ranges for neutrophil counts (2.5 - 7.5 x 10^9/L). Sixty-three individuals are neutropenic (**Figures 1 & 2**). b) Sixty-four percent of Omani population is within the currently used Omani ranges for neutraphi1s counts (2.0 - 7.5 x 10^9/L. Thirty-six individuals are neutropenic (**Figures 1 & 2**). c) Ninety-five percent of Omani population are having neutrophil ranges between (0.5 and 4.4 x 10^9/L (**Figures 1 & 2**).

Apparently there are some blood donors who fit within the international ranges for neutrophils. That means more than 60% of Omani population are having abnormal neutrophil count. But it covers only 64% of normal Omani population, in other words more than 30% of normal Omani individuals are regarded as having abnormal level of neutrophils. At least in this study, none of these ranges cover or reach 95% of normal population. Statistical analysis of these data showed that a range between 0.5 and 4.4 x 10^9/L of neutrophil is more convenient and covers 95% of the normal population. This range needs further evaluation. To be representative for Omani population, it needs a large study sample to cover the whole Sultanate. Obviously, the current range needs to be change for the reason it is limited to approximately 64% of the population.

In this study, there is a considered number of Omani individuals having neutropenia according to the international and Omani reference ranges. The majority of Omani (95%) are having a neutrophil count between 0.5 - 4.4 x 10^9/L.

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Typhoid fever due to multiresistant *Salmonella enterica serovar typhi* having reduced susceptibility to ciprofloxacin and nalidixic acid resistance

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Salmonella typhi (*S.typhi*), the etiological agent of typhoid fever is pathogenic only to humans. It is endemic in developing countries, where around 33 million cases occur every year, leading to high morbidity and mortality. Early effective antimicrobial therapy of typhoid fever, without waiting for the blood culture results is necessary for the prevention of complications and to avoid mortality. Chloramphenicol remained the drug of choice for the treatment of typhoid fever until 1972, when extensive outbreaks of chloramphenicol resistant *S.typhi* occurred in India and Mexico.[1] Until the middle of 1980 to 1990, ampicillin and trimethoprim-sulfamethoxazole were the alternative drugs for treatment of typhoid fever and resistance to these drugs appeared along with resistance to chloramphenicol in the strains causing outbreaks in Indian subcontinent and Vietnam.[2] Fluoroquinolones have become the first line drugs for treatment of multi drug resistant typhoid fever for their proven efficacy. Subsequently resistance to these drugs was observed in strains of *S.typhi*.[3] The nalidixic acid resistant *S.typhi* strains with reduced susceptibility to ciprofloxacin is an emerging problem in the developing countries. Limited reports are available from the Indian subcontinent and some of the Asian countries where such strains were sensitive to ciprofloxacin by the disc diffusion test but clinically there was treatment failure, leading to complications and longer period of hospitalization.[4-5] This study presents a report of a self-limiting outbreak of typhoid fever due to multi drug resistant strains of *S.typhi* with nalidixic acid resistance and reduced susceptibility to ciprofloxacin, from the Al-Hasa region of the Kingdom of Saudi Arabia (KSA).

The study was conducted at a 500-bed, King Fahad Hospital and Tertiary Care Center, Al-Hofuf, an Ancient City and oasis of the Eastern Province of KSA, with native population of approximately 1 million. Indoor admissions in the medical wards during September 2003 with clinical suspicion based on the symptoms and signs of typhoid fever and confirmed through blood culture were enrolled for the study. A detailed history, findings on clinical examination, the progress and a close follow-up was recorded for each patient. Blood samples were collected in Bactec blood culture bottles and processed in Bactec 9240 blood culture system (Becton Dickinson Company, United States of America (USA)). *Salmonella typhi* strains were biochemically identified by API20E identification system (Bio Merieux SA France) and serotyped using Salmonella O9, Vi, d-H antisera (Difco Laboratories, USA). Antibiotic susceptibility was performed by disc diffusion technique according to the criteria of the National Committee for Clinical Laboratory Standards. Following concentrations of the antibiotics µg/disc (Becton Dickinson Company, USA) was used for the susceptibility test, ampicillin-25, amoxicillin/clavulanic acid 20/10, cefoxitin-30, cephalothin-30, cefotaxime-30, ceftriaxone-30, cefepime-30, chloramphenicol-30, trimethoprim/sulfamethoxazole 1.25/23.75, tetracycline-30, streptomycim-10, gentamicin-10, amikacin-30, imipenem-10, aztreonam-30, piperacillin-100, nalidixic acid-30 and ciprofloxacin-5. Minimum inhibitory concentration (MIC) to nalidixic acid and ciprofloxacin was performed by agar dilution method.

The study involved 12 patients admitted within a short span of 15 days with clinical symptoms of typhoid fever and confirmed by positive blood culture for *S.typhi*. All these patients were native from the Al-Hasa region and none of them were expatriates. Of these, 10 patients were directly admitted to this tertiary care center and 2 patients were admitted to the peripheral hospital and subsequently transferred to this center for treatment. Blood culture of these 2 patients were positive in the peripheral hospitals. All these patients were admitted with the history of fever and dry cough of 5-10 days duration. Mean age of the patients was 24.5 years (range 5-46 years), 5 of them were male and 7 female. Diarrhea, abdominal pain and fever were the main presenting symptoms in 8 patients. Laboratory investigations revealed mean white blood cell (WBC) count of $4.3x10^3$/µl (range 3.1-7.6), platelet count mean $131x10^3$/µl (range 57-189), AST mean 180 U/L (range 32-376) and ALT mean 116 U/L (range 40-330). *Salmonella typhi* strains isolated from the blood of all these patients were resistant to ampicillin, amoxicillin/clavulanic acid, chloramphenicol, trimethoprim/sulfamethoxazole, tetracycline, streptomycin, piperacillin and nalidixic acid. While all were sensitive by disc diffusion test to ciprofloxacin, cefotaxime, ceftriaxone, cefepime,

cefoxitin, cephalothin, gentamicin, amikacin, aztreonam, imipenem. Minimum inhibitory concentration of all the strains to nalidixic acid was >256 µg/ml and all the strains had reduced susceptibility to ciprofloxacin (MIC 0.20-0.25 µg/ml). Each patient was treated with ceftriaxone 80mg/kg body weight for 7 days. All became afebrile after average of 4.8 days of ceftriaxone therapy. Mean period of hospital stay of these patients was 16.5 days (**Table 1**). Patients who remained afebrile for 6 consecutive days following ceftriaxone therapy and had negative stool culture for *S.typhi* were discharged from the hospital. On the other hand, 2 patients (aged 13 and 15 years) transferred from the peripheral hospital who received initial ciprofloxacin therapy for 6 days with out any clinical improvement also became afebrile 4 days following commencement of ceftriaxone therapy. Only 6 patients had 4 folds rise in antibody titer by Widal test (Initial titer of 1:80 increased to 1:320 in 2 patients and from 1:40 to 1:160 in 4 patients). The endemicity of typhoid fever and appearance of multi drug resistance in *S.typhi* to the cost effective drugs such as chloramphenicol, trimethoprim-sulfamethoxazole has added to the burden of already overstretched health budget of developing countries. These multi resistant strains are responsible for massive outbreaks in the countries with scarce resources. An outbreak of typhoid fever with such strains in Tajikistan, in 1997 affected more than 8000 people causing 150 deaths.[6] The potential spread of such strains of *S.typhi* to other areas of the world through international travel is of serious concern. In the United Kingdom (UK) multi drug resistant strains of *S.typhi* with nalidixic acid resistance and reduced susceptibility to ciprofloxacin, increased from 3% in 1995 and 23% in 1999. Most of the patients from whom such strains were isolated had recently traveled to Indian subcontinent.[5] In the USA, most of the identified ciprofloxacin resistant *Salmonella* infections were acquired from outside. In the present study none of the affected patients traveled to any of the country which is endemic for multi drug resistant and nalidixic acid resistant *S.typhi* during last one year. Drinking water in this region is safe and is procured by the consumer from the reverse osmosis units. These units use chlorinated under ground water for desalination by the reverse osmosis process. The typhoid cases were distributed in the wider urban and rural area of the region; the drinking water was not procured from one particular source. High quality hygiene standards are maintained by the restaurants and food stores. All the food handlers are regularly screened for carriage of *salmonella*. There was no history of taking food or eatables from one particular source among these patients and there was no other common factor among these patients admitted with typhoid fever. All the patients were native Saudis and belonged to different areas of this region (both rural and urban) and there was no concentration of cases to specific area. There are many people from Indian subcontinent and Far East (where such strains are prevalent) working in this region, the possibility of introduction of this *S.typhi* strain through

Table 1 - Patient characteristics admitted with typhoid fever.

Sex	age	Duration of stay (days)	Afebrile after CRO (days)	Diarrhea	WBC count x103/µl	Platelet count x103/µl	AST U/L	ALT U/L	Widal test
F	28	20	10	+	3.7	187	162	134	+
M	16	18	5	-	2.8	156	81	122	-
M	28	10	5	-	4.4	143	51	77	-
F	30	20	4	+	3.5	128	62	78	+
M	32	20	5	+	3.8	112	122	130	+
M	22	22	4	+	4.2	128	82	110	-
M	37	7	3	+	3.2	90	376	330	+
F	5	21	4	+	5.6	57	217	78	-
F	13	20	4	+	7.6	74	32	34	-
F	23	13	6	-	6.2	158	32	40	-
F	15	10	4	-	3.1	139	172	115	+
F	46	17	4	+	4.2	189	61	60	+
Mean	24.5	16.5	4.8	8	4.3	130	118	109	6

F - female, M - male, CRO - ceftriaxone, WBC - white blood cell, AST - alanine aminotransferase, ALT - antilymphocyte serum

asymptomatic carrier in this region cannot be completely ruled out. However distribution of the cases to a wider area does not support this possibility. During last 4 years, no expatriate patient having typhoid fever with multi drug resistant strain was admitted to this hospital and such multi drug resistant *S.typhi* strains with resistance to nalidixic acid and reduced susceptibility to ciprofloxacin were isolated for the first time in this region. All the affected patients were native, possibly this was an autochthonous infection leading to a short self limiting outbreak, the source of which could not be traced. Appearance of fluroquinolone resistance in non typhoidal *salmonella* in the UK and the USA has been linked to use of fluoroquinolones in the poultry and animal feed. *Salmonella typhi* is pathogenic to human only, the source of selective pressure leading to development of fluoroquinolone resistance is not certain, possibly the widespread use of quinolone in treatment of diarrheal disease could be a source of selective pressure.

In the present study apart from dry cough and fever, 8 patients had diarrhea, this was an unusual finding, as constipation has been commonly described in typhoid fever. The majority of the patients had thrombocytopenia, leucopenia and altered liver enzymes, which improved with ceftriaxone therapy. Most of the patients became afebrile after 4.8 days of ceftriaxone therapy and none of them had treatment failure or relapse, where as fever clearance time of 6.1 days with ceftriaxone therapy has been reported.[7,8] Ceftriaxone therapy for the treatment of typhoid fever with multi resistant nalidixic acid resistant strains of *S.typhi* appears to be safe and an effective alternative. Two patients who had treatment failure with the ciprofloxacin therapy, responded to ceftriaxone therapy and both of them became afebrile 4 days after treatment. Widal test had 4 folds rise in titer only in 6 patients indicating the poor reliability of the test. Incidentally this is the only cost effective diagnostic test available in the developing countries, which needs to be replaced by a more sensitive test.

Resistance to quinolone is mediated by point mutation in the quinolone resistant determining region of gyrA gene at position 83 of the deoxyribonucleic acid gyrase enzyme. In the present study, all the nalidixic acid resistant strains of *S.typhi* had reduced susceptibility to ciprofloxacin (MIC 0.20-0.25 µg/ml) although they were sensitive (zone diameter >21 mm) to this drug by disc diffusion test. The routine disc diffusion test with ciprofloxacin cannot detect the reduced susceptibility and can lead to treatment failure if typhoid fever due to *S.typhi* strain having reduced susceptibility is treated with this drug. Sensitivity to nalidixic acid should be carried out routinely for the *S.typhi* strains and nalidixic acid resistance should be taken as an indicator of reduced susceptibility to ciprofloxacin. As first line of treatment of typhoid fever ciprofloxacin should be avoided to prevent the treatment failure, in the areas where nalidixic acid resistant strains of *S.typhi* are prevalent or the patient has recently visited the country known to have the prevalence of such strains. Ceftriaxone therapy for 7 days appears to be an effective alternative for typhoid fever due to multi drug resistant *S.typhi* with nalidixic acid resistance and reduced susceptibility to ciprofloxacin.

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Treatment of cutaneous leishmaniasis by intralesional metronidazole

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Cutaneous leishmaniasis (CL) is a specific skin infection caused by *Leishmania* parasite and is endemic in tropical and subtropical areas.[1] Optimal treatment for the old world CL is not well established and there have been few controlled clinical trials of different therapeutic modalities of this condition. The recommendation of the use of intralesionally administered pentavalent antimony compounds by the World Health Organization,[2] as well as other substances such as zinc sulfate and hypertonic saline are the mainstay local therapy of CL. However, with these modalities there is a failure rate and always there is a need for an alternative treatment.[3] One ß-hydroxyethyl, 2 methyl and 5 nitroimidazole, now called metronidazole, was found to have particularly high activity in vitro and in vivo against *trichomonas vaginalis* and *entamoeba histolytica.*[4] Oral metronidazole had been used in the treatment of CL but the results were unsatsifactory.[5-7] The current trial was therefore designed to evaluate local infiltration of the drug in healing CL lesions. Patients with single or multiple typical lesions of CL presenting at the Department of Dermatology, College of Medicine, University of Baghdad, Baghdad, Iraq, fulfilled the following criteria, 1. confirmed cases of CL by smear and culture or in combination, 2. acute CL with history of 12 weeks or less. This criterion was applied to exclude any possibility of self-healing of lesions during the period of follow-up, 3. cases of re-infection were excluded. For each patient admitted to the study, a detailed history was taken including name, age sex and residence. Details of the lesions were recorded, including the site and size of induration, duration and type of lesion and whether it was wet or dry. Associated features such as lymphatic involvement or satellite lesions were noted. To confirm the clinical diagnosis, parasitological confirmation was sought for all cases. Thus, for a case to be admitted to the study, demonstration of the *Leishmania* organism was prerequisite. The following was conducted either alone or in combination, 1. Smear, using a dental broach, from more than one site from the lesion, smeared on a clean glass slide and stained with *Leishmania*'s stain. It was examined microscopically for amastigotes inside or outside macrophages. 2. Culture, material obtained from the lesion by dental broach was cultured on either semisolid or biphasic medium (Novy MacNeal Nicolle,) . The culture was incubated at 26°C and examined after 5 days and subsequently at close intervals to demonstrate promastigotes of *Leishmania*. A negative culture was sub passaged at 10 days interval and not discarded until after 30 days.

Seventy-three patients were included in this study. Their ages ranged from 1-66 years. Patients were divided into 3 groups, metronidazole 5% group (27 patients), CL lesions were infiltrated with 5% metronidazole solution intralesionally; metronidazole 0.5% group (31 patients), patients were injected intralesionally with 0.5% metronidazole solution. These 2 solutions were prepared by dissolving 5g and 0.5g of metronidazole powder (obtained from Samara Drugs Industry, Iraq) in 100ml of bidistilled deionized water. The solutions were then sterilized in an autoclave at 121°C for 20 minutes in suitable screw capped bottles with rubber caps to allow for sterile injection. Controls (15 patients), a few lesions on unimportant and unexposed parts of the body were left as controls after obtaining the consent of the patients. The lesion was infiltrated with the drug solution, thoroughly using disposable tuberculin syringe until complete blanching was achieved. The amount of solution required was 0.1-4ml and occasionally more, depending on the size of the lesion. No local anesthesia was added to any solution. Patients were seen at 10-15 day intervals after injection. At each visit, the lesions were re-examined and the response graded using the following system, slight (decreased erythema and edema of the lesion), mild (reduction in the size of the lesion up to 30%), moderate (reduction in the size of the lesion of more than 30% but less than 60%), marked (reduction in the size of the lesion by 60% or more and parasite not detected in the lesion by smear or culture or in combination) and total clearance of the lesion with parasites not detected in the affected area by smear or culture or in combination. Both marked improvement and total clearance were considered as a cure. In cases where there was slight or mild improvement, another injection was given. At the end of the 6-week follow-up, the lesions were reassessed and parasitological proof of cure or otherwise were obtained by smear or culture or in combination. In the 5% group, 56 lesions were treated with this concentration, 51 lesions were of the dry type while 5 lesions were of the wet one. Forty-nine lesions showed complete clearance (87%), while 7 lesions showed slight improvement. Twenty-one lesions showed marked improvement or total clearance within 10 days by a single injection. However, 22 lesions showed total clearance by 2 injections while

6 lesions required 3 injections to show complete clearance. The patients during the intralesional infiltration of the drug noticed slight pain. After healing, scarring was minimal or absent, but hyperpigmentation was noted in all patients which later disappeared. In the 0.5% group, 65 lesions were treated, 55 lesions of the dry type and 10 lesion of the wet one. Marked improvement or complete clearance was observed in 55 lesions (85%). Only 2 patients showed total clearance after a single injection. However, 24 lesions showed total clearance by 2 injections while 29 lesions required 3 injections to show complete clearance. Regarding controls, 33 lesions were included in this group and were followed-up for 45 days. After the end of follow-up, there was minimal reduction in the size of lesions. Moreover, some lesions especially on the lower limb showed signs of infection. Parasites could be still detected in smear and culture or both at the end of the follow-up period.

In the design of this trial, only acute lesions, which had been present for 12 weeks or less, were included, and the follow up period was 6 weeks. This gave a total of 18 weeks, which is less than the healing time reported for lesions caused by both *L. major* (9 months or more) and *L. tropica* (one year or more).[8] In addition, a number of lesions were left untreated and followed-up as controls to demonstrate that no self healing took place within the follow-up period. It can therefore be assessed that the healing which occurred after drug administration in this trial is due to the effect of the drug and not due to self-healing lesions. The results of this trial show that intralesional infiltration with metronidazole gives high cure rate using low concentration (0.5%) or high concentration (5%). However, with higher concentration, healing occurs faster and requires less frequent injections. Metronidazole had been reported as an effective treatment of CL when the drug is orally administered. However, the cure rate is not high and there is the controversy regarding its use.[5,6] This is probably due to the low concentration of this antiprotozoal drug at lesional site following oral route of administration. In case of intralesional infiltration the high cure rate is owed to high concentration of the active ingredient at tissue level.

On the basis of this trial, the use of 5% metronidazole solution, injected intralesionally, in the treatment of CL is highly recommended. The treatment is safe with no serious side effects, gives high cure rates and the final cosmetic effect is very good. Local injections for the treatment of CL are advised when there are few lesions, to avoid systemic side effects, to increase the concentration of drug at the lesional site and to increase its effectiveness and reduce the cost of therapy.

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Comparison of intravenous aminoglycoside therapy with switch therapy to cefixime in urinary tract infections

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Urinary tract infections (UTI) cause acute morbidity and may result in severe problems, including hypertension and reduced renal function. Diagnosis of UTI is extremely important as prompt treatment could prevent damage. As intravenous (IV) antibiotic therapy is associated with side effects, toxicity, high cost, and long hospitalization period in treatment of UTIs, switch therapy (IV-to-oral antibiotic) is considered to reduce above-mentioned harms. In the present study, we compared the efficacy of IV aminoglycoside

therapy with IV ceftriaxone plus switch therapy to cefixime in children with UTIs.

This prospective randomized clinical study was conducted from February to June 2003. Written consent was obtained from all children's parents. Children aged ≤10-years with UTI were eligible for the study if they required initial parenteral antimicrobial therapy and if the infection was caused by a pathogen susceptible to the study drugs. Criteria for acute pyelonephritis included fever, flank pain or costovertebral angle tenderness, pyuria (≥10 white blood cells), and positive urine culture [10^5 colony forming unit (CFU) of a uropathogen/ml] within 48 hours (h) of enrollment. Patients with any of the following were excluded from the study: history of serious allergy to study therapy, complete obstruction of the urinary tract, perinephric or intrarenal abscess, any rapidly progressive disease, immune-compromising illness or therapy, the need for concomitant antimicrobials, acute hepatic failure, requirement for peritoneal dialysis or hemodialysis, treatment with a systemic antimicrobial agent for ≥24h within 72h prior to the baseline urine culture, creatinine clearance of <30 ml/min, aspartate aminotransferase or alanine aminotransferase levels of >6 times the upper limit of normal (ULN), bilirubin or alkaline phosphatase levels of >3 times the ULN, absolute neutrophil count of ≤1,000 per µl, platelet concentration of <75,000 per µl, hematocrit level of <25%, or coagulation tests of >1.5 times the ULN. Patients were enrolled and divided in 2 groups, A and B. Children in group A (n=30) were treated with IV amikacin (15mg/kg daily) or gentamicin (3mg/kg daily) with ampicillin (100mg/kg daily) for 7-10 days. Patients in group B (n=24) were treated with IV ceftriaxone (50mg/kg daily) for the first 2 days and then switched to cefixime (8mg/kg daily) orally for 8 days. After at least 2 days of hospital or clinic-based infusion therapy, study therapy could be completed in the hospital or at clinic or home. Consistent with current pyelonephritis treatment guidelines,[1] at the investigator's discretion and after 2-3 days of IV therapy, patients could be switched to oral cefixime (8mg/kg daily) if they were afebrile; nausea and vomiting had resolved; signs, symptoms, and leukocytosis had improved; and a urine culture was obtained. Other oral agents were permitted if the patient could not tolerate cefixime or if the causal pathogen was resistant. The suggested total duration of IV plus optional oral therapy was 10-14 days. Patients were evaluated within 24h of enrollment and daily thereafter while on parenteral study therapy. The clinical response was measured on day 3-5 of parenteral therapy, at the discontinuation of IV therapy, 5-9 days post therapy, and 4-6 weeks post therapy. Urine and blood culture were performed at the baseline. All isolates were identified at the site laboratory, and pathogens were tested for in vitro susceptibility to different antibiotics, following the guidelines of the National Committee for Clinical Laboratory Standards.[2] Microbiologic efficacy was assessed at each time point by quantitative urine culture. After at least 48h of study IV therapy, failure was defined as a urine culture with a 10^4 CFU/ml concentration of any uropathogen present in the admission culture at a concentration of 10^5 CFU/ml.

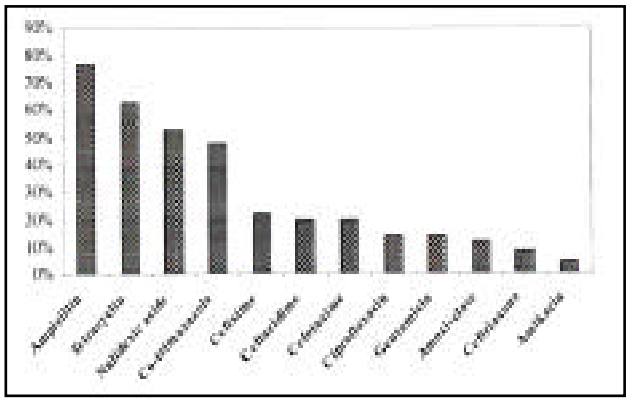

Figure 1 - Antimicrobial resistance pattern.

Baseline demographics and disease characteristics of the 2 treatment groups in the randomized populations were generally similar. *Escherichia coli* and *Klebsiella spp* were the most common microorganisms isolated from the patients. **Figure 1** shows antibacterial resistant pattern in this study. Rate of response (clinically and microbiologically) to IV aminoglycoside therapy in patients of group A was 80% (24/30). Children of group B, who received ceftriaxone and switched to cefixime, had 88% (21/24) response rate. However, there was no statistical significant difference between the rate of response in both groups (p=0.82). Cefixime is a third-generation oral cephalosporin that is highly active against a broad range of gram-negative and some gram-positive aerobic bacteria.[3] In UTIs, it is at least as effective as other usual treatments, and has a low rate of side effect.[3] Several clinical studies have been performed on cefixime in UTIs both in adults and children.[3] Different studies have recently shown that an early switch from parenteral antimicrobials to an oral substitute, provides an effective means of treating different infection diseases in pediatric patients.[4] Also, on the basis of the literature data, cefixime could be indicated in the treatment of UTIs in children either as monotherapy or as switch therapy.[5] In this randomized clinical study, the efficacy and safety of ceftriaxone with a switch to

cefixime were compared with those of IV aminoglycoside therapy for the empirical treatment of UTI, judged by the investigator to require initial therapy with a parenteral antimicrobial agent. The study design was consistent with standard clinical practice. After 2-3 full days of parenteral study therapy, investigators had the option to switch to oral cefixime if the patient had clinically improved. Results of this study show that ceftriaxone with switch to cefixime, 8 mg/kg once a day, was highly effective and equivalent to treatment with IV aminoglycoside therapy. Approximately 88% of patients in treatment group B (treated with switch therapy) had a favorable clinical/microbiologic response assessment at the 7 days post therapy. Although rate of response (clinically and microbiologically) to children of group B, who received ceftriaxone with switch to cefixime, was higher than children treated with IV aminoglycoside (88 versus 80%), there was no statistical significant difference between the rate of response in 2 groups (p=0.82). Although we did not measure psychological, aspects of mother's support during oral therapy at home compared to IV therapy in the hospital, we suggest that oral therapy at home associated with a mother's psychological support could be considered a positive aspect of switch therapy. Switch therapy with cefixime in children with UTIs increases effectiveness and convenience. Switch therapy shortens duration of hospitalization, and decreases costs and risk of nosocomial infections. Cefixime could also be considered as switch therapy in children with UTIs.

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The services provided for combined oral contraceptive users in health care centers, Kerman, Iran

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Combined oral contraceptives (OC) are the most effective reversible form of contraception available. They have also several health benefits on genital system, breast, bones, and others.[1] Some misconceptions regarding the safety of these compounds and also insufficient knowledge regarding their beneficial effects cause irregular use or stopping and consequently the occurrence of unwanted pregnancies. Therefore, physicians and other health care providers should consult their patients regarding safety of these compounds and urge them to take their pills regularly. As the main reason for stopping oral contraceptives is fear of their probable side effects, regular visit and consultation may help the continuity of using OC.[2] Mentioning of health benefits in each visit is necessary. Moreover, taking a complete history, blood pressure and weight measurements, breast, liver and pelvic physical examination and doing Pap smear for early diagnosis of probable problems are necessary. In this descriptive cross-sectional study, the rate of services provided for the combined OC users in the health care centers of Kerman City was evaluated. Sample size was determined in 600 women. Subjects were selected randomly from 33 health care centers. Receiving of OC pills from health centers at least for one year prior to the study was criteria inclusion. Subjects were questioned regarding the control of blood pressure and weight measuring, the examination of breast, liver and pelvis or recommendation for that and Pap smear carried out during the recent year. It should be mentioned that in regard to the physical examination of breast, liver and pelvis, in centers having educated midwives the rate of performed examinations and in centers lacking midwives the rate of recommendations were considered. Data were collected by interviewing subjects and were analyzed by descriptive statistical methods. In order to study the services provided for the combined OC users, 6 factors based on the health center facilities were considered. Blood pressure measuring had been carried out in 500 subjects (83.3%), weight measuring in 506 (84.6%), examination of breasts or recommendation to carry out in 322 (53.7%), pelvis in 120 (20%), liver in 6 (1%) and finally Pap smear that is one of the main responsibilities of these centers and had been performed in only 246 ones

(41%). Oral contraceptives are one of the most effective methods of contraception used around the world. Contraceptive use data from 1965-1995 shows that OC continue to be the method chosen consistently by more than one-quarter of women contraceptors. Probably even more women would use the pill if they had more accurate information regarding the higher failure rate with barrier method, if misconceptions regarding OC safety put to rest and if greater awareness of the noncontraceptive health benefits of OC could be achieved. Increased education and awareness of women as well as their health care providers has the potential to positively affect future contraceptive use.[3] In addition to clinical benefits of the OC, which outweigh the risks and adverse effects, these compounds cause some metabolic changes in body such as change in lipids, lipoproteins and carbohydrate metabolisms. In healthy women with no high risk factor, these metabolic changes are trivial and have no risk. Oral contraceptives may increase the risk of breast, cervix and liver cancer. They can also have some cardiovascular effects such as arterial thrombosis, cerebral stroke, hypertension and myocardial infarction. Cardiac and cerebral diseases that are the most serious effects are observed mostly in smoking women aged more than 35. Risk of mortality from OC is very low in non-smoking women, younger than 35 who have no systemic disease and it is definitely less than the risk of mortality due to pregnancy.[1] There is little evidence to suggest any persistent adverse effect 10 or more years after use of OC and mortality in past users is similar to that nonusers. In order to increase the safety of OC at least yearly follow-up is necessary. A sufficient follow up depends on the knowledge of both users and health care providers regarding the side effects of these compounds. Brayden and Fletcher[4] showed that knowledge concerning the health risks and benefits of OC use is a contributor to OC compliance and the number of correct responses to questionnaire increased with academic year, indicating that younger women were less knowledgeable regarding OC. The results of this study indicate that despite increased efforts to educate women, knowledge of OC remains a major problem even in a sample of women with relatively high socio-economic status. Poor knowledge regarding the benefits and side effects of OC is the main contributing factor to pill failures and to approximately 20% unwanted pregnancies.[5] Knowledge in contraception is important for avoiding pregnancy and yet very few know the basic rules for it. Health professionals should provide leaflets and ask questions on knowledge of contraception at consultations for repeat prescriptions of the contraceptive pills, as education seems to improve knowledge of contraception even after one consultation. Therefore, The ideal time for consulting users and detecting the probable side effects is at the time of users referring for follow up and receiving their pills. Preparation of educational leaflets containing the health benefits, side effects and schedule of pill taking can be very useful.[5] In developing countries, a lack of appropriate family planning information and services is more of an immediate obstacle to increased use of contraceptives than is low demand. Based on the results of the present study follow up of OC users in Kerman City is not good. Training of health care providers and OC users in relation to this effective contraceptive method will have useful potential effects and consequently will lead to the better OC compliance and use of these compounds consistently.

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Safety of vaginal breech delivery

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Breeches are more common at the end of the second trimester of pregnancy than at near term, factors other than gestational age that appear to predispose on breech presentation include uterine relaxation with multiparity, multiple fetuses, hydramnios, oligohydramnios, hydrocephalus, anencephalus, previous breech delivery, uterine anomalies and tumors in the pelvis. Implantation of the placenta in either cornuel-fundal region of the uterus has been suspected to be a predisposing factor to breech presentation.[1] In Europe, in 1970, 11.6% of breech presentation were delivered by cesarean section (CS) and this has increased to 79.1% by 1985 as the obstetrician recommended CS for breech delivery.[2] In Salmaniya Medical Complex (SMC), Manama, Bahrain, there were 13,806 deliveries in the period of January 1998 to January 2001. We conducted a retrospective study to obtain the incidence of breech presentation, to determine weather a set of clinical factors could predict successful vaginal delivery in breech presentation and to compare the maternal and neonatal outcome according to the mode of delivery.

This is a retrospective study performed on 203 singleton pregnancies with breech presentation at term >37 weeks gestation delivered. The following cases were excluded: preterm breech, multiple pregnancy, intra-uterine death, placenta previa, and fetuses with major congenital anomalies. It was thought that these cases might affect the mode of delivery and its success. From 203 women, only 166 women were allowed to attempt the trial of vaginal birth. In these women, the only factor to determine the possibility of vaginal delivery was normal progress during the first stage without secondary arrest or signs of fetal distress. The remained 47 women advised elective SC in view of anticipated difficulties as fetopelvic disproportion, previous CS, bad obstetric history, macrosomia, severe oligo or polyhydramnios and severe intrauterine growth retardation. The women wishes concerning mode of labor also played a very important part in making decision. The maternal variables included maternal age, which was subdivided into <35 years and ≥35 years. The parity was subdivided into nullipara, multipara and grand multipara of more than 5. The maternal and neonatal early morbidity and mortality were submitted and analyzed in this study. The maternal outcomes were third and fourth degree perinatal tear, postpartum hemorrhage, wound infection, wound rupture, puerperal pyrexia, urinary tract infection and thromboembolic disease. The neonatal outcomes were as follow, intracranial injury, wide spread bruising, intrapartum stillbirth, neonatal death, low apgar scores of ≤7 at 5 minutes requires for neonatal ventilation, jaundice, convulsion and admission to special care baby unit (SCBU). The outcomes were studied during the early first week of postpartum period. During the study period, the total number of deliveries in SMC were 13,806, whereas 592 were breech delivery giving the incidence of 4.3%. The singletons breech deliveries at term were 203, which have been studied, 166 were given a trial of vaginal breech delivery, while 37 were planned to deliver by elective CS. Successful vaginal delivery was achieved in 120 cases (72.3%, were 46 cases (27.7%) failed to deliver vaginally and required emergency CS. The effect of maternal characters in the form of maternal age and parity had been studied, the mothers who were above 35 years had less incidence of successful vaginal delivery (6.9%) than maternal age below 35 years old (7.5%), however this differences were statistically not significant. Maternal parity was studied and show higher incidence of successful vaginal delivery among grand multipara (82%) than nullipara (52%), this relation found to be statistically significant, x^2=14.755, p=0.0006250, degree of freedom=2.

The maternal and neonatal outcomes were studied in relation to mode of delivery, the incidence of neonatal morbidity was higher among emergency CS (8.7%) than successful trial of vaginal delivery (6.8%) and elective CS group.[5,4] There was no neonatal death and the majority of neonatal complication occurred in emergency CS group (8.7%) than elective CS group (5.4%) while vaginal delivery group shows 6.8% of neonatal morbidity. Most of the cases where admitted to SCBU for observation, which did not necessitate longer stay (more than 4 days). There were only one case with neurological deficit in the forms of Erbs palsy, all neonatal complication resolved by the time of discharge, there were no maternal or neonatal mortality. The maternal complication found to be higher among elective CS group (0.8%) as compared to emergency CS (6.5%) while the least in vaginal delivery group (1.6%) only. The maternal complication was mainly due to pyrexia with infection, which required longer hospital stay and antibiotics.

There have been always debates in the method of delivering baby in breech presentation. A review of literature shows vaginal delivery for breech to be safe in well-selected cases.[3,4] While the critical review of literature concluded that there may be an increase in neonatal morbidity and mortality in

planned vaginal delivery group.[5] A comparative study was carried out by Gifford et al[6] and found a successful vaginal delivery in 74% of patients. This was comparative to our study, where the successful vaginal delivery rate was 72.3%. Our observation shows that the increase in maternal age might have adverse influence in successful vaginal breech delivery, however the association in our study failed to reach a statistical significance. Many obstetrician consider parity as an important criterion for selection of parturient to deliver vaginally, in our study, grand multipara (p>0.5) had a significant higher successful rate than nullipara group. The increase in maternal parity was a positive influence in successful vaginal delivery. This could be explained by the fact that, the history of previous successful vaginal delivery might affect the obstetrician decision regarding the choice of delivery. The pelvis of multipara has been already tested by the previous vaginal deliveries. Kayam et al[7] his study did not show any increase in maternal or neonatal morbidity rate attributable to vaginal delivery. Iron et al[8] found significantly lower maternal complication in planned vaginal delivery than elective CS and there was no differences in neonatal morbidity between the planned vaginal delivery and the elective CS group. Thropo-Beesteon et al,[4] had a large retrospective study on 3447 singleton breech term fetus and concluded that good neonatal outcome with elective CS group than vaginal delivery. This study corresponds to our result on neonatal morbidity; it can be explained that the important issue to be consider when planning vaginal delivery includes careful selection of patient, obstetrical experience and judgment of intrapartum attendant. Although the recommendation now to do elective CS for flexed or complete breech singleton. We suggest that a trial of vaginal breech delivery is more likely to be successful if both mother and baby are of normal proportion with presentation either frank or complete and clinically adequate pelvis with no fetopelvic disproportion, the presence of an experience team of obstetrician, anesthetist and pediatrician in labor room may be more important than the planned mode of delivery.

A trial of vaginal delivery in carefully selected patients with breech presentation at term might be safe procedure that was successfully completed in almost 72.3% of cases in our experience. In our retrospective study we found that, low maternal parity and increase maternal age have a negative influence on maternal progress of labor.

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Arteriovenous fistulas for hemodialysis. *Patency rates and complications*

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In the last 20 years, a rapid increase in the number of hemodialysis patients is seen.[1] This situation was constituted by the scientific improvement causing a longer life expectancy in the chronic renal failure cases. For this reason, longer-lasting vascular access interventions are needed. Brescia-Cimino type distal interventions are used as the first choice in patients undergoing arteriovenous fistula (AVF) operations. In cases of thrombosis of these fistulas, more proximal AVF's are performed. If a patient's chances of performing autogenous AVF are consumed, synthetic materials may be used. In the hemodialysis-dependent patients, Brescia-Cimino type AVF's have been considered to be the most convenient procedure from 1966 when it was performed for the first time.[1] Due to repeated venous interventions, it is sometimes difficult to find a proper vein to form an AVF although a proper artery can be found easier. Internal or external shunting may be necessary. However, the probability of facing with significant complications due to use of synthetic grafts is high.[2] In this study, we aimed to show the details of the surgical technique we used and the possibility of constituting fistula without using synthetic graft.

Between January 1997 and December 2002, AVF operations were performed in 486 hemodialysis-dependent chronic renal failure patients at our department. The non-dominant upper extremity was preferred and patients are warned for taking care of their chosen arms 2 weeks before the operation in terms of not permitting vascular interventions. In patients having more than one convenient area on the same extremity, the most distal ones are preferred in order to protect parts that are more proximal. In order to prevent postoperative ischemia, brachial and ulnar pulses were evaluated manually and by Doppler ultrasound before the operation in all cases. Regarding the adverse effect of high venous pressure on the short-term patency rates, it was avoided to choose the areas intervened by central or peripheral venous catheters due to higher possibility of venous hypertension. All the interventions were carried out by applying bupivacaine (Citanest®) using local infiltration anesthesia. Single dose sodium cefoperazone prophylaxis was introduced to all cases intravenously before the operation. After the dissection, the arteries and veins were exposed and freed. Heparin (100 U/kg) was injected intravenously 5 minutes before clamping the vessels. After arteriotomy and venotomy of no longer than 5 mm, a side-to-side anastomosis was carried out using 7/0-10 mm polypropylene suture material. When the thrill reaches an adequate quality, the distal part of the vein was ligated close to the anastomosis site by silk ligatures to convert the anastomosis to end-to-side form. The tissues covering the vein were removed in order to prevent flow blockage. Skin and subcutaneous tissues were sutured by mattress technique using 3/0 Dexon suture material. All the operations were carried out by using 3.5x magnification loop. Antiaggregants and anticoagulants were not administered postoperatively.

The mean age of 486 patients (293 males, 193 females) who underwent AVF operation was 47.3±5.3 (range 14-72 years). Left upper extremity was operated in 391 (80%) patients. Around 392 patients (80%) underwent fistula operation only once, as early patency was obtained following the first operation. Among 94 cases whose fistulas did not function, 40 cases (42%) underwent re-operation at the level of brachial artery, whereas the remaining 54 at the contralateral radial artery and cephalic vein. Functioning fistula was obtained in 73 patients with the operation increasing the total number of functioning fistulas to 464 (96%). In spite of the second operation, 21 cases needed re-operation using either cephalic or basilic vein with brachial artery. As a consequence, in our series of 486 cases, functioning fistulas were provided without using an additional intervention at femoral artery level or a synthetic graft material in a total of 601 operations. The average follow-up time was 25.1 months. Brescia-Cimino type, radial artery and cephalic vein fistulas in 540, brachial artery and either one of cephalic or basilic veins in 61 interventions were used. Eighty-percent (436) of radial artery and 100% (61) of brachial artery fistulas were functioning. The patency rate was significantly higher in brachial artery fistulas than radial arteries ($p<0.05$ with Mann-Whitney U test). In 28 (5.1%) patients who underwent Brescia-Cimino type fistula operation at radial artery level, complications developed in 24 hours following the operation. Among the cases underwent revision, in 17 patients (3.1%) hematoma, in 7 patients (1.2%) bleeding and in 4 patients (0.8%) acute thrombosis were observed and all were completely treated by either one of drainage, bleeding control or thrombectomy. None of our patients had ischemic complications.

The patients with end stage renal disease should admit hemodialysis programs until getting the chance of renal transplantation. Therefore, arteriovenous fistulas performed should have the highest patency rates for the longest duration with least discomfort during the operation. Blood flow required for hemodialysis is 250 cc per minute on an average. This flow rate can be maintained by arterialized veins via fistulas constituted surgically between superficial veins and arteries, especially on the arms. For this purpose, Brescia-Cimino type arteriovenous fistulas are mostly preferred.[1] A low complication rate, long duration of patency and easy applicability to children made this procedure a standard method in a short period of time.[3] The most appropriate localization for Brescia-Cimino type AVF operation is defined to be between radial artery and cephalic vein at wrist level. The patency rate of 80% of fistulas between radial artery and cephalic vein after the first operation in the present study was within the reported range of 73-93%.[1] Unfortunately, during the diagnostic and therapeutic procedures many venous interventions are performed around this area and therefore, it is not always possible to carry out the optimal procedure defined. The AVF between brachial artery and basilic or cephalic vein was used as the second choice due to from periphery to the center principle in our series and the patency rate was 100%. It was revealed that the early patency rates are lower at the anatomical snuffbox level than those of more proximal. This was emphasized in some other article previously.[4]

Our technique is based on the side-to-side type of anastomosis between radial artery and cephalic vein. The early thrombosis rate is found to be lower in side-to-side type of anastomosis than that of end-to-side type of anastomosis. Regarding that we ligated the proximal part of vein after the

side-to-side type of anastomosis, converting it to end-to-side type, it can be said that the change in the early patency rates originates from the easy applicability of this side-to-side type of anastomosis technique. On the other hand, after completing the anastomosis, if there was thrill of low amplitude a venotomy was carried out on the distal part and a coronary dilator of proper calibration or an embolectomy catheter of 3 Fr. were inserted through. It was irrigated then with heparinized saline solution. The patency of AVF is affected adversely by the venous hypertension.[4,5] The primary reason of this venous hypertension is mostly the stenosis occurred due to previous venous interventions. Therefore, in the present study, it was avoided to use localizations intervened previously via central or peripheral venous catheters. The congenital and acquired arteriovenous fistulas usually do not increase cardiac output; however, sometimes heart failure of high cardiac output may be seen. The closer to the heart AVF is located, the more and earlier are the complications. On the other hand, autogenous grafts should be preferred, as synthetic grafts have a higher probability of infection in early period. Thus, an autogenous source via comfortable surgical procedure with a single anastomosis is the best option with a lower cost. This comfort shows itself via easy applicability of bleeding control after hemodialysis and a very low probability of infection.[6] We prefer Brescia-Cimino type AVF operation routinely as it does not necessitate synthetic grafts, is localized far away from the heart and fits, from the periphery to the center principle. In order to avoid congestive heart failure or aneurysm complications, the arteriotomy should be kept shorter than 5 mm.[7] Edema distal to AVF was not observed in any of our cases. It is likely that ligation of the distal vein with Nr.[1] silk at 2 to 3 mm in diameter during the fistula procedure at the brachial level minimized distal edema and aneurysm formation. Nevertheless, it is recommended to ligate the deep branch of the median antecubital vein to prevent edema whenever side-to-side anastomosis between artery and vein at brachial level is preferred.[8]

In conclusion, in the present study, functional anastomosis was obtained via Brescia-Cimino type distal AVF operation without using a synthetic graft material and additional surgical intervention at the femoral artery level.

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Effects of Ramadan fasting on cardiovascular diseases

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The present paper pooled all the available data on cardiovascular diseases and Ramadan fasting. Bibliographic data have generally shown that Ramadan fasting did not impair the health of patients with a cardiovascular disease when they were monitored. Few reports have demonstrated the impact of Ramadan fasting on cardiovascular diseases but still, it is not enough to establish a consensus on Ramadan and cardiovascular diseases. The changes in meal and activity schedules during Ramadan, induced chronobiological and metabolic modifications on healthy volunteers. These changes could have repercussions on chronic diseases. The aim of this article was to analyze all the available bibliographic data on cardiovascular diseases and Ramadan fasting. Little is known regarding the clinical implications associated with the observance of Ramadan fast in the management of patients with cardiovascular diseases such as hypertension and stroke. The comparison of hospital admission frequency, before and during Ramadan, of 2337 patients showed a slight decrease of hospital admissions for hypertension and angina. No difference was seen for cerebrovascular diseases, heart failure or acute myocardial infarctus.[1] These

observations were confirmed by a retrospective study that was carried out between 1991 and 1997 to evaluate the effect of Ramadan fasting on patients with coronary heart disease. The results showed that the incidence of acute coronary heart disease events did not increase in Ramadan.[2] The attitude of patients with hypertension concerning fasting during Ramadan is strongly influenced by religious convictions, as only 1.8% of the patients accepted not to fast following clinicians advice. In fasting hypertensive patients, headaches, illness and dizziness were reported and these symptoms are related to the usual effects of fasting. Moreover, an improvement of hypertensive patient's general state of health was observed during Ramadan. It is well known that blood pressure (BP) changes according to physical activity and to sleep and wake cycle. This circadian variation in BP must be taken in consideration when evaluating the effect of fasting on this variable. A 24-hour BP recording showed that its circadian rhythm did not change significantly during Ramadan in healthy volunteers.[3] A slight increase of mean diastolic BP has been observed in healthy volunteers after the fasting period, the rate of this low difference was in the normal range.[4] However, the reduced fluid intake and the disturbance in fluid balance may influence the BP. A decrease of systolic and diastolic BP during Ramadan was observed in healthy subjects.[5] In hypertensive subjects, a slight decrease of BP was found.[6] Moreover, a one-hour shift was reported in hypertensive patients BP. The mean BP was similar before and during Ramadan in treated hypertensive patients with continuous medication.[7] Even if there are some slight changes in BP, it is important to take care of each patient during this religious month. A circadian variation was demonstrated for the occurrence of cerebral infarct in normal conditions, with a high incidence in the morning. A study on 815 patients with stroke showed a diurnal variation of cerebral infarct incidence in Ramadan similar to the month prior to Ramadan.[8] However, a significant difference was seen in the diurnal variation of intracerebral hemorrhage. During the month of Ramadan, the incidence was lower in the afternoon and higher in the evening. Under normal conditions, it was lower at night and higher at noon. Waking up for a meal before dawn (sohor) did not affect the circadian rhythm of intracerebral infarct incidence and the chronobiological change during Ramadan did not have any effect on cerebral infarct occurrence.[8] In another retrospective study, stroke incidence did not vary during Ramadan and no variation was observed according to sex or age.[9] The fasting in the month of Ramadan did not seem to affect the cardiac risk factors negatively. Patients with stable cardiac diseases such as congestive heart disease, valvular heart disease and cardiac arrhythmia, could fast safely without any significant detrimental effect. No significant changes occurred in any of the hematological or biochemical standard (urea, creatinine, cholesterol, triglycerides, LDL, HDL, blood sugar, uric acid) of cardiac patients during Ramadan.[10]

Ramadan fasting did not have any harmful effect in hypertensive and cardiac stable patients. However, most of the studies carried out concerning Ramadan fasting and cardiovascular diseases were epidemiological and retrospective studies and only few controlled clinical assays were carried out. Patients with any cardiovascular disease should, prior to Ramadan, get the advice of their physicians whether they can fast or not. If a patient were allowed to fast, the physician would then suggest a treatment schedule adapted to Ramadan. This new schedule should be started before the beginning of Ramadan.

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Rheumatic valvular heart surgery and Maze III procedure

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Atrial fibrillation (AF) is a frequent complication in patients with mitral valve disease causing systemic embolism, cardiac chamber dilatation and decreased cardiac output.[1] Adequate treatment of mitral valve disease often does not relieve the cardiac rhythm disorder and AF persists or recurs.[2] Maze III procedure was proposed as a surgical treatment for patients with sustained AF. In this report, we describe our initial experience with the Maze III procedure in patients with rheumatic valve disease. From September 2000 to September 2002, 10 consecutive patients underwent the Cox-Maze III procedure concomitantly to mitral or other valve operation. All patients had an indication for cardiac surgery. Inclusion criteria for AF surgery was AF lasting for more than one year, medical history of previous thromboembolic events and large left atrium on preoperative transthoracic echocardiography. Exclusion criteria were non-cardiac disease, redo operation, severe left ventricular dysfunction and severe pulmonary artery hypertension. After establishing cardio-pulmonary bypass (CPB) and cross-clamping of the ascending aorta, the left atrium (LA) incision was carried out behind the interatrial septum and extended encircling around the pulmonary veins. The interatrial septotomy was made in the posterior to the orifice of the superior vena cava. In large sized LA, reduction size operation was carried out. The LA appendage was excised and incision made from its base to the encircling incision. This incision and remanent of LA appendage was closed. Extensive sutures were used to close the encircling incision. An incision was made from the LA to the middle portion of the posterior mitral valve annulus until coronary sinus was exposed. Fat tissues and remanent of muscle fibers around the coronary sinus and mitral valve annulus was cauterized and incision was closed. The mitral valve was excised and replaced with prosthesis or bioprosthesis valve according to patient's condition. After mitral valve replacement, the encircling incision was completely closed. In cases with aortic regurgitation, aortic valve replacement was carried out. After repairing ascending aorta, aortic clamp was removed and right side portion of the maze III procedure was performed. A long incision from the upper part of the right atrium to inferior vena cava is made and extended T-incision from the inferior right atrial free wall to the tricuspid annulus. At this time, tricuspid valve repair was performed. After cauterization of fat tissue and muscle fibers around tricuspid annulus, the incision is partially closed. An incision from the right atrial appendage to the near tricuspid annulus in the free wall of right atrium was made and closed. Right atrial appendage was saved. All patients weaned off CPB with low dose inotrope. Standard 12 leads as well as right sided leads of electrocardiography (EKG) was checked daily during the postoperative hospital stay and first, third, sixth and twelfth months postoperatively. After operation, sinus rhythm on EKG was defined when the P-wave was present. In early postoperation, to evaluate cardiac function and the recovery of atrial function, transthoracic echocardiography was performed and a peak A-wave velocity was considered evidence of effective atrial contraction.

There were 2 men and 8 women with a mean age of 40±8 years. All patients had rheumatic mitral stenosis or regurgitation. Severe aortic regurgitation in 2 patients and tricuspid regurgitation in 4 patients were found. **Table 1** shows the demographic data of patients before operation. **Table 2** shows the operative variables and concomitant cardiac procedures. In early postoperative period, 2 patients required re-operation due to suture line bleeding. Normal sinus rhythm was restored in 6 patients and atrial contractility was demonstrated in 5 patients. There was no occurrence of low cardiac output syndrome, thromboembolic events, stroke or need for permanent pacemaker implantation. All patients were followed up for 470±230 days. Six months postoperation, normal sinus rhythm was found in 8 patients and LA contractility in 7 patients. In all patients, in early or late period of postoperation, supra ventricular tachycardia or thromboembolic events do not occur.

All of the patients undergoing the maze in our series were referred specifically for correction of rheumatic valvular pathology rather than correction of symptomatic AF. The New York Heart Association class in patients with rheumatic disease was higher than in patients with other diseases and the technique of operation is distinct from isolated AF, with regard to mitral valve and multiple valve procedures. The combined valve procedure required significantly longer aortic clamping time than the isolated maze procedure. It has been shown that some patients would restore sinus rhythm with only the mitral valve procedure.[3] Association of maze in those patients may have additional

Table 1 - Patient's characteristics (N=10).

Variable	N
Male/Female	2/8
Age (years)	40±8
NYHA	
Class 2	1
Class 3	9
LAD (mm)	68±15
PAP (mmHg)	
Systolic	55
Diastolic	19
LVEF (%)	50±7
Mitral stenosis	8
Mitral regurgitation	1
Mixed lesion	6
Aortic valve disease	2
Tricuspid valve disease	4
History of embolic event	2
AF duration (year)	> 1

Data expressed as mean ± SD
NYHA - New York Heart Association, LAD - left atrial dimension, PAP - pulmonary artery pressure, LVEF - left ventricular ejection fraction, AF - atrial fibrillation

Table 2 - Operative variables and concomitant cardiac procedure in 10 patients.

Variable	N
CPB time (min)	144±18
AXC time (min)	90±11
Prosthesis	
Mechanical	10
Biological	2
MVR	8
MVR + AVR	2
TAP	3
TVR	1
Need to permanent pace maker (n)	0

Data expressed as mean ± SD
CPB - cardio-pulmonary bypass, AXC - aortic cross clamp, MVR - mitral valve replacement, AVR - aortic valve replacement, TAP - tricuspid annuloplasty, TVR - tricuspid valve ring

morbidity with no benefit. For this reason, it is necessary to carefully identify those patients who need maze procedure preoperatively.

Interruption of macroreentrant circuits responsible for AF requires performance of several incisions in both atriums. Given this complexity of the technique, bleeding from less accessible suture line has been a significant consideration.[4] In our early experience, 2 patients had bleeding from suture lines.

In some of our cases, LA diameter was more than 75 mm. In these patients, we excised portions of the inferior and dome of the left atrium to reduce the left atrial size. In others, extensive suturing of the LA during the maze procedure lead to significantly decrease in LA dimension. In all patients we were faced with a relatively thin and fibrotic atrial wall. We suppose lower success rate of recovering atrial rhythm and contractility in our series have direct relation to the replacement of fibrosis in atrial wall due to LA dilatation and rheumatic pathology. It has been reported that LA function and sinus rhythm are gradually recovered after the maze procedure.[5] In the present study, both the electrical and mechanical atrial activities were recovered in the first 6 months and maintained for 2 years after operation. It seems reduction of atrial size, volume load and inflammation lead to the gradual recovery of electrical and mechanical atrial activities.

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The outcome of non-operative treatment for undisplaced patellar fractures

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The objective of this study is to assess both clinical and radiological out come of non-operative treatment of none displaced patellar fractures. As the treatment of none displaced patellar fractures remain controversial, a question weather prophylactic surgery is indicated and what is the functional outcome of non-operative management were asked and answered in this study. Undisplaced patellar fractures can be safely and effectively managed none operatively with good outcome results.

Data were collected by retrospectively reviewing all files and roentgenograms of patients with patellar fracture treated none operatively at McGill University Health Center, Montreal, Canada from 1999 to 2003. This information was obtained from the trauma database of McGill University Health Center Records. The criteria applied for sample collection are patellar fracture with less than 3mm step and intact extensor mechanism. Exclusion criteria include patellar fractures with more than 3 mm step in the articular cartilage, open fractures, ligaments injury, pathological bone, and preprosthetic fractures. The outcome of the treatment was recorded as healed fracture with no further displacement radiologically and asymptomatic functioning knee clinically. Other relevant information, namely age, gender, mechanism of injury and follow up period were collected.

Twenty-eight patients were extracted from the database, however, only 18 of these patients fulfilled the selection criteria. All of them had clinical and radiological assessment. Ten patients (2 pathological, 3 preprosthetic, 2 failed conservative treatment and 3 lost for follow up) were eliminated from the study. Patients demographic data, 8 (44.4%) males, 10 (55.6%) females, age (20-90 years) mean of 58 years, 15 patients (83%) independent and 3 (17%) from a nursing home. Mechanism of injury included sports injury in 5 patients (27.7%), accident at home in 6 patients (33.3%), motor vehicle accident (MVA) in 4 patients (22.2%) and 3 (16.7%) patients in work injuries. All 18 patients were treated with immobilization (cast or brace) for 2 weeks and early physiotherapy. Follow up period ranged from 6-48 months with a mean of 24 months in which patient had documented clinical and radiological finding in the medical records. Radiological evaluation at 3 months showed no further displacement, osseous union were evident in 16 patients (**Figures 1a & 1b**), 2 patients developed fibrous union, which is asymptomatic. Clinically, 17 patients had no or mild pain and 16 patients had full range of motion and power documented in file notes both in clinical visit and physiotherapy notes. When called for evaluation in this study they were having full range of motion and normal power and we used the contra lateral (uninjured) knee to compare our finding.

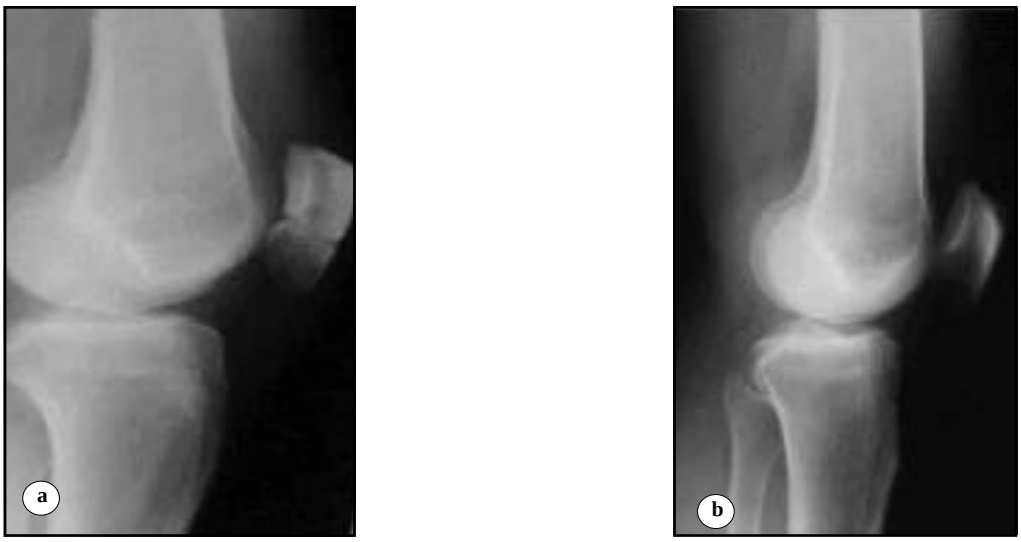

Figure 1 - Radiological evaluation of 37-year-old male with fractured patella following sport injury **(a)** minimally displaced fracture at the mid-portion of the patella, **(b)** nine months later with a healed fracture.

Fractures of the patella are generally caused by a direct blow that results in a transverse or slightly oblique fracture of the mid-portion of the patella. Occasionally, fractures can occur from the strain placed on the patella from exertion of the quadricep muscles. Many patellar fractures have separated fragments due to the strain placed on the patella from exertion of the quadriceps.

In this study, patient treated non-operatively for minimally to none displaced patellar fracture, fitting the inclusion criteria were having no risk of further displacement and their functional out come in the long term were favorable. Patellar fractures are relatively common and the displaced ones may be treated by a variety of methods with different complication risks (knee stiffness, loss of reduction, osteoarthrosis, hardware irritation, infection and nonunion). In an experimental investigation by Fortis et al[1] of the tension in fractures of the patella it showed that there are 2 forces acting on patella surfaces. In principle, compression force posteriorly on the articular surface due to femoral condyles, tensile force anteriorly with 22% displacement and 18.5% loosening or malunion. A study of 104 transverse by Sanderson,[2] comminuted and polar patella fractures with a follow up period ranging from 3-11 years after being treated by conservative, open reduction internal fixation or patellectomy (partial or total).[2] It was noted in his study that conservative treatment was good when indicated. Braun et al[3] looked at 40 patients with congruous, stable patella fractures followed up for 30 months. They found 80% pain free and 90% full range of motion while Levack et al[4] concluded that anatomical open reduction internal fixation is difficult when they studied 64 patella fractures and found out that patellectomy gave 60% versus 31% for open reduction and internal fixation. In a study by Pritchett,[5] an evaluation of nonoperative treatment of widely displaced patella fractures with up to 1 cm gap in 18 low-function and low-demand patients with 4 patients were available in the end of 2 years follow-up with no severe pain.

Several investigators have performed different studies including biomechanical study of cadaver knees and various clinical studies, which have shown what we concluded in our study. We concluded that undisplaced patella fractures could safely be treated by conservative means without risk of further displacement. Prophylactic surgery is not indicated and finally good functional out come can be expected in the long-term.

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Frequency of anemia in pregnancy in Northern Jordan

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Anemia is the most common medical disorder in pregnancy in developing countries.[1] According to the World Health Organization, the prevalence of anemia in pregnancy ranges from 18% in developed countries to more than 55% in developing countries.[2,3] The development of anemia early in pregnancy is associated with increased risks of inadequate gestational gain, low birth weight, preterm delivery, and increased risk of maternal mortality.[4] Furthermore, anemia in pregnancy is associated with an increased risk of iron deficiency anemia in infants which may cause adverse behavioral and cognitive development if it is not corrected.[5] In 1996, the Jordanian Ministry of Health reported a 29% prevalence of anemia in non-pregnant women, which rose to 38% in rural areas.[5] These values are high enough to require alertness and concern. The present situation of this common and serious health problem is less than ideal and indicates that a lot has to be carried out to detect women at risk and to correct anemia at an earlier stage during pregnancy.

This study attempts to determine the current prevalence of anemia during pregnancy in Northern Jordan, to investigate the possible etiology of anemia in the study region, and to assess the use of iron and folate supplementations. Two-hundred pregnant women were randomly selected from different hospitals in Northern Jordan, during a 3-month period. All subjects were interviewed during regular antenatal visits. The hemoglobin level during first, second and third trimester were

recorded for all patients. Anemia was defined as hemoglobin values of less than 11 g/dl, and severe anemia if hemoglobin was less than 7 g/dl. Data were analyzed using Statistical Package for Social Sciences (SPSS) program. Correlation studies were carried out by using paired T test. A *p*-value of 0.05 or less was considered as indicative of statistical significance. Anemia during pregnancy was detected in 84 pregnant women (42%). A significant association was found with education and socioeconomic status, family income, parity and rural residence. Thirty percent of the subjects were anemic during the first trimester. Sixty percent of anemic women had a monthly income of less than 200 JD. The prevalence of anemia increases among pregnant women living in rural areas and among pregnant women of low educational level. Multiple parity was also associated with increased risk of anemia 45.2% (had more than 3 children).

The study showed that 59.5% of pregnant women with anemia were prescribed folic acid, and 92.9% iron supplementation. Prophylactic iron was given to 67.2% of pregnant women. Compliance with iron supplementation use was 62.6%. Forgetting the drug was the major reason for poor compliance, whereas side effects were not a major problem. Around 30% of the subjects did not like drugs and were afraid of taking them during pregnancy. Only few patients (5.3%) didn't comply with iron therapy due to side effects (**Table 1**). Among the reported side effects are constipation (12.8%), diarrhea (2.6%), epigastric pain (5.8%), vomiting (0.6%) and heartburn (1.9%). The overall prevalence of anemia in our study was 42%. This value is close to that found in other studies in the region,[5] which means that the problem is persistent and practical solutions are needed. The following factors were associated with increased anemia frequency: low income, low level of education, living in a rural area, and higher number of previous children. An effort should be made to improve women's health during and in-between pregnancies. Improving economic, educational, and social conditions of women might help. Anemia during pregnancy compromises the health of mothers in traditional cultures as Jordan where women tend to have multiple pregnancies soon after marriage, with inadequate intervals between pregnancies to replenish nutritional stores. Infants born to anemic women also appear to be at increased risk of developing iron-deficiency anemia. Infants with anemia have been shown to have delay cognitive and psychomotor development with long-term consequences.[4,5] For better infant and mother health, it is important to encourage family planning schemes for lower number of children and proper childbirth spacing.

In this study, poor compliance was observed with iron supplementation, mainly due to forgetting to take supplementation and being afraid of taking drugs during pregnancy. Side effects of iron were not very common, probably as most of the women were taking low prophylaxis doses. The side effects increase as the doses increase. Strategies to overcome poor compliance with supplementation such as fortification of food items and dietary changes resulting from education interventions were somehow successful in developed countries.[6] Fortunately, a study in Jordan to evaluate folate concentration during pregnancy showed that most mothers had an adequate serum folate concentration antenatally. That was expected to be due to high content of leafy salads in Jordanian diet, so enough folic acid can be taken in spite of traditional prolonged heating of cooked food.[7]

We conclude that anemia is a significant problem during pregnancy in Jordan. It is difficult to have a single identifiable cause of anemia, so solutions should cover different aspects; social, economical and medical, to be successful.

Table 1 - Iron supplementation.

Classification	Anemic %	Non-anemic %	Total %
Prescribed			
Yes	92.9	67.2	**78**
No	7.1	32.8	**22**
Regular use			
Yes	61.5	63.6	**62.6**
No	38.5	36.4	**37.4**
Reasons of poor compliance			
Side effects	0	11.1	**5.3**
Forgetting	70	55.6	**63.2**
Hating drugs	30	33.3	**31.6**

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Specific chromosomal satellite association among infertile male patients

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It has been observed that certain chromosomes tend to occupy positions in the mitotic cells close to each other.[1] The most obviously associated chromosomes are the acrocentric chromosomes, which in human karyotype involve chromosome numbers 13, 14, 15, 21, and 22. Accordingly, this phenomenon has been designed as satellite association (SA) or acrocentric association (AA). Indeed, a large body of data is now accumulating to suggest the involvement of SA in the occurrence of chromosomal non-disjunction[2] and Robertsonian translocation.[3] Furthermore, it appears that D/D translocation (13/14, 13/15 and others) is not associated with phenotypic abnormality except for a possible association with male infertility.[4]

Based on the above data together with our previous finding, which suggested a high frequency of SA in metaphases of infertile male patients,[5] we were pushed to carry out more extensive work to assign the most frequent associated chromosomes that might predispose the chromosomes to centric fusion and might have indirect effect on spermatogenesis and to conclude as well, whether those association occur at random or non-random pattern. During the 2-year period starting from October 1998 to October 2001, a total of 75 infertile male patients were subjected to the present investigation. One hundred normal controls were included and investigated in parallel. Culture media, chromosomes, cytology, satellite association scoring and G-banding techniques were conducted according to standard methods. The present investigation revealed a high frequency of association between chromosomes numbers 13-14 among the oligospermia patients compared to normal control. The chi-square analysis showed the association is highly significant (**Table 1**). Again, the 2x2 association particularly between chromosome numbers 13-13, 13-14, 13-15 and 13-21 were significant (X^2=303.77, p>0.005) (**Table 2**). No such observation has been noticed among the azoospermia patients. A high frequency of association was observed between chromosome number 13-14 among the azoospermia though it is non significant (**Table 1**).

Based on the above data, the present investigation showed that the association tendency among the oligospermic groups is non-random, specially when chromosome numbers 13 and 14 are involved. Indeed, the result of Mattei et al[6] also suggested that the unequal frequency observed in the

Table 1 - Number of association for each acrocentric chromosome in metaphase among the oligospermia patients.

Patient n	Association scored for each pair acrocentric per 25 cells					Association /cell
	13	15	14	21	22	
1	10	9	7	10	5	1.64
2	12	10	8	7	8	1.80
3	10	9	10	5	5	1.56
4	11	8	7	0	7	1.32
5	8	7	6	10	4	1.4
6	8	6	2	0	3	0.76
7	9	7	10	6	0	1.28
8	4	4	3	2	2	2.12
9	9	7	10	7	6	1.56
10	13	11	5	10	17	2.24
11	5	4	11	3	3	1.04
12	14	10	5	13	5	1.88
13	15	14	14	3	16	2.48
14	16	14	4	12	0	1.84
15	18	14	7	8	6	2.12
16	13	16	0	8	4	1.64
17	18	14	12	11	8	2.52
18	20	15	14	13	9	2.84
19	12	12	6	6	13	1.96
20	16	10	6	9	7	1.96
21	11	16	11	12	13	2.12
22	16	20	13	12	11	2.84
23	14	12	10	3	5	1.76
24	9	8	11	10	10	1.76
25	15	12	10	6	7	1.88
26	15	14	12	0	12	2.12
27	12	11	10	8	9	2
28	10	9	12	13	12	2.24
29	9	4	6	4	7	1.2
30	18	9	12	8	7	2.16
31	11	10	18	11	8	2.32
32	19	13	10	19	0	1.88
33	13	11	1	10	15	2
34	15	14	10	8	7	2.16
35	16	13	9	8	7	1.88
Total	**444**	**367**	**302**	**275**	**258**	**1.894**

$\chi^2 = 268.84$

Table 2 - Distribution of 2x2 association chromosomes among patient with oligospemia.

Patient n	Association chromosomes per 25 cell														
	13-13	13-14	13-15	13-21	13-22	14-14	14-15	14-21	14-22	15-15	15-21	15-22	21-21	21-22	22-22
1	2	6	2	0	3	4	5	4	0	2	1	3	2	4	3
2	4	7	3	6	2	3	4	5	3	2	1	1	1	2	1
3	3	5	2	3	3	4	3	3	1	1	2	3	0	3	3
4	1	4	3	4	4	2	2	1	2	0	3	2	0	2	3
5	2	5	4	4	2	3	3	4	3	1	0	2	0	1	1
6	3	4	2	0	0	0	2	0	1	1	0	0	0	2	4
7	3	5	2	7	3	1	3	4	1	0	2	1	0	0	0
8	7	8	7	4	2	5	2	2	3	0	3	2	3	3	2
9	0	8	0	0	2	3	5	6	4	0	3	1	2	4	1
10	8	6	5	9	4	4	3	4	4	0	2	2	2	3	0
11	6	1	7	5	1	0	1	3	0	1	0	0	0	0	1
12	0	8	5	0	8	1	5	4	3	2	2	4	0	3	2
13	14	7	0	0	8	3	4	5	4	3	3	3	2	4	2
14	5	8	0	0	0	2	4	4	5	2	4	4	3	3	2
15	0	9	9	0	0	4	7	6	6	0	0	6	2	4	0
16	4	10	0	0	1	3	3	5	4	2	3	2	1	2	1
17	9	6	7	0	8	4	2	3	5	2	3	4	4	2	4
18	5	4	9	8	8	6	5	4	6	2	3	2	2	4	2
19	0	7	9	8	0	2	3	4	4	1	4	2	1	2	3
20	8	7	0	0	0	4	3	3	5	3	3	5	2	3	2
21	0	8	6	2	7	2	1	4	3	3	4	3	3	5	5
22	8	6	10	6	6	3	2	5	2	2	1	3	4	4	7
23	0	9	0	0	0	1	3	6	4	3	4	1	5	4	4
24	4	5	4	3	1	2	2	4	3	4	2	4	2	3	3
25	3	3	3	2	5	1	4	4	1	3	4	2	4	4	3
26	1	5	4	4	4	3	2	5	4	4	5	3	3	5	3
27	3	4	2	5	6	2	1	6	0	0	4	5	5	4	2
28	5	6	6	2	2	2	6	6	3	2	2	4	4	3	3
29	0	7	0	0	1	1	5	5	1	1	2	3	2	1	1
30	4	6	7	7	2	2	0	1	5	4	1	5	4	2	4
31	9	7	7	0	2	1	3	4	3	4	0	4	6	3	5
32	0	8	3	0	3	4	3	4	2	5	3	3	3	3	3
33	4	4	4	2	5	3	2	5	1	4	3	3	5	4	1
34	5	6	5	3	4	2	4	5	2	5	1	1	4	3	4
35	3	7	5	1	3	1	3	1	1	5	4	2	4	4	3
Total	**133**	**216**	**142**	**95**	**110**	**81**	**121**	**139**	**99**	**74**	**80**	**95**	**85**	**103**	**88**

p<0.005, 13-14 and 13-13 (X^2=56.3), 13-14 and 13-15 (X^2=55.70), 13-14 and 13-22 (X^2=53.62), total X2=303.77, degrees of freedom = 136

distribution of Robertsonian translocation constituted an argument, supporting the view that association between acrocentric chromosomes did not occur at random. It is also suggested that the close proximity of the short arms of specific D-group and specific G-group could explain the occurrence of exchange between them, leading to Robertsonian translocation. It is well established that there are 2 factors considered to play a major role in acrocentric chromosome association. Those factors are the presence of satellite deoxyribonucleic acid in the short arm of those chromosomes and the nucleolar organizer regions activity. Indeed, the non-random distribution of Robertsonians translocation can be explained by the meiotic distribution of acrocentric association. Furthermore, the tendency for specific acrocentric chromosome to be in Robertsonian translocation could result from the homology at molecular level.

In conclusion, it seems that the non-random tendency of acrocentric chromosome is evident particularly between chromosome numbers 13-14 among the oligospermic. This tendency could be considered as predisposing factor to Robertsonian translocation. Our finding is supported by previous work, which revealed that, approximately 4% of the oligospermic patients have 45,XY,t(13,14) karyotypes.[5]

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Hajj caravan 1423

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The Kingdom of Saudi Arabia (KSA) occupies four-fifths of the Arabian Peninsula, with a land area of 2 million square kilometers. The KSA holds a unique position in the Islamic world, as the custodian of the 2 holiest places of Islam, Makkah and Medina.[1] This extraordinary emeses migration is a unique forum for the study of travel epidemiology and our study is a part of it. Health services occupy a high priority in developing the agenda of the KSA, Saudi culture-devotion to Islam.[2]

Caravan, by a definition is a camper equipped with living quarters or a company of travelers journeying together specially across a desert, but in our study, Hajj caravan comprises a group of people who were Hajj pilgrims, got some illness and admitted in a tertiary care, 550 bedded, Al-Noor Specialist Hospital, Makkah, KSA and on the 9th of Dhu-Al-Hijjah corresponding to 10th February 2003 were taken to Arafat to perform Hajj by hospital management. Anyone who enters Arafat on 9th of Dhu-Al-Hijjah Waqfa or Arafat day, his Hajj is complete. A special arrangement in the presence of doctors with all emergency measures was made for such patients so that they may perform Hajj. Their medication and recommended food was also organized as it takes approximately 3-4 hours. This study includes all the Hajj pilgrims admitted in Al-Noor Specialist Hospital during Hajj 1423 Hejre, at any time before the Hajj day but still present on 9th of Dhu-Al-Hijjah in the hospital. There were 118 Hajj patients on 9th of Dhu-Al-Hijjah in the hospital, 40 patients were allowed in the morning to go for Hajj but Hajj caravan comprises of 33 patients only as 6 of them became critical at the time of departure and one refused to go. The inclusion criteria was that their vitals should be stable, they were allowed by the doctors and as well as their own will was highly considerable as there was one patient who was fit to go but refused to go.

The data collected summarizes, sex, nationality, their diagnosis, duration of stay before and after Arafat day and their general condition. They all went to Arafat at 3 p.m. and returned by 7 p.m. after Maghrib in good condition. The demographic data and clinical picture of Hajj pilgrims on Arafat day is shown in **Table 1**. The results highlight that out of 33 patients, 60% were males and 40% were females justifying the male dominancy. There was a total of 14 nationalities that accompanied the caravan. The majority was from Arab countries comprising 42.4% of which Egyptians were 24.2%. An overall condition of patients was quite stable, 18.1% had

Table 1 - Demographic and clinical characteristics of Hajj caravan (N=33).

Characteristics/parameters	n	(%)
Gender		
Male	20	(60)
Female	13	(40)
Nationalities		
Arab countries	14	(42.4)
Indo-Pak subcontinent	10	(30.3)
Others	9	(27.3)
Vitals stable at departure*		
Good†	6	(18.1)
Acceptable‡	27	(81.8)
Duration of stay before 9th Dhu-Al-Hijja		
1 or same day	6	(18.1)
2-4 days	16	(48.5)
5-7 days	7	(21.2)
> 1 week	4	(12.1)
Duration of stay after 9th Dhu-Al-Hijja		
1 or same day	14	(42.4)
2-4 days	13	(39.3)
5-7 days	3	(9.1)
> 1 week	3	(9.1)

* pulse, blood pressure and temperature at standard normal levels, †vital signs normal independently mobile and not in agony, ‡vital signs normal, nearly 1-2 postoperative, 1-day back recovered from acute situation

Table 2 - Diagnosis of Hajj caravan patients according to ICD-10.

Diagnosis	ICD-10 codes	n	(%)
Disease of musculoskeletal and connective tissue	M00-M99	8	(24.2)
Disease of respiratory system	J00-J99	7	(21.2)
Disease of nervous sytem	G00-G99	5	(15.1)
Disease of gastroenteritis	K00-K93	5	(15.1)
Cases of general surgery as hernia, amputation, acute abdomen and others	R00-R99	4	(12.1)
Disease of blood and blood forming organs	D50-D89	2	(6.1)
Disease of skin and soft tissue	L00-L99	2	(6.1)
Total		**33**	**(100)**

good and 81.8% had acceptable condition. **Table 1** also highlights the duration of stay of patients before and after Hajj day showing that majority of patients 48.4% staying for 2-4 days until 9th of Dhu-Al-Hijjah but after 9th of Dhu-Al-Hijjah maximum patients 42.4% left the hospital on the same or next day. **Table 2** shows us the presentation of different diagnosis with their ICD-10 codes.[7] There were only 7 codes in which various diagnoses fall but the diagnosis of patients with musculoskeletal and connective tissue disorder were at higher rate 24. 2%.

Our study gives us a picture of how it was made possible for the ill to perform Hajj by the hospital management. Other studies regarding Hajj,[3-6] and more than this had been conducted in past but it is a different type of study ever done for the first time in the KSA. Our study indicates that the provided selection criteria is followed closely and no undue effects were experienced by allowing patients to attend Hajj. Moreover, hospital should carefully select patients who should be allowed to go with the Hajj caravan in order to avoid unnecessary morbidity and mortality.

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Acetylator phenotype in Iraqi patients with discoid lupus erythematosus

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Lupus erythematosus (LE) is usually divided into 2 main types, discoid (DLE) and systemic (SLE). Discoid lupus erythematosus is a relatively benign disorder of the skin most frequently involving the face. There are hematological and serological changes in half of the patients.[1]

Polymorphic N-acetylation has been linked to variation in drug response, susceptibility to adverse reactions and increased incidence of certain spontaneous disorders including cancer.[2] The association between LE and acetylation has received much attention with conflicting results. While drug–induced lupus syndrome is more frequent in slow than rapid acetylators,[2] the association of spontaneous SLE with the slow acetylator status is controversial. Although some reports confirmed this association, other repots failed to find any association.[3] The association between DLE and acetylation has received little attention. There are only 2 reports that failed to show an association between acetylation and DLE.[4,5] The present paper examined the acetylator status in Iraqi DLE patients. Iraqi population as well as other Middle Eastern populations are characterized by a predominance of slow acetylators.[6] Therefore, it is interesting to

examine this problem in a predominantly slow acetylator population.

Twenty DLE patients and 30 healthy volunteers participated in the study. Approval to conduct this study was granted by the appropriate local ethical committee. The nature of the trial was explained to each subject and the consent of each was obtained. Excluded from this study were individuals with glucose-6-phosphate dehydrogenase deficiency or allergy to sulfonamides. Non of the subjects had a history of drug-induced lupus prior to phenotype determination, were receiving drugs that would interfere with acetylation, or were on any drugs known to be polymorphically N-acetylated. The study included a total of 20 patients with DLE who attended the Department of Dermatology, Baghdad Teaching Hospital, Medical City, Baghdad. Diagnosis of DLE patients was carried out by a specialist dermatologist and was based upon clinical and histological criteria and the absence of lupus related articular or visceral damage (gut, liver, or heart disease were excluded). Investigations included a complete blood picture and erythrocyte sedimentation rate, a general urine examination, anti-nuclear antibody titer, venereal disease research laboratories test, and anti double stranded deoxyribonucleic acid antibody. Patients included 8 (40%) males, and 12 (60%) females, whose ages ranged from 17-58 years, with mean 37.20±10.88. The age at the onset of the disease ranged from 7-48 years (mean 29.40±9.28). The mean duration of disease was 7.81 years (range 0.25-30). All patients had negative antinuclear antibodies. Thirty healthy volunteers were recruited, and all had no history of major illness and no abnormal physical findings during examination or investigation. Their age ranged from 16-52 years (mean 26.30±9.81). The group included 9 (30%) males and 21 (70%) females. After an overnight fast, each subject received a single oral 100mg of dapsone, obtained from (Al-Nile Company for Pharmaceuticals and Chemical Industries, Cairo, Egypt). Drinking of caffeine containing beverages was not allowed throughout the study period. A blood sample (5ml) was obtained 3 hours after drug intake by venepuncture that was added to a 10ml polyethylene tube containing 50µl of heparin (Heparin Leo 5000 iu/ml, Leo Pharmaceutical Products, Denmark). Plasma was separated within one hour after collection by centrifugation at 3000rpm for 10 minutes. The samples were subsequently stored frozen at -20°C pending analysis. A rapid, simple, one-stage protein precipitation method for the estimation of plasma dapsone (DDS) and monoacetyldapsone (MADDS) concentrations by a high performance liquid chromatography was used,[7] as was described in a previous study.[6] Statistical analyses were carried out, using SPSS software, version 10. Results were presented as mean±standard deviation, differences between groups were assessed by chi square test and an estimate was considered to be statistically significant if p value was <0.05.[8]

The frequency of slow acetylators in DLE patients, whose MADDS and DDS ratios were <0.30, was 13 of 20 (65%), with a 95% confidence interval (CI) of 49.4-80.6%, (7, 53.8% females, and 6, 46.2% males). Their ages ranged from 17-58 years (mean 37.38±12.58), their ages at onset of the disease ranged from 7-48 years (mean 28.46±11.30), and the duration of disease ranged from 1-30 years (mean 8.92±9.53). The plasma concentrations of DDS ranged from 0.19-7.77 µg/ml (mean 1.83±2.12), and MADDS ranged from 0.01-1.20 µg/ml (mean 0.23±0.33). The plasma MADDS and DDS ratios ranged from 0.03-0.27 µg/ml (mean 0.12 ±0.07) **Table 1**.

The frequency of non-acetylators in DLE patients whose MADDS and DDS ratio are zero, was 7 of 20 (35%), (5, 71.4% females and 2, 28.6% males). Their ages ranged from 29-52 years (mean 36.86±7.63), their ages at onset of disease ranged from 27-36 years (mean 31.14 ± 3.39), and the duration of the disease ranged from 0.25-20 years (mean 5.75±7.03). The plasma concentrations of DDS ranged from 0.49-2.66 µg/ml (mean 1.51±0.92 µg/ml). The plasma concentrations of MADDS were zero. There were no rapid acetylators in DLE patients.

The frequency distribution of the plasma MADDS and DDS ratio in 30 healthy volunteers (control) revealed that the frequency of slow acetylators whose MADDS and DDS ratios were <0.30 was 22 (73.3%) of 30 with a 95% CI of 59.9-86.7%. They included 17 (77.3%) females and

Table 1 - Frequency distribution of acetylator phenotype in lupus patients and healthy controls with their statistical significance.

Acetylator phenotype	Subjects n	Frequency %
None		
DLE	7	35
Control	0	0
Slow*		
DLE	13	65
Control	22	73.33
Rapid		
DLE	0	0
Control	8	26.66

DLE - discoid erythematosus lupus, * Not significant compared to control *p=0.28*

5 (22.7%) males, their ages ranged from 16-52 years, (mean 27.86%±10.74). Their plasma MADDS and DDS ratios were from 0.01-0.28 µg/ml (mean 0.11±0.088). While the frequency of rapid acetylators in control whose MADDS and DDS ratios were >0.30 were 8 (26.7%) of 30. They included 4 (50.0%) females and 4 (50%) males. Their ages ranged from 16-29 years, (mean 22.00±4.87). Their plasma MADDS and DDS ratios were from 0.36-1.63 µg/ml (mean 0.86±0.57). There were no non-acetylators in healthy controls (**Table 1**). The slow acetylators in the DLE patients, as a group, was not significantly different from the slow acetylators in the control group ($p>0.05$).

In this study, patients with DLE were shown to be either slow acetylators or non-acetylators, that is the plasma concentration of MADDS was undetected in plasma. In this respect, the results of this study differs from the 2 previous reports from the European countries which concluded that the frequency of slow acetylators was not different between DLE patients and normal control group.[4,5] In a parallel study, the incidence of slow acetylators in patients with spontaneous SLE was reported not different from that found in the control group.[3] Taken together, the 2 studies about the acetylator phenotype in SLE and DLE support the held view that the 2 diseases do not represent a spectrum but can be considered to be overlapping diseases with different etiologies.[1] An interesting finding in this study was that some patients were non-acetylator. In a previous report about half of the patients with Behcets' disease were found to be non-acetylators.[6] This finding can not be explained by a technical error in the method used since non-acetylator in this study as well as the previous were found in the patients and not in the control group. On both occasions patient and control samples were run together. The significance of this finding, needs further investigation to determine the genotype of non-acetylators, in order to understand this phenomena.

In conclusion, in a population of slow acetylators, it appears that slow or very slow acetylators phenotype can be considered as genetic trait predisposing to the development of DLE. This finding as well as the occurrence of non-acetylators needs further investigation to determine the genotype in a lager sample.

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Risk factors of coronary heart disease among Jordanians

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Coronary heart disease (CHD) is the first leading cause of death in developed countries. According to Ministries of health statistics, it was also found to have a significant prevalence in Jordan and the rest of the Arabic countries.[1] Prevention is of primary importance, and proper prevention requires correction of risk factors in persons at high risk. This will significantly lower the mortality rate, which reduces the economic burden resulting from stroke on patients' families and health service organizations. Numerous surveys and epidemiological studies revealed the major risk of coronary heart disease (CHD), which included diabetes, low-density lipoprotein-cholesterol (LDL-C), hypertension (HTN), smoking, inflammatory diseases and others, which could be managed effectively.[2] However, the relative significance of these factors remains controversial among many publications.[3] Nevertheless, it was well established that some environmental, genetic and ethnic factors played a significant role in these controversial conclusions.

We have conducted this study, which retrospectively involved a total of 201 patients who underwent catheterization at the Islamic and Ibn-Al-Hytham Hospitals, Amman, Jordan, in the period between 1995 and 2000. Experienced

cardiologists were consulted to determine inclusion criteria of patients. A special data form was designed. Thereafter, baseline demographic criteria (including height, weight, and body mass index), blood pressure and family history were collected with a common protocol details of which are described in another publication.[4] Monitoring parameters during follow-up included lipid profile (LDL-C, triglyceride and high-density lipoprotein-cholesterol [HDL-C]), as well as fasting blood sugar. Measurements of each lipid profile item were further stratified into various risk categories that have been defined by the National Cholesterol Education Program (NCEP) Expert Panel for detection, evaluation and treatment of high blood cholesterol in adults. To determine the significant predictors of CHD in this population, 2 multiple logistic regression models were fitted for lipid and nonlipid variables separately. In the first model, the independent effects of different age groups, gender, diabetes, diabetic types, hypertension, congestive heart failure, previous history of myocardial infarction (MI), smoking status, family history, and documented diagnosis of hyperlipidemia were tested. However, all lipid parameters were included for evaluation in the second model. **Table 1** and **Table 2** displays the adjusted odds ratios (OR) of CHD with their 95% confidence intervals, which were obtained for the nonlipid (Model l) and lipid variables (Model 2). As shown, male gender was the most significant nonlipid variable with an estimated risk for CHD of 16.7 times higher than female gender. In particular, males of age greater than 45 years had 92 times higher risk than males of age less than 45 years. In addition, other variables including hypertension, family history of any type (family history of hypertension, diabetes, or more than one type), diabetics type II, and history of previous MI were also significantly associated with CHD. An interesting finding is the impact of smoking cessation on modifying the cardiovascular morbidity with an OR=0.058. While the variables; diabetes mellitus, congestive heart failure (CHF) and hyperlipidemia were dropped out of the final model when forward and backward stepwise regression methods were applied due to their insignificance. In the second analytical model, LDL ≥220 (mg/dl) level and total cholesterol ≥200 (mg/dl) level were the only lipid parameters, which remained in the backward regression model with OR=3.75 and 10 times. Although HDL level >35 mg/dl was inversely associated with CHD (OR=0.38), the relationship did not reach the statistical significance (*p*=0.09). However, the LDL and HDL ratio had a positive trend for prediction of CHD, which has started at the "gray zone" level (ratio between 4 and 5). Patients with LDL is to HDL ratio of >5 were 20

Table 1 - Adjusted odds ratio of prevalence of coronary heart disease by nonlipid variables.

Variables (mg/dl)	Odds ratio (95% confidence interval)		*p* values
Gender	16.7	(3.4 - 82.17)	0.0005
Male	0.02	(0.007 - 0.08)	0.00
Female			
Age (years)			0.0045
30-39	0.0349	(0.0008 - 1.6)	0.08
40-49 versus >60	92	(8 - 1.57)	0.0003
Male >45	1.99	(0.9 - 261.6)	0.11
Diabetes mellitus	16.05		0.05
Diabetic type II	2.68		0.02
Hypertension	0.54		0.27
Congestive heart failure	0.38		0.015
Family history	59.9	(1.7 - 2082)	0.023
HTN			0.009
Diabetes mellitus			0.02
More than one	1.7	(0.02 - 3.1)	0.2
Hyperlipidemia	1.12		0.78
Current smokers	0.058	(0.0023 - 1.5)	0.09
Ex-smokers	28.8	(2.4 - 343.5)	0.007
History of myocardial			

HTN - hypertension disease

Table 2 - Adjusted odds ratio of prevalence of coronary heart disease by various lipid parameters.

Variables	Odds ratio (95% confidence interval)		p values
Low-density lipoprotein			
Very high risk (190-219)	3.75	(0.4 - 35.1)	0.037
Extremely high ≥220	753748	(0 - 1.87)	0.04
Total cholesterol			
Borderline-high risk (200-239)	64.4 10	(2 - 2.44)	0.018
High risk (≥240)		(0.7 - 138.8)	0.08
High-density lipoprotein			
Desirable >35	0.38	(0.125 - 1.19)	0.09
LDL:HDL ratio			
Gray zone "4-5			0.07
High risk >5	20.8	(2 - 1017)	0.12
Triglyceride			
Borderline-high risk (200-239)	0.72	(0.04 - 12)	0.3
High risk ≥240	0.11	(0.005 - 2.5)	0.8

times more likely to develop CHD than patients with ratio of <5. For triglyceride levels, none of their risk categories were independently associated with CHD incidence. The total cholesterol and HDL ratio was also of minor significance compared to other lipid parameters and therefore it was removed with the triglyceride variable from the final model.

Overall, this cross-sectional survey has revealed the high prevalence rate of CHD among the Jordanian society referred to cardiac catheterization units at 2 major medical centers in Amman in which medical services are provided for a broad range of public and private sectors. Although the prevalence of dyslipidemia of various types showed greater positive trends in patients with CHD (N=145) than non-diseased patients (N=56). The overall distributions of various risk categories of total cholesterol, triglyceride, LDL-C, HDL-C, triglyceride/HDL-C, and LDL-C/HDL-C were not significantly different between the 2 groups, probably due to the smaller number of non-diseased patients.

Nevertheless, it was concluded that hyperlipidemia of any type was not the only crucial determinant of vascular stenosis in all admitted cases of CHD. Therefore, it was recommended that further large-scale, prospective surveys should be carried out to define other "nonclassical" variables, which were recently in question as predictors of CHD, such as infectious agents, markers of inflammation, homocysteine and Lp(a).[5] However, conflict go on regarding their exact role in pathogenesis of atherosclerosis.

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