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**Note:** Please make sure that you Register only **once** for all your Manuscripts
In this issue of SQUMJ, Dr. Deepali Jaju and her colleagues have shown the effects of a yoga technique known as Pranayam breathing (PB) on the pulmonary system. These authors have demonstrated that PB has different effects on healthy controls compared to those with chronic obstructive pulmonary disease (COPD). PB invoked clear improvement in maximum inspiratory pressure (MIP) in normal controls; however, PB was not able to produce MIP changes in subjects with COPD. There was however, a significant increase in the visual analogue score (VAS) in COPD patients, which suggested reduction in respiratory distress. While the improvements were limited, and perhaps variable in different people, it does indicate that there is indeed some validity in yogic intervention.

In modern parlance, health care systems outside the realm of modern biomedical sciences, also termed ‘allopathic medicine’, are often labelled ‘traditional medicine’. The increasing acceptance of ‘non-allopathic’ health care systems, has led to some of them have being accepted as ‘complementary and alternative medicine’ (CAM). The term ‘integrative medicine’ has also emerged to describe the concurrent use of different healing systems to increase vitality, cure disease, or as integral part of a regimen for a healthy lifestyle or prevention of diseases.

In the SQUMJ February 2011 issue, Dr. Rahma Al-Kindi and her colleagues studied the use of alternative medicine among adult diabetics. The study population was 146 patients, attending diabetic clinics at four primary health centres in the Muscat area of Oman. This study demonstrated that 52% of the subjects had used alternative medicine at some time in the past. Most importantly, 42% of the cohort had used herbs and food supplements specifically to manage their diabetes. As half of the patients were satisfied with such interventions, the study sends a clear message: alternative medicine is widely used in the Muscat area for conditions such as diabetes. Such findings imply that physicians should be better prepared to discuss the use of CAM with patients, with all the implications this may have including the consideration of potential side effects and drug interactions.

It is no surprise that SQUMJ has attracted manuscripts on CAM in its recent issues since this is consonant with international trends. There is evidence in the literature to suggest that there is widespread increased use of CAM even in developed countries like the United States. In addition to the widespread general increase in use, CAM is also being increasingly used to treat some specific diseases of major concern to society, such as arthritis and cancer in developed countries, and malaria in Africa. In developing countries, where modern health care systems have remained rudimentary, traditional medicine continues to meet a significant proportion of health care needs.

Many healing systems owe their origin to ancient civilizations. In the Middle East, numerous records show the existence of pre-Islamic healing systems. This healing system bloomed in ancient Mesopotamia, which encompassed the area around the Tigris and Euphrates rivers, corresponding to...
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Present-day Iraq, Syria, Turkey, and part of Iran. This cradle of civilization competes with historic Egypt in the development and application of such healing systems. During the heyday of the Islamic civilization, various healing systems came into prominence and some of them were employed in early experimental studies, the precursors of modern clinical trials.

Historically, India is one of the countries that has given humanity a unique healing system known as Ayurvedic medicine which originated at least 4,000 years ago. The term Ayurveda is a combination of Ayu (life) and Veda (science). Ayurvedic medicine is based on a humoral interpretation of disease and health with the idea of balancing the three humours “Vata,” “Pitta” and “Kapha.” Ill health results when these three are out of balance. Just like India, China developed its own unique health care system that eventually spread to Japan, Korea and some other parts of the Far East. The cardinal idea of the Chinese health system was symmetry or balance, as in Ayurvedic medicine, and echoed the philosophy of ‘Galen’s medicine’ in ancient Greece. In Chinese medicine, illness is due to an imbalance in the flow of energy through established channels or meridians. A normal flow is essential for good health and self-healing; bamboo sticks, fish bones and now needles are used to stimulate points along the energy meridians and referred to as acupuncture. Healing systems in Europe were strongly influenced by Galen and Arab/Islamic medicine until the end of medieval period. With the emergence of science and experimentation during the European Renaissance, scientific medicine started to take root. This, in turn, led to the current domination of the modern allopathic biomedical health care system in Europe and North America. Nonetheless, even in these regions, there is still wide popular use of various CAM healing practices such as hydrotherapy, naturopathy, and herbalism, as well as chiropractic therapy, breathing, meditation and the use of mega-vitamins. The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institute of Health (NIH) in the USA has instituted scientific studies to explore the efficacy of both the remaining traditional medicine systems and newly emerged healing systems.

With respect to Oman, the health system is a hybrid of of allopathic medicine and traditional healing practices, the latter being deeply rooted in society. It is thus not surprising that Dr. Rahma Al-Kindi found a high use of herbal treatments for the self-management of diabetes. Oman also has other types of CAM including the well known ‘physical treatments’ such as “Al Wasam” (المسح) cauterization and “Al Hujama” (الحجامة) vacuum cup suction of the body surface. Traditional Omani ‘orthopaedic’ interventions include the use of “Al Jabirah” (الجبرة), a homemade equivalent of plaster of Paris used by a traditionally trained person (a “Mugabbir” – مجابير) for fractures and sprains. There are also various ‘spiritual’ interventions often employed for combatting what would in Western medicine be deemed to be psychological disorders; these include “Al Bassar” (المسح) and “Zar” (زور), both exorcism practices. In addition, like other countries round the world, Oman also uses a variety of herbs (“Marameiah” – المرميه) for different medical conditions. There is also a specific type of deep massage which is used for the treatment of infertility in Oman (“Al Maasah” – المسح). Other CAM physical treatments used in Oman include using a twin to treat migraine by massaging the affected side of the person’s forehead with his/her foot.

Despite the wide current use of non-allopathic treatment, there are still highly polarized views on the topic among modern practitioners of biomedical health care system. Many doctors who practice conventional allopathic medicine do not ‘believe’ in the efficacy of CAM at all—“it neither works nor does it have any basis on which it can possibly work”. Then, there are those doctors who practise both allopathic medicine and CAM, but unfortunately, some of these are doing it only for profit.

There is however, a glimmer of hope as evidenced in the American NCCAM Center, where millions of dollars are spent on studying various forms of CAM including naturopathy, chiropractic medicine, Ayurveda, meditation, yoga, biofeedback, hypnosis, homeopathy, acupuncture and nutrition-based therapies among other therapies. NCCAM aspires to establish the evidence-based efficacy of CAM. More recently, some clinical research has been employed to shed light on the efficacy of CAM, employing vigorous research methodology such as controlled clinical trials. To understand CAM better, NCCAM has classified CAM into 5...
major groups:11 1) Whole medical systems such as Ayurvedic medicine, Chinese medicine and homeopathy; 2) Mind-body medicine which include yoga and meditation; 3) Biological-based substances such as herbs, foods and vitamins; 4) Manipulative and body based practices such as chiropractic and osteopathy manipulations; 5) Energy medicine including biofield therapists and bioelectromagnetic-based therapies. The Cochrane Center has also reviewed some scientific studies on CAM and published them on website of the Danish Knowledge and Research Center for Alternate Medicine (ViFABS).15

Those of us who practise conventional allopathic medicine need to have a better understanding of CAM, how it works, and what the potential benefits and side effects are. We need to be more willing to discuss the use of CAM with our patients. There is indeed potentially great danger in combining the two without proper knowledge of both. This is of particular concern when a serious illness threatens the confidence of patients in modern allopathic medicine and they resort to CAM as adjunctive therapy, and, at times, as the sole treatment. It is not clear why people use CAM, but their reasons are related to social and cultural issues, as well as the nature and severity of their disease. Somehow, CAM has a major persuasive appeal to patients.16,17 In developed countries, wide usage of CAM among patients with chronic and debilitating disease may be due to a culturally-based wish to "leave no stone unturned" and a patient's 'loss of hope' of regaining their pre-morbid self as in the case of people with aggressive types of cancers or other progressive debilitating diseases that are impervious to conventional medical treatment. There is no evidence to suggest that oncologists are fully aware of the trend for cancer patients to use CAM concomitantly with their chemotherapy. This, needless to say, is potentially dangerous as major toxicities may arise. Ernst et al. reviewed several publications and out of the 21 studies on adult cancers, 50% reported that 27% of respondents used CAM while the average percentage of adults using CAM was 31.4%.8

Why patients use alternative medicine and which patients do this has yet to be empirically charted. John Astin, from Stanford Center for Disease Prevention, has studied the socio-demographic characteristics of people who use CAM and found that those who used CAM were likely to be well educated, but have poor health status.18 It was found in this study that people utilised CAM not because they were dissatisfied with conventional medicine, but because they found it "more congruent with their valued beliefs and philosophical orientations towards health and life."14 It is not known how widely CAM is used in different communities or clinical conditions. Most of the available studies are marred by poor design and methodological limitations. Harris and Rees have reviewed 12 studies and could not come to a clear conclusion.9

However, there is hope for humanity as a whole because it is gradually getting clearer that there is a lot of potential benefit from CAM, even though currently there is some misuse or improper use. As more and more clinical and basic scientific studies are carried out, it becomes clearer that the boundaries between CAM and conventional Western medicine are becoming blurred. On the whole, what is considered complementary and alternative practice in one country maybe considered conventional practice in another, e.g. some herbs in standard use in Europe are considered CAM therapy in the United States.13 An increasing number of robust studies are appearing in the literature showing the potential benefits of using CAM alone or as part of integrative medical therapy. One of these is a recent Norwegian study from the Norwegian University of Life Sciences (UMB). It is a scientific study of the plants extracts derived from the bark of Cinchona tree and the Sweet Wormwood plant (Artemisia Annua) that have been used since dawn of history in African traditional medicine against malaria. Interestingly, contrary to the case with some of the conventional drugs available to treat malaria today, the malaria parasite has not yet developed resistance to the formula employed in African traditional medicine.9 Another recent clinical research study has studied the effects of omega-3 fatty acid and fish intake on development of age-related macular degeneration (AMD) amongst the 38,022 women who were followed up by questionnaire.19 The results showed a significant decrease of the incidence of AMD over 10 years follow-up. It is postulated that the fatty acid in fish and omega-3 fatty acid helped improved choroidal blood flow in the eye. AMD and cardiovascular disease have been hypothesised to share similar mechanisms and risk factors. Intake
of fish and omega-3 fatty acid has been linked to reduced cardiovascular events possibly related to the anti-inflammatory and anti-atherosclerotic effects of these products.

Where do we go from here? We, as modern allopathic medicine practitioners, need to take a long and good look at our attitude towards CAM. We need to be well-versed in this subject so that we are able to discuss it intelligently with the ‘e-patients’ of the 21st century. We need to understand the role of CAM when used alone or in conjunction with other treatment protocols that are an integral part of biomedical care. We need more scientific research devoted to understanding how and which CAM treatment has benefit to those who use it. The future of health care would be best served if an enlightened and amicable merger of the two branches of medical treatments were contemplated. More studies are therefore imperative. This means physicians need to open their eyes and apply their minds to this endeavour.

References


The Role of Pharmacokinetics and Pharmacodynamics in Early Drug Development with reference to the Cyclin-dependent Kinase (Cdk) Inhibitor - Roscovitine

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ABSTRACT: Pharmacokinetics, pharmacodynamics and pharmacogenetics play an important role in drug discovery and contribute to treatment success. This is an essential issue in cancer treatment due to its high toxicity. During the last decade, cyclin-dependent kinase inhibitors were recognised as a new class of compounds that was introduced for the treatment of several diseases including cancer. Cyclin-dependent kinases (Cdk's) play a key role in the regulation of cell cycle progression and ribonucleic acid transcription. Dereulation of Cdk's has been associated with several malignancies, neurodegenerative disorders, viral and protozoa infections, glomerulonephritis and inflammatory diseases. (R)-roscovitine is a synthetic tri-substituted purine that inhibits selectively Cdk1, 2, 5, 7 and 9. Roscovitine has shown promising cytotoxicity in cell lines and tumor xenografts. In this paper, we present several aspects of pharmacokinetics (PK) and pharmacodynamics (PD) of roscovitine.

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Clinical approval of new drugs is preceded by intensive research consisting of two steps, drug discovery and drug development. In the drug discovery stage, target enzymes and/or receptors for a particular disease are identified, and new molecules are designed and screened for their biological activities. Promising drug candidates are evaluated for their toxicity and efficacy in the development stage.

Studies on the metabolism and pharmacokinetics (DMPK) of candidate drugs have become an essential part in drug discovery and development programmes and start usually concomitantly with the screening for biological activity. It is estimated that approximately 10–40 % of drug candidates fail due improper pharmacokinetic properties. Further, DMPK studies provide vital information about the PK/PD (pharmacokinetics/pharmacodynamics) relationship. This knowledge is prerequisite for safety phase I clinical trials and prediction of a clinical effective dose.

Moreover, PK is essential for further investigation of drugs in phase II and III clinical trials. PK/PD also play important roles in dose optimisation, personalised treatment and prevention of side effects. This in turn determines the clinical outcome. These aspects are especially important in anticancer drugs due to their toxicities and the narrow therapeutic window.

Age is one of the important factors affecting the PK and efficacy of drugs. Variability in drug exposure and efficacy occurs among the different age populations, i.e. children, adults and elderly. It is essential to investigate the PK parameters in the age population that is treated with the drug. In the younger aged population, doses of many drugs are still not optimised due to lack of knowledge about drug disposition and PK in this particular population. Several factors such as the ontogeny of the metabolising enzymes and drug transporters are responsible for the variability of DMPK. Continuous efforts are being made to develop accurate PK models to predict the PK parameters in this population without conducting a large scale investigation which might be difficult due to technical and ethical restraints. Age-dependent pharmacokinetics in young animals at different stages of development should be considered before clinical use.

Cyclin-Dependent Kinases

Cyclin-dependent kinases (Cdks) are a family of serine/threonine kinases that are activated through binding to regulatory subunits called cyclins. Cdk enzymes are homologues and highly conserved in their cyclin binding domain. Despite the fact that the human sequencing programme has successfully indentified 20 Cdks and 25 cyclins, their functions are still not fully understood and a limited number of active Cdk/cyclin complexes have been identified so far.

Cyclin-dependent kinases are regulated by several mechanisms including, transcription and translation of their subunits, heterodimerisation with cyclins, post-translational modification by phosphorylation and dephosphorylation and interactions with the natural inhibitors. The natural inhibitors CIP/KIP (p21, p27, p57) suppress the Cdk/cyclin complexes and INK4 proteins (p15, p16, p18 and p19) inhibit the Cdk4 and Cdk6 monomers.

Cdk/cyclin complexes play an essential role in the regulation of the cell cycle progression. Cyclins transcription and degradation varies during the different phases of the cell cycle and lead to the activation or inactivation of the corresponding Cdks.

During the last decade, the roles of Cdks in several diseases including cancer were extensively studied. Over expression of cyclin B1 and hyperactivation of Cdk1 has been observed in a number of primary tumours including breast-, colon- and prostate carcinoma. Inactivation of Cip–Kip inhibitors and over expression of cyclin E and/or cyclin A lead to deregulation of Cdk2 in various malignancies, including melanoma, ovarian...
carcinoma, lung carcinoma and osteosarcoma. Cdk5 has been found to modulate the metastatic potential of some malignancies including breast and prostate carcinomas.

Cdk2 and Cdk5 have been shown to play important roles in apoptosis in various tissues. Cdk2 was found to regulate apoptosis in thymocytes, while subcellular localisation of Cdk2 have been found as a determinant of the apoptotic or proliferative fate of mesangial cells.

Cdk5 has an essential role in the central and peripheral nervous system. Cdk5 regulates the cytoarchitecture of the developing brain and mediates the neuronal migration in the post mitotic neurons. Cdk5 has also many important functions in the neuronal cytoskeleton dynamics, synaptic plasticity, drug addiction, synaptic endocytosis and neurotransmitter release. Cdk5 may be involved in the pathogenesis of several neurodegenerative disorders such as Alzheimer’s and Parkinson’s disease. It has been shown that Cdk9 induces the differentiation in distinct tissues and the degree of expression of Cdk9 correlates with differentiation of primary neuroectodermal and neuroblastoma tumours.

Due to the important role of Cdk5 in several diseases including cancer, intensive efforts to find selective cyclin-dependent kinase inhibitors (Cdki) have been made during the last 15 years. Several classes of different Cdki have been identified. In spite of their chemical diversity they share common characteristics: 1) Cdkis have low molecular weights (about 600); 2) Cdkis are flat hydrophobic heterocyclic compounds; 3) Cdkis act by competing with adenosine triphosphate (ATP) for binding in the kinase ATP-binding site, and 4) Cdkis bind mostly by hydrophobic interactions and hydrogen bonds with the kinase.

Cdki have been classified according to their selectivity into three groups: 1) Pan-Cdki that inhibit Cdk1, 2, 4, 5, 6, 7 and 9 with almost similar potency like flavopiridol; 2) Selective Cdki for Cdk5 1, 2, 5, 7 and 9 such as the 2, 6, 9 tri-substituted purines (olomoucine, roscovitine and purvalanol), and 3) Selective Cdki for Cdk4 and 6 (PD-0332991 or P-276–00).

**(R)-Roscovitine (CYC202)**

Roscovitine belongs to the 2, 6, 9 tri-substituted purines [Figure 1]. Roscovitine was found to be a selective inhibitor for Cdk1, 2, 5, 7 and 9. In the kinase inhibitory assay, roscovitine has been shown to inhibit these kinases with the IC50 at the nanomolar range. Roscovitine was also found to inhibit several other kinases such as CaM Kinase 2, CK1α, CK1δ, DYRK1A, EPHB2, ERK1, ERK2, FAK, and IRAK4 at the micromolar range (1-40 µM). However, other kinases including Cdk4, Cdk6 and Cdk8 were not sensitive to roscovitine.

Since Cdk5s have an important role in a wide range of cellular functions, roscovitine has been suggested as a potential treatment for several pathophysiologically different diseases. The effects of roscovitine have been studied in vitro in cell lines and in vivo in animal models. The in vitro effects of roscovitine have been studied in more than 100 cell lines. Several studies have reported the IC50 required to inhibit cell proliferation including the NCI 60 cell line panel (average IC50 = 16 µM), the McClue et al. panel (19 cell lines; average IC50 = 15.2 µM), and the Raynaud et al. panel (24 cell lines; average IC50 = 14.6 µM). The IC50 average required for inhibition of cell proliferation in cancer cell lines does not exceed 17 µM; moreover, roscovitine was shown to be cell cycle phase non-specific. Direct inhibition of several Cdk5 results in inhibition of the exit from G0 (Cdk3/cyclin C), G1/S transition (Cdk2/cyclin E), S phase progression (Cdk2/ cyclin A), G2 phase (Cdk1/Cyclin A) and G2/M transition (Cdk1/Cyclin B). Depending on the cycling status of the cells, the antimitotic effects of roscovitine may comprise combinations of these mechanisms.
Indirect inhibition of the cell cycle by roscovitine is mediated through the inhibition of the activity of Cdk7/ cyclin H/ MAT1 (CAK) resulting in prevention of the phosphorylation of the T loop threonine of various Cdns. This finally decreases the activity of Cdk1, 2 and 4. Also phosphorylation of the natural inhibitor p27 by Cdk2 will be diminished leading to its stabilisation and more inhibition of the cell cycle. In addition, roscovitine was shown to inhibit the initiation of DNA synthesis, the formation of centrosomes and the formation of the nucleolus.

Roscovitine has been shown to induce apoptosis in several cell lines regardless of the p53 status; however, roscovitine has a higher potency to induce apoptosis in wild type p53 cells compared to p53 null cells. Cell death has been detected in all phases of the cell cycle and different mechanisms may be involved including inhibition of the cell cycle due to p53 activation and inhibition of Cdk7/Cdk9-dependent transcription inhibiting RNA polymerase II enzyme. Effects of roscovitine on global transcription have been shown to be limited and only few proteins such as Mcl-1, XIAP, and survivin have been found to be severely reduced. Induction of cell death by roscovitine, thus, seems to correlate rather well with inhibition of transcription of essential cell survival factors.

Down regulation of survivin and XIAP by roscovitine was shown to contribute to the activation of caspases in glioma cell. Alvi et al. have reported that roscovitine induced apoptotic cell death in chronic lymphocytic leukaemia B-lymphocytes at significantly higher level than in normal blood mononuclear cells, purified B- or T-lymphocytes. Apoptosis was caspase-dependent but p53- independent and was accompanied with down regulation of Mcl-1 and XIA.

Anti-proliferative and pro-apoptotic effects of roscovitine have been implicated in cancer treatment and used in studies on the antitumour effects of roscovitine. So far, no cell line resistant to roscovitine has been reported until now.

Interestingly, tumour cells are more dependent on the short-lived survival factors compared to normal cells, and thus, down regulation of these factors by roscovitine treatment has a higher impact on tumour cells. Synergistic effects of roscovitine in combination with other chemotherapeutic agents such as camptothecin in MCF-7 breast tumour, irinotecan in p53-mutated colon cancer, histone deacetylase (LAQ824) in HL60 and Jurkat leukaemic cells and doxorubicin in sarcoma cell lines have been shown in vitro.

Antitumour effects of roscovitine as a single treatment, or in combination with conventional cytostatics, have been studied in vivo in various tumour xenografts models. Nude mice bearing human colorectal cancer or human uterine cancer xenografts were treated with roscovitine at different dosing schedules. Roscovitine inhibited the tumour growth rate and reduced tumour volumes and weights. Roscovitine was also shown to be effective in reducing the growth of A4573 (Ewing’s sarcoma) and PC3 prostate tumour xenografts.

The efficacy of roscovitine in non-nude BDF1 male mice bearing Glasgow osteosarcoma xenografts was investigated in relation to biological circadian rhythm. Roscovitine was administered orally (300 mg/kg x1 daily) for 5 days Zeitgeber time 3 (ZT3, 3 hours after light onset) or at ZT11 or ZT19. Roscovitine reduced the tumour growth by 35% when administered in the active time of the mice (ZT19) and 55% when administered during their rest span (ZT3 or ZT11).

Roscovitine showed higher antitumour activity when combined with other antitumour treatments. Maggiorella et al. have reported better reduction in tumour volume from 54% to 72% when a single dose of 100 mg/kg was given intraperitoneal (i.p.) and combined with radiation therapy in mice bearing MDA-MB 231 (breast cancer). Roscovitine was shown to have a synergistic effect in inhibiting HT29 colon cancer xenografts when combined with irinotecan.

**Pharmacokinetics and Metabolism of Roscovitine**

The PK of roscovitine have been reported in mice, rats and human. Vita et al. reported the PK and biodistribution of roscovitine in rats after a dose of 25 mg/kg. Roscovitine PK was described by a two-compartment open model and short elimination half-life (<30 min). The highest distribution of roscovitine was observed in lungs followed by liver, fat and kidney, while exposure to roscovitine in brain was 30% of that observed in plasma. Three major metabolites were detected in plasma, but no metabolites were detected in brain.
The PK of roscovitine was investigated in BALB/c and Tg26 mice. These studies showed rapid and biphasic clearance of roscovitine from plasma following intravenous (i.v.), i.p. or oral administration. Roscovitine had rapid tissue distribution and rapid elimination with a half-life of 1.19 hr. Plasma concentrations above 15 µM (the average IC50 values obtained with various tumour cell lines) were observed for 4, 12, and 24 h following oral administration of 50, 500, and 2000 mg/kg, respectively.

The PK of roscovitine in humans were reported in two phase trials. Roscovitine was administered orally as a single dose (50 to 800 mg) to healthy volunteers and the concentrations of roscovitine and its carboxylated metabolite were followed in plasma and urine. Roscovitine was found to undergo slow absorption from the gastrointestinal tract, but food intake did not affect the bioavailability of the drug. Roscovitine was found to have rapid metabolism and non-saturated high protein binding.

In the second investigation, twenty-one patients with a median age of 62 years (range: 39–73 years) were treated with roscovitine in doses of 100, 200 and 800 mg twice daily for 7 days. The elimination half-life ranged between 2–5 hrs depending on the dose of roscovitine. Neither objective tumour responses, nor inhibition of retinoblastoma protein phosphorylation (suggested as a suitable PD endpoint) in peripheral blood mononuclear cells were observed. High protein binding of roscovitine (92% to 96%) was shown in human and mice plasma.

In vitro and in vivo metabolism of roscovitine was reported recently. Several metabolites were indentified including the carbonylated metabolite (oxidation of the alcohol group at C2 of the purine ring), CYP3A4 and CYP2B6 enzymes have been shown to be the main enzymes in roscovitine metabolism. Roscovitine was found to undergo phase II metabolism through conjugation with glucoronic acid by the phase II UGT1A3, 1A9 and 2B7. Moreover, roscovitine was able to inhibit its own metabolism in vitro through inhibition of CYP3A4 with the IC50 of 3.2 µM. Thus, possible drug-drug interactions should be considered in the clinic.

PK/PD of Roscovitine in the Bone Marrow in Mice

Myelosuppression is one of the most frequent complications and a dose limiting factor for the majority of conventional chemotherapeutic agents. Depending on the dose, several cytostatics may induce complete myeloablation of the bone marrow. Studies on haematotoxicity in vitro and in animal models help to predict the possible side effects prior to clinical trials.

In order to investigate the myelosuppressive potential of roscovitine we studied the effect of roscovitine on bone marrow cells in vitro and in vivo in Balb/c mouse. Crude bone marrow was incubated in vitro with roscovitine at concentrations of 25–250 µM for 4 hrs and viability was studied using resazurin assay. The viability of bone marrow cells was decreased in a concentration-dependent manner. Concentration of 250 µM significantly reduced the viability of the cells to 70% compared to controls ($P = 0.015$) while lower concentrations did not have a significant effect. Our results were in agreement with the findings that roscovitine induced apoptosis of mature neutrophils, eosinophils and proliferating T-cells in a concentration and exposure-time dependent manner. The myelosuppressive effect of roscovitine on haematopoietic progenitors was studied using a clonogeneic assay. Bone marrow cells were exposed to roscovitine (1 - 100 µM) in semisolid MethoCult media containing growth factors. Suppression of
The Role of Pharmacokinetics and Pharmacodynamics in Early Drug Development with reference to the Cyclin-dependent Kinase (Cdk) Inhibitor - Roscovitine


...colony formation in a concentration- and cell type-dependent manner was observed. CFU-GEMM were most sensitive and were completely blocked at 25 µM concentration, followed by BFU-E which were also significantly inhibited at 25 µM while CFU-GM were least sensitive and were inhibited at 100 µM only [Figure 2].

We further studied the myelosuppressive effect of roscovitine in vivo in female Balb/c mice. Roscovitine was administered to the mice and bone marrow cells were cultured in the MethoCult media and assessed for colonogenic growth. No myelosuppressive effect was detected after the administration of a single dose of roscovitine up to 250 mg/kg. Then, roscovitine was administered at a dose of 175 mg/kg twice daily for 4 days. Only transient inhibition of the BFU-E colonies occurred one day after the last dose of roscovitine. The colony formation capacity of bone marrow was recovered 5 days after the last dose of roscovitine [Figure 3].

The lack of activity of roscovitine on haematopoietic progenitors in vivo was not expected after its proven inhibitory effect in vitro and the reported activity on different xenografts in vivo. Therefore we decided to study the distribution and PK of roscovitine in Balb/c mice. Roscovitine was administered as a single i.p. injection in a dose of 50 mg/kg. As presented in Table 1, roscovitine had a short half-life (less than 1 hr) and only a small fraction of roscovitine (about 1.5%) reached the bone marrow compared to plasma. Thus, low distribution of roscovitine to bone marrow may explain the low haematotoxicity in vivo. This example illustrates the importance of PK/PD and biodistribution in preclinical studies. This may be also implicated in the fact that, despite a good cytotoxic effect of roscovitine in leukaemic cell lines in vitro, the therapeutic potential of roscovitine in haematological malignancies may be limited.

Age-Dependent Kinetics and Dynamics of Roscovitine in Rat Brains

Age-dependent PK is an important issue when the drug may be used in the treatment of paediatric patients and/or when the drug has a narrow therapeutic window. Unfortunately, scaling down the PK data from adults to paediatrics, has been proven not to be sufficiently predictive for many drugs. Roscovitine has been found to inhibit different solid and haematological tumour cell lines including acute lymphoblastic leukaemia (ALL), which is frequent in children and is correlated with a high central nervous system (CNS) relapse rate.

Recently, we have explored the effect of age on the PK of roscovitine and investigated the effect of roscovitine on two neuronal targets, Cdk5 and Erk1/2, in different brain regions. Fourteen day-old pups and adult Sprague-Dawley rats were...
found in plasma (Table 2). The $C_{\text{max}}$ was significantly ($P < 0.05$) higher (>22 µg/g) in pups brain compared to that found in plasma, while 4-fold higher $C_{\text{max}}$ was found in plasma compared to that observed the brain (17.7 µg/ml and about 4 µg/g, respectively) in adult rats. The high concentrations of roscovitine found in the pups’ brains indicate the free passage of roscovitine into the brain.

This difference in exposure might be due to the immaturity of the CYP450 enzymes responsible for roscovitine metabolism or immaturity of BBB. Roscovitine is metabolised in humans mainly by CYP3A4 and CYP2B6 enzymes. Several CYP450 enzymes are not fully matured at the age of 2 weeks in rats. A similar situation was also reported in humans and CYP3A4, for example, approaches the adult full capacity only after first year of life.

Most chemotherapeutic agents do not cross the BBB and do not reach the CNS in enough high concentrations to eliminate tumour cells despite treated with a single i.p. injection of roscovitine in a dose of 25 mg/kg and plasma and brain were sampled at different time points. Table 2 shows the pharmacokinetic parameters of roscovitine in plasma and in different brain regions in pups and adult rats. The PK of roscovitine was best described by a 2-compartment open model with distribution half-lives of 0.6 hrs in pups and 0.06 hr in adult rats. A significantly longer elimination half-life (7 hrs) was observed in the plasma and brain of the rat pups compared to 30 and 20 min found in the plasma and brain in adult rats, respectively.

The area under the concentration–time curve (AUC) of roscovitine was 22-fold higher in the pups’ plasma and 100-fold higher in the pups’ brains compared to that found in adult rats [Figure 4]. No significant difference between roscovitine AUC in plasma and AUCs in different brain regions in pups was found. On the contrary, in adult rats, the AUC of roscovitine in the brain was about 25% of that found in plasma (Table 2). The $C_{\text{max}}$ was significantly ($P < 0.05$) higher (>22 µg/g) in pups brain compared to that found in plasma, while 4-fold higher $C_{\text{max}}$ was found in plasma compared to that observed the brain (17.7 µg/ml and about 4 µg/g, respectively) in adult rats. The high concentrations of roscovitine found in the pups’ brains indicate the free passage of roscovitine into the brain.

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Most chemotherapeutic agents do not cross the BBB and do not reach the CNS in enough high concentrations to eliminate tumour cells despite
the high systemic exposure. Roscovitine was highly distributed over the BBB in the pups and the brain exposure in all studied regions (e.g. hippocampus, cerebral cortex and cerebellum) was 100% of that found in plasma which can be compared to about 25% that has been found in the brain of adult rats. The high distribution to the brain could be explained by an age-dependent variation in the maturity and function of BBB. Butt et al. have shown that the BBB of the rat fully matures 3–4 weeks postnatal.68 No roscovitine metabolites were found in the brains of both adult and young rats.

In pups, roscovitine concentrations in plasma and brain were higher than the reported IC50 (10-15 µM) for cancer cell lines for more than 8 hours. However, this level of exposure was achieved for less than 30 minutes in plasma and brain of adult rats. These results may be implicated in the treatment of paediatric malignancies especially brain tumours.

Roscovitine is a potent inhibitor of Cdk5 which has important function in the developing brain such as neuronal migration.15 Moreover, the negative

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**Table 2**: Pharmacokinetic parameters in plasma and brain of adult and pups rats. Results are presented as mean ± standard deviation (SD) (n = 3)

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Plasma (h.μg/ml)/ (h.μg/g)</th>
<th>Frontal Cortex</th>
<th>Hippocampus</th>
<th>Cerebellum</th>
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<tr>
<td>AUC</td>
<td>Pups 66.79 ± 7.15, 69.57 ± 15, 74.92 ± 12, 78.72 ± 11.2</td>
<td>Adults 3.01 ± 0.21, 0.71 ± 0.14, 0.58 ± 0.03, 0.62 ± 0.06</td>
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<td></td>
<td>Adults 0.50 ± 0.09, 0.48 ± 0.19, 0.43 ± 0.1, 0.59 ± 0.14</td>
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<td></td>
<td>Pups 0.081 ± 0.05, 0.045 ± 0.02, 0.062 ± 0.012, 0.062 ± 0.018</td>
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<td></td>
<td>Adults 7.2 ± 1.4, 6.8 ± 1.3, 8.0 ± 1.7, 7.7 ± 2.2</td>
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<tr>
<td></td>
<td>Adults 0.54 ± 0.26, 0.35 ± 0.13, 0.36 ± 0.15, 0.42 ± 0.18</td>
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<tr>
<td></td>
<td>Pups 15.79 ± 0.38, 24.9 ± 1.8, 24.75 ± 1.9, 23.69 ± 1.4</td>
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<tr>
<td></td>
<td>Adults 17.71 ± 4.42, 4.47 ± 0.70, 4.64 ± 0.81, 3.81 ± 1.22</td>
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<tr>
<td></td>
<td>Pups 88 ± 15.3, 90 ± 21, 86 ± 20, 102 ± 13</td>
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</tr>
<tr>
<td></td>
<td>Adults 650 ± 223, 1095 ± 167, 2056 ± 219, 1909 ± 484</td>
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</tr>
<tr>
<td></td>
<td>Pups 9.7 ± 1.2, 10.2 ± 1.5, 11.1 ± 2, 11.3 ± 1.2</td>
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</tr>
<tr>
<td></td>
<td>Adults 1637 ± 118, 7262 ± 1612, 8737 ± 452, 8139 ± 727</td>
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</tbody>
</table>

Legend: AUC = Area under the concentration–time curve; Tα,Tβ = distribution and elimination half-lives; Cmax = maximum concentration; Vss = volume of distribution; Cl = clearance.
feedback regulation of mitogen activated protein kinases (MAPK) signalling by Cdk5 has been suggested to be important for neuronal survival.69

High concentrations of roscovitine found in the brain of pups raised the question about the effects of roscovitine on target enzymes. We assessed the expression of p35 as an indicator of Cdk5 activity. Inhibition of p35 phosphorylation by Cdk5 stabilises it and delays its proteasomal degradation.70,71 Roscovitine induced a transient and significant accumulation of p35 protein in all brain regions in rat pups that indicates the inhibition of the Cdk5 enzyme. An increase in p35 was found in the frontal cortex 1–2 hrs post-administration (140% of controls, Figure 5, P < 0.05), in the hippocampus and in cerebellum at 2 hrs post-administration (150% and 200%, respectively, Figure 5). The levels of p35 were normalised at 6–15 h [Figure 5]. No change in p35 levels was observed in the adult brain which probably is due to the low concentration and the rapid elimination half-life.

Cdk5 was found to inhibit Erk1/2 phosphorylation by a MEK1 and RasGRF2 mediated mechanism and the inhibition of Cdk5 by roscovitine increased the levels of phosphorylated Erk1/2 (active form) in neuronal cells in vitro.69,72 At early time points after administration of roscovitine, the accumulation of p35 protein was accompanied by increased levels of the phosphorylated (activated) form of Erk1/2. In the frontal cortex and hippocampus, a transient activation of Erk1/2 was observed at 1 and 2 hrs after injection [Figure 6]. In the cerebellum, significant increases of pErk1/2 levels at 2 hrs were followed by a significant decrease at 6 hrs after administration [Figure 6]. At later time points, levels of pErk1/2 returned to control levels in all brain regions [Figure 6]. Altogether, roscovitine was presented in the brain of rat pups in sufficient amounts to inhibit the Cdk5 resulting in increased phosphorylation of Erk1/2.

Discussion

Cyclin-dependent kinases (Cdks) are serine/threonine kinases that play key roles in cell cycle progression and RNA transcription. Deregulation of Cdks has been shown in several diseases including several types of cancer in which increased activity of Cdks has been observed. Synthetic cyclin dependent kinase inhibitors (Cdkis) are small heterocyclic compounds which compete with ATP and inhibit the phosphorylation of the target substrates. Exposure of tumour cells to Cdkis results in both cell cycle arrest and apoptosis.

The family of 2,6,9-trisubstituted purines are one of the first described Cdk inhibitors.73 The (R)-stereoisomer of roscovitine is a member...
of this family and has now reached phase II clinical trials for non-small cell lung (NSCL) cancer and nasopharyngeal cancers and phase I trials for glomerulonephritis. Preclinical investigations of the role of roscovitine in the treatment of neurodegenerative disorders such as Alzheimer’s disease, viral infections, protozoal infections and inflammatory diseases are ongoing. Roscovitine has a rapid metabolism and short elimination half-life in rodents and man.44,50,52,53 The poor pharmacokinetic profile and the insufficient exposure to the drug in cancer patients may explain the modest success in the clinical trials.54 Current research is focusing on overcoming pharmacokinetic barriers that limit the clinical use of roscovitine. Moreover, a novel class of second generation analogues of roscovitine has been designed and is under development. Studies on the pan-Cdk inhibitor flavopiridol confirmed the importance of optimising the schedule of dosing according to the PK/PD relationship. By changing the dose schedule from 72 hrs infusion to 30 minutes i.v. bolus followed by a 4-hrs infusion, a significant difference in the clinical outcome and final response of refractory CLL patients was achieved.74

No myelosuppression has been reported until now in the preclinical and clinical studies with roscovitine.53,54 However, clinically beneficial low haematotoxicity of roscovitine may reflect in reality poor distribution of roscovitine to the bone marrow. In vitro, the haematopoietic progenitors were inhibited by roscovitine within the same exposure range as the tumour cells when comparing the inhibitory AUC reported for tumour cell lines 26,44 with the inhibitory AUC of the haematopoietic progenitors found in our study.

Under certain circumstances the haematotoxicity of roscovitine may become more evident: 1) Changes in the form of administration, aiming to increase the half-life of the drug, may result in higher exposure to roscovitine and changes in biodistribution. This in turn may change the toxicity profile; 2) A combination of roscovitine with radiation therapy, which increases the permeability of blood-bone marrow barrier,75 and thus the distribution of some drugs to the bone marrow, may increase the myelotoxicity of roscovitine, and 3) In pediatric patients where age-dependent longer elimination half-life is most likely leading to higher exposure of haematopoietic progenitors to roscovitine and thus toxicity risk.66

Age dependent PK is an important issue concerning toxic drugs and drugs with a narrow therapeutic window such as anticancer drugs, where underdosing may lead to relapse while overdosing can cause severe side effects. Age dependent kinetics were reported for several drugs including cis platin, busulfan, thioguanine, etoposide, lamivudine and

Figure 6: Effect of roscovitine on p-Erk in different brain parts of rat pups 14 days old after single intraperitoneal (i.p.) injection of 25 mg/kg. Pups were killed at different time points after injection, brains dissected, homogenized, and immunoblotted for active phosphorylated Erk1/2. Control animals were injected with vehicle. The figure show densitometric analysis of the Western blotting bands for pErk1/2 in the frontal cortex, hippocampus and cerebellum until 48 hr after single i.p. injection of roscovitine. Data are presented as mean ± standard deviation (SD) of values expressed as percentage of control animals (*, P < 0.05 is the significant level for analysis of p-ERK data; Analysis of variance (ANOVA) followed by all pairwise Fisher’s Protected Least Significant Difference (PLSD) post-hoc test).
Our studies showed that roscovitine elimination half-life was 14-fold higher in young rats compared to adults. Moreover, the exposure to the drug was 22-fold and 100-fold higher in the plasma and brain, respectively. These results indicate the importance of early determination of the PK-parameters in different age groups.

Conclusion

Roscovitine inhibits mouse haematopoietic progenitors in vitro within the same concentration range required to inhibit malignant cells; however, the cytotoxic effect of roscovitine on haematopoietic progenitors in vivo is transient due to a short half-life in combination with low distribution to the arrow compartment.

Roscovitine demonstrates age-dependent PK. Prolonged systemic and brain exposure to roscovitine was found in pups compared to adult rats, which may be due to immature CYP450 enzymes as well as the BBB. Moreover, roscovitine was able to induce a transient effect on critical neuronal targets and signalling pathways in the brain of young rats. These studies show the importance of early pharmacokinetic and pharmacodynamic studies in drug development.

ACKNOWLEDGMENTS

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References


The Role of Pharmacokinetics and Pharmacodynamics in Early Drug Development with reference to the Cyclin-dependent Kinase (Cdk) Inhibitor - Roscovitine


Diabetes mellitus is a growing public health concern and a common chronic metabolic disease worldwide.1-4 Diabetes mellitus represents a group of metabolic diseases that are characterised by hyperglycaemia due to a total or relative lack of insulin secretion and insulin resistance or both. The metabolic abnormalities involve carbohydrate, protein and fat metabolism. Diabetes mellitus affects all age groups, but is more common in adults. The World Health Organization (WHO) has recently declared it to be a pandemic.2 Its prevalence has increased dramatically over the past few decades and it is expected to triple in the next decade. Diabetes mellitus is considered a leading cause of death due to its microvascular and macrovascular complications.5,6 The most common types of diabetes are type 1 (also known as insulin dependent) and type 2 (also known as non-insulin-dependent).2,9 Type 2 is the more prevalent type. Countries with the highest rates of diabetes in the Eastern Mediterranean region and the Middle East are the United Arab Emirates, Saudi Arabia, Bahrain, Kuwait and Oman.9 Oman is one of the countries that has a high prevalence of diabetes mellitus, especially type 2 diabetes, and its prevalence is expected to increase in the next twenty years.10,11

Various inflammatory diseases and soft tissue pathologies in oral cavities are associated with diabetes mellitus;12-14 however, awareness of these complications is lacking worldwide.15-18 Periodontal diseases have been proposed as the sixth most prevalent complication of diabetes mellitus following the other diabetic complications.19 It has been reported as a more frequent oral complication of diabetes compared to other oral manifestations.
such as dry mouth and caries. Periodontitis is more frequent and severe in patients with diabetes with poor glycaemic control. Early identification and/or management of these oral manifestations may help in the early diagnosis of diabetes and in attaining better glycaemic control. Therefore, diabetic oral complications need to be identified and included in the ultimate care of diabetes in order to fight this chronic metabolic disease effectively.

Oral Complications and Manifestations of Diabetes Mellitus

Several soft tissue abnormalities have been reported to be associated with diabetes mellitus in the oral cavity. These complications include periodontal diseases (periodontitis and gingivitis); salivary dysfunction leading to a reduction in salivary flow and changes in saliva composition, and taste dysfunction. Oral fungal and bacterial infections have also been reported in patients with diabetes. There are also reports of oral mucosa lesions in the form of stomatitis, geographic tongue, benign migratory glossitis, fissured tongue, traumatic ulcer, lichen planus, lichenoid reaction and angular cheilitis. In addition, delayed mucosal wound healing, mucosal neuro-sensory disorders, dental carries and tooth loss has been reported in patients with diabetes. The prevalence and the chance of developing oral mucosal lesions were found to be higher in patients with diabetes compared to healthy controls.

Periodontal Diseases

PATHOPHYSIOLOGY OF PERIODONTITIS

Periodontitis is one of the most widespread diseases in the world affecting the oral cavity, and is highly prevalent in both developed and developing countries. Periodontitis is a chronic inflammatory disorder affecting the gingivae and the periodontal tissue initiated by bacteria. The micro-flora in the dental plaque that forms daily adjacent to the teeth causes this inflammatory process. Eventually, the toxins that are released by the microorganisms in the dental plaque will start the gingival inflammation as a result of failure to remove the dental plaque on a daily basis. A periodontal pocket is formed as a result of the progression of the gingival inflammation causing the gingivae to detach from the tooth surface. This periodontal pocket is filled with bacteria and its toxins. As the disease worsens, the pocket will get deeper carrying the dental plaque until it reaches the alveolar bone that will eventually be destroyed with the periodontal attachment. This process is very common and causes destruction of periodontal tissues, loss of alveolar bone and, finally, tooth loss [Figure 1]. There are many factors contributing to this type of inflammation beside the presence of bacteria in dental plaque; a susceptible host is one of them.

PERIODONTITIS AND DIABETES MELLITUS

The link between diabetes mellitus and periodontal disease is not well recognised by the medical community. Periodontal disease has been reported with increased prevalence and severity in patients with type 1 and type 2 diabetes. The mechanism by which hyperglycaemia can induce periodontal destruction is not yet fully understood. However, there are many theories which propose factors such as advanced glycation end products, changes in collagen statue, and altered immune function that causes impaired polymorphonuclear leukocyte function which may facilitate bacterial persistence in the tissue and the accumulation of advanced glycation end products, which results from prolonged and chronic hyperglycaemia and increased secretion of pro-inflammatory cytokines such as tumour necrosis factor-α and prostaglandin E-2. The increase in collagenase activity together with the reduction in collagen synthesis will adversely influence collagen metabolism. This
would result in compromised wound healing as well as periodontal tissue destruction. Recent studies indicate that periodontitis has a bidirectional effect on glycaemic control in patients with diabetes.\textsuperscript{31} There is a cluster of research studies, which support the hypothesis of periodontitis occurring more frequently in patients with diabetes with poor glycaemic control.\textsuperscript{33-38} In addition, there is enough evidence to support the hypothesis that poor periodontal conditions could worsen glycaemic control as well. Many studies report that diabetes is a risk factor for gingivitis and periodontitis and it is more severe with poor glycaemic control [Figure 2].\textsuperscript{39} The risk of developing periodontitis in patients with diabetes has been reported to be three times higher than the general population.\textsuperscript{40}

Numerous risk factors have been reported that make patients with diabetes more susceptible to periodontal disease, especially those with poor oral hygiene, poor metabolic control, longer duration of diabetes and who are smokers.\textsuperscript{41-43} Smoking was identified in many studies as being a major preventable risk factor for periodontal disease and tooth loss in the general population and in patients with diabetes.\textsuperscript{44-46} The dentist and the physician should play an important role in advising and supporting patients with diabetes regarding smoking cessation. The dentist should be engaged in counselling these patients and referring them to a specialist organisation which deals with smoking cessation.\textsuperscript{49}

Several studies showed that the treatment of periodontal disease has an influence on glycaemic control in both type 1 and type 2. A recent meta-analysis of the efficacy of periodontal treatment on glycaemic control in patients with diabetes suggested that such treatment could lead to a significant reduction in HbA1c.\textsuperscript{50} However, they also recommended that the results need to be viewed with caution due to a lack of strength and limitations in the designs of some of the studies included. Periodontitis and diabetes are related to each other therefore further larger studies are required to determine the effect of periodontal treatment on glycaemic control.

**Salivary and Taste Dysfunction**

**SALIVARY DYSFUNCTION**

Saliva has a major role in maintaining a healthy oral cavity. Saliva is produced by major salivary glands (parotid, sub-mandibular and sub-lingual) and numerous minor salivary glands distributed in the oral cavity. Salivary dysfunction has been reported in patients with diabetes.\textsuperscript{51,52} A cross sectional epidemiological study was conducted in 2001 to look at the prevalence of hyposalivation and xerostomia (dry mouth) and to determine the relationship between salivary dysfunction and diabetes complications. This study was conducted in type 1 diabetics and control subjects without diabetes. They found that symptoms of reduced salivary flow rate and xerostomia were more frequently reported by patients with diabetes than the controls, especially by those diabetics who had developed neuropathy.\textsuperscript{53} Other studies conducted in type 2 diabetics also confirmed that xerostomia and hyposalivation were more prevalent in this group of patients.\textsuperscript{54} It has been shown that poorly controlled type 2 diabetics have a lower stimulated parotid gland flow rate compared to well-controlled patients and patients without diabetes.\textsuperscript{55} An increase in salivary pathogens was also reported in these patients.\textsuperscript{56} Patients with diabetes usually complain of xerostomia and the need to drink very often (polydypsia and polyuria). The constant dryness of the mouth would irritate the oral soft tissues, which in turn will cause inflammation and pain. Patients with diabetes with xerostomia are more predisposed to periodontal infection and tooth decay. The cause of this is not yet fully understood in patients with diabetes, but may be related to polydypsia and polyuria or alternation in the basement membrane of the salivary glands. It is known that diabetes mellitus is associated with...
chronic complications such as neuropathy, microvascular abnormalities and endothelial dysfunction that lead to deterioration of microcirculation and this may play a role in reduction of the salivary flow rate and composition. Sialosis is defined as asymptomatic, non-inflammatory, non-neoplastic, bilateral chronic diffuse swelling mainly affecting the parotid glands. Sialosis has been found to be more prevalent in patients with diabetes mellitus.

**TASTE DYSFUNCTION**

There are many factors that have been implicated in altered taste sensation in the oral cavity. Metabolic and endocrine diseases were proposed as causative factors for this disturbance; nevertheless, salivary dysfunction can contribute to altered taste sensation or elevation of detection thresholds. Taste dysfunction has been reported to occur more frequently in patients with poorly controlled diabetes compared to healthy controls. Diabetic patients who suffer from neuropathy have a higher taste threshold. Taste disturbance has also been reported to lead to poor glycaemic control by inhibiting the ability to maintain a good diet.

**Oral Infection**

**FUNGAL INFECTIONS**

Oral candidosis is an opportunistic infection frequently caused by *Candida albicans* species. Many predisposing factors can lead to this infection; these include smoking, xerostomia and endocrine and metabolic diseases. Other factors were also implicated such as old age, medications, Cushing’s syndrome, malignancies, and the use of dentures. Oral candidosis has been classified into primary and secondary. Primary oral candidosis is subclassified into acute (pseudomembranous and erythematous), chronic (pseudomembranous, erythematous and hyperplastic) and candida associated lesions.

Pseudomembranace candidosis is also known as oral thrush. It is characterised by the presence of a creamy white patch which, when wiped, reveals underlying erythematous and bleeding oral mucosa. The soft palate is the most commonly affected area followed by the cheek, tongue and gingivae. It could be chronic in immuno-compromised patients. Erythematous candidosis can present as acute or chronic infection. It is believed to result from the usage of steroid and broad spectrum antibiotics and mainly affects the tongue. Hyperplastic candidosis is known as candidal leukoplakia. It appears as an irregular whitish raised plaque-like lesion commonly seen in the buccal mucous membrane near the commissures.

Candida associated lesions include denture induced stomatitis, angular cheilitis and median rhomboid glossitis which have mixed bacterial and fungal etiology. Denture induced stomatitis is mainly seen in full denture wearers in the underlying surface of the upper denture. Angular cheilitis is seen in the lip commissures as an erythematous crusting lesion. The lesion has been reported to occur in diabetics with poor glycaemic control. Median rhomboid glossitis is seen on the dorsal surface of the tongue as adepopulated erythematous diamond-shaped patch at the midline.

The incidence of fungal infections in patients with diabetes mellitus has been recognised for many years. Candidal infection is reported to be more prevalent in patients with diabetes especially in those patients who smoke, wear dentures, have poor glycaemic control and use steroids and broad spectrum antibiotics. In addition, salivary dysfunction in patients with diabetes can also contribute to higher carriage of fungi in this group of patients. It is clear from these studies that both local and systemic predisposing factors might increase candidal carriage rate and hence increase the risk of oral candidal infection in patients with diabetes.

**BACTERIAL INFECTIONS**

Patients with diabetes are more susceptible to developing oral bacterial infections. They are well known to have an impaired defense mechanism hence considered to be immuno-compromised. Diabetics with diabetic complications and poor metabolic control are more prone to spreading and recurrent bacterial infection. Several studies have reported that patients with diabetes are more prone to deep neck bacterial infection compared to patient without diabetes. A four-year prospective study by Rao et al. investigated the severity of maxillofacial space infection of odontogenic origin, the type of micro-organism, the sensitivity of the micro-organisms to
antibiotics, and the length of hospital stay of patients with diabetes compared with patients without diabetes. They concluded that the spread of the bacterial infection to the submandibular space was more common in patients and controls and that the second commonest area was the buccal space. *Streptococcus* species was more commonly isolated in both groups. Patients with diabetes were found to stay longer in hospital due to more severe infection and required more time to control their blood glucose levels.74

**Poor Oral Wound Healing**

Poor soft tissue regeneration and delayed osseous healing in patients with diabetes are known complications during oral surgery. Therefore, the management and treatment of patients with diabetes undergoing oral surgery is more complex. It was reported that delayed vascularisation, reduced blood flow, a decline in innate immunity, decreased growth factor production, and psychological stress may be involved in the protracted wound healing of the oral cavity mucosa in patients with diabetes.75

**Non-Candidal Oral Soft Tissue Lesion**

Oral lesions that are not caused by candidal infection have been reported to occur in patients with diabetes such as fissured tongue, irritation fibroma and traumatic ulcer. These lesions were more prevalent in diabetes compared to the controls.27 Altered or delayed wound healing may play a role in traumatic ulcer.

**Oral Mucosal Disease**

Both lichen planus and recurrent apthous stomatitis have been reported to occur in patients with diabetes.76,77 Oral lichen planus (OLP) is a skin disorder that produces lesions in the mouth. OLP is reported to occur more frequently in patients with type 1 diabetes compared to type 2 diabetes.76 The reason for this is that type 1 diabetes is considered an autoimmune disease, and OLP has been reported to have an underlying autoimmune mechanism. Patients with diabetes are subjected to a prolonged state of chronic immune suppression especially in type 1 diabetes. In addition, acute hyperglycaemia causes alteration in the immune responsiveness in diabetes mellitus. Atrophic-erosive oral lesions are more common in patients with diabetes with OLP.77

**Neuro-Sensory Oral Disorder**

Oral dysesthesia or burning mouth syndrome (BMS) is a painful condition affecting the oral cavity (palate, tongue, throat and gingivae).78,79 Other abnormal oral sensations may co-exist with the burning mouth sensation such as tingling, numbness, dryness or sore mouth at the same time. The exact cause of BMS is unknown, but it has been attributed to several conditions such as dry mouth, menopause, candidal infection, diabetes mellitus, cancer therapy, psychological problems and acid reflux. BMS is classified into two types: primary idiopathic, and secondary as a result of a systemic process; secondary BMS has been reported to occur with diabetes mellitus. It could adversely affect the ability to maintain good oral hygiene in patients with diabetes. Diabetic neuropathy could be the underlying cause of BMS in patients with diabetes. The nerve damage in diabetic neuropathy has been reported to show an increase in the Langerhans cells that are associated with immune disturbance.80, 81 Therefore, it is crucial to screen patients who have symptoms of BMS for diabetes mellitus.

**Dental Caries and Tooth Loss**

It is well known that patients with diabetes are susceptible to oral infections that lead to tooth decay and loss.82 Salivary secretion dysfunction, periodontal and sensory disorders could increase the likelihood of developing new and recurrent dental caries and tooth loss [Figure 3]. The relationship between diabetes and development of dental caries is still unclear. It is well-known that the cleansing and buffering capacity of the saliva is diminished in patients with diabetes mellitus resulting in increased incidence of dental caries, especially in those patients who suffer from xerostomia.
Conclusion

Diabetes mellitus is a chronic, non-communicable and endemic disease. Type 2 compared to type 1 diabetes mellitus is more prevalent worldwide and increasing, especially in Oman. Oral manifestations and complications in patients with diabetes mellitus have been recognised and reported recently as a major complication of diabetes mellitus. There is increasing evidence that chronic oral complications in patients with diabetes adversely affect blood glucose control. Prevention and management of oral complications, especially periodontal disease, in patients with diabetes is important due to their possible adverse effect on glycaemic control. Promotion of a healthy oral cavity in patients with diabetes is paramount. Epidemiological and research data on this problem in Omani patients with diabetes should be expanded by further studies.

There are several clinical implications from this review. These include: 1) a lack of awareness of oral complications among both diabetics and health providers; 2) an understanding of the way diabetes affects oral health is necessary for both clinicians and patients, therefore research in this field should be encouraged; 3) the need for regular follow-up of patients with diabetes mellitus by both dentist and physicians; 4) the major role that dentists should play in recognising the signs and symptoms of diabetes and their oral complications; 5) advice and counselling for diabetic smokers regarding smoking cessation, and 6) vigorous treatment of oral infection either bacterial or fungal in these patients, especially if they have poor glycaemic control.

References


The Sultanate of Oman is a Muslim Arab country located in the southeastern Arabian Peninsula. The strategic position of Oman, particularly as a marine centre connecting the Arabian Peninsula with the Indian Subcontinent and East Africa, contributed largely to creating the dynamic cultural hub which characterises the country. For many people in Oman, the year 1970, when the current Sultan took power, marked the leap of Oman into an independent state and the move towards modernisation. The health care sector has been one of the essential priorities in the evolving state.¹ Looking today at the public, state-wide biomedical health care system, the presence and evolution of biomedicine over the last two centuries could be easily overlooked by future generations. As even the seemingly minor traces of history do contribute to shaping and explaining current health care policies in the country,² and because of significant rising challenges to the existing system in Oman,³⁴ the need to look back at the roots of current practice and identify historical learning points seems more imperative than ever.

Few papers have attempted to address, even in brief, some of the aspects related to the history of medicine in Oman. The College of Medicine
at Sultan Qaboos University took an interesting initiative in The Dean’s Prize Essay in the History of Medicine for medical students which existed for several years during the 1990s. The award-winning essays touched on various aspects related to the history of medicine in general although often with a focus on Oman. Essays such as Folk Medicine in Oman through the Eyes of Traditional Healers, The Early History of Modern Medicine in Oman and The History of Medicine in Relation to Medical Education in Oman could form the seed for a deeper insight on the subject.\textsuperscript{5,6,7} Unfortunately, such initial efforts have neither been nurtured further nor sustained. Alas, there are at present no organised or sustainable efforts to study the historical development of the system of medical practice in relation to health and health care in the country.

The aim of this paper, therefore, is to trace the introduction and evolution of biomedicine in Oman during the 19\textsuperscript{th} century in relation to internal and external factors. It is an attempt to ignite interest in the medical humanities in general, and to break new grounds for investigation and research on the history of medicine by relating it further to health and health care in the country. As such, the article is expected to generate more questions and open more new doors for enquiry than it may present ready-made answers on the subject.

Methods

This study, to the best of the author’s knowledge, is the first to investigate and document in detail the very beginning and development of biomedicine in Oman in the 19\textsuperscript{th} century. Labelling medical and healing practices poses always a dilemma of terminology and definitions, particularly when it comes to Western medicine and its counterparts in other cultures.\textsuperscript{8,9} The term “biomedicine” is used in this paper specifically to connote biological medicine which is based on a positivist approach,\textsuperscript{10,11,12} so as to differentiate it from other forms of local medical practices that were present in the community.

Since writing a global history of biomedicine in Oman is virtually impossible, this study has to be limited in time to the 19\textsuperscript{th} century and in content to the evolution of biomedicine. The introduction of biomedicine in Oman corresponded largely with the increased Western involvement and intrusion into the region during late 18\textsuperscript{th} and the 19\textsuperscript{th} centuries. The pattern almost parallels the development of Western imperialism through the stages of exploration and discoveries, military and economic interests and religious imperialism. Investigating such a historical issue is hindered by the lack of documentation for this period. Moreover, socio-political events and internal conflicts were the topics of interest for local historians, but they rarely documented the health status of the general population, or healing practices in the community.

In studying history, there are usually three types of source materials.\textsuperscript{13} Primary sources include all materials produced at the time of an event by people with direct knowledge of it. Secondary sources are those that discuss, analyse or review primary sources. Tertiary sources are usually collections that organise data from secondary sources. This study utilised primary sources from travelogues written by visitors to Oman during the period under study. It also utilised the information contained in the administration reports sent by the British Naval Resident Surgeon in Muscat to headquarters. American Mission reports contributed as well to the documentation of medical practice in the country starting from the 1890s onwards. The study would have not been complete without referring to the few local resources that addressed health-related aspects of Omanis. In addition, secondary sources were also consulted and used to augment this study.

Why Study the History of Medicine?

Medical humanities, including the history of medicine, are as essential to medicine as basic sciences are. Medicine is an art and a science,\textsuperscript{14,15} and both aspects therefore should be considered whether one is dealing with an individual patient or with a medical system. Just like the vital importance of patient history in the clinical context, the history of medicine attempts to place people, institutions and events in the broader context in which they happened, lived or interacted.\textsuperscript{16} Among other functions, it questions the past in order to provide answers to current or expected problems of health and health care.

Being rather a dynamic social organism and not simply a mechanical structure, a health care system should be understood, evaluated and enhanced within its context and locale. Medical
humanities are essential for a practice that is suffering proliferating ethical dilemmas, frequent patient-carer miscommunication and increasing customer dissatisfaction despite skyrocketing costs. It can operate, as well, as a countermeasure against the “dehumanizing atmosphere that technology brings to medicine”. In addition, humanities may also contribute positively to medical education and practice in an age of crisis.

Medical humanities could also improve the art of medical practice and guide the rethinking of current health policies. Although it is thought commonly to deal with the past, studying history is about affecting the future course of events differently from what already happened or is happening. This makes the link between history and policy unambiguous, and as Rosenberg stated: “Policy is always history”. As such, history is indispensable for health systems in order to understand current public health challenges and affect, directly or indirectly, related future policies. In brief, the history of medicine can be a compass showing where health care was, where it stands now and in which future direction it should be steered.

### Brief History of Oman During 19th Century

Throughout history, Oman has remained an independent land, apart from short periods when mainly coastal areas were under Persian and, later, Portuguese control. Toward the end of the 18th century, Omani dominion had expanded beyond the south eastern Arabian Peninsula eastwards to the coast of Baluchistan in the Indian subcontinent and westwards to the shores of Mozambique. By the 19th century, its influence extended across the Gulf, Persia, Asia, and East Africa. This was the epoch of the “Omani Empire”.

The 19th century had also witnessed the struggle between western powers to gain a foothold in the area as part of their imperial expansion. As a consequence of rising western interests and competition in the region, the East India Company established a British Political Agency in Oman. This was moved in 1843 to Zanzibar when the capital was shifted there earlier under Sultan Said. In 1861, the British Residency was re-established by re-appointing a European political officer at Muscat. This was an important landmark for the institutionalisation of biomedicine in Oman as the nucleus of an organised biomedical practice was soon established by the British Army. Although the Omani empire had receded since the mid-19th century to occupy its original lands in the Arabian Peninsula, Oman continued to influence and be influenced by the external competing forces in the region, especially following the discovery of oil in the Gulf.

### Biomedicine in Oman: The Early Days

The rise of biomedicine and its first contact with people in Arabia coincided with the rising tide of Western colonialism and evangelisation in the region. Soldiers, missionaries, administrators and capitalists became almost simultaneously interested in Arabia. These different “invaders” attempted to enlighten the people they encountered, albeit by different means and for different reasons, but commonly toward “civilisation”. Doctors and nurses had diverse motivations for working away from home including economic, practical, social, professional and religious reasons; nevertheless, “they were all culturally determined”. Wendell Phillips portrays this civilising mission as he describes the work of Dr. Krause in the desert of Oman: “Here is one of the wildest, least known areas of the world, a primitive badawi lies in the sand extremely ill. Then, without warning, one of America’s leading medical specialists drops down as from heaven to serve his most grateful patient”. They were simply missionaries of a new culture, a new way of life and a new Weltanschauung.

Moreover, invading forces used medicine as a tool for penetration into Arabia, making the connection between biomedicine and these forces unavoidable. As an instrument used by various groups of politicians, armies and missionaries, and practised by professionals and non-professionals to gain entry into the region including Oman, biomedicine could be considered as a Trojan Horse of Arabia. Major Ross “believed that in the coming (20th) century the success of Imperialism would depend largely upon success with the microscope”. Members of the royal family and rich people who had more contact with the Westerners were more ready to welcome and adopt the biomedical approach to healing as they had access to it. Gradually, however, several
pushing and pulling factors contributed to the incorporation of biomedicine in the local Omani community as a mode of healing practice.

Pushing Factors

External pushing factors probably preceded the internal pulling ones. Politicians, discoverers, investors and missionaries guarded by military troops all used, or abused, biomedicine to fulfill their agenda in this region as they had in other parts of the world such as China, India and Africa. As will be noted later in the discussion, physicians were used to bargain for political and military advantages. They also helped the newcomers to cope with the harsh, “unhealthy” environment of their new “settlements”. Biomedicine was, initially at least, more of a condition for survival of the foreigners in the country than a requirement for the locals.

Toward the end of the 19th century, with increasing wealth and urban growth, new social hierarchies and influential relationships were being shaped by the imperial powers in the region. Medicine served a dual role for both the local elite and the invaders. It was a means for the elite to strengthen their relationships with the military powers and to prove their devotion in order to protect their interests in the region. As noted by Ghubash et al., “pro-British personalities played a substantial part in motivating Britain to introduce medical services into the region. That was their natural role, taking into consideration the status they enjoyed at that time.” On the other hand, medicine was utilised as a tool for those military powers to gain the confidence and satisfaction of the rulers and local people.

Pulling Factors

Pushing factors, no matter how forceful they could be, would not have exerted the required influence without a significant accompanying change in the social milieu. Pulling, or internal, factors calling for biomedicine to be part of local culture were related mostly to the pushing factors. The need was partly created by the new epidemics, illnesses and injuries shipped in by soldiers, merchants and missionaries. Ibn-Ruzaiq, a prominent Omani historian who died in 1857, described the cholera epidemic in 1821 as an ‘unusual plague’ leading to an assumption that cholera was probably not a known disease in this country until that date. This is consistent with various historical data that linked the 1821 Omani cholera epidemic with British troops sent from India to aid the Sultan against a local rebellion.

The industrial revolution and its surge of scientific discoveries had been associated with a new set of illnesses and injuries. The introduction of guns, for example, led to injuries previously unknown to locals. As Peter J. Zwemer noted, a man was brought over 600 km from Abu-Thabi (Abu-Dhabi, UAE, today) to the British military hospital in Muscat because of a gunshot wound, and a bullet was extracted successfully by the attending surgeon. Major surgery, in its modern practice, was indeed an incredible treatment modality for a population that largely used herbal medicines and other simple “surgical” procedures such as tajbeer (bone-setting) and wasm (cauterisation or branding).

In addition, and as happened in other cultures, the perceived inability of local healers to cope with new epidemics and types of illnesses and injuries paved the road for biomedicine to claim its effectiveness among the locals. People even copied new healing practices from others, probably with the hope of combating the ‘new plagues’. The Omani princess Sayyida Salma, in her memoirs published first in 1886, noted that some superstitious practices were unknown to Omanis until they mixed with people in the African part of their empire. Probably she was referring to the zar cult which has been used to treat spirit possession victims. This is consistent with other sources that refer the origin of this practice to Africa, and might explain earlier observations that this cult flourished in coastal rather than interior areas of Oman. Biomedicine was being accepted as a mode of healing practice to combat the new illnesses, but never as the sole one.

Evolution of Biomedicine in Oman

Biomedicine in Oman can be traced back to the late 18th century. The development can be categorised into three eras, distinctive in their characteristics, but yet having limited time overlap:

1. First Era (Sent to explore): the era of casual
medical practice by physician and non-physician explorers extended for the first six decades of 19th century.

2. Second Era (Sent to conquer): the era of organised military medicine services extended from the seventh decade of 19th century and beyond.

3. Third Era (Sent to heal): the era of missionary medicine extended from the 1890s onward.

These eras represent more topical than chronologic stages of biomedicine in Oman. The labelling of the eras reflects the general dominant trend of western powers in the region rather than individual practitioners’ objectives. The first and second eras correspond closely to phase 1 (exploration phase) and phase 2 (colonial phase) in the Basalla model for explanation of the spread of Western sciences to non-Western dominions.33

Sent to Explore

The last decade of 18th century witnessed a peak in the strife between the British and the French. Sayyid Sultan, the ruler of Muscat, had at that time a French military surgeon in his service.44 This prompted the British in 1799 to suggest sending Assistant Surgeon A. H. Bogle as a personal physician to the Sultan if the later agreed to exclude the French, and their physician, from Muscat. The Sultan did, and Dr. Bogle became the first British Political Agent in Muscat.25 Dr. Bogle, who died in less than a year, was then succeeded by Captain David Seton of the Bombay Army. Biomedicine has entered Oman on military ships as a door opener for the colonials and the doctor was the bait!

One of the earliest encounters during the early 19th century was with the Italian traveller, Vincinzo Maurizi, known to local people in the region as Shaik Mansur. He was appointed as the Sultan’s physician in 1809, shortly after his arrival in Oman.45 In addition to this position, he also had his own private medical practice, which he described as being ‘very extensive’. Nevertheless, he described the suspicions raised by some people regarding his claim of being a physician and how luck helped him overcome it! Apart from casual stories of patients he successfully treated, he did not elaborate much on the population health status, common illnesses, or medical and healing practices.

Not surprisingly, this era coincided with Western geographical exploration and is the most difficult to track as biomedical practice was not yet organised. Most of the information is in the writings of travellers who visited the country, or in the political history records. A few journals also referred to some biomedical practitioners in Oman, but mainly for their contribution to geographic explorations rather than their medical practice. Many military surgeons visited and toured the country, such as Dr. W. S. W. Ruschenberger of the United States Navy,46 Dr. Hulton, and John Henry Carter of the British Navy.47,48,49 Their accounts on the culture, geology, and topography of Oman reflect the trend of Western explorers in Asia and Africa at that time, but contain no elaborate medical reports.

The British Navy in Muscat had medical staff to care for its employees and also the royal family. Grant is probably referring to this in his statement: ‘The British Residency started medical work in Muscat in 1800, and maintained a medical staff throughout the century’.50 Bosch also asserted that a medical officer was maintained at that time by the British Residency as ‘Port Quarantine Officer’.51 The proposition that the quarantine officer was maintained throughout 19th century cannot be substantiated since the regulations were not present till 1867. In addition, the British Political Agency had been shifted to Zanzibar from 1843 until 1861, and it was represented in Muscat by an illiterate Jew during that period.52 Thus, it is hard to assume that any organised biomedical practice was undertaken by British Residency medical staff during the first half of the century. Nevertheless, this was the exploratory era when such visits probably had an impact on the elite society, in particular, and prepared it for the “new medicine” to come.

Sent to Conquer

During the 19th century, Western commercial interests in Oman developed into political as well as military affairs. Although the Arabian Gulf was never formally a part of the British Empire, it is acknowledged that the Gulf was indeed British.52 The British government of India was the only foreign government that could maintain a permanent mission in Muscat throughout the second half of the 19th century.53 The re-establishment of the
British Residency in Muscat in 1861 was a driving force to provide other supporting services for the permanent troops, including medical facilities.

In fact, this was the first time biomedical services were institutionalised in Oman, and probably in the Arabian Peninsula. A hospital was maintained within the Agency compound and was run by a surgeon major from the Indian Medical Services. The Sultan had donated a building that was suitable for the hospital and its dispensary.

The doctor during this period assumed multiple roles. Doctors not only treated their fellow soldiers, but they were also pioneers in reporting on local flowers and species, documenting socio-cultural practices and informing headquarters about political and military issues. The regular administration reports that were sent by the resident surgeon to the headquarters in India documented, among other things, the health of the population at that time.

Surgeon Major Mr. Apothecary Gaspar de Rozario was appointed as the British Political Agent in 1866. Rozario wrote an account of Muscat, which included a two-page briefing on the prevailing diseases, mainly small pox, measles and whooping cough. He had also documented the malaria and cholera epidemics in the summer of 1865. Rozario asserted that vaccination was started for the people of Muscat after nine years of "haranguing and illustration". Although this report was not dated, it could be assumed that it was written around 1875, i.e. 9 years after appointment of Rozario in Oman.

Surgeon Major A. S. G. Jayakar succeeded Rozario in Muscat and is probably better known to zoologists than to physicians as he identified three important Omani species that now carry his name: Tahr (\textit{hermitragus jayakari}), Fakhakh (\textit{agama jayakari}), and the small boa (\textit{eryx jayakari}). He seemed to have travelled extensively throughout Oman during the 21 years that he spent in the country before his retirement in 1900.

Jayakar deserves the credit for the first comprehensive biomedical report on Oman, entitled, \textit{Medical Topography of Muscat}. This 14-page account offered valuable information on the geology, climate, water supply, food, sanitation, streets and population of Muscat. It also included a detailed description of the prevailing diseases and related health issues in the country. Interestingly, Jayakar noted the very uncommon prevalence of organic diseases of the heart and large blood vessels and the rare occurrence of kidney and bladder diseases, dysentery, rheumatism and brain diseases. On the other hand, malaria was the prevailing disease in the region, and cases of consumption (tuberculosis) were common. According to him, bronchitis, dyspepsia, haemorrhoids, ulcers, and eye and skin diseases were also common in the region.

The 19th century witnessed a remarkable increase in the frequency of epidemics in the country. Much of the burden of these epidemics could be attributed to poor sanitation, unavailability of clean water, and the ‘harsh’ climate of the country as described by many Western travellers. Nevertheless, the contribution of population movement to and from their new dominions in Asia and Africa, combined with increased use of the Muscat port by military and trading ships, cannot be overlooked. Following the first cholera epidemic in Oman in 1821, a second outbreak took place in 1864, and a third in 1899. Although Jayakar reported that that "plague" had never been known to prevail in Oman, a breakout of plague was indeed reported in Mutrah, the twin city of Muscat, in 1899–1900.

As noticed above, despite the fact that many epidemics were related directly or indirectly to imperial activities in the region, there was neglect of the health of the general population in favour of a focus on health of the troops, western travellers and the elite. For example, ‘Maskat Quarantine Regulations’ were issued in 1867 for British subjects and British-protected subjects who entered Oman.

This may not be surprising since “[t]he first priority of imperial medicine prior to the First World War was to keep soldiers and officials functioning in unhealthy environments.” However, this era paved the road for the next when missionaries came to a country which was suffering from diseases and epidemics both contributed to and neglected by their fellow countrymen.

Sent to Heal

Toward the end of the 19th century, evangelical missionary activities were flourishing in Arabia. Oman was a strategic area to the missionary
enterprise, just as it was for the foreign political and military powers. General F. T. Haig of the British Army suggested Oman, Bahrain, and the Najd region in Saudi Arabia as profitable places for establishing permanent missionary stations.54 Missionaries realised early on that it would be futile to start out with empty hands on the adventure of “healing souls”. Healing bodies with biomedicine, tried already in some other areas such as China and Africa with success, could pave the way toward “God” in Arabia as well, or so it was thought. Despite the fact that the Muslim people of the region did not consent to any evangelisation, medical missionaries were still of particular importance as they were the key to the people and area.

The Arabian (American) Mission started its work in Oman in 1893. It was customary for non-medical missionaries to practice medicine and dispense drugs to people in the region during their tours, just as earlier explorers did. Samuel Zwemer, for example, was known to do this, and he used it as a door-opener during his tours in Arabia, including Oman.60 In 1896, the first recorded exploratory visit by a medical missionary to Oman was made by Dr. Worrall.61 Although missionaries frequented the country with their ‘medicine chests’ during the 1890s, it was not until 1904 that a medical clinic was started in Mutrah, the port area of Muscat, and run by Mrs. James Cantine.

Female medical practitioners were of particular importance to the missionary enterprise in the region and they were awarded a central role in Arabia. In fact, women’s medical services were among the most effective agents of cultural change in the region.62 Sayyida Salma, who converted to Christianity, called particularly for female physicians, as ‘there is a great opening here for Christian charity, that would bear fruit a hundredfold, without any great obstacles in the way’.63 It seemed that “Oman and all Arabia offer untold opportunities for the [missionary] medical profession”.63

At the turn of the 19th century, the Arab Gulf region was sandwiched between the tight military grip of the British Army on one side and the soft, “humanitarian” services of the American missionaries on the other. In contrast with the already existing British military hospital, missionary medical services were primarily public and sought to serve otherwise impenetrable parts of the country. Medical missionaries, just as in other parts of the world, blended in with the people as no other “foreigners” did. They lived their life, ate their food and shared their joys and sorrows. Their work included not only conquering the diseases of the poor, but also civilising the “heathen” with their Western cultural values.64,65,66 As Etherington has noted: “although missions and the official empire were quite different operations, they play related parts in a larger drama—the spread of modernisation, globalisation, and Western cultural hegemony”.67

Until the end of the 19th century, biomedical work was restricted mostly to the Muscat area although missionaries also started exploratory visits to the Batinah.67 Their activities expanded in the 20th century to include the interior of Oman, an area that had remained largely unreached by other foreigners. Medical missions with two operating hospitals were the active force in Omani biomedical practice until a national health care system was established in the 1970s.

Agenda for Future Research

The history of the evolution of biomedicine in Oman is intriguing and raises many questions that could form an agenda for future research on the topic. The nature of the interaction between state power, Western powers in the region, biomedicine, culture and traditional healing practices in Oman, and factors that affected such interactions, is a virgin area for investigation. Missionary medicine and missionaries in Oman and Arab Gulf is another almost untouched topic despite a wealth of primary sources. In addition, it would also be worth investigating social milieu changes in relation to health and healing practices, particularly following the establishment of missionary medical centres. Such studies should address these issues and relate them to the then health and healing practices, as well as probing possible implications for the current health system.

Conclusion

The introduction and evolution of biomedicine in Oman, which began in the 19th century, is a fascinating topic. What started out as casual exploratory visits further crystallised into a
permanent British military hospital that served mainly military staff and the elite, but occasionally the poor as well. The last decade of the 19th century witnessed the growing interest of American missionaries in the country, who were particularly influential in opening doors for not only the evangelising enterprise in the community, but for foreign intrusion in general. The history of changes in biomedicine and health in Oman is an interesting subject that needs more attention from local scholars and researchers. Humanities, in general, are still a subject which is lacking, or thought to be auxiliary, in the medical scene of most developing countries. Literature, history, philosophy, ethics and religion should be addressed in medical education not as a supplementary, but as a core subject. In addition, focused research and practice in these disciplines should be encouraged in order to explore and assess their contribution to current and future health and health care in Oman.

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References
ONLY A SMALL AMOUNT OF VITAMIN D comes from dietary sources, e.g. fish and meat, while most of it is known to be made by the body as a natural by-product of the skin’s exposure to sunlight. In the early 1900s, the discovery of the link between rickets and vitamin D deficiency helped to ensure that exposure to the ultraviolet B (UVB) fraction of sunlight became popular as a preventative medical intervention.

UVB rays enter the epidermis and release energy that changes a pre-existing cholesterol metabolite to previtamin D3, which is then slowly converted nonenzymatically to vitamin D3 (cholecalciferol). Vitamin D3, bound to a specific vitamin D-binding protein (DBP), is then transported to the liver, where it is enzymatically hydroxylated to 25-hydroxyvitamin D (calcifediol or 25(OH)D). Although 25(OH)D is only weakly biologically active, its circulating level furnishes a good index of the bioavailability of vitamin D because it has a long serum half-life (2 weeks). Then, 25(OH)D, bound to DBP, is transported to the kidney and other organs, where it is hydroxylated at the 1 position to produce 1,25(OH)2D, the most biologically active form of vitamin D.

However, sun education then started to emphasise the importance of protection from harmful ultraviolet rays (UVR), especially after...
the strong involvement of the United Nations (UN) in work to understand the health effects of UVR exposure. This was established at the UN Conference on Environment and Development in 1992. The trigger for that was the recognition that the ozone layer was being depleted and that the risk of diseases resulting from excessive exposure to UVR, particularly skin cancers, would probably increase.5

Several studies have demonstrated that exposure to environmental levels of UVR alters the activity and distribution of some of the cells responsible for triggering immune responses in humans. Consequently, sun exposure may enhance the risk of infection with viral, bacterial, parasitic or fungal infections, which has been demonstrated in a variety of animal models.6 The known health effects of UVR include also photokeratitis and photconjunctivitis. Moreover, sun exposure, in particular exposure to UVB, appears to be a major risk factor for cataract development.7 Regarding skin, exposure to UVR is considered to be a major aetiological factor for three common cancers: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM). Non-melanoma skin cancers, BCC and SCC, are most frequent on parts of the body that are commonly exposed to the sun such as ears, face, neck and forearms. This implies that long-term, repeated UVR exposure is a major causative factor. Moreover, there is a clear relationship, in some countries, between an increasing incidence of non-melanoma skin cancers and decreasing latitude, i.e. higher UVR levels.6 On the other hand, the causes of malignant melanoma (MM) are not fully understood. However, several epidemiological studies support a positive association with a history of sunburn, particularly sunburn at an early age. Tumour development may be linked to high, intermittent exposure to solar UVR,6 such as at weekends or on holiday.7 The higher incidence of malignant melanoma in indoor workers compared to outdoor workers supports that notion.7 Studies show also that malignant melanoma risk is higher in people with a history of non-melanoma skin cancers and of solar keratoses, both of which are indicators of cumulative UV exposure.6

In assessing how much sun exposure is needed for adequate vitamin D production, one should be aware that there is a threshold level of UVB required to induce vitamin D production.6 However, the exact dose of UVR exposure for optimal vitamin D levels is not known, particularly as the required UVR dose will be influenced by host factors. Whole body exposure in a bathing suit to one minimum erythemal dose (MED) of UVR is equivalent to ingesting 10,000 international units of vitamin D.9 MED is defined as the UVR exposure that will produce a just perceptible erythema 8–24 hours after irradiation of the skin. The MED is specific to each individual and varies with the source of UVR, the tanning capacity and any adaptation from previous exposures.10

A low level of casual sun exposure, even during summer, will result in only very small amounts of endogenous vitamin D3 production.11 The effects of sunlight exposure on vitamin D3 synthesis are also decreased by the use of sunscreens and in individuals with darker skin pigmentation12 because of the presence of high concentrations of melanin in the stratum corneum that severely inhibits vitamin D3 production.10 In addition to that, concentrations of 25(OH)D in blood serum—the best clinical index of vitamin D status—decline with age due to declining intake, decreased sun exposure and, perhaps most importantly, less efficient skin synthesis of vitamin D3.13 Thus, for a person with moderately fair skin, exposure of face, hands and arms for 6–7 minutes at 10:00 or 14:00 in summer (or 9–12 minutes in winter) in northern Australia (latitude 17° south), should produce around 1,000 IU of vitamin D, an amount sufficient to maintain vitamin D concentrations in the normal range. The equivalent exposure required at a higher latitude such as Tasmania (41–43° south) is 7–9 minutes in summer, but 40–47 minutes in winter.14 However, some argument remains over the range of concentrations of vitamin D in blood that should be considered ‘normal’. Currently, 50 nmol/L is accepted as the lower limit of sufficiency,5 although a study from Finland, suggested 80 nmol/L as the minimum level in blood able to prevent physiological changes associated with vitamin D insufficiency.15

Although a low prevalence should be expected, studies carried out in the last two decades show a high prevalence of vitamin D deficiency in many tropical countries,16 including Oman. In 2004, the Ministry of Health (MOH), Oman, in collaboration with the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO) and the United Nations International Children’s
Emergency Fund (UNICEF) conducted a cross-sectional household-based survey of micronutrient status using the sophisticated technique of high-performance liquid chromatography (HPLC) in the MOH Central Public Health Laboratory to analyse vitamin D and other micronutrients in serum samples from 832 households. The survey clusters were selected using the PPS (proportional to population size) sampling methodology. A sub-sample of 298 non-pregnant women of child bearing age was analysed for serum 25(OH)D. Alarmingly 21.4% of the women included in the survey were found to be vitamin D deficient (<27.0 nmol/L). Almost half of the women (47%) tested had serum 25(OH)D levels below 37.5 nmol/L, while only 10% of the women had levels above 75 nmol/L.

A more recent study by Al-Kindi in 2010 investigated serum 25(OH)D levels among 41 apparently healthy Omani women of childbearing age. All the women had a 25(OH)D level <50 nmol/L as the cut-off for deficiency. Another study conducted by Al Kalbani et al. in 2010 investigated the vitamin D status of pregnant Omanis by measuring their circulating 25(OH)D levels. In that study, blood samples were obtained from a cohort of 103 consecutive healthy pregnant Omanis on their first antenatal visit to the hospital. The study revealed that vitamin D deficiency ([25(OH)D] <25 nmol/L) was present in 34 cases (33%), ‘at risk’ levels ([25(OH)D] = 25–50 nmol/L) were found in 67 cases (65%); two cases (1.9%) had values between 50 and 75 nmol/L, and not one case was found in the optimal range (25(OH)D >75 nmol/L). The results confirmed that vitamin D3 stores are low in Omani females of reproductive age. The findings of the study were found by Al Kalbani and her colleagues to be similar to those reported earlier in Saudi Arabia and recently in the UAE and Qatar.

These recent studies conducted in Oman give a warning that subclinical vitamin D deficiency may be prevalent amongst Omani women and indicate the need for vitamin D replacement especially during pregnancy and lactation. This situation is surprising as Oman is known to be one of the sunniest countries in the world and its people are thus expected to have adequate sun exposure. This unexpected situation may be attributed to social and cultural factors as the conservative dress of Omani women, especially those who wear the veil, blocks exposure to sunlight. Added to that, the reduction in outdoor leisure time that has accompanied urbanisation in Oman and the rise in office-based work has lead to an increased lack of sunlight exposure. Females, particularly those who are sensitive to the sun’s UV rays, are more concerned about their appearance and health. They are unwilling to get dark-coloured skin or sunburn, and so avoid being exposed directly or indirectly to sunlight.

So, the boundaries between the risks and the benefits of UVR are unclear and the question therefore arises: “What is the balance between healthy sun exposure that provides sufficient UVR to maintain adequate vitamin D levels in blood serum, and excessive exposure that leads to an increased risk of skin cancer?” Unfortunately, public health campaigns aiming to decrease the incidence of skin cancer urged people to limit exposure to ultraviolet light, which is important for maintenance of vitamin D levels, especially in at-risk groups such as those who are elderly, who suffer from malabsorption or who have dark skin (particularly if they wear a veil). It is important also to mention that the guidelines for decreasing exposure included directives from the American Academy of Pediatrics (AAP) that infants younger than 6 months should be kept out of direct sunlight, children’s activities that minimise sunlight exposure should be selected, and protective clothing as well as sunscreens should be used. Accordingly, one consequence of avoiding possibly harmful sun exposure could be a reduced amount of physical activity, especially when school, work and recreational activities are usually scheduled outdoors between 10:00 and 16:00. Sun protection messages may, thus, inadvertently increase health risks related to physical inactivity such as obesity and cardiovascular disease.

All these irritatingly contradictory relationships make it very difficult to determine what the adequate sunshine exposure time is for any given person. The message to protect against excessive UVR exposure was seen to be correct in countries with abundant sunshine and populated by fair-skinned inhabitants. Even for populations that remain in the physical environments for which they are evolutionarily suited, marked changes in the social environment now predispose people to diseases associated with under- or over-exposure to UVR. Similarly, in populations that have moved from their traditional habitats, problems of both excess sun exposure and
vitamin D insufficiency are clearly evident. 5

The first national cancer council to recognize the importance of balance in recommendations about sun exposure was the Cancer Council Australia in its 2005 position statement “Risks and benefits of sun exposure”. 23 The statement did provide sufficient guidance on optimum levels of exposure. 5 However, the correct answers to several questions are still under debate: “What is the optimal level of vitamin D?”, “What is the amount of UVR needed to maintain an adequate vitamin D level?”, and “What is the optimal age-appropriate UVR dose?”

The conclusion is that increased UVR exposure is known to have harmful health consequences; however, UVR exposure also has some beneficial effects, especially in relation to vitamin D production. Therefore, a ‘one message fits all’ approach is not appropriate. Sun exposure or protection messages may need to be shaped to different situations, in recognition of the complex combination of host factors, e.g. age, sex, race, skin pigmentation, and sun-seeking or sun-avoidance practices. This matrix of considerations becomes even more complex when a diversity of cultural and social environments are taken into account. Added to that, the lack of clear guidelines may lead to inappropriate personal solar exposure. The substantial challenge for health workers is to translate their knowledge into readily comprehensible public health messages and, subsequently, to take account of the accretion of upcoming evidence-based information.

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To Be or Not To Be Exposed to Direct Sunlight
Vitamin D Deficiency in Oman


Health care professionals are dedicated individuals who require minimal direction and supervision to perform their duties. They are professionals in that they are bound to their code of ethics and their fiduciary responsibility to perform well and render quality services to their clients. It is believed that health care providers are the type of professionals that embody such beliefs and behaviour. These professionals are seldom found committing intentional mistakes or causing harm to their clients, but errors do occur in health care and “unacceptable” behaviour occasionally happens as well. For this reason, one has to question these practices and wonder why such highly regarded individuals who are extremely dedicated to their profession, clients and profession still commit errors. Some of these individuals also raise such questions as “What’s in it for me?” to do this or that and have been increasingly asking, “Why do I need to continue to work hard?” especially if there is no system of appreciation. One cause of the problem could be that there is a system that punishes errors, but no system to reward productivity.

Pay-for-Performance

One of the performance incentives models being used in the USA is Pay-for-Performance (P4P). This is a model that was initiated to improve measures of quality and efficiency, and eliminate excessive cost. It provides a financial incentive that allows payers and providers to link economic incentives and operational quality outcomes. The underlying assumption is that P4P will improve, motivate, and enhance providers to pursue aggressively and
ultimately achieve the quality performance targets thus decreasing the number of medical errors with less malpractice events.\(^1\)

In 2005, 75% of American companies and employers paid part of their employees’ salaries by a P4P method.\(^2\) Payment systems have been known traditionally to reward and pay health care providers for the quantity of their services rather than their quality. On the other hand, health care providers were still able to increase their incomes by providing quality service, but only as part of a payment for performance incentives system. In 2004, The UK’s National Health Service (NHS) began a system of P4P, where 8,000 general practitioners and family physicians agreed to increases in their incomes based on 146 quality indicators. A study showed that British health care providers have increased their average income by $40,000 by adhering to the P4P system.\(^3\) Therefore, incentives in any form combined with other methods to improve performance may prove successful to change provider behaviour.

Rewarding employees is becoming the norm in most successful organisations in the USA and worldwide. A recognised employee is a loyal employee and a loyal employee is a dedicated employee. A dedicated employee will perform at a higher level, but when dedication is not recognised it causes employees to lose their enthusiasm. Those unrecognised employees will gradually lose morale as well as their desire to work for improvement and innovation. It behoves an organization to recognise its employees often and continuously. However, recognition without sincerity may not have the same effect and in some cases, may even backfire. For example, saying thank you to employees who help a facility provide quality service can go a long way when facility managers are sincere. It is believed that a happy employee is one who innovates and competes with others to be the best.

Dedicated employees impact their organisations positively. On the other hand, a struggling organisation generally has a minimum number of dedicated employees. Dedication is critical for sustainability and continuous success. Without dedicated employees, organisations will not do well.

Having a rewards and recognition programme in place lets valued employees know that their contributions are important and their efforts are appreciated. Not only will the employees appreciate it, but clients may appreciate it as well. When employees are happy and satisfied with their work, their attitude will be reflected in the services they provide. When managers “go the extra mile” to keep the employees happy and treat team members well, employees will often go the extra mile to ensure clients are happy. Treating people well is reflective of how employees expect others to treat them.

Again with P4P, physician reimbursements will be partly dependent on patient outcomes, and it is widely assumed that a doctor can only do so much. In a study reported in the New England Journal of Medicine in 2003, patients only received 55% of the care they were supposed to get regardless of whether it was preventive, acute or chronic care.\(^4\) P4P is intended improve this situation. Another study found that hospitals participating in a P4P programme had modestly superior outcome measures compared to those who did not participate in such incentive programmes.\(^5\)

Although monetary rewards are important, recognition is even more important for professionals. High performing employees expect to be recognised, but do not necessarily expect to be rewarded. Sometimes a small token of appreciation may go a long way towards motivating dedicated employees. In fact, recognising employees (sincerely, often and on a timely basis) will improve retention and have a major and positive impact on attracting new staff. Employees want to be appreciated, valued and recognised and not all are motivated by money alone.\(^6\)

Nelson suggests that, “The best praise is done soon, specifically, sincerely, personally, positively, and proactively.”\(^7\) When employees feel valued, they are more satisfied and happier at work, and in turn will provide better service to patients. Putting an employee rewards and recognition programme in place does not have to be difficult or costly. There are many ways to show the team that their efforts are appreciated, not only for large accomplishments, but also for the smaller daily ones.

Incentives of all forms have two main goals: 1) to motivate the employee to perform or continue to perform better and 2) to have a long lasting effect on their performance. Motivations coming from any type of incentive should spur the recipients to meet these two goals by sparking an interest and a change in behaviour in the recipient and having a lasting effect on that individual’s desire to perform better. To achieve this, most researchers and experienced
organisations try to customise rewards based on employees’ preferences and expectations. Rewards may have different effects on different individuals depending on their education, culture and status in the organisation. Therefore trying different rewards and motivational methods may be necessary to engage employees more and to stimulate them to improve their performance.

On the other hand, W. Edwards Deming, a leading quality management scholar and consultant, taught and demonstrated that motivation efforts are a form of tampering because they try to make improvements to individual components of what is largely a common cause (or routine system) variation. He argued that the overall performance of a unit was much more a function of the quality of materials, process design and management, quality specifications and machine performance—in other words, the “system.” Deming went on to demonstrate that the result of an improvement strategy based on trying to lift the performance of each worker one-at-a-time would not be system improvement; rather, it would simply be an increased variation in performance. He encouraged management to find ways to lift the performance of the whole system.6,9

Putting together an incentive programme is, nonetheless, a great step toward improving employee morale and encouraging productivity. If employees are happy and motivated, it follows that clients will be happier and will reap the benefits as well. Saying thank you to everyone for a job well done is important.

Incentives can be either monetary or non-monetary. Monetary incentives include: P4P, cash, non-cash gift cards, certificates, merchandise, travel and experiential rewards. These and other such incentives have a varying impact on performance and behaviour.9 Examples of non-monetary incentives include: payroll or premium contributions, flexible work hours, health savings or reimbursement accounts, training, or even paid sabbaticals. Also, plaques, thank you letters, recognition certificates, stickers, and t-shirts with a logo are used. Other no-cost or low-cost awards include: presentation of a certificate of appreciation for a job well done at a staff meeting; nomination of department employee of the month; allowing employees to take classes and improve skills; sending a handwritten note of thanks for the completion of a challenging task; sending flowers to an employee’s family thanking them for sharing their loved one with the organisation during the preparation of an important project; making time to stop and chat with your employees; bringing treats for the office; encouraging participation in organisation’s activities; sending an employee to a conference, and development of a flexible work schedule.12

Payment-for-Performance for Health Care Providers

P4P programmes are designed to measure employees’ performance accurately while aligning pay such that it rises and falls in accordance with variations in performance. The use of P4P comes from a simple desire to motivate employees towards more constructive behaviour.13

P4P is an emerging movement in health insurance (initially in Britain and USA). Providers (and in some instances consumers) under this arrangement are rewarded for meeting pre-established targets for delivery of (or increased use) of health care services. This is a fundamental change from the fee for service payment system. The P4P or “value-based purchasing,” model rewards physicians, hospitals, medical groups, and other health care providers for meeting certain performance measures for quality and efficiency.

Disincentives, such as eliminating payments for negative consequences of care (medical errors) or increased costs, have also been proposed. In developed nations, the rapidly ageing population and rising health care costs have recently brought P4P to the forefront of health policy discussions. Pilot studies underway in several large health care systems have shown modest improvements in specific outcomes and increased efficiency, but no cost savings because of the added administrative requirements. Statements by professional medical societies generally support incentive programmes to increase the quality of health care, but express concern with the validity of quality indicators, patient and physician autonomy and privacy, and increased administrative burdens.14

In the United States, the Centers for Medicare and Medicaid Services (CMS), in an attempt to reform payment to providers for services rendered, designed and implemented a basic P4P system; one for hospitals and one for doctors’ offices.
Based on the commonest and most effective and evidence-based clinical practice guidelines of high volume medical conditions, CMS designed and implemented a programme to reward high performers. For hospitals, CMS identified some 20 plus process and outcome indicators related to three medical conditions: congestive heart failure, acute myocardial infarction and community acquired pneumonia. Hospitals were asked to volunteer in the programme by submitting their performance against those indicators to be ranked with other hospitals in the national database of these indicators. The high performing hospitals in the top 4% would receive a bonus on top of their reimbursements for maintaining a high level of performance. A similar system was designed for physician offices, but this one was based on medical conditions most frequently seen in an outpatient setting namely, diabetes, asthma, hypertension, back ache, etc. Again a number of indicators were identified and those doctor’s offices who volunteered to submit their measurements of performance against those indicators were entered in the national database and ranked against the performance of their peers. High performers will be rewarded with an annual bonus as a percentage of their reimbursement amount.

The CMS programme is in its early stages and has already experienced some challenges related to design, communication and impact on performance. Common design challenges include: difficulties in measuring performance; setting payouts at the correct level; managing factors outside the control of individuals being paid for performance; discomfort that managers and peers have with rating employees differentially; limited funding for payouts; resistance to adjusting payout levels as technology or market conditions change; avoiding perceptions of unfairness, and quality of implementation.

Communication challenges stem from the difficulties about how the programme works and what is required to achieve rewards. Additionally, there is little evidence so far that there is a marked impact on performance in general of those enrolled in the programme compared to those who are not. In fact, providers (hospitals and physicians) can easily manipulate the system by concentrating their performance improvement interventions on the specific indicators which will make their “focused” performance look good, but ignoring other indicators or medical conditions not included in the programme. In addition, the cost of designing, maintaining and evaluating the system is another burden that needs attention and perhaps a re-design.

Pay-for-Performance for Health Care Clients

Yet the P4P system has led to marked improvement in outcomes in several other locations and projects. The Bolsa Familia, a results-based financing for health project in Brazil, provides small monetary incentives for poor and very poor families on condition that they use certain health care services. Several health indicators showed marked improvements in these families: 1) Decrease in income inequity and poverty levels by 81%; 2) Decrease in child mortality, and 3) Improvements in maternal health.

Monetary incentives for consumers have been introduced not just in Brazil, but in a number of countries world-wide. The common factor between these projects was improving performance or enhancing behavioural change through incentives (primarily monetary). These practices showed a positive impact on health care outcomes and health indices. It was noticed that even small monetary incentives in certain populations (low or very low income families) had a positive impact on the health indices of these families’ mothers and children. According to the Center for Global Development, these projects were so successful that the number of families wishing to participate increased dramatically from the first year of these programmes.

As part of the Millennium Development Goals, in a project in 2006, conditional cash transfer (family stipends) was provided (US $26–55 per month/family) to more than 11 million families (or 46 million individuals) in Latin America. Once again, marked and tangible improvements were recorded in child health related to weight, vaccinations, school attendance, and nutrition. Similar results were noted in other conditional cash transfers projects in such countries as Guatemala and Nicaragua (combining demand and supply side incentives), Haiti (performance incentives model), Afghanistan, (paying NGOs for performance in post-conflict settings), Rwanda (performance
based financing in the public sector) and several Latin American countries and world-wide to offer incentives for TB diagnosis and treatment.\textsuperscript{19–21}

Two models were implemented in these projects: one targeted primarily to providers to increase the demand for health care services and another targeted at consumers to increase their use of health care and related services. In the all projects, workers reported that to ensure success of these projects the following characteristics should be present: 1) Designed in collaborative manner; 2) Development of realistic goals; 3) Development of indicators that are SMART (specific, measurable, achievable, realistic, and timely); 4) Tailoring of incentives (types and amounts) according to the target population; 5) Putting in place a system to monitor and validate performance, and 6) Development and execution of contracts.

**Pay-for-Performance Outside the Health Sector**

Outside the health sector, national and international companies have been using performance based incentives for their employees for a long time. For example, Conoco-Philips has long offered what they call a Viable Cash Incentives Programs (VCIP) to their employees based on the performance of the organisation, i.e. a share in the business success.\textsuperscript{22} Employees are rewarded for advancing company objectives and are accountable to their performance outcomes. Other practices elsewhere include the rewarding of employees in terms of monetary incentives or discounts for their participation in health enhancing programmes (exercise, dieting, smoking cessation, alcohol and drug abuse awareness programmes etc.) Insurance companies on the other hand also use monetary incentives to encourage their consumers to live and practice a healthy life style.\textsuperscript{23,24}

**Conclusion**

An incentive programme represents a substantial investment for most organisations. Receiving a sufficient return on that investment requires the full participation of the programme participants. Incentive programmes are based upon the concept that effort increases as people perceive themselves progressing towards their goal. Therefore programmes should offer participants a variety of products and services based on their unique interests and diverse needs. Successful programmes need to develop their reward methods carefully to keep participants eager to approach a new goal once they have achieved a reward.\textsuperscript{25}

There is often a poor level of incentives given to providers. Unless incentives are worthwhile, providers may not be interested or encouraged to participate. Incentives have to be based on a sound system of performance measurements that is both comprehensive and valid. Measures have to be reliable, valid and clear while comparisons between provider performances based on these measures should be risk adjusted and unbiased. These conditions are almost impossible to achieve in the current system of performance.\textsuperscript{26,27}

P4P and similar incentives programmes are a major improvement in the right direction. Providers must be accountable. Performance must be measured and levels must be ranked and compared with one another. Basing reimbursements of providers on quantity should be changed and payment based on performance should be encouraged.\textsuperscript{28}

Workers in general (even the most dedicated) thrive on constant encouragement, effective rewards and suitable recognition. Rewards tend to motivate people to do more and to do it better or continue to do it better. Without rewards, workers tend to lose interest in excelling and innovating. If not properly recognised, they will lose their enthusiasm for perfection and that will in turn diminish their morale and happiness. It is documented that unhappy employees are less productive, but worse still they will negatively affect the satisfaction of their clients.

There are many types of incentive programmes and a variety of options within each type. Not all incentives are applicable to all organisations and not all successful programmes will be successful in all organisations. For these programmes to be effective they must be customised, well-focused and suitable to the organisation’s culture and setting.

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Incentives for Better Performance in Health Care

Factors Affecting the Quality of Diabetic Care in Primary Care Settings in Oman
A qualitative study on patients’ perspectives

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ABSTRACT: Objectives: The quality of services delivered to type 2 diabetic patients in primary health care has an important impact on long-term outcomes. The aim of this study is to explore diabetic patients’ views of factors affecting quality of diabetic services delivered in primary care in Oman, a developing country with a high burden of diabetes. Methods: Semi-structured face to face interviews were conducted with 19 type 2 diabetic patients recruited from four selected primary healthcare centres (PHCs) in Muscat region, the capital city of Oman. A framework approach was used to analyse the qualitative data. Results: Participants identified several factors which could affect the quality of diabetic services provided in PHCs: delays in the follow-up process; lack of continuity of care; diabetes educational materials unavailable in waiting areas; shortage of Omani nurses able to speak the patients’ language; inadequate explanations from the attending primary care physician (PCP); under involvement of dieticians in patient management; delays in provision of laboratory results; inadequate supplies of diabetic medication between appointments, and long waits to see ophthalmologists. Conclusion: Several factors were identified by diabetic patients that may influence the quality of diabetic care in the PHC setting in Oman. Health care professionals and decision makers in the Ministry of Health (MOH) and other health care sectors in Oman should consider patients’ views and concerns in order to improve the quality of diabetic care services in primary health care.

Keywords: Quality; Interviews; Type 2 diabetes; Primary care; Oman
DIABETES HAS BEEN CONSIDERED AS the greatest challenge in primary care and primary care physicians (PCPs) play a major role in the care of diabetic patients. Evidence showed that good diabetic control reduces the risk of cardiovascular and micro-vascular complications; hence, the quality of care delivered to type 2 diabetic patients has an impact on the long term outcomes. Nonetheless, the quality of care provided to diabetic patients in primary care in some developing countries appears to be suboptimal.

Oman, a high income country with a total population of 3.2 million (2.0 million Omanis and 1.2 expatriates), has experienced substantial socioeconomic development. This development has been accompanied by remarkable changes in lifestyle towards a “Westernised pattern”; this is reflected in changes in nutrition, less physical activity and thus an increased burden of diabetes, obesity, hypertension and hyperlipidemia. Currently, Oman is among the top ten countries worldwide in terms of high prevalence of diabetes. In a study published in 2006, the prevalence of diabetes (fasting blood glucose ≥ 7 mmol/l) in Muscat, the capital city of Oman, was 17.7% and in rural areas was 10.5%. Furthermore, the estimated death rate from diabetes in the year 2002 in Oman was 16.8 per 100,000 population.

Despite the immense advances that have been made in the management and treatment of diabetes in recent years, many patients do not achieve optimal outcomes and continue to experience devastating complications that result in decreased length as well as quality of life. A cross-sectional observational study conducted in 2009 at six general health centres in Muscat showed that more than 70% of Omanis with type 2 diabetes obtained all their diabetic care service requirements at every visit; however, only 2.4% of them achieved the indicators of good outcomes of diabetic care.

Patients with type 2 diabetes often feel challenged by their disease and multiple personal, psychosocial factors influence their daily decisions which in turn could affect their diabetic metabolic state, long-term glycaemic control, and risk of developing long-term complications. In addition, there are other factors at multiple levels that impede health care systems’ ability to deliver high-quality diabetic services including provider-oriented factors (e.g. lack of knowledge about guidelines, lack of time with patients), and system-oriented factors (e.g. lack of specialty care services, lack of interdisciplinary team approaches, long patient waiting times for services). Furthermore, some health care providers tend to view their own management strategy as scientifically legitimate and have focused on managing numbers rather than attempting to understand the patient’s concept of their disease and their treatment goals. This could lead to frustration, unsatisfactory outcomes and serious obstacles in achieving the optimum outcomes. Patient’s views on the quality of primary health care are vital for better health care delivery. The aim of this study was, therefore, to explore diabetic patients’ views of factors affecting the quality of diabetic services delivered in primary care in Oman, a developing country with high burden of diabetes.

Methods

The study was carried out in four public primary care health centres (PCHCs) in the Governorate of Muscat, the political and the economic hub of Oman. PCHCs in Muscat have specific days (1–2 per week) when they provide free diabetic care...
services for patients with type 2 diabetes through special diabetic clinics. Usually, diabetic patients would have a regular follow-up every month or sometimes every two or three months depending on the progression of the disease and on outcomes. Patients are seen first by a diabetic nurse who checks their blood pressure, fasting blood sugar, weight, height and body mass index (BMI). Patients are then be seen by PCPs who might use specific guidelines in the management of diabetes. Moreover, a dietician visits the health centre twice a week to offer advice on lifestyle modifications for referred patients.

In this study, a qualitative research approach was selected to collect data from patients. Qualitative enquiry helps in exploring areas where there is likely to be complexity and diversity of experiences and perspectives of patients with diabetes. Therefore, we developed a topic guide for individual interviews using some of the available literature and our local experience. The topic guide was piloted in the first two interviews to assess the comprehensibility of the language, the relevance and logical progression of the questions. All the patients were selected based on convenient sampling. Potential rich-informant patients were identified by their PCP and then invited by the research team to participate in the study. Patients suffering from diabetes for less than two years were excluded from the study. The number of patients was based on the saturation of the data. A quiet consultation room in the PCHC was selected for the interviews. The interviews were in Arabic language and each interview lasted 30 to 45 minutes. The interview was carried out by two researchers with one of them questioning the participant and other was observing as well as helping with logistical issues such as recording and taking notes. All the interviews were recorded and transcribed verbatim.

Using the interview guide, participants were asked and probed about their experiences and views of different aspects of diabetic care services provided in the diabetic clinic at their PCHC including: the effectiveness of appointment system; suitability of the waiting area; waiting time before consulting doctor; the role of nurses and doctors and nutritionists; the efficiency of laboratory test and pharmacy procedures, and the availability of diabetes health education. Also, they were asked for their views on the services provided in the clinic including those of the laboratory, pharmacy and the dietician. The study was approved by the Research and Ethics Committee (REC) of the Ministry of Health (MOH). Prior to each individual interview, written informed consent was obtained from participants who agreed to participate in the study. The study was conducted between March and June 2010.

The framework approach, widely used for qualitative analysis, was employed to analyse data. As the framework highlights the associations between participants’ attitudes, perceptions and experiences, it fitted well with the aims of this study. Data analysis was conducted by the research team; findings emerging from the analysis were regularly discussed and refined as part of an ongoing interactive process. The final analysis and findings were mutually agreed by the research team. The recruitment of participants continued until data saturation was achieved. Significant findings from patients’ quotes were translated to English and translated back into Arabic by a blinded researcher.

Results

Nineteen patients, 11 males and eight females, were interviewed in the study. Their age ranged from 21 to 67 years with an average of 41 years. Ten patients were educated up to secondary level and the remaining had college and postgraduate education. Ten patients had had type 2 diabetes for 2–4 years; seven for 5–9 years and three had suffered from it for more than 10 years. Two main themes emerged from the data analysis of the factors affecting quality of care from the patients’ perspective. The first was communication and continuity of care with health care professionals; the second was the timely provision and convenient location of certain services.

**THEME ONE: COMMUNICATION AND CONTINUITY OF CARE WITH HEALTH CARE PROFESSIONALS**

In many health centres, there are still expatriate nurses from India and south Asia and they cannot communicate well with patients in their native Arabic language. Thus, some participants stated that they prefer the diabetic nurse to speak Arabic so that their problems could be understood. “She
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A qualitative study on patients' perspective

Participants commented that there was lack of detail explanation about the importance of lifestyle modification on their health when consulting their PCPs. "The doctors advise me to exercise, but they do not tell me why it is important" (Patient 3).

Other participants felt unhappy because the attending PCP did not explain the results of the previous investigations and the actions that they should consider; thus, they had to remind the PCP to give them the results at every visit. "Doctors don't tell me about my results unless I remind them... and they take no action" (Patient 5).

Although participants appreciated the importance of seeing the dietician for the benefit of their health, some of them felt that PCPs did not refer them as expected. "It is necessary to see the dietician at least twice a year ... I need to know more about my diet but I did not get any referral..." (Patient 1).

Participants highlighted the importance of continuity of care; they should be able to consult the same PCP when attending the clinic. Most of them preferred to be seen by the same PCP at every visit so that their problems could be understood; they also highlighted their unwillingness to repeat the same story when consulting with a different PCP. "I prefer to see the same doctor on every visit, so we can understand each other well .... I do not like to repeat my history on every visit" (Patient 6).

**THEME TWO: PROVISION OF SERVICES AT THE RIGHT TIME AND PLACE**

Participants expressed their discomfort regarding the intervals between visits to the diabetic clinic. They felt that their regular visits should be every month or maximum every two months and should not to be delayed because of difficulty in obtaining an early appointment. "Sometimes I need to take appointment within a month, but the nearest appointment is available only after 3 months" (Patient 7).

Other participants expressed their concern regarding the long waiting time to see the PCP in the diabetic clinic in the day of their appointment. "Sometimes, I go for my appointment on time, but, I have to wait for two hours until the doctor finishes with the patients who came before me ... I feel tired and bored" (Patient 9).

Participants were dissatisfied because of the difficulty in obtaining early appointments with the ophthalmologist in the hospital, which is part of the annual diabetic review. "I have not seen the eye doctor for last 5 years .... I am not reminding the doctor because I do not like to go to the hospital .... I will only get an appointment after months" (Patient 14).

Other participants commented that their medications finished before their next appointment. The regulations of the MOH prevent the PCP from prescribing drugs for more than one month. This is not enough to cover the patients' needs until next appointment in the diabetic clinic. "If my medicine finishes before my appointment, I have to see the walk-in doctor, if there is crowding I get bored and I leave ..." (Patient 16).

Some participants were unhappy about the delay of their laboratory results report when coming for their follow-up as the majority of investigations are sent to the nearest hospitals and it can take several weeks to get the results. "They (doctors) asked me to come after two weeks for the results, but my results were not ready..." (Patient 2).

Therefore, some participants suggest that a copy of the laboratory results be sent by e-mail and that they are informed by a telephone based system (SMS) when their results are ready so that they can make appointments with their PCP accordingly. "I suggest if they can send a copy of the results through e-mail .... at least send an SMS when the results are ready" (Patient 8).

Some participants commented on the waiting area in the clinic. They prefer the male waiting area to be separate from the female waiting area so they feel more at ease. Other participants suggested that the patient waiting area for the diabetic clinic should be separated from the general patients waiting area. This would enable them to get the chance to share their experiences of diabetes with other diabetic patients while waiting to see the PCP. "I will feel more comfort if they separate the males from the females in the waiting area..."(Patient 10). "I like it if they separate the diabetic patients from the general clinic patients ... so I can share my experience with other diabetic patients" (Patient 12).

Other participants suggested keeping some diabetic educational materials in the waiting area so they can utilise their time for something beneficial such as reading about diabetes while waiting to see
the PCP. “In the waiting area there are no pamphlets or health education materials about diabetes …. I would like to sit and read something that could benefit me …” (Patient 11).

Discussion
To our knowledge this is the first study conducted in Oman to explore the factors which influence the quality of diabetic care provided in the PHC setting from the perspective of type 2 diabetic patients. Several factors were identified which could affect the quality of diabetic care including delays in getting appointments; lack of proper utilisation of the waiting area for the purpose of health education; language barriers with diabetic nurses; inadequate provision of continuity of care; lack of sufficient clarification of disease related issues; delays in obtaining investigation results; long waits for ophthalmology appointments, inadequate supplies of prescribed medications to cover the time between appointments, and lack of referrals to dieticians.

Participants in some health centres found it difficult to communicate with the diabetic clinic nurses as they were expatriates and could not speak Arabic. Research from elsewhere found that language barriers can be a risk factor for adverse outcomes and quality of care in diabetes; nurses, on the other hand, perceived language barriers with their patients as an impediment to quality care delivery and as a source of workplace stress.19-21 In the case of Oman, large numbers of expatriate nurses contribute to the health care workforce. Nonetheless, the overall Omanization rate (replacement of expatriate professionals by Omanis) in Ministry of Health and other health care institutions in Oman has grown over the years; the percentage of Omani nurses in 2007 was 64% of total nurses compared to only 12% in the year 1990.3 This Omanization of the health care workforce, which includes nurses, could help to overcome the language barriers in the future.

Participants emphasised the importance of continuity of care in diabetic clinics. Good continuity of care is associated with better outcomes and improves the quality of care among diabetes patients in primary health care, for example by reducing macrovascular complications and associated non-vascular comorbidity.22 Indeed, continuity is highly valued and preferred by most diabetic patients and other patients with chronic diseases compared with acute or minor problems.23,24 It has been found that maintaining continuity of care with the same health care provider improves the quality of life for diabetic patients and enhances the clinical management of the disease by improving the outcomes and decreasing diabetic related complications.25

Patients with diabetes should be able to consult the same physician frequently as this would increase their satisfaction, trust and confidence and hence they would be more likely to adhere to the doctor’s recommendations, thus improving their outcomes and quality of life.24,25 Also, as a result of continuity, the doctor would know the patient well and would be more likely to identify appropriate therapies and, thereby, also improve the outcomes.26 However our patients identified significant lack of continuity which led to difficulties in building good patient-doctor relationships (e.g. familiarity, understanding, explanations). This could impede the provision of a good standard of care.27

Participants’ also emphasised that the quality of their diabetic care could be affected by long waiting times either for getting their next appointment at the diabetic clinic at their health centre, or at specialty clinics such as the ophthalmology one in the hospital. Long appointment waiting times limit the opportunity for the early detection, evaluation and management of new diabetic problems leading to poor diabetic control, increased risk of complications and poor quality of life.28 The availability of more PCPs to manage patients with diabetes in primary care on a regular basis was found to improve the process of diabetic care such as regular measurements of haemoglobin A1c, lipid profiles and retinal eye examinations which ultimately improve the outcomes.29

Participants highlighted the importance of utilising the waiting room for diabetes education and they also wanted to have group-based health education about diabetes and lifestyle modifications. Using waiting rooms for educational purposes has been shown to be effective for patient education.30 Patient education has been found to be an important factor in patient adherence to therapy; educating diabetic patients about lifestyle changes is an important factor for good diabetic control.31 Group-based study for diabetic patients has also been shown to be effective in improving patients’
knowledge and confidence about their diabetes.32

Although the emerging findings from the analysis were discussed and refined by the research team which increased the credibility of the study, we believe that similar studies should be repeated in other countries as diabetic patients’ views and experiences might be different within the context of their national primary health care system setting. Furthermore, the sample of patients was homogenous selected by convenient sampling methodology, thus, they might not represent all diabetic users of PHCs in Oman.

Conclusion

This study is an attempt to explore diabetic patients’ perceptions regarding the quality of health care services provided in primary care setting in Oman. Several recommendations emerged from this study relevant for the practice and policy of primary care organisation in order to improve diabetic care services and hence improve the quality of diabetic care. Waiting areas could be used to educate patients about their diabetes as the level of literacy in Oman is rising. Thus, providing patients with educational materials and leaflets highlighting important information about diabetes (complications, need for compliance with lifestyle changes and medication) might help increase patients’ awareness and improve outcomes.

Another challenge for the quality of diabetes care in the PHC is the shortage of local specialised diabetic nurses. The MOH and other governmental education bodies in Oman should consider developing postgraduate programmes to train Omani nurses in the proper management of diabetes care. This would avoid communication problems and misunderstandings that may occur with patients which can increase chances of medical errors which could affect the quality of care.

According to the current prescribing policy in Oman, PCPs can write prescriptions and repeat prescriptions for chronic diseases such as diabetes for only one month. Patients sometimes travel from a long distance to their PCHC so it could be difficult for them to obtain medication every month and therefore they could run short of medication before their next diabetic appointment. The MOH should consider changing the current prescribing strategy by allowing PCPs to prescribe drugs for diabetics for at least 3 months.

CONFLICT OF INTEREST

The authors reported no conflict of interest.

ACKNOWLEDGMENTS

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**Abstract:** Objectives: This study aimed to assess the incidence and trend of childhood leukaemia in Basrah.

Methods: This was a hospital-based cancer registry study carried out at the Pediatric Oncology Ward, Maternity & Children’s Hospital and other institutes in Basrah, Iraq. All children with leukaemia, aged 0 to 14 years diagnosed and registered in Basrah from January 2004 to December 2009 were included in the study. Their records were retrieved and studied. The pattern of childhood leukaemia by year of diagnosis, age at diagnosis, morphological subtypes, and geographical distribution was analysed. Rates of childhood leukaemia over time were calculated for six years using standard linear regression. Results: The total number of cases of childhood leukaemia in Basrah was 181. The number of cases ranged from 21 in year 1, to 31 in the final year reaching a peak of 39 in 2006. Leukaemia rates did not change over the study period (test for trend was not significant, $P = 0.81$). The trend line shows a shift towards younger children (less than 5 years). The commonest types of leukaemia were acute lymphoblastic leukaemia (ALL), then acute myeloid leukaemia (AML) and finally chronic myeloid leukaemia (CML).

Conclusion: Annual rates of childhood leukaemia in Basrah were similar to those in other countries with a trend towards younger children. This raises the question about the effect of environmental catastrophes in the alteration of some specific rates of childhood leukaemia, rather than the overall incidence rate. There is a need for further epidemiological studies to understand the aetiology of childhood leukaemia in Basrah.

Keywords: Childhood leukaemia; Incidence; Time trend; Cancer registry study; Basrah; Iraq

**Advances in Knowledge**

1. This article is based on one of many studies by the Basrah Cancer Research Group and looks at the time trends and geographical distribution of childhood leukaemia in Basrah.
Leukaemia is the most common childhood cancer, accounting for 25% to 35% of the incidence of all childhood cancer among most populations.\(^1,2\)

The commonest type of childhood leukaemia is acute lymphoblastic leukaemia (ALL), which occurs in approximately 80% of leukaemia cases, followed by acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML), and a few in other categories.\(^3\)

The incidence of childhood leukaemia is higher in resource rich countries, ranging from 4.0 to 4.4 per 100,000 per year,\(^4\) and lower in less-income countries\(^5\) although these variations may reflect a lack of registrations of cancer in low-income countries.\(^6\) Studies from different parts of the world have indicated an increase in recent decades in the incidence of childhood leukaemia in some countries,\(^7,8\) while rates have stayed largely stable in the USA and Nordic countries.\(^9,10\) In most countries, the incidence of childhood leukaemia is higher among boys than girls.\(^11,12\) Although the aetiology of most childhood leukaemias is unknown,\(^13\) several factors have been associated with the disease, including socioeconomic status,\(^14,15\) environmental exposures including ionising radiation and benzene,\(^16\) infectious agents,\(^17\) and parental exposure risk factors.\(^18,19\)

Basrah is Iraq's second largest city and its main port. It is located along the Shatt Al-Arab waterway, approximately 545 km southeast of Baghdad and adjacent to Iran and Kuwait. Basrah is composed of a flat alluvial plain formed by the combined flood plains and deltas of the Tigris, Euphrates, and Shatt Al-Arab rivers. The area surrounding Basrah has substantial petroleum resources with many oil wells. Basrah has been exposed to massive environmental pollution as a consequence of military conflicts and lack of an efficient protective policy from 1980 to 2003. Previous research work and growing impressions among physicians and lay people suggest that childhood leukaemia has increased in Basrah since the second Gulf war.\(^20,21,22\)

However, these suggestions were criticised for being inadequate proof of a real increase in the risk of childhood leukaemia because of incomplete case registration and/or inaccurate population denominators before 2003. In order to study the subject properly, the Basrah Cancer Research Group (BCRG) was established in 2004. BCRG initiated a project to improve registration, identify risk factors, and improve care. This group has achieved good results in registration of cancer, including childhood leukaemia.\(^23\)

The purpose of this study was to assess the rates and trends of childhood leukaemia in Basrah, Iraq, from 2004 to 2009. The data reported here can be used for comparison with past figures or future findings.

### Methods

The Basrah governorate is divided into five areas congruent to the health sectors established by the Basrah health authorities: City centre, South Basrah, West Basrah North Basrah and East Basrah (see map, Figure 4). Information related to the population of Basrah was based on data available from Basrah Health Authorities, electronic lists and the Statistical Office in Basrah. The authors depended on the information from ration cards to assess the size of the population in Basrah. The ration card system was established from the 1990s to provide basic foodstuffs to Iraqi people during...
the economic sanctions after the 1991 Gulf War. It is therefore the best way to assess the Basrah population’s size under the prevailing circumstances, because the Iraqi government monitors it carefully for economic reasons. It is renewed annually to take into account migration, death, and births in the population. In comparison with other parts of Iraq, the population in Basrah is more stable and, due to a stable political and economic environment migration is not an important issue.

This hospital-based cancer registry study was based on all new cases of childhood leukaemia which were registered at the Pediatric Oncology Ward of the Basrah Maternity & Children’s Hospital and other institutes, e.g. the main oncology centre in Basrah, the cancer registration section at the Department of Pathology, College of Medicine University of Basrah, and data from some specialist doctors who keep their own collection of cancer cases as part of their routine clinical work. The research protocol was approved by the Scientific Committee in the Department of Community Medicine, College of Medicine, University of Basrah, in December 2009. The permission of the Directorate of Health in Basrah was obtained prior to the research implementation.

In Basrah, all childhood leukaemia cases are referred to the Pediatric Oncology Ward in Basrah’s Maternity & Children’s Hospital, which is responsible for the treatment and registration of all childhood malignancies in Southern Iraq. Many of the children are treated outside Iraq, but they are diagnosed and registered in Basrah before travelling. Diagnosis was based on the histopathology of the bone marrow and complete blood counts. Two haematologists agreed on all diagnoses, and no changes in diagnostic techniques occurred over the study period. Standard criteria are used to diagnose leukaemia, which for the purpose of this analysis have been divided into acute lymphoblastic leukaemia (ALL), acute myeloblastic leukaemia (AML), chronic myeloid leukaemia (CML), and chronic lymphocytic leukaemia. Cases identified by various sources were entered first on Excel spreadsheets in most centres, or identified from their original documents and entered by BCRG on Excel. Then, all the Excel files were merged, matched and checked for any duplications.

All analyses were carried out with the Statistical Package for the Social Sciences (SPSS) programme (Version 15.0). Some of the figures were constructed using Excel 2007. Incidence data were reported for each year by dividing the incidence by the population (aged 0–14 years) for each year, then multiplying by 100,000. To assess whether the increase in leukaemia rates over time was statistically significant, we calculated rates for the six years 2004–2009 and used standard linear regression to test whether the slope of the line between each year average rates was different from 0. This method is similar to that used by Linet et al. in their study of the changes in leukaemia rates in the USA.24 Age standardised incidence was derived using the world standard population by the direct method.25

### Results

There were 181 cases of leukaemia in children aged 0–14 years registered in Basrah during the six years 2004 to 2009. This represented 46.2 % of the total percentage of cancers among children in Basrah. The number of cases ranged from 21 cases in the first year to 31 cases in the final year and reached a peak of 39 cases in 2006 [Table 1].

Leukaemia rates in children aged 0 to 14 years did not change over the 6 year period (ratio of 2008–2009 rate to 2004–2005 rate = 0.96; 95% confidence interval = 0.96 – 1.01). By using the parameter estimate from the regression model of untransformed values, it was found that leukaemia rates decreased by 0.123 per 100,000 during the 6

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Table 1: Leukaemia rates for children aged 0 to 14 years in Basrah, Iraq, from 2004 to 2009.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of leukaemia cases</th>
<th>Population</th>
<th>Rate per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>21</td>
<td>777,709</td>
<td>2.70</td>
</tr>
<tr>
<td>2005</td>
<td>32</td>
<td>837,293</td>
<td>3.82</td>
</tr>
<tr>
<td>2006</td>
<td>39</td>
<td>866,896</td>
<td>4.49</td>
</tr>
<tr>
<td>2007</td>
<td>27</td>
<td>946,377</td>
<td>2.85</td>
</tr>
<tr>
<td>2008</td>
<td>31</td>
<td>971,929</td>
<td>3.18</td>
</tr>
<tr>
<td>2009</td>
<td>31</td>
<td>998,171</td>
<td>3.10</td>
</tr>
</tbody>
</table>

Note: The data were collected from the cancer registry at the Pediatric Oncology Ward in Basrah Maternity & Children’s Hospital.

Legend:
- a = cases of acute lymphoblastic leukaemia, acute myeloid leukaemia, and chronic myeloid leukaemia.
- b = population aged from 0 to 14 years.
year period: beta (B) = -0.123; standard error (SE) = 0.17); the test for trend was not significant, with \( P = 0.81 \). We were satisfied that presentation of rates in Figure 1 was a robust finding of no change in childhood leukaemia in Basrah over the period of our study.

The total reported cases during the years 2004–2009 shows that leukaemia was more frequent in boys (59.8%) than in girls (40.2%), with a male to female ratio of 149:100. The total leukaemia rate among boys was 3.63 per 100,000 during the years 2004–2005 and 4.18 per 100,000 for 2008–2009. For girls, the rates were 3.03 during the earlier period and 2.07 during the most recent two year period (data not shown).

The trend line in Figure 2 shows the shift of the incidence of leukaemia in recent years towards younger children (below 5 years of age). In the 2004–2005 period, children ages 0 through 4 had overall annual leukaemia rates of 3.04 per 100,000, compared with 3.46 for children aged 10 to 14 years. In the 2008–2009 period, children aged 0 to 4 years had an annual rate of 4.36 per 100,000, compared with 1.73 for children aged 10 to 14 years.

Different trends in incidence were observed for ALL, AML, and CML from 2004 to 2009 [Figure 3]. In the period 2004–2005, there were 40 cases of ALL, 8 cases of AML, and 6 cases of CML. These case number reflect rates of 2.47 per 100,000 children for ALL, 0.49 for AML, 0.37 for CML. During the period 2008–2009, the case counts and rates were 50 for ALL, 9 for AML, and 3 for CML, reflecting rates of 2.53, 0.45, and 0.15 per 100,000, respectively (data not shown).

The rates of childhood leukaemia in each region of Basrah over the five years are shown in Figure 4. The highest rate was found in West Basrah (4.01/100,000), followed by East Basrah (3.88/100,000), North Basrah (3.69/100,000), South Basrah (3.58/100,000), and Basrah city centre (2.77/100,000) respectively.

Discussion

The aim of this study was to describe rates and changes in childhood leukaemia for the population of Basrah, Iraq, in recent years. Data for this study were taken from the cancer registry of the Pediatric Oncology Word of the Maternal & Children's Hospital in cooperation with the College of Medicine of the University of Basrah and the BCRG.

Basrah is confronted with a range of environmental problems, some of which can be directly linked with the effects of recent military conflicts. Others have been triggered by internal Iraqi policies and actions, and were exacerbated by factors such as the impact of economic sanctions. During the 2003 Gulf war, there were reports of oil wells having been deliberately set on fire in the Rumelia oilfield in Basrah, while a thick haze of dark smoke could be seen from Kuwait City the following day. The broad categories of contaminants are volatile hydrocarbons, hydrogen sulphide, and naturally occurring radioactivity. Since the aromatic hydrocarbons (like benzene), which are known to be leukaemogenic, are the most volatile of hydrocarbons, exposure even at low levels can be very harmful.

Also, in Gulf wars of 1991 and 2003, the US
and UK Governments acknowledged that known depleted uranium munitions were used in Iraq. Many tons of this radioactive substance was targeted at the Basrah governorate.28

Our data show that the rates of leukaemia in children aged 0 to 14 years did not change over the 6 year period. This finding is inconsistent with Hagopian et al. study which reported that the average annual incidence of childhood leukaemia in Basrah has risen substantially.22 In the Hagopian et al. study, the average annual rates of childhood leukaemia were measured by dividing the incidence by the population (aged 0–14 years) for each year, then multiplying by 100,000. The incidence included all new cases of childhood leukaemia that were diagnosed and treated in Basrah (included cases from Basrah and those who came from other provinces in southern Iraq) and divided by the estimated size of the population from Basrah province only; this led to an increase in the average annual rate to about 12 per 100,000. Also, the change in the trend of childhood leukaemia in Hagopian et al. study might be attributed to the underestimation of cancer cases, because of incomplete cancer registration prior to 2003 in Basrah.23

In the present study, leukaemias make up about 46% of paediatric cancers in Basrah, whereas international percentages ranged from 27% of paediatric cancers in the United States, 30% in Ireland and France, 33% in Germany, 35% in Shanghai, China, and India.29–34 The high percentage of leukaemia in the present study may reflect the underestimation of other types of paediatric cancer, or it may be suggest a relatively higher risk of leukaemias in Basrah reflecting an exposure to certain risk factors, like the exposure to environmental leukemogens.

Another finding in the present study is the shift of the incidence of leukaemia in recent years towards younger children (below 5 years of age). Our results are similar to those from the United States and Great Britain,35 where the peak occurs between the age of 2–5 years, but the peak is less marked in less developed countries.36,37 This observation may also be attributed to the effect of environmental pollution and/or the changes in the life style of the population in Basrah in recent years compared to the West.

The highest average rate of childhood leukaemia is present in West and East Basrah. These two regions were exposed to great environmental pollution during recent decades. West Basrah was exposed to many environmental carcinogens in the wars of 1991 and 2003 such as depleted uranium and aromatic hydrocarbons. East Basrah was also affected by environmental pollution as a result of the military conflict in the period from 1980 to 1988, during the Iraq-Iran War.

On the other hand, our data show that the average annual rate of all types of childhood leukaemia (per 100,000 children aged 0 – 14) did not noticeably rise in Basrah during the six years under review. Also, the rates of childhood leukaemia subtypes (ALL, AML, and CML) were not elevated. Because ALL was by far the commonest type, the trends in the rates of all leukaemias combined should mostly reflect trends in the incidence of ALL.
Conclusion

Although we observed no temporal increase in the incidence rates for childhood leukaemia during the 6 year period from 2004 to 2009, there is a shift in the incidence of leukaemia in recent years towards younger children and there is an increase in the percentage of childhood leukaemia in comparison with other studies worldwide. This result raises the question about the effect of environmental pollution on the specific characteristics of childhood leukaemia rather than on the overall incidence rate.

It is known that the Basrah region was exposed to environmental insults including the known leukemogen benzene \(^2^7\) and pyrophoric depleted uranium, \(^2^1,2^8\) but also, and still ongoing, undifferentiated water and air pollution; however, no data are available on the doses to which the leukaemia patients in our study were exposed. There is a need for further epidemiological studies to understand the effect of environmental pollution on the pattern of childhood leukaemia in Basrah.

CONFLICT OF INTEREST

The authors reported no conflict of interest.

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References


Effects of Pranayam Breathing on Respiratory Pressures and Sympathovagal Balance of Patients with Chronic Airflow Limitation and in Control Subjects

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ABSTRACT: Objectives: The objective of this study was to compare the effects of Pranayam breathing on respiratory muscle strength measured as maximum expiratory and inspiratory pressures (MEP and MIP) and relevant spirometry parameters in patients with chronic obstructive pulmonary disease (COPD) and in control subjects, and on the sympathovagal balance in both the groups. Methods: The research was performed in the Clinical Physiology Department, Sultan Qaboos University Hospital, Oman. Eleven patients (mean age 43.91 ± 20.56 yr; mean BMI 21.9 ± 5.5 kg/m²) and 6 controls (43.5 ± 14.6yr; 25.4 ± 3.2 kg/m²) learnt and practised Pranayam. Their respiratory and cardiovascular parameters were recorded. Their respiratory ‘well being’ was noted as a visual analogue score (VAS). The respiratory parameters were expressed as a percentage change of predicted values. Results: Patients’ respiratory parameters were significantly lower than those of controls. Patients’ maximum respiratory pressures did not improve after Pranayam; however, they showed significant improvement in VAS 5.4 ± 2.4 to 7.2 ± 1.2 (P < 0.03). Controls showed significant increase in MIP after Pranayam exercises. There were no changes in other spirometry indices. Controls showed significant increase in their systolic blood pressure and stroke index after exercise. The vaso-sympathetic balance shifted towards sympathetic in both patients and controls after exercise. Conclusion: The improvement in MIP in controls indicated the positive effect of Pranayam exercise; however, it may not be an adequately stressful exercise to produce changes in the respiratory parameters of COPD patients. The increase in VAS in patients suggested improvement in respiratory distress and quality of life. Keywords: COPD; Pranayam Exercise; Autonomic Nervous System; Respiratory Pressures; VAS

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Effects of Pranayam Breathing on Respiratory Pressures and Sympathovagal Balance of Patients with Chronic Airflow Limitation and in Normal Subjects

By definition, chronic obstructive pulmonary disease (COPD) is “a state that is characterised by the presence of airflow limitation which is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. COPD is a preventable and treatable disease with significant extrapulmonary effects that may contribute to its severity in individual patients. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). The relative contribution of these may vary from person to person.” COPD has also been associated with inspiratory and expiratory muscle weakness which may contribute to the sensation of dyspnea. Respiratory muscle weakness was confirmed by the low maximal inspiratory (MIP) and expiratory (MEP) pressures generated by patients with COPD. Enhancing respiratory muscle strength with physical training has been found to have some success in alleviating the respiratory distress of such patients. Most of this training involved breathing against pressure loads or endurance training. Respiratory muscle training in patients of COPD decreased the sense of dyspnea during exercise and improved tolerance to exercise, but the effect on MEP and MIP was contradictory. The intense training may have caused distress to the already compromised patients.

A respiratory manoeuvre which does not accentuate the respiratory distress of COPD patients, but at the same time improves respiratory muscle strength and spirometry parameters while allaying the sense of dyspnea and fatigue, would be a more acceptable proposition.

Sub-clinical cardiovascular autonomic neuropathy has been known to occur in patients of COPD even in the early stages of the disease. The basic pathophysiology involved is likely to be chronic hypoxia as autonomic modulation could be brought about by supplemental oxygen breathing. Patients with chronic airflow limitation are thus under a constant physiological stress which needs to be alleviated if their quality of life is to be improved.

Pranayam is a non-distressing, slow, yogic breathing exercise which modifies autonomic functions in control subjects. Others have used it with varying success as an adjunct to existing therapy for COPD patients. However, respiratory pressures were not measured in any of the studies involving Pranayam. We hypothesised that Pranayam breathing exercises might lead to clinical improvement with positive changes in MIP and MEP as well as readjustments of the vago-sympathetic balance of the cardiovascular system. This study aimed to examine this hypothesis and compare their respiratory, haemodynamic and autonomic parameters with control subjects who also undertook Pranayam breathing exercises.

**Methods**

Eleven patients (7 males; 4 female; mean ± standard deviation (SD): age 43.9 ± 20.6 yr; body mass index (BMI) 21.9 ± 5.52 kg/m²) and 6 control subjects (6 males; 2 female; 43.5 ± 14.6y, BMI 25.4 ± 3.2 kg/m²) volunteered for the study which was approved by the Ethical Committee of the College of Medicine & Health Sciences at Sultan Qaboos University (SQU). Written consent was obtained from all participants. Inclusion criteria for patients were: 1) registered as patients of COPD/chronic airflow limitation with the Respiratory Clinic at SQU Hospital; 2) forced expiratory volume 1 sec (FEV₁) < 60% of predicted, and forced expiratory flow (FEF) of 25–75% at < 40% predicted. None of the selected patients suffered from diabetes mellitus, hypertension or congestive cardiac failure. They continued with their prescribed treatment, if any,
throughout the experiment. The control subjects were volunteers from among departmental staff.

The patients and the control subjects were asked to follow the breathing sequence as per Pal et al.,
as follows: Close one nostril with the thumb; inhale slowly over a count of 6 seconds; At the end of the inhalation, close both the nostrils; Count to 6; Open the second nostril and exhale slowly over a count of 6 seconds; Inhale with the same nostril slowly over 6 seconds; This constituted a single sequence. This was to be repeated for 30 minutes each day for at least 5 days a week for 3 months.

Spirometry indices were measured using Medgraphics (Elite Dx, USA) which was calibrated daily at the start of the day, and zero flow of the pneumotach was confirmed prior to testing. All measurements were performed by one/two trained technologists, and measurements were made using standard procedures. Minimum and maximum respiratory pressures (MIP, MEP) were measured as described in the American Thoracic Society/European Respiratory Society statement. To elaborate, for the measurement of the MEP, after connecting to the pneumotach, the subjects breathed normally at tidal volume for six breaths. Following this, s/he inspired maximally to total lung capacity (TLC). At this point, the shutter of the body box was occluded, and the patient breathed out using maximal force which could be sustained for at least 3 seconds against the closed shutter.

At least three to four satisfactory attempts were recorded, and the best effort was included for the analysis. For recording the MIP, the patient/subject started the manoeuvre at the end of a maximal expiration to residual volume (RV), and inhaled maximally against the closed shutter. Follow-up lung function testing was done after three months practice of Pranayam breathing. Most studies also have this time sequence in assessing effects of respiratory training in COPD patients. The VAS (visual analogue score) for respiratory well being (scale 0–10) was recorded at the first visit and after 3 months of breathing exercise.

Haemodynamic and autonomic measurements were taken as follows. Beat-to-beat haemodynamic and autonomic parameters were obtained non-invasively at rest using Task Force Monitor (TFM) (CNS Systems, Graz, Austria). Haemodynamic measurements of heart rate and R-R interval were acquired with a 6-lead electrocardiogram. Beat-to-beat blood pressure (BP), systolic and diastolic, (SBP and DBP) was measured with the vascular unloading technique using finger cuffs. Beat-to-beat BP was automatically counterchecked and corrected every minute by the oscillometric BP measurements recorded from the contralateral upper arm.

Impedance cardiography measurements were also taken. Derived haemodynamic parameters were computed from continuous BP and heart rate (HR) and the impedance signal. The latter was acquired from a small constant sinusoidal alternating current passing through the thorax between an electrode placed around the neck and another placed at the lower end of the sternum. The voltage between the electrodes is proportional to the thorax impedance. Left ventricular ejection time (LVET), the time between points ‘B’ and ‘X’ (opening and closure of aortic valve, respectively) of the impedance signal, was considered in further calculations of haemodynamic parameters using the standard Kubisek’s formula. The haemodynamic parameters calculated and indexed for body surface area were stroke index (SI), cardiac index (CI) and total peripheral resistance index (TPR, TPRI).

Autonomic measurements were made as follows. An adaptive autoregressive model (AAR) was used to compute online beat-to-beat time varying spectral analysis of the heart rate variability (HRV) in the frequency domain. Very low frequency (VLF 0.01–0.05 Hz band); low frequency (LF 0.05–0.17 Hz band), and high frequency (HF 0.17–0.5 Hz band) were calculated in absolute values (ms²) and in normalised units: low frequency (LFnu) and high frequency (HFnu). There is a general agreement that HF, HFnu reflect the parasympathetic or vagal activity, and LF, LFnu reflect the sympathetic modulation of the sinoatrial node and vasomotion.

The change in status of the sympatho-vagal balance was indicated by the LF/HF ratio. All experiments were done in the morning at a comfortable room temperature of 27 °C. An informed consent was obtained after explaining the procedure. All subjects underwent the same protocol. After spirometry and respiratory pressure measurements, subjects were connected to the TFM with electrodes. They were made to rest supine on a comfortable bed in a quiet room. Beat-to-beat recordings of haemodynamic and autonomic parameters were obtained at rest for 10 mins. All
Effects of Pranayam Breathing on Respiratory Pressures and Sympathovagal Balance of Patients with Chronic Airflow Limitation and in Normal Subjects

Table 1: Baseline haemodynamic and autonomic parameters, respiratory pressures and spirometry indices in control subjects and patients—value (standard deviation)

<table>
<thead>
<tr>
<th>Anthropometric, haemodynamic and autonomic parameters</th>
<th>Controls n = 6</th>
<th>Patients n = 11</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.5 (14.5)</td>
<td>43.9 (20.5)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4 (3.2)</td>
<td>21.9 (5.4)</td>
<td>NS</td>
</tr>
<tr>
<td>VAS</td>
<td>7.0 (2.1)</td>
<td>5.4 (2.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>HR</td>
<td>72.0 (13.6)</td>
<td>78.6 (13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP</td>
<td>108.8 (15.5)</td>
<td>112.3 (14.5)</td>
<td>NS</td>
</tr>
<tr>
<td>DBP</td>
<td>78.6 (9.3)</td>
<td>74.5 (7.3)</td>
<td>NS</td>
</tr>
<tr>
<td>SI</td>
<td>47.4 (12.9)</td>
<td>47.4 (7.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>TPRI</td>
<td>2218.5 (639.2)</td>
<td>1885.4 (431.5)</td>
<td>NS</td>
</tr>
<tr>
<td>LFnu</td>
<td>56.8 (13.7)</td>
<td>41.5 (26.1)</td>
<td>NS</td>
</tr>
<tr>
<td>HFnu</td>
<td>43.1 (13.7)</td>
<td>60.3 (23.2)</td>
<td>NS</td>
</tr>
<tr>
<td>VLF</td>
<td>102.3 (102.7)</td>
<td>113.6 (117.8)</td>
<td>NS</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.5 (0.9)</td>
<td>1.1 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>PSD</td>
<td>731.0 (103.6)</td>
<td>677.4 (313.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory pressures and spirometry indices</th>
<th>Controls n = 6</th>
<th>Patients n = 11</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEP</td>
<td>153.5 (32.4)</td>
<td>98.5 (27.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>pcMEP</td>
<td>79.5 (18.6)</td>
<td>60.8 (16.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>MIP</td>
<td>113.5 (34.1)</td>
<td>65.4 (37.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>pcMIP</td>
<td>106.0 (21.3)</td>
<td>57.8 (26.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>FVC</td>
<td>4.0 (1.3)</td>
<td>2.4 (0.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>pcFVC</td>
<td>95.8 (9.5)</td>
<td>73.2 (10.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>FEV₁</td>
<td>3.1 (0.9)</td>
<td>1.5 (0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>pcFEV₁</td>
<td>90.5 (5.8)</td>
<td>58.2 (12.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEVF/VFC</td>
<td>78.6 (5.7)</td>
<td>63.8 (12.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>pcFEVF/VFC</td>
<td>98.3 (6.3)</td>
<td>80.2 (15.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>FEF25-75%</td>
<td>2.75 (0.8)</td>
<td>0.9 (0.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>pcFEF25-75%</td>
<td>68.1 (12.3)</td>
<td>25.5 (12.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PEFR</td>
<td>9.0 (1.3)</td>
<td>4.4 (1.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>pcPEFR</td>
<td>112.7 (14.5)</td>
<td>61.4 (15.5)c</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Legend: Age (years); BMI = body mass index (kg/m²); VAS = visual analogue score; HR = heart rate (bpm); SBP = systolic blood pressure (BP) (mmHg); DBP = diastolic BP (mmHg); SI = stroke index (ml/min); TPRI = total peripheral resistance index (dyne·S·M²/cm²); LFnu = low frequency normalized units (%); HFnu = high frequency normalized units (%); VLF = very low frequency (ms²); LF/HF = sympatho-vagal balance; PSD = power spectral density (ms³); MEP = maximum expiratory pressure (cmH2O); pcMEP = % predicted of MEP (cmH2O); MIP = maximum inspiratory pressure (cmH2O); pcMIP = % predicted of MIP (cmH2O); FVC = forced vital capacity (L); pcFVC = % predicted of FVC; FEV₁ = forced expiratory volume 1 sec (L); pcFEV₁ = % predicted of FEV₁; FEF25-75% = forced expiratory flow 25-75% (L/sec); PEFR = peak expiratory flow rate (L/sec); pcPEFR = % predicted of PEFR (L/sec); NS = not significant; P > 0.05.

The difference between baseline and post Pranayam values of cardiovascular and respiratory parameters was taken as measure of responses to Pranayam exercises. This estimated reactivity was compared between control subjects and patients using the Wilcoxon rank test for non-parametric samples.

Results

Anthropometric and baseline cardiovascular and respiratory parameters for control subjects and patients are given in Table 1. Both groups were comparable for age and BMI. The VAS was significantly lower in the patients (P = 0.03). There were no differences in haemodynamic and autonomic parameters between two groups [Table 1]. All respiratory pressures and spirometry indices were within normal physiological range in control subjects and were significantly lower in patients [Table 1]. This confirmed the impaired pulmonary
functions in patients.

Responses of cardiovascular and respiratory parameters and VAS to Pranayam exercise are given in Table 2 for the control subjects and in Table 3 for the patients. The comparison of cardiovascular and respiratory responses to Pranayam exercises between control subjects and patients are given in Table 4.

In the control subjects, there was a significant increase in SBP ($P = 0.01$) and SI ($P = 0.05$) after Pranayam exercise [Table 2]. There was also an increase in sympathetic parameters (LFnu and LF/HF) after Pranayam exercise; however, the difference was not significant. The MEP and MIP both increased in response to Pranayam exercise; however, the difference was significant only for MIP ($P = 0.03$). There was no difference in other respiratory pressures and indices in response to Pranayam exercise.

Patients showed significant improvement in VAS ($P = 0.04$) after Pranayam exercise [Table 3]. Paradoxically, they did not show a significant change in cardiovascular parameters, respiratory pressures and indices in response to the Pranayam exercise [Table 3].

There were no differences in cardiovascular responses to Pranayam exercises between control subjects and patients [Table 4]. Amongst respiratory pressures, the control subjects showed a significant increase in percent predicted MIP (pcMIP; control subjects $24.7 \pm 18.3$ versus patients $0.9 \pm 19.5$; $P = 0.03$) compared with patients. There were no differences in the responses of other respiratory pressures and indices between control subjects and patients [Table 4]. In patients, the measure of respiratory well being, VAS, showed a significant increase in response to Pranayam exercise (control subjects $0.5 \pm 1.5$ versus patients $1.8 \pm 1.2$; $P = 0.05$).

Discussion

The major findings of this study were, first, that Pranayam exercise produced significant increase...
only in the MIP of control subjects; second, in patients, there were no significant changes in cardiovascular parameters, respiratory pressures and indices in response to the Pranayam exercise; and third, patients showed significant improvement in the score of respiratory well-being in response to the Pranayam exercise.

The impaired respiratory muscle function in COPD patients leading to exertional dyspnoea is well established. We hypothesised that Pranayam, a non-distressing slow yogic breathing exercise, may train respiratory muscles and improve their performance. However, our study showed significant increase in MIP only in control subjects and not in patients. Inspiratory muscles of respiration are an important factor contributing to exertional dyspnoea. The improvement in MIP in control subjects suggested that Pranayam worked positively for them. It is possible that Pranayam was not a sufficiently stressful breathing exercise to produce the change in patients. However, the significant increase in VAS in our study group indicated that the Pranayam exercise improved the respiratory distress and quality of life. The positive outcome from the respiratory muscle training depends upon the overload principle applied to the training which includes increase in frequency, duration and intensity of the training. The respiratory muscle training would be of benefit to patients if respiratory muscle function is a major limiting factor during performance of the training. Reid suggested that an exercise training programme should be tailored to an individual patient’s needs and abilities. Rigorous aerobic exercise has not consistently produced benefit on MIP and MEP values. Gemeniz et al. showed that maximally intense aerobic exercise significantly improved MEP and MIP and decreased dyspnoea at rest. In COPD patients, however, De Lucas Ramos et al. found that progressive maximal exercise tolerance decreased the sense of dyspnoea, but had no effect on respiratory pressures. Cooper et al. showed that the Buteyko breathing technique (a device that mimics paranayama) attenuated the symptoms and reduced bronchodilator use, but...
Table 4: Comparison of responses of visual analogue score (VAS), haemodynamic and autonomic parameters, respiratory pressures and spirometry indices before and after Pranayam exercise between control and patients

<table>
<thead>
<tr>
<th>VAS, haemodynamic and autonomic parameters</th>
<th>Controls</th>
<th>Patients n = 6</th>
<th>Patients n = 11</th>
<th>P</th>
<th>Respiratory pressures and spirometry indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>Controls n = 6</td>
<td>0.5 (1.5)</td>
<td>1.8 (1.2)</td>
<td>0.05</td>
<td>MEP</td>
</tr>
<tr>
<td>HR</td>
<td>3.5 (3.7)</td>
<td>-1.1 (14.1)</td>
<td>NS</td>
<td>pcMEP</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>9.8 (3.8)</td>
<td>1.3 (2.3)</td>
<td>NS</td>
<td>MIP</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>3.5 (6.6)</td>
<td>-2.7 (12.5)</td>
<td>NS</td>
<td>pcMIP</td>
<td></td>
</tr>
<tr>
<td>SI</td>
<td>3.4 (8.30)</td>
<td>-0.2 (5.1)</td>
<td>NS</td>
<td>FVC</td>
<td></td>
</tr>
<tr>
<td>TPRI</td>
<td>112.8 (445.0)</td>
<td>-31.6 (593.8)</td>
<td>NS</td>
<td>pcFVC</td>
<td></td>
</tr>
<tr>
<td>LFnu</td>
<td>10.3 (14.7)</td>
<td>9.9 (22.7)</td>
<td>NS</td>
<td>FEV1</td>
<td></td>
</tr>
<tr>
<td>HFnu</td>
<td>-10.4 (14.6)</td>
<td>-12.7 (21.7)</td>
<td>NS</td>
<td>pcFEV1</td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>14.0 (51.0)</td>
<td>18.8 (90.4)</td>
<td>NS</td>
<td>FEV/FVC</td>
<td></td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.3 (0.9)</td>
<td>0.7 (1.7)</td>
<td>NS</td>
<td>pe FEV/FVC</td>
<td></td>
</tr>
<tr>
<td>PSD</td>
<td>-337.7 (650.4)</td>
<td>187.8 (462.6)</td>
<td>NS</td>
<td>pcPEFR</td>
<td></td>
</tr>
</tbody>
</table>

Legend: VAS = visual analogue score; HR = heart rate (bpm); SBP = systolic blood pressure (BP) (mmHg); DBP = diastolic BP (mmHg); SI = stroke index (ml/m²); TPRI = total peripheral resistance index (dynes*S*m⁻²); LFnu = low frequency normalized units (%); HFnu = high frequency normalized units (%); VLF = very low frequency (ms²); LF/HF = sympatho-vagal balance; PSD = power spectral density (ms⁻¹); MEP = maximum inspiratory pressure (cmH₂O); pcMEP = % predicted of MEP (cmH₂O); MIP = maximum expiratory pressure (cmH₂O); pcMIP = % predicted of MIP (cmH₂O); FVC = forced vital capacity (L); pcFVC = % predicted of FVC (%); PEFR = peak expiratory flow rate (L/sec); pcPEFR = % predicted of PEFR (L/sec); NS = not significant, P>0.05.

it did not change lung functions. Yoga therapy which included asanas (body postures) and timed Pranayam breathing improved the tolerance of COPD patients for the 6 minute walk test. However, Donesky-Cuenco et al. did not study the effect of yogic therapy on respiratory parameters. A recent meta-analysis of respiratory muscle training in chronic air flow limitation suggested that there is little evidence of clinically important benefits of respiratory muscle training in patients with chronic air flow limitation. The meta-analysis also suggested that benefit may result if resistance exercises are conducted in a fashion that ensures the adequate generation of mouth pressures.

The inspiratory muscle training schedule which improves MIP is 15–50 min exercise/day 5 days a week for 1–6 months. Although the schedule of the training offered in our study was adequate, the type, intensity and duration of exercise were probably not adequate to produce beneficial changes in COPD patients. Our subjects were asked to follow the schedule at home. The reliability of compliance from patients thus remains questionable. Conducting the exercises in controlled environment could have provided better results. Most studies involving respiratory muscle strength were conducted in COPD patients who had a FEV₁/FVC ratio of 50% or less. In comparison, our patients were less compromised (FEV₁/FVC ratio 63.8% ± 12.3). It is possible that patients with more severe limitation may have responded more positively to the exercise.

Our study did not find any significant differences between resting haemodynamic and autonomic parameters between patients and control subjects. The autonomic dysfunction was documented in COPD patients using interventions that excite cardiovascular reflexes like Valsalva manoeuvre, 30:15 ratio, handgrip or postural challenge. Few studies correlated the autonomic dysfunction with hypoxaemia and severity of the disease in these patients. Camillo et al. associated autonomic dysfunction not with severity of disease, but with a lower level of…
of physical activity in daily life along with poor health-related quality of life, functional status and respiratory and peripheral muscle force.\textsuperscript{30} Correction of hypoxaemia may not have any effect on improvement of autonomic functions,\textsuperscript{12,29} but the 6 weeks aerobic exercise training significantly improved the submaximal performance in the 6 minute walk test and it was associated with increased parasympathetic activity.\textsuperscript{31} Our study investigated the autonomic activity at rest and not during the cardiovascular challenges. The similar autonomic functions in patients and control subjects could be attributed to normal resting oxygen saturation in them (\textit{PO}$_2$; Control subjects: 99.0 ± 1.1; patients: 97.0 ± 1.3%).

Pranayam exercise is known to activate the parasympathetic limb of the autonomic nervous system.\textsuperscript{15} Although non-significant, we found that Pranayam exercise activated the sympathetic limb of the autonomic nervous system in both control subjects and patients. The improvement in quality of symptoms as indicated by VAS could be attributed to the correction of autonomic balance.

In this study, we compared the effect of Pranayam breathing in COPD patients and control subjects by investigating both improvement in respiratory muscle strength and also the relief of stress. The small sample size posed a limitation in drawing conclusions. In the future, a well organised clinical trial with adequate sample size and strict supervision of the breathing exercises may give a better understanding of the usefulness of Pranayam breathing exercise for these patients.

\textbf{Conclusion}

Our study did not show significant alterations in the autonomic studies or in the pulmonary functions status of COPD/chronic airflow limitation patients. The improvement in MIP in control subjects indicated the positive effect of Pranayam. Although Pranayam was not an adequately stressful breathing exercise to produce the change in COPD patients, it improved the respiratory distress and quality of life as indicated by the significant increase in VAS in patients. It was also interesting to note the shift of the autonomic balance towards sympathetic which may suggest that this could be a better coping mechanism induced by Pranayam breathing.

\textbf{CONFLICT OF INTEREST}

The authors reported no conflict of interest.

\textbf{ACKNOWLEDGEMENTS}

This project (RS/06/041) was funded by the College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman. We sincerely acknowledge the help of Ms. Adila Al-Touqui, Superintendent, Department of Clinical Physiology, Sultan Qaboos University Hospital, Oman for the Arabic translation.

\textbf{References}


Abstract: Objectives: This study aimed to investigate the clinical and therapeutic profiles of heart failure (HF) cases admitted to Aseer Central Hospital (ACH), Saudi Arabia. Methods: A retrospective cohort of 300 consecutive patients admitted with the diagnosis of HF to ACH from 1 June 2007 to 31 May 2009 were included in the study. Data on demographic variables, aetiological factors, risk factors, and therapeutic profiles of patients with HF were collected and analysed. Results: The patients' mean age was 67.4 ± 13.7 years and 68.7% of them were male. The commonest aetiologies for HF were ischaemic heart disease (IHD) and hypertension in 38.3% and 33.3% of patients, respectively. A total of 61.3% of patients were diabetics. Other risk factors for HF included renal failure in 9.7%, atrial fibrillation in 13%, and anaemia in 48.3% of patients. Echocardiography was performed in 98.7% of cases: the average ejection fraction (EF) was 33% ± 17. Angiotensin converting enzyme inhibitors (ACEI) or angiotensin 2 receptor blockers were used in 68.3% of cases, β-blockers in 51.6% of cases and digoxin in 28.3% of cases. Conclusion: The major causes of HF in our study were IHD and hypertension. Diabetes and anaemia were common risk factors. The cohort constituted an intermediate HF risk group (ejection fraction (EF) 33%). Important therapeutic agents like angiotensin converting enzyme inhibitor, β-blockers and digoxin were underutilised. Fostering such therapy in practice will lead to a better outcome in the management of HF patients. Anaemia was a significant risk factor in our HF patients and should be managed properly.

Keywords: Heart failure; Therapeutics; Saudi Arabia

Advances in Knowledge
1. This study provides information on the pattern and aetiology of heart failure in Saudi Arabia and the pattern of risk factors for heart failure in Saudi population.
2. It highlights the underutilisation of important drug therapies in heart failure for Saudi patients.
Heart failure (HF) is defined as a complex syndrome resulting from inability of the heart to meet peripheral tissues metabolic demands at a normal filling pressure. It is a common final pathway of many chronic disorders namely hypertension, diabetes, and ischaemic heart disease (IHD). The global prevalence of heart failure varies from 2.3% to 3.9% per annum. Annually, an estimated 23 million people have heart failure worldwide and 2 million new cases are diagnosed each year. Due to therapeutic improvement in the treatment of acute myocardial infarction and hypertension and improved survival, the incidence of heart failure has increased and become a real public health issue. It is characterised by decreased quality of life with high morbidity and mortality. The HF mortality rate is approximately 25% within one year of initial diagnosis.

The aetiology of HF varies from different reports around the world, but ischaemic heart disease, hypertension, rheumatic heart disease and to a lesser extent cardiomyopathy and anaemia are the leading causes of HF. Ischaemic heart disease is becoming a major leading cause of heart failure in developed countries, where more than two thirds of HF cases are due to IHD. Despite clear evidence of the beneficial effect of certain therapeutic agents like angiotensin converting enzyme inhibitors (ACEI), β-blockers and K-sparing diuretics on survival, these agents continue to be underutilised globally.

The Aseer Region (population 1,200,000) is located in the southwest of Saudi Arabia covering an area of more than 80,000 km². The region extends from the high mountains of Sarawat (with an altitude of 3,200 m above the sea level) to the Red Sea. Health services delivery in Aseer region is provided by a network of 244 primary health care centers, 16 referral hospitals and one tertiary hospital, Aseer Central Hospital (ACH). ACH, with 500 beds, is run by the Ministry of Health and the College of Medicine of King Khalid University (KKU), Abha.

We aimed in this study to analyse the demographic data, clinical and therapeutic profiles of patients admitted with the diagnosis of heart failure to Aseer Central Hospital (ACH) and to find out how close we were to the recommended international standards of management of heart failure.

**Methods**

A retrospective cohort of all consecutive patients admitted to Aseer Central Hospital (ACH) with the diagnosis of heart failure according to medical records, during the two-year period 1 June 2007 to 31 May 2009, were included in this study. Approval of the local medical ethical committee was obtained. Demographic data, underlying aetiologies, risk factors for heart failure (diabetes, hypertension, anaemia, atrial fibrillation and renal failure), echocardiographic features and ejection fraction (EF) values were collected. Conventionally patients with EF < 30% were labelled as having severe left ventricular dysfunction, 30–44% as moderate left ventricular dysfunction, and 45–54% as mild left ventricular dysfunction.

Records on all medications used conventionally for treatment of heart failure were collected. The main angiotensin converting enzyme (ACE) inhibitor agent used was captopril, and the target recommended dose was considered to be one 50 mg tablet taken three times a day, with any lower dose considered to be below the target dose. The main β-blocker agent used was carvedilol and the target recommended dose was considered to be one 25 mg tablet taken twice daily, with any lower dose considered to be below the target dose.

Data were analysed using the Statistical Package for the Social Sciences (SPSS) software package (Version 15.0). Frequency, percentage, mean, standard deviation and median were used to present the data.

**Application to the patient care**

1. This study highlights the need to improve the use of proven important drug therapies for heart failure.
2. Physicians should recognise and address the problem of drug underutilisation in heart failure management.
3. The study also provides information on important risk factors for heart failure development and how to improve their prevention.
**Results**

The present study included 300 patients with the diagnosis of heart failure. The age ranged from 26 to 101 years with an average 67.4 ± 13.7 years. A total of 206 patients (68.7%) were male. The commonest aetiology for heart failure was IHD in 38.5% of cases followed by hypertension in 33.3% of cases. Other aetiologies included dilated cardiomyopathy in 10% and valvular heart disease in 3% of patients. The commonest risk factors were diabetes in 61.3%, hypertension in 59% and anaemia in 48.3% of patients. Other risk factors were atrial fibrillation in 13% and renal failure in 9.7% of patients. Table 1 shows the demographic and clinical characteristics of heart failure patients in Aseer region, Saudi Arabia.

Echocardiography was performed in 98.75% of patients and the average EF was 33% ± 17 for the study group. Our patients lay in the moderate left ventricular dysfunction group. Table 2 shows the distribution of heart failure patients according to their ejection fraction values. Table 3 shows the frequency of types of treatment used in HF patients in the study cohort.

The use of ACEI or angiotensin 2 receptor blockers (A2RB) was reported in 68.3% of patients, and among patients on ACEI, the majority (91.85%) were on lower than the target dose, thus only 8.15% of patients were on the recommended target dose. Captopril was the main ACEI agent used in this cohort.

**Discussion**

The literature on clinical and therapeutic profiles of heart failure patients in Saudi Arabia is scarce. This makes it difficult to plan policies for the prevention and management of heart failure in Saudi Arabia. The only study in neighbouring countries was the Omani study which included 1,164 patients with symptomatic heart failure and showed a prevalence of heart failure in an Arab population to be 5.17/1,000 population.

In our series, the mean age was 67.4 years which is similar to the Framingham series of a Western population, where the most susceptible age for the onset of HF was 60 years and older. In our cohort, more than two thirds of patients were older than 60 years.

IHD and hypertension were the commonest aetiology of heart failure in our series, this concurs with similar findings both the Framingham and the Omani study. Among risk factors for heart failure, we found the incidence of diabetes in our group to be high (61.3%); this data corroborates well with Al-Nozha’s findings of a high prevalence of diabetes in Saudi society.

An important relevant finding in our study...
is the high prevalence of anaemia (defined as haemoglobin level less than 12 gm/dl in females and less than 13 gm/dl in males according to the WHO definition). In our series, anaemia was detected in 48.3% of patients with heart failure. Evidence from previous studies showed that anaemia is a long term predictor of poor prognosis in patients with severe heart failure. This group of patients requires special attention as correcting their anaemia will improve their clinical and haemodynamic status. The reasons for this relatively high prevalence of anaemia in our cohort could be due to different factors among them the fact that the Assir region is considered to be one of the major pockets of sickle cell genes in Saudi Arabia. Other important risk factors for heart failure include atrial fibrillation and renal failure which we found in our series (13% and 9.7% respectively); similar incidences of these two disorders were reported in other studies. These disorders were found to contribute to a high need of hospitalisation for elderly patients with heart failure.

The rate of echocardiography performance was adequate in our series where the vast majority of heart failure patients (98.7%) underwent echocardiographic assessment. The majority of our patients were in the moderate risk group according to the EF value categorisation. In large trials, ACEI was clearly found to improve survival, functional capacity and to reduce the need for hospitalisation when given to heart failure patients. Despite these studies, the drugs are underutilised and, when used, the optimal dose is not achieved. In the current study, only 68.3% of heart failure patients were prescribed ACEI, and the majority of them were not on the recommended target dose. In contrast to this finding, in the USA ACEI is used in 89% of patients with heart failure. This low rate of use in our cohort can be due to several factors: 1) lack of awareness of the important role of ACEI in improving mortality in HF patients; 2) inappropriate broadening of the scope of the contraindications by clinicians; 3) lack of adherence to the recommended guidelines; 4) patient’s poor compliance with medications, or the economic cost of prescribing multiple medications to heart failure patients.

Similar findings regarding the underutilisation of ACE inhibitors in heart failure patients was observed in other studies and multiple factors were found to contribute to such a practice; among these were the older age of patients, the presence of renal dysfunction, the presence of only diastolic dysfunction, and the substandard quality of care given to heart failure patients.

β-blockers were found to reduce mortality and frequency of hospital admissions when given to patients with heart failure. The meta analysis of 21 trials showed that β-blockers improve left ventricular ejection fraction by 25%. In our study, we found only 51.6% of HF patients were prescribed β-blockers, and the majority of those were not on the recommended target dose. The same reasons postulated for ACEI underutilisation can be applied to the underutilisation of β-blockers.

Digoxin was found to decrease the need for admissions, but did not reduce mortality when given to patients with heart failure. Digoxin was used in only 28.3% of our cohort which is lower than the rate reported in the USA (50%). This low rate in our series could be due to clinicians giving more priority to drugs that reduce mortality only and less importance to drugs that only improve morbidity. The use of oral anticoagulation warfarin in HF patients, especially those with severe left ventricular dysfunction, was found to reduce stroke, sudden death, and myocardial infarction. In large HF trials like SOLVD (Study of Left Ventricular Dysfunction), oral anticoagulation warfarin was used in 12% of patients. In our series, it was used in 16% of patients which is close to the international figure.

Amiodarone was found to reduce arrhythmia,
but not mortality, in HF patients. The rate of amiodarone use in large HF trials was 14.4%, which is clearly higher than our rate of 1.3%. The reason for such a discrepancy is not obvious.

The observed underutilisation of different evidence-based therapeutic agents for the treatment of heart failure patients in our cohort was also reported in other larger studies such as the Euro Heart survey on heart failure.

Conclusion

In conclusion, we believe that this study shed some light on the clinical and the therapeutic profile of HF patients treated in the tertiary hospital in Aseer Region, Saudi Arabia. It has shown that IHD and hypertension were the leading causes of HF in this cohort. Diabetes is a highly prevalent risk factor and anaemia is a significant problem in our HF patients and should be corrected. Furthermore, this study showed underutilisation of the important treatment modalities used for HF, mainly ACEI, β-blockers and digoxin, and when used, the doses were not optimal. Awareness of this data will contribute to improvement in management of HF patients and encourage clinicians to adhere to the recommended guidelines for HF management. This study also calls for an urgent need to establish a national registry for heart failure in Saudi Arabia in order to evaluate the economic burden of such a common medical disorder and therefore plan a better health care system.

CONFLICT OF INTEREST

The author reported no conflict interest.

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Effects of Hydrogen Sulphide on the Isolated Perfused Rat Heart

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Abstract: Objectives: Hydrogen sulphide has been identified as a gas signalling molecule in the body, and has previously been shown to have vasorelaxant properties. The aim of the study was to investigate the effects of sodium hydrosulphide (NaHS), a hydrogen sulphide donor, on heart rate (HR), left ventricular developed pressure (LVDP) and coronary flow (CF) in the isolated perfused rat heart.

Methods: A Langendorff isolated heart preparation was used to investigate the effect of a dose range of sodium hydrosulphide, in the presence and absence of inhibitors, on heart rate, left ventricular developed pressure and coronary flow.

Results: Sodium hydrosulphide caused a significant decrease in heart rate at a concentration of 10−3 M (P < 0.001). This decrease was partially inhibited by glibenclamide, a KATP channel blocker (P < 0.05); L-NAME, a nitric oxide synthase inhibitor (P < 0.001), and methylene blue (P < 0.001), but not by H-89, a protein kinase A inhibitor. Sodium hydrosulphide significantly increased coronary flow at concentrations of 10−4 – 10−3 M (P < 0.05). This response was significantly increased in the presence of L-NAME (P < 0.001) and methylene blue (P < 0.001), but not by H-89, a protein kinase A inhibitor. Sodium hydrosulphide significantly decreased LVDP at all concentrations (P < 0.001). In the presence of glibenclamide and H-89, the time period of the decrease in LVDP due to sodium hydrosulphide was extended (P < 0.001), whereas methylene blue and L-NAME caused a significant reduction in the response to sodium hydrosulphide (P < 0.05, P < 0.01 respectively).

Conclusion: Sodium hydrosulphide reduced heart rate and LVDP and increased coronary flow in the isolated perfused rat heart; however, the mechanisms of action could not be fully elucidated.

Keywords: Hydrogen sulphide; Heart; Langendorff; H2S gasotransmitter; Vasorelaxation

Advances in Knowledge

1. This study identifies a sodium hydrosulfide dependant decrease in heart rate and left ventricular pressure and an increase in coronary flow.

2. This study also identifies the potential cell signalling pathways via which these physiological changes take place.

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Application to Patient Care

1. Hydrogen sulphide has been identified as a gaseous signalling molecule alongside nitric oxide and carbon monoxide mediating a range of physiological processes.
2. Hydrogen sulphide has been shown to abrogate the effects seen during myocardial ischaemia reperfusion injury and has the potential of being translated into a clinical setting.

It is now well established that hydrogen sulphide (H\textsubscript{2}S) gas has effects on the heart; however, to date, the cardiovascular effects of both endogenous and exogenous H\textsubscript{2}S have not been fully elucidated. Zhao et al. reported that an intravenous bolus injection of H\textsubscript{2}S at 2.8 and 14 µmol/Kg body weight caused a significant transient decrease in blood pressure in anaesthetised rats, which was partially antagonised by glibenclamide (a potassium adenosine triphosphate [K\textsubscript{ATP}] ion channel blocker).\textsuperscript{1} The heart rate was not significantly affected by H\textsubscript{2}S injection. An early study on sulphhydril reagents on the isolated perfused guinea-pig heart reported an increase in coronary flow and heart rate.\textsuperscript{2} Geng et al. reported that sodium hydrosulphide (NaHS), a H\textsubscript{2}S donor, inhibited left ventricular developed pressure in the isolated perfused rat heart in a concentration-dependent manner over a range of 10-6–10-3 M.\textsuperscript{3} However, they found a decrease in heart rate and coronary flow only at a concentration of 10-3 M NaHS which was partially inhibited by glibenclamide.\textsuperscript{4} Sun et al. found that NaHS impeded contraction of isolated rat cardiomyocytes by inhibiting L-type calcium channels.\textsuperscript{5} No effects on K\textsubscript{ATP} channel currents or on levels of cAMP (cyclic adenosine monophosphate) or cGMP (cyclic guanosine monophosphate) were found. H\textsubscript{2}S was found to have a negative chronotropic action on pacemaker cells in the sinoatrial node of rabbit heart, possibly via the opening of K\textsubscript{ATP} channels.\textsuperscript{5}

A number of recent studies have shown that H\textsubscript{2}S is cardioprotective in myocardial ischaemia and ischaemia-reperfusion injury.\textsuperscript{6–12} Some of these studies found evidence that the cardioprotective mechanism is mediated via the opening of K\textsubscript{ATP} channels;\textsuperscript{7,10,11,13,14} however, it is controversial whether mitochondrial K\textsubscript{ATP} channels are involved.\textsuperscript{11,13,13} Inhibition of nitric oxide production attenuated the cardioprotective effects of NaHS, suggesting some synergy between nitric oxide (NO) and H\textsubscript{2}S.\textsuperscript{11} There is some evidence that the protein kinase C pathway,\textsuperscript{15,16} upregulation of cyclooxygenase-2\textsuperscript{17,21} or upregulation of heat shock protein 72\textsuperscript{12} could be involved in cardioprotection.

H\textsubscript{2}S is produced endogenously from the amino acid L-cysteine by two enzymes, cystathionine \(\beta\)-synthase (CBS) and cystathionine \(\gamma\)-lyase (CSE). CBS has been shown to have no activity or expression in human cardiovascular related tissues.\textsuperscript{18,19} Conversely, CSE expression and endogenous production of H\textsubscript{2}S have been shown in the rat portal vein, thoracic aorta\textsuperscript{20} and heart.\textsuperscript{1} The expression of CSE has been identified in vascular smooth muscle cells, but not in the endothelium, whereas CBS expression was not detected in vascular tissue.\textsuperscript{1}

There appears to be some similarities between H\textsubscript{2}S, NO and carbon monoxide (CO) in terms of their effects, and mechanisms of action and interactions between them have been reported.\textsuperscript{21} Hosoki et al. were the first to suggest synergy between H\textsubscript{2}S and NO in relaxing vascular smooth muscle.\textsuperscript{19} They demonstrated a left-ward shift in the dose-response curve for relaxation of rat thoracic aorta by NaHS in the presence of two different NO donors, sodium nitroprusside and morpholinosydnonimine. They reported that a low concentration of H\textsubscript{2}S enhanced the smooth muscle relaxant effect of NO by up to 13-fold. However, Zhao and Wang found that low doses of NaHS shifted the dose-response relaxation curve for sodium nitroprusside to the right in rat aortic rings, suggesting that H\textsubscript{2}S inhibited the vasorelaxant effect of NO.\textsuperscript{22}

The primary aim of this study was to investigate the effects of a concentration range of NaHS, a H\textsubscript{2}S donor, on heart rate, left ventricular developed pressure and coronary flow in the isolated perfused rat heart using the Langendorff model.

Methods

Male Sprague-Dawley male rats (250–300g body weight) were used in all the experiments. All animals were from the same source, fed a standard diet and housed in the same conditions. All animals received humane care in accordance with the UK Guidance on the Operation of the Animals (Scientific Procedures) Act 1986. Animal protocols
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were approved by the Committee of Animal Care and Supply of Coventry University, UK.

All chemicals were obtained from Sigma (Poole, UK). The Krebs Heinseleit buffer contained (mM) NaCl 118.5, NaHCO₃ 25, KCl 4.8, MgSO₄ 1.2, KH₂PO₄ 1.2, CaCl₂ 1.7, and glucose 12, methylene blue (a guanylate cyclase inhibitor), glibenclamide and H-89 (a protein kinase A inhibitor) were dissolved in dimethyl sulphoxide (DMSO) initially and then diluted with a KH buffer. L-nitro-arginine-methyl ester (L-NAME) was dissolved in distilled water. NaHS (a H₂S donor) was dissolved in a KH buffer. The rate of infusion of agents was 1% of coronary flow to achieve the final concentrations indicated.

The animals were killed by cervical dislocation followed by exsanguination. Hearts were rapidly excised and placed in ice-cold Krebs-Heinsleit (KH) buffer solution. The aortic stump was rapidly mounted onto a cannula attached to a standard Langendorff set up. Hearts were perfused with KH buffer, gassed with 95% O₂ 5% CO₂ (pH 7.4) and maintained at 37.5°C. The temperature was constantly monitored by a thermocouple inserted into the right ventricle.

A latex balloon was positioned in the left ventricle via an insertion performed in the left atrial appendage and inflated to 5–10 mmHg. The balloon was attached to a pressure transducer connected to a Harvard amplifier to determine the left ventricular developed pressure (LVDP). Heart rate was monitored via the electrocardiogram (ECG) recorded using electrodes connected to a Harvard isolated preamplifier. Hearts exhibiting arrhythmia were discarded. Readings were taken at 5 min intervals using a Thermo array recorder WR7700 (Western Graphtec, USA).

Hearts were allowed to stabilise for 20 mins following mounting on the Langendorff set up. Hearts were randomly assigned to the following protocols:

a) Control group (n = 5): hearts were infused using a Harvard infusion/withdrawal pump with KH buffer at room temperature without the addition of any agents for 15 minutes at an infusion rate of 0.13 ml/min and allowed to recover for a further 20 mins;

b) Concentration-effect group: hearts were infused with a range of concentrations of NaHS (M) of 10⁻⁵ (n = 6), 10⁻⁴ (n = 5) and 3x10⁻³ (n = 5) for a period of 15 minutes, followed by a further 20 minutes of recovery;

c) Hearts were allowed to stabilise for
20 mins with KH buffer perfusion and were then exposed with either 10 µM glibenclamide (n = 5), or 10 µM MB (a guanylate cyclase inhibitor) (n = 5), or 10 µM L-NAME (n = 5) for 35 mins; d) Hearts were allowed to stabilise for 20 mins with KH buffer and were then exposed to either 10 µM glibenclamide (n = 5), 10 µM MB (n = 5), 10 µM L-NAME (n = 5) or 1 µM H-89 (n = 5) for 15 minutes. Hearts were then exposed to 10^{-3} M NaHS for 15 mins followed by a further 20 mins for recovery.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, Version 10.5). Data were compared using analysis of covariance (ANCOVA) or one-way analysis of variance (ANOVA) with Fisher’s protected least mean squares difference post hoc test. Differences were considered significant where \( P < 0.05 \). All data are expressed as mean ± standard error of the mean (SEM).

Results

Results are presented as the percentage mean of the stabilisation period. NaHS caused a significant decrease in heart rate compared with control at a concentration of 10^{-3} M (\( P < 0.001 \)) [Figure 1a]. This decrease was partially, but significantly, inhibited by glibenclamide (\( P < 0.05 \)), by L-NAME (\( P < 0.001 \)), and by methylene blue (\( P < 0.001 \)), but not by H-89 [Figure 1a]. Glibenclamide, L-NAME and methylene blue alone had no significant effect on heart rate, but H-89 alone caused a significant increase in heart rate compared to control subjects (\( P = 0.05 \)) [Figure 1b].

NaHS caused a significant increase in coronary flow compared to control at a concentration of 10^{-3} M (\( P < 0.001 \)) [Figure 2a]. Glibenclamide did not block the response to NaHS [Figure 2a]. H-89 alone caused a significant increase in coronary flow (\( P < 0.001 \)) [Figure 2b], but it significantly inhibited the increase in coronary flow due to NaHS (\( P < 0.001 \)) [Figure 2a]. Methylene blue alone had no significant effect on coronary flow, but it significantly augmented the increase due to NaHS (\( P < 0.001 \)) [Figure 2a]. L-NAME alone had no significant effect on coronary flow, but it significantly augmented the increase due to NaHS (\( P < 0.001 \)) [Figure 2a]. L-NAME with NaHS caused a profound, highly significant increase in coronary flow compared to control (\( P < 0.001 \)) and compared to NaHS alone (\( P < 0.001 \)) [Figure 2b].

NaHS significantly decreased LVDP at all concentrations (\( P < 0.001 \)) compared with control (data not shown). Glibenclamide did not affect the initial response to NaHS, but significantly inhibited

Figure 2a: Percent change in coronary flow over time due to infusion of Sodium hydrosulphide (NaHS) (10^{-3} M) in the presence of glibenclamide (10 µM), H89 (1 µM), methylene blue (10 µM) and L-nitro-arginine-methyl ester (L-NAME) (10 µM) (mean ± Standard error of the mean (SEM), n = 5). The initial coronary flow in each case was taken as 100%. Hearts were infused with the inhibitors for 15 minutes, followed by NaHS for 15 minutes and then recovery was monitored for a further 20 minutes.

Note: *** \( P <0.001 \) vs. NaHS; ### \( P <0.001 \) vs. Control.

Figure 2b: Percent change in coronary flow above over time due to infusion of glibenclamide, H89, methylene blue and L-nitro-arginine-methyl ester (L-NAME) (mean ± Standard error of the mean (SEM), n = 5). The initial coronary flow in each case was taken as 100%. Hearts were infused with the inhibitors for 35 minutes. H-89 alone caused a significant increase in coronary artery flow (\( P <0.001 \)).

Note: *** \( P <0.001 \) vs. Control.
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Figure 3a: Percent change in Left ventricular Developed Pressure (LVDP) over time due to different concentrations of Sodium hydrosulphide (NaHS) (10-3 M) in the presence of glibenclamide, H89, methylene blue and L-nitro-arginine-methyl ester (L-NAME) (mean ± Standard error of the mean (SEM), n = 5). The initial LVDP was taken as 100% in each case. Hearts were infused with the inhibitors for 15 minutes, followed by NaHS for 15 minutes and then recovery was monitored for a further 20 minutes. Note: *** P <0.001 vs. Control, ### P <0.001 vs. NaHS; * P <0.05 vs. NaHS, ** P <0.01 vs. NaHS.

However, Geng et al. reported a decrease in LVDP over time due to infusion of glibenclamide, H89, methylene blue and L-nitro-arginine-methyl ester (L-NAME) (mean ± Standard error of the mean (SEM), n = 5). The initial LVDP in each case was taken as 100%. Hearts were infused with the inhibitors for 35 minutes. Note: * P <0.03 vs. Control.

![Figure 3b](image)

The negative chronotropic effect on heart rate, which agrees with the findings of Geng et al., must presumably be due to H₂S influencing ion channels and ion currents in the pacemaker cells. Xu et al. have reported that NaHS decreases the rate of pacemaker firing in the sinoatrial node in rabbit. In previous reports of the effects of H₂S on the heart in vivo, Zhao et al. and Geng et al. reported that an intravenous bolus injection of H₂S or NaHS caused a significant transient decrease in blood pressure, but the heart rate was not significantly affected. The heart may well respond differently in vivo compared to in vitro. There are probably differences in dose between these experiments and the present study. A crude estimate of the maximum dose range was exposed to in the in vivo experiments of Zhao et al. is 4.5 x 10⁻⁵ – 2.4 x 10⁻⁴ M, assuming a rat body weight of 375 g and a blood volume of 22 ml. Geng et al. used a dose of 2.8 µmol/Kg body weight.

In the present study, the effect of H₂S on heart rate seems to partially involve K_ATP channels, as it was inhibited by glibenclamide. This agrees with the findings of Xu et al. who suggested that H₂S influences pace maker cell depolarisation by opening K_ATP channels. H₂S, acting by opening K_ATP channels, would hyperpolarise the membranes of pacemaker cells, thus reducing their rate of

Discussion

The H₂S donor NaHS caused significant reductions in heart rate and LVDP, but increased coronary flow. The effect on LVDP concurs with the known role of H₂S as a muscle relaxant, and suggests that it has a similar effect on cardiac muscle. The effects of NaHS on LVDP reported here support the findings of Geng et al. In a study on isolated rat cardiomyocytes, Sun et al. reported that NaHS reduced contraction and inhibited L-type calcium channels. The vasodilatory effect of H₂S in increasing coronary flow agrees with reported effects on peripheral blood vessels in vitro.
depolarisation and decreasing heart rate. The lack of effect of H-89 suggests that \( \text{H}_2\text{S} \) is not exerting its negative chronotropic effect via the Cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway. The significant increase in heart rate due to H-89 alone might be due to the fact that H-89 is not very specific in its action of inhibiting PKA. Alternatively, the normal control of heart rate could involve the (cAMP/PKA) pathway. The effect of L-NAME and methylene blue in inhibiting the action of \( \text{H}_2\text{S} \) in decreasing heart rate suggests that the mechanism involves the stimulation of production of NO and the guanylate cyclic guanosine monophosphate (cGMP) pathway. In comparison, Kojda et al. found that L-arginine had a positive chronotropic effect in rat heart, whereas methylene blue reduced heart rate.29

\( \text{H}_2\text{S} \) has been previously shown to have vasodilatory effects in the rat heart20,22 and, in the present study, \( \text{H}_2\text{S} \) increased coronary flow in isolated perfused hearts indicating dilation of coronary blood vessels. Conversely, Geng et al. reported a decrease in coronary flow by NaHS in a similar model.3 Blockade of \( K_{\text{ATP}} \) channels with glibenclamide, in the present study, did not inhibit the vasodilatory effect of \( \text{H}_2\text{S} \), suggesting that the mechanism of action of \( \text{H}_2\text{S} \) was not via opening \( K_{\text{ATP}} \) channels. This is in contrast to the findings of Zhao et al. using peripheral blood vessels.1 H-89 alone significantly increased coronary flow which could be due to its other actions apart from inhibiting PKA. However, H-89 inhibited the vasodilatory effect of NaHS, suggesting that the mechanism of action of \( \text{H}_2\text{S} \) in this case is via the cAMP/PKA pathway. This finding agrees with that of Kimura who showed that physiological concentrations of \( \text{H}_2\text{S} \) increased the production of cyclic AMP in neurones and oocytes in culture.27

Methylene blue and L-NAME both caused a highly significant increase in the vasodilatory effect of NaHS, which shows that inhibition of nitric oxide synthesis and signalling via guanylate cyclase augmented the effect of \( \text{H}_2\text{S} \). These findings were reproducible and were highly statistically significant. This suggests that endogenous production of NO inhibits the vasodilatory effect of \( \text{H}_2\text{S} \) in coronary blood vessels; however, it is well known that NO is a vasodilator of coronary blood vessels. Zhao et al. showed that L-NAME, an inhibitor of endogenous NO production, significantly shifted the \( \text{H}_2\text{S} \) dose-response relaxation curve to the right, decreasing the potency of \( \text{H}_2\text{S} \), in rat aortic rings, and similar effects were obtained by removing the endothelium from the aortic rings.1 They also showed that the addition of a specific inhibitor of soluble guanylate cyclase, 1 H-[1,2,4]oxadiazolo[4,3-c]quinoxalin-1-one, significantly increased the relaxant effect of \( \text{H}_2\text{S} \); however, synergy between NO and \( \text{H}_2\text{S} \) has also been reported. Hosoki et al., demonstrated a leftward shift in the dose-response curve for relaxation of rat thoracic aorta by NaHS in the presence of two different NO donors, sodium nitroprusside and morpholinosydnonimine.13 Cheung and Schulz reported that glutathione and glutathione disulphide caused coronary vasodilation which was mediated by a NO and guanylate cyclase-dependent mechanism.26 It is possible, in the current study, that endogenously produced NO could stimulate the production of a factor which opposes the actions of \( \text{H}_2\text{S} \).

Both H-89 and L-NAME caused a significant reduction in LVDP. The reduction in LVDP by H-89 could be due to effects other than on PKA. The depressor effect of L-NAME would suggest that the maintenance of LVDP requires the production of NO, although NO is generally known to be a muscle relaxant. It has been previously reported that a NO donor SPM3672 increased maximal left ventricular pressure in the isolated rat heart and increased levels of cGMP in rat cardiomyocytes.28 The positive inotropic effects of NO donors in rat heart have been confirmed by the same group and others.25,26 H-89 extended the time period of the decrease in LVDP following NaHS treatment, suggesting that normal recovery involved the cAMP/PKA pathway. L-NAME and methylene blue significantly inhibited the response to NaHS, suggesting that the mechanism of relaxation of cardiac muscle by \( \text{H}_2\text{S} \) involves NO production and guanylate cyclase. As \( \text{H}_2\text{S} \) binds to heme groups, similarly to NO, it is possible that guanylate cyclase is a target. Glibenclamide did not inhibit the initial depression of LVDP by NaHS, suggesting that the mechanism of action did not involve the opening of \( K_{\text{ATP}} \) channels. Indeed, glibenclamide extended the time period of the depression of LVDP due to NaHS and thus inhibited recovery of the heart from NaHS treatment. This could be interpreted as an involvement of the opening of \( K_{\text{ATP}} \) channels in the recovery from \( \text{H}_2\text{S} \) treatment. However, it is unclear how the opening of \( K_{\text{ATP}} \) channels and the resultant hyperpolarisation
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could increase LVDP.

Conclusion

NaHS, an H$_2$S donor, significantly reduced heart rate and LVDP, and increased coronary flow in the isolated perfused rat heart; however, the mechanisms of action could not be fully elucidated.

CONFLICT OF INTEREST

The authors reported no conflict of interest.

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References


Trends and Characteristics of Head and Neck Injury from Falls
A hospital based study, Qatar

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ABSTRACT: Objectives: The aim of this retrospective descriptive hospital-based study was to determine the trend in the number, incidence and pattern of head and neck injuries involved with falls. Methods: A retrospective analysis was carried out of 1,952 patients who were treated at the Accident and Emergency and Trauma centres of Hamad Medical Corporation, Qatar, for head (n = 1,629), neck (n = 225) and both (n = 98) injuries during the period 2001–2006. Head and neck injuries were determined according to the International Classification of Disease, ICD-10 criteria. Details of all the trauma patients who were involved in falls were extracted from the database of the Emergency Medical Services (EMS), Hamad Medical Corporation. Results: The majority of the victims were non-Qatars (78.6%), men (86.6%) and in the age group 20–29 years (26.8%). There was a disproportionately higher incidence of head and neck injuries from falls during weekends (27.1%). Nearly half of the head and neck injuries from falls occurred at work (49.4%). Neck injuries (10.2%) were more severe than head injuries (7.3%). The incidence rate of head and neck injuries per 10,000 population increased from 2.1 in the year 2001 to 5.5 in 2006, particularly among the elderly population above 60 years of age (13.1 in 2003 to 18.6 in the year 2006). Superficial injury to the head (29.4%) was more common among trauma patients.

Conclusion: The present study findings revealed that the incidence of head and neck injuries was higher among young adults and the elderly population.

Keywords: Head injury; Neck injury; Occupational falls; Home falls; Incidence; Morbidity; Trauma; Qatar

Advances in Knowledge
1. This is the first study in Qatar to investigate the number, incidence and trends of head and neck injuries from falls.
2. The high risk groups of fallers were elderly people and younger workers.
3. This study highlighted the emerging trend of traumatic morbidity from fall induced head and neck injuries in the general population.

Application to Patient Care
1. The findings of this study emphasise the need for urgent steps to be taken in Qatar for injury prevention, especially among workers and those in the elderly population.
Falls and fall-induced injuries are a major public health problem in modern societies with ageing populations.1 As a measure of burden, disability adjusted life years (DALYs) quantify the total amount of healthy life lost because of disease or injury. In high income countries, injuries due to falls are the fourteenth leading cause of DALYs for all age groups combined.2 In industrialised countries like the USA, Canada and Japan, injuries caused by falls have increased dramatically.3 Falls are the second leading cause of unintentional injury deaths in the USA. It was reported that an estimated 3.4 million non-fatal injuries occurred among workers of all ages and were treated in US hospital emergency departments in 2004.4

Falls are the most common cause of head injuries in children and adolescents, followed by motor vehicle crashes, pedestrian and bicycle accidents, sports-related trauma, and child abuse.5 Falls are a common source of traumatic injuries, and it was revealed that fall injury patterns differ between adults and children. Fall rates are highest for children age 0 to 4 years and adults aged 75 years and older. Falls are usually the most common cause of injury seen in hospitals, accounting for 25–52% of all treated child injuries.6 Falls and subsequent head injuries among the elderly are the result of a complex interaction between physical changes due to ageing, disease, lifestyle and environment related and social factors. Also, older fallers are more likely to fall indoors than outdoors.7

Head injury is a common and serious consequence of falling among older adults, and a great majority of elderly people's non-fatal and fatal head injuries are caused by falls.8 Although the head, face and neck comprise only 12% of the total body surface area exposed during impact, injuries sustained in these areas are more likely to be fatal.9 Head and neck injuries from falls are a common cause of occupational morbidity and mortality, resulting in significant losses of life and wages, as well as significant medical expenses. Males are at greater risk of sustaining a fall-related injury while at work and during recreational activities.

Although fall injuries comprise a major health burden, the risk factors for such injuries have not been examined in a systematic and comprehensive manner. In practice, knowledge of risk factors for head and neck injuries from falls can assist injury practitioners, programme developers, and policy makers in determining appropriate intervention. Only two previous studies have been conducted in Qatar to document trends in traumatic brain injury10 and traumatic spinal injury.11 Both of these studies were very preliminary and neither study specifically focused on head and neck injuries as a result of falls. In fact, to our knowledge, no nationwide study investigating the number, incidence and trends of head and neck injuries from falls has been published from Qatar. Therefore, this study aimed to determine the trends of head and neck injuries from falls in absolute number, incidence and pattern of injuries during the period 2001 to 2006.

Methods

This is a retrospective, descriptive hospital based study. This study included a total of 1,952 patients with head and neck injuries who were treated in the Accident & Emergency Department of the Hamad General Hospital (HGH) and other 8 Trauma Centres of the Hamad Medical Corporation (HMC) following fall incidents during the period 2001 to 2006. All trauma cases occurring in the State of Qatar are treated in the Accident and Emergency Department of the HGH and the 8 trauma centres of the HMC. Hence, the data collected in this study not hospital based, but covers all head and neck injuries occurring in Qatar during the period of the study. The electronic Emergency Medical Service database has complete information on trauma cases year by year. We took the frequency of head and neck injury from falls by year and population of the respective year. Then, we calculated the incidence of the head and neck injury per 10,000 of the population based on the population of the country for the respective year.

This is a retrospective, descriptive hospital based study. This study included a total of 1,952 patients with head and neck injuries who were treated in the Accident & Emergency Department of the Hamad General Hospital and other 8 Trauma Centres of the Hamad Medical Corporation following fall incidents during the period 2001 to 2006. The population in Qatar was estimated to be 838,065 in the year 2006 and has a unique distribution of population according to gender and ethnicity.12 Only about 30% of the total population are nationals and the majority of the total population (66.7%) are...
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Male. The study was based on the Emergency Medical Services (EMS) registry, an electronic database in Qatar. This registry records complete information of the patients who had accidents and were brought to the Accident & Emergency Department and Trauma centres for treatment. The details of the falls were

<table>
<thead>
<tr>
<th>Variables</th>
<th>Head n = 1,629, n (%)</th>
<th>Neck n = 225, n (%)</th>
<th>Both n = 98, n (%)</th>
<th>Total N = 1,952, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± Standard deviation)</td>
<td>30.4 ±18.1</td>
<td>29.8 ± 15.0</td>
<td>32.2 ± 17.6</td>
<td>30.4 ± 17.6</td>
</tr>
<tr>
<td>Age groups in years §</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>243 (14.9)</td>
<td>19 (8.4)</td>
<td>5 (5.1)</td>
<td>267 (13.7)</td>
</tr>
<tr>
<td>10–19</td>
<td>150 (9.2)</td>
<td>29 (12.9)</td>
<td>13 (13.3)</td>
<td>192 (9.8)</td>
</tr>
<tr>
<td>20–29</td>
<td>419 (25.7)</td>
<td>71 (31.6)</td>
<td>33 (33.7)</td>
<td>523 (26.8)</td>
</tr>
<tr>
<td>30–39</td>
<td>368 (22.6)</td>
<td>53 (23.6)</td>
<td>19 (19.4)</td>
<td>440 (22.5)</td>
</tr>
<tr>
<td>40–49</td>
<td>225 (13.8)</td>
<td>25 (11.1)</td>
<td>16 (16.3)</td>
<td>266 (13.6)</td>
</tr>
<tr>
<td>50–59</td>
<td>104 (6.4)</td>
<td>20 (8.9)</td>
<td>6 (6.1)</td>
<td>130 (6.7)</td>
</tr>
<tr>
<td>≥60</td>
<td>120 (7.4)</td>
<td>8 (3.6)</td>
<td>6 (6.1)</td>
<td>134 (6.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qatari</td>
<td>343 (21.1)</td>
<td>52 (23.1)</td>
<td>22 (22.4)</td>
<td>417 (21.4)</td>
</tr>
<tr>
<td>Non Qatari</td>
<td>1,286 (78.9)</td>
<td>173 (76.9)</td>
<td>76 (77.6)</td>
<td>1,535 (78.6)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,415 (86.9)</td>
<td>192 (85.3)</td>
<td>84 (85.7)</td>
<td>1,691 (86.6)</td>
</tr>
<tr>
<td>Female</td>
<td>214 (13.1)</td>
<td>33 (14.7)</td>
<td>14 (14.3)</td>
<td>261 (13.4)</td>
</tr>
<tr>
<td>Day of the week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week days</td>
<td>1,189 (73.0)</td>
<td>167 (74.1)</td>
<td>6 (67.0)</td>
<td>1,422 (72.9)</td>
</tr>
<tr>
<td>Weekend‡</td>
<td>440 (27.0)</td>
<td>58 (25.9)</td>
<td>32 (33.0)</td>
<td>530 (27.1)</td>
</tr>
<tr>
<td>Place of fall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At work</td>
<td>817 (50.1)</td>
<td>99 (44.2)</td>
<td>50 (50.7)</td>
<td>965 (49.4)</td>
</tr>
<tr>
<td>Home</td>
<td>519 (31.9)</td>
<td>85 (37.6)</td>
<td>30 (31.0)</td>
<td>635 (32.5)</td>
</tr>
<tr>
<td>School</td>
<td>106 (6.5)</td>
<td>14 (6.1)</td>
<td>3 (2.8)</td>
<td>123 (6.3)</td>
</tr>
<tr>
<td>Recreational places</td>
<td>187 (11.5)</td>
<td>27 (12.2)</td>
<td>15 (15.5)</td>
<td>229 (11.8)</td>
</tr>
<tr>
<td>Status at the time of admission*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conscious</td>
<td>1,510 (92.7)</td>
<td>215 (95.6)</td>
<td>87 (88.8)</td>
<td>1,812 (92.8)</td>
</tr>
<tr>
<td>Breathing</td>
<td>1,619 (99.4)</td>
<td>225 (100)</td>
<td>98 (100)</td>
<td>1,942 (99.5)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>677 (41.5)</td>
<td>59 (26.2)</td>
<td>39 (39.8)</td>
<td>775 (39.7)</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe score 3–8</td>
<td>119 (7.3)</td>
<td>23 (10.2)</td>
<td>7 (7.2)</td>
<td>147 (7.5)</td>
</tr>
<tr>
<td>Moderate score 9–12</td>
<td>149 (9.1)</td>
<td>30 (13.3)</td>
<td>11 (11.2)</td>
<td>186 (9.5)</td>
</tr>
<tr>
<td>Mild score 13–15</td>
<td>1,361 (83.6)</td>
<td>172 (76.5)</td>
<td>80 (81.6)</td>
<td>1,619 (82.9)</td>
</tr>
</tbody>
</table>

Notes: § = significant P value = 0.005; ‡ = weekend is Friday and Saturday; *Multiple options: sum of percentage may not add to 100%.
collected regularly by the EMS staff using a standard questionnaire. The questionnaire included variables such as age, sex, time of injury, place of fall, the type of injury, the region of the body injured and the severity of injury. The data provided by this register are well suited for epidemiological purposes.

Medical records of the victims were thoroughly reviewed in the event of any missing information. The patient information was extracted from the EMS registry and analysed. Head and neck injuries were defined according to the International Classification of Disease (ICD) ICD-10 criteria and external causes of injury recorded. Head injuries, neck injuries and a combination of both injuries together were mutually and exclusively reported. Fall-induced head and neck injuries were recorded by evaluating the primary and secondary diagnosis. Descriptive statistics were performed on the socio-demographic characteristics, place of fall, status of the injury at the time of admission and diagnosis. According to ICD-10, injuries to the head were classified under categories S00–S09 and injuries to the neck were classified under S10–S19. The age-specific incidence rate was calculated based on the population in that specific age group in that year.

The severity of head or neck injury was classified by Glasgow Coma Scale (GCS). This a tool for measuring degree of unconsciousness and is thus a useful tool for determining severity of head injury.13 The GCS classifications are as follows: 1) Severe: score of 3–8; 2) Moderate: score of 9–12, and 3) Mild: score of 13–15. The GCS score of patients was taken when they were examined and, for the intubated patients, the score was taken prior to intubation. Informed consent by all participants was not required in this study, as it was a retrospective hospital based study. The study was approved by the Research Ethics Committee at Hamad General Hospital of Hamad Medical Corporation.

Data are expressed as mean and standard deviation (SD) unless otherwise stated. The Fisher exact and chi-square test for trend were used to compare frequencies between two or more than two categories. A P value of <0.05 was considered as the cut-off value for significance.

Results

Table 1 shows the socio-demographic characteristics of patients with head and neck injuries resulting from falls during the period 2001–2006. A total of 1,952 patients were diagnosed with head and neck injuries from falls. The majority of them were non-Qatars (78.6%), males (86.6%) and in the age group 20–29 years (26.8%). Men outnumbered women by 6.5:1. A total of 27.1% of the head and neck injuries from falls occurred during weekends, while 72.9% occurred on week days. Nearly half of the head and neck injuries from falls occurred at work (49.4%), followed by falls at home (32.5%), then at recreational places (11.8%) and school (6.3%). According to the GCS score, 7.5% had severe and 9.5% had moderate injury. The majority of the patients had mild head (83.6%) and neck injury (76.5%). Neck injuries (10.2%) were more severe than head injuries (7.3%) among trauma patients. A significant difference was observed in the age group of fallers and the injuries occurred between week days and weekends (P=0.005).

Table 2 shows the distribution of diagnosis of injuries and place of fall according to the age group of trauma patients. Most of the head and neck injuries were occupational injuries (49.5%) and 32.5% of injuries happened at home. Older people above 60 years-old had more frequent injuries to the head and neck region from falls at home (70.9%), followed by children below 10 years (66.7%). Major fall related injuries included superficial injury of the head (29.4%), followed by an open wound on the head (23.4%), then blunt injury (19.5%). Superficial injury of head was more frequent among children below 10 years (33%). An open wound to the head was more common among patients above 60 years (32.8%).

Table 3 shows the incidence rate of head and neck injuries sustained from falls per 10,000 of the population according to age group and year during the period 2001–2006. There was a clear increase in the incidence of head and neck injuries: 2.1/10000 in 2001 to 5.5/10000 in 2006. The elderly population above 60 years of age had the highest increase in incidence of head and neck injuries from falls (6.7 to 18.6/10,000) across the study period. There was a significant difference found in the number of injuries in different age groups of fallers (P <0.001).

Figure 1 shows the incidence rate of head, neck injuries and both together per 10,000 of the population resulting from falls during the period 2001–2006. The number of neck injuries also increased to 4.9/10,000 population in 2006.
Trends and Characteristics of Head and Neck Injury from Falls
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Discussion
Falls are the commonest cause of head and neck injuries in children, adults and elderly people. Although fall-induced injuries among older adults are said to be a major public health concern in modern societies with ageing populations, reliable epidemiologic information on their trends and the pattern of injuries is limited. To our knowledge, this is the first study in Qatar examining and comparing fall related head and neck injuries in young, middle-aged and older men and women. The focus was on the faller’s activity, the incidence of head and neck injuries, and the severity and type of injuries. Of all hospitalisations with head and neck injuries, 18.4% had head and neck injuries from falls, while 7.5% had a GCS score of <9 (severe), 9.5% a score of 9–12 (moderate) and 82.9% a score of 13–15 (mild). Most of the patients with head and neck injuries were conscious (92.7%) at the time of admission after the fall. Head injuries accounted for the majority of the fall cases (83.5%), followed by neck injuries (11.5%). A similar result was observed in another study where 63.2% of the fall cases were compared to 1.8/10,000 population in 2001.

Table 2: Place of fall and diagnosis by age group (N = 1,952)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age group in years</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10 n (%)</td>
<td>10–19 n (%)</td>
</tr>
<tr>
<td>Place of fall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At work</td>
<td>0 (0.0)</td>
<td>22 (11.5)</td>
</tr>
<tr>
<td>Home</td>
<td>178 (66.7)</td>
<td>49 (25.5)</td>
</tr>
<tr>
<td>Recreation</td>
<td>0 (0.0)</td>
<td>91 (47.4)</td>
</tr>
<tr>
<td>School</td>
<td>89 (33.3)</td>
<td>30 (15.6)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial injury to head</td>
<td>88 (33.0)</td>
<td>48 (25.0)</td>
</tr>
<tr>
<td>Open wound on head</td>
<td>57 (21.3)</td>
<td>36 (18.8)</td>
</tr>
<tr>
<td>Blunt head injury</td>
<td>62 (23.2)</td>
<td>38 (19.8)</td>
</tr>
<tr>
<td>Superficial injury of neck</td>
<td>16 (6.0)</td>
<td>31 (16.1)</td>
</tr>
<tr>
<td>Soft tissue contusion</td>
<td>23 (8.6)</td>
<td>17 (8.9)</td>
</tr>
<tr>
<td>Traumatic amputation on head (ear &amp; nose)</td>
<td>3 (1.1)</td>
<td>13 (6.8)</td>
</tr>
<tr>
<td>Dislocation, sprain, strain of joints of head</td>
<td>6 (2.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Fracture of skull &amp; Facial bone</td>
<td>4 (1.5)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Multiple injuries of head</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Open wound of neck</td>
<td>2 (0.7)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Burns &amp; corrosions</td>
<td>3 (1.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Injury of nerves &amp; spinal cord</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Penetrating head injury</td>
<td>1 (0.4)</td>
<td>2 (1.0)</td>
</tr>
</tbody>
</table>
head injuries, followed by neck injuries (19.8%).14

Our findings revealed that both the head and neck injuries from falls were higher in young adults in the age group 20–29 years (25.7%) and 30–39 years (22.6% and 23.6%). A study by Hausdorff et al. documented that more than a third of older adults fall each year and 10–20% of falls cause serious injuries such as fractures or head trauma.15 This runs contrary to the study in Canada on fall-related emergency department visits, where the head and neck were injured most often (49%) among children below 20 years.16 In Ontario, 80% of head injury hospitalisations were reported among people aged 65 years and older, while only 17% were reported in the 15 to 34 years age group.17 Another study by Cheng et al. also reported that there was a trend for the elderly to have more frequent injuries to the head (53.2%) and neck (47.5%) region.18

The reason for the low proportion of falls among elderly people in Qatar is that the majority of the fall-induced head (78.9%) and neck injuries (76.9%) occurred in the non-Qatari population. These people leave Qatar once they reach their retirement age of 60 years. This is evident from the data as half of the head and neck injuries were occupational injuries (49.5%). Thus, falls are a common cause of occupational morbidity and mortality, resulting in significant losses of life, wages, as well as significant medical expenses. Falls are a risk factor for disability and frailty and exacerbate disablement among the adult non-Qatari population. Even in the United Arab Emirates, occupational injuries resulting from falls were frequent with 66.7% of hospitalisations.18 Similar to Qatar, falls were the most frequent cause of head and neck injuries among non-nationals in the United Arab Emirates, whereas for injuries among nationals the main cause was road traffic crashes.18 Many studies indicate that falls continue to pose a serious problem to the elderly population, whereas it was a more serious issue for both the middle-aged working population and the elderly in Qatar.18,19

The incidence rate of fall induced head and neck injuries among the general population rose considerably in the study period: from 2.1 in 2001 to 5.5 in 2006. Although the frequency of fall induced head and neck injuries was higher in young adults, the incidence rate in the elderly population above 60 years of age seemed to show an alarming rise with a rate that cannot be explained merely by demographic changes: from 2.8 in 2001 to 19/10,000 in 2005 and 18.6/10,000 in 2006. The incidence rate in people above 60 years-old was four times higher than the incidence rate observed in younger people. A similar finding was observed in

### Table 3: Incidence rate of head and neck injuries resulting from falls per 10,000 population during the period 2001–2006

<table>
<thead>
<tr>
<th>Age group</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1.4</td>
<td>3.5</td>
<td>5.5</td>
<td>4.5</td>
<td>5.5</td>
<td>2.4</td>
</tr>
<tr>
<td>10–19</td>
<td>2.4</td>
<td>3.4</td>
<td>2.7</td>
<td>3.4</td>
<td>4.1</td>
<td>4.0</td>
</tr>
<tr>
<td>20–29</td>
<td>3.4</td>
<td>6.1</td>
<td>4.8</td>
<td>5.4</td>
<td>8.7</td>
<td>8.7</td>
</tr>
<tr>
<td>30–39</td>
<td>1.7</td>
<td>2.4</td>
<td>4.0</td>
<td>4.4</td>
<td>6.2</td>
<td>5.4</td>
</tr>
<tr>
<td>40–49</td>
<td>1.3</td>
<td>2.7</td>
<td>3.8</td>
<td>3.5</td>
<td>4.8</td>
<td>4.0</td>
</tr>
<tr>
<td>50–59</td>
<td>3.4</td>
<td>4.4</td>
<td>3.6</td>
<td>3.3</td>
<td>4.9</td>
<td>5.4</td>
</tr>
<tr>
<td>60+</td>
<td>2.8</td>
<td>6.7</td>
<td>13.1</td>
<td>11.9</td>
<td>19.0</td>
<td>18.6</td>
</tr>
<tr>
<td>All Ages</td>
<td>2.1</td>
<td>3.7</td>
<td>4.4</td>
<td>4.4</td>
<td>6.3</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Note: P < 0.001.

### Figure 1: Incidence rate of head injury, neck injury and both injuries per 10,000 of the population resulting from falls during the period 2001–2006.
a study by Stevens and Soglow where the incidence rates for fall related head injuries increased with advancing age with a rate four to five times higher in people aged 85 years and older compare to those aged 65–74 years. Rubenstein et al. reported that beyond 50 years of age, there is a steady increase in the occurrence of falls and the magnitude of fall related complications. In Qatar, after the elderly population, young adults in the age group 20–29 years were the most frequent victims of head and neck injuries from falls; 8.7/10000 in the years 2005 and 2006.

The relationship between fall and injury varies by gender. In the study sample, 86.6% of the head and neck injuries were reported among men. Men outnumber women by 6.5:1. It was found that men sustain more fall injuries than women, perhaps due to the underlying causes or circumstances of their falls. This result differs to that of another study where women had a higher risk of falling than men in general population studies, a trend not seen in the present study. Jenson et al. reported that the cause of the gender discrepancy may lie in divergent activity patterns between men and women over separate periods of the day and night or in differences in personal risk assessment between the genders.

In Qatar, expatriates (70% of the total population), especially the male labour force, are greater in number than nationals. A good proportion of the expatriate men are employed on construction sites where they are at high risk for occupational injuries. Elderly people are mostly nationals and they have a better life expectancy due to better health care and a higher standard of living.

In Qatar, superficial injuries of head have been observed overall with a frequency up to 29.4% in falls, followed by open wound on the head (23.4%). Superficial injury was more common among children below 10 years (33%) and in elderly population above 60 years (31.3%). However, an open wound to the head was more frequent among people above 60 years (32.8%). Nonetheless, blunt head injury was more frequent in children (23.2%) and the elderly population (22.4%) compared to other age groups. In another study by Turk and Tsoko, a higher frequency of blunt neck injuries were observed (33%) in falls from heights. Neck injuries were less common in falls in the studied population compared to head injuries. In Canada, 74% of fall related hospital admissions are due to fractures and dislocations, with serious head injuries (20%). Elderly trauma patients differed from younger adult trauma patients in their injury patterns and the mode of presentation of significant injuries.

The present study showed some differences and some similarities when compared to other studies related to fall injuries. The risk in our study increased with age and was higher among men, a similar finding to other studies. The findings of our study confirm the findings of previous studies with regard to older age which is a well-recognised risk factor for falling in the general population. Additional efforts in Qatar are needed to reduce the occurrence of fall related occupational injuries. It is important to identify the risk factors related to fall induced head and neck injuries and develop comprehensive intervention programmes to reduce the risk for such falls. Falls have significant economic impact on the country, including costs to individuals and their families, to work places and the health system as well as to community and social services.

Conclusion

A relatively high rate of head and neck injuries from falls was demonstrated in this study. The incidence of head and neck injuries rose during the study period. Occupational fall injuries were most frequent in the general population, particularly among non-nationals. Findings show that the age-specific incidence of fall-induced severe head injuries in the Qatar population above 60 years of age has increased steeply during the study period and also has not declined in more recent years. According to the GCS score, neck injuries were more severe than head injuries. The injuries represent an alarming epidemic and the predicted ageing of populations will soon exacerbate the burden on our health care systems.

CONFLICT OF INTEREST

The authors reported no conflict of interest.

References


The Disinfecting Potential of Contact Lens Solutions used by Sultan Qaboos University Students

B. C. Nzeako and Sara H. Al-Sumri

ABSTRACT: Objectives: This study aimed to determine the disinfecting potential of some contact lens solutions used by some university students in Oman. Methods: This work was carried out from January to June 2010 in the Department of Microbiology & Immunology, College of Medicine and Health Sciences, Sultan Qaboos University, Oman. Fifty disinfecting solutions, in which contact lenses were disinfected according to the manufacturers’ instructions, were collected from the students and plated on various microbiological culture media. Bacterial isolates were identified by API-20E, API-20NE and Phoenix automated systems while fungi were identified by their cultural characteristics and biochemistry. Results: From 98 isolates, Pseudomonas aeruginosa was 23.5%; Penicillium, 13%; Candida species, 9.2%; coagulase negative staphylococci, 9.2%; Serratia marcescens, 6.1%; Bacillus, 5.1%; Aspergillus flavus, 5.1%; Serratia liquefaciens, Pseudomonas fluorescens, Enterobacter cloacae and Aspergillus niger, 4.1% each; Chryseomonas luteola and Chryseomonas indologenes, 3.1% each; Stenotrophomonas maltophilia, Serratia odorifera, 2.0% each; Enterobacter aerogenes and Klebsiella pneumoniae, 1% each. Most isolates (65%) came from polyhexanide containing solutions. Conclusion: Contact lens disinfecting solutions with the same formulations, but manufactured by different companies, possessed different disinfecting activity. Keywords: Lenses; Disinfecting; Bacteria; Contamination; Fungi; Oman

ADVANCES IN KNOWLEDGE
1. This is the first time this type of study has been done at Sultan Qaboos University.
2. It was observed that different disinfecting solutions for contact lenses are used by students at Sultan Qaboos University.
3. Contact lens disinfecting solutions with the same formulation, but manufactured by different companies, possessed different disinfecting activity.
4. There is great need to revisit the US Food and Drug Administration guidelines on the use of multipurpose disinfecting solutions for contact lenses and storage cases.

APPLICATION TO PATIENT CARE
1. Manufacturers’ guidelines for the decontamination of contact lenses and storage cases should be rigorously followed by the wearers.

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The soft contact lens industry has expanded rapidly over the past four decades because of the demand for a convenient alternative to wearing spectacles for various purposes. Contact lenses wear can be for correction of eye defects (myopia, hypermetropia, astigmatism and presbyopia), may be cosmetic (decorative) or therapeutic (for the treatment and management of bullous keratopathy, dry eyes, corneal ulcers and keratitis). It is estimated that 125 million people worldwide use contact lenses of which 28–38 million are from USA and 13 million from Japan.

Soft hydrogel contact lenses are categorised according to their structure, water content, oxygen permeability and mode of wearing (daily wear, removed each night), extended wear (worn for 6 nights) and continuous wear (worn for 30 consecutive nights). Their ability to aid vision, give comfort to the wearer and prevent microbial keratitis is highly advocated.

Silicone hydrogel contact lenses were introduced in 1999 for this purpose. Unfortunately, they are not better than other soft contact lenses for controlling microbial keratitis. Corneal infections continue to be the most serious complication of wearing contact lenses.

However, many people who wear contact lenses are unaware of the likelihood of developing eye infections for some bacteria colonise and form biofilms inside lens storage cases. In this state, they become resistant to disinfecting solutions. A study on 252 soft contact lenses, lens storage cases and disinfecting liquids found that 84.1% of the contact lenses, 80.9% of the lens storage cases and 63.1% of the disinfecting liquids were contaminated by Staphylococcus aureus, Staphylococcus epidermidis, Viridans streptococci, Klebsiella pneumoniae, Pseudomonas aeruginosa, Pseudomonasfluorescens, Citrobacteramalonaticus and Stenotrophomonas maltophilia. Another study found 9% of lenses, 34% of lens storage cases and 11% of lens solutions contained Serratia spp, S. aureus, coagulase negative staphylococci and P. aeruginosa. The contamination was traceable to users’ dirty hands, or the tap water used to rinse the lens storage cases, and/or air contamination during drying of the cases.

Flynn et al. found contact lenses to harbour mostly Gram negative and coagulase negative staphylococci. Their mode of adhesion to lenses was through deposits of proteins, mucins, lipids and inorganic compounds produced by the eye.

However, the results of studies on the efficacy of some contact lens solutions as effective disinfectants are conflicting. The Federal Drug Administration (FDA) recommended the mode of assessing the efficacy of multipurpose contact lens disinfecting solutions using 'stand alone' (ISO/CD 14729) testing procedures. In this procedure, all multipurpose solutions are required to ensure a 3-log reduction in numbers on three bacterial strains (S. aureus (ATCC6538), Serratia marcescens (ATCC 13880) and P. aeruginosa (ATCC 9027), 1-log reduction on Candida albicans (ATCC 10231) and Fusarium solani (ATCC 36031). Although the recommendation ensured good disinfection of lenses by achieving 3-log reduction in cell numbers, some researchers found many laboratory isolates viable in the solution while others observed that many microbes associated with microbial keratitis were not represented in the approved panels of microbes used for the test.

Disinfecting solutions containing polyhexanide were found to kill Escherichia coli, S. epidermidis, P. aeruginosa, and S. marcescens while solutions containing biguanides killed E. coli and S. epidermidis, but not C. albicans. The reduced efficiency of some disinfecting solutions may be attributable to their formulations and mode of use.

The aim of this study was to assess the disinfecting potential of some contact lens solutions used by some students at Sultan Qaboos University. It is envisaged that the results of this investigation can help establish the type of microbes in the solutions so that wearers can appropriately be advised.

2. Wearers of contact lenses should be aware of the risk of developing microbial keratitis and corneal ulcers.
3. Good personal hygiene during decontamination of lenses and storage cases and during removal or placement of lenses on the eyes is essential.
Methods

This study was carried out from January to June 2010 in the Department of Microbiology & Immunology, College of Medicine and Health Sciences, Sultan Qaboos University, Oman. Fifty disinfecting solutions, in which contact lenses were disinfected according to the manufacturers’ instructions, were collected from the students and plated on various microbiological culture media. No patient or patient’s sample was utilised.

Each contact lens user was given three sterile bijou bottles, one for the disinfecting solution for the contact lens of the right eye, the second for the left eye, while the third served as a control (same as solution for disinfecting right or left eye lenses). This was done to check the degree of sterility of the solutions before immersion of the lenses. The lenses were immersed in the solutions at night and brought to the laboratory in the morning. Twelve brands of disinfecting solutions marketed by different manufacturers were investigated. The solutions were coded 1-12 to mask the manufacturers’ names and to avoid brand name promotion.

**INOCULATION OF MEDIA**

Fifty microlitres of each solution were streaked on blood agar (BA, Oxoid, UK), cystine electrolyte deficient (CLED, H-Media Laboratories, India), and Sabouraud (SAB, Biotec, UK). All the plates were incubated at 37°C for 48 hrs except Sabouraud plates which were incubated at room temperature for one week. Bacterial growths on the plates were identified using API 20-E, 20-NE (Biomerieux, France) and Phoenix automated system (Becton Dickinson, Maryland, USA) while fungal growths were identified by their growth characteristics, the colour of aerial spores and structural differences using lactophenol cotton blue.

The FDA mode of testing disinfecting solutions for contact lenses (ISO/CD 14729) was not followed because of non-availability of the test organisms. However, any solution that allows growth of any microbe was regarded as contaminated and the contaminating organism was identified.

<table>
<thead>
<tr>
<th>Table 1: Active agents in some contact lens disinfecting solutions and organisms isolated from them</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solutions (code)</strong></td>
</tr>
<tr>
<td>Code 1</td>
</tr>
<tr>
<td>Code 2</td>
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<tr>
<td>Code 3</td>
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<tr>
<td>Code 4</td>
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<tr>
<td>Code 5</td>
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<tr>
<td>Code 6</td>
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<td>Code 7</td>
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<td>Code 8</td>
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<tr>
<td>Code 9</td>
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<tr>
<td>Code 10</td>
</tr>
<tr>
<td>Code 11</td>
</tr>
<tr>
<td>Code 12</td>
</tr>
<tr>
<td>Totals</td>
</tr>
</tbody>
</table>
Results

Although the sample sizes of the solutions were small and their manufacturers different, the same formulations marketed by different manufacturers gave different results [Table 1]. Forty percent (40%) of the solutions showed growth of various types of microbes. Solutions containing polyhexanide had 65% growth and were used by 66% of the students. This was followed by polyaminopropyl biguanide with 5% growth and used by 14% of the students. All the microbes contaminating control solutions were present in the solutions used for the right or left contact lenses, but not all the isolates contaminating the right or left contact lenses solutions were present in the control solutions [Table 2]. However, where the lens solutions and their aliquots (controls) were sterile, no organism was found. *P. aeruginosa* (23.5%) and *Penicillium* spp. (13.3%) were the most common isolates while *Klebsiella pneumoniae* and *Enterobacter aerogenes* were the least, 1% each [Table 3].

Discussion

Soft hydrogel contact lenses are used for various purposes (corrective, cosmetic or therapeutic) and are either for daily, extended or continuous wear. Users are advised to clean their contact lens cases and change disinfecting solutions daily except if they are silicone hydrogels for extended or continuous wear. Contact lenses offer some advantages over spectacles in terms of convenience and better visual acuity. However, the wearing of contact lenses may lead to serious complications including microbial keratitis and corneal ulcers which may lead to blindness.7-9,30-31

In this experiment, polyhexanide containing solutions, although greater in number, were the most contaminated. In contrast, polyaminopropyl and polyhexamethylene biguanides inhibited the growth of some microbes and allowed growth of others. Though their sample sizes were few, they possessed more antimicrobial properties than polyhexanides. This finding agrees with Santos et al.3 and Hume et al.,23 but disagrees with Cano-Parro et al.28 who found polyhexanides better than biguanides.

In this study, *P. aeruginosa* had a prevalence of 23.5%. The factors contributing to its survival in some lens disinfecting solutions were traceable.

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**Table 2: Microbes isolated from various solutions**

<table>
<thead>
<tr>
<th>Solution used for right eye lenses</th>
<th>Solution used for left eye lenses</th>
<th>Control solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase negative staphylococci</td>
<td>Coagulase negative staphylococci</td>
<td><em>P. aeruginosa</em></td>
</tr>
<tr>
<td><em>E. aerogenes</em></td>
<td><em>E. cloacae</em></td>
<td><em>C. indolegenes</em></td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td><em>P. aeruginosa</em></td>
<td><em>S. marcescens</em></td>
</tr>
<tr>
<td><em>C. luteola</em></td>
<td><em>C. luteola</em></td>
<td><em>Penicillium</em></td>
</tr>
<tr>
<td><em>C. indolegenes</em></td>
<td><em>K. pneumoniae</em></td>
<td><em>A. flavus</em></td>
</tr>
<tr>
<td><em>Candida spp</em></td>
<td><em>S. marcescens</em></td>
<td><em>S. liquefaciens</em></td>
</tr>
<tr>
<td><em>A. flavus</em></td>
<td><em>Candida spp</em></td>
<td><em>A. niger</em></td>
</tr>
<tr>
<td><em>S. hominis</em></td>
<td><em>E. cloacae</em></td>
<td><em>Bacillus spp</em></td>
</tr>
<tr>
<td><em>Bacillus</em></td>
<td><em>A. flavus</em></td>
<td></td>
</tr>
<tr>
<td><em>S. liquefaciens</em></td>
<td><em>S. liquefaciens</em></td>
<td></td>
</tr>
<tr>
<td><em>Penicillium</em></td>
<td><em>Candida spp</em></td>
<td></td>
</tr>
<tr>
<td><em>S. marcescens</em></td>
<td><em>S. odorifera</em></td>
<td></td>
</tr>
<tr>
<td><em>C. indolegenes</em></td>
<td><em>S. marcescens</em></td>
<td></td>
</tr>
<tr>
<td><em>S. marcescens</em></td>
<td><em>C. indolegenes</em></td>
<td></td>
</tr>
<tr>
<td><em>A. niger</em></td>
<td><em>A. niger</em></td>
<td></td>
</tr>
<tr>
<td><em>A. flavus</em></td>
<td><em>Bacillus</em></td>
<td></td>
</tr>
<tr>
<td><em>Penicillium spp</em></td>
<td><em>P. fluorescens</em></td>
<td></td>
</tr>
<tr>
<td><em>P. fluorescens</em></td>
<td><em>P. maltophilia</em></td>
<td></td>
</tr>
<tr>
<td><em>P. fluorescens</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. odorifera</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
<td></td>
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</tr>
</tbody>
</table>
to its adaptability to adverse environmental conditions and capability to attach easily to corneas and contact lenses (rigid, hydrogel, high and low water content contact lenses).16,32-33

In contrast, *Enterobacter, Serratia* and *Klebsiella* species which are usually of faecal origin can be transferred to the disinfectants by the wearers during the process of immersion or removal of the lenses from the solutions. In addition, some of the organisms like *Serratia* and *Pseudomonas* species are resistant to some disinfecting solutions.20 Fungi like *Candida, Penicillium* and *Aspergillus* species are adaptive to diverse environments and require little moisture and organic substrate for growth. They are likely to come from poor or inadequate cleaning of contact lens cases since bacteria interacting with contact lens storage cases form biofilms that make them resistant to disinfecting solutions.17 The nutrients for growth are acquired from lipids, proteins and glycoproteins present in the tears of the eyes.20 However, when they are present on the lenses and lens cases, the efficacy of the disinfecting solution can be neutralised by their presence.11 The isolates contaminating the control solutions also contaminated the solutions used for disinfecting left and right eye lenses. This indicates that the solutions were contaminated before the immersion of the lenses. In this study, it is observed that some control solutions were sterile although microbes were isolated from their aliquots used for disinfecting the right or left lenses [Table 2]. Such contamination is inferred to originate from the user (poor hand hygiene), the lenses or from the storage cases. Some researchers observed that non-compliance with the guidelines for caring for contact lenses and lens cases was a major issue in the use of contact lenses.32 Their observation was supported by the finding that 11% of the contamination of solutions was due to poor hand hygiene, 13% to inadequate disinfection of lenses, and 61% to inappropriate cleaning practices of storage cases.31,32 From whatever source and by whatever means, the organisms got into the solutions and some of the disinfectants could not eliminate the organisms. This experiment appears to establish the fact that disinfecting solutions for lenses are not sterilising solutions, but agents meant to reduce the microbial numbers on lenses and cases.

### Table 3: Percentage distribution of isolates from all solutions

<table>
<thead>
<tr>
<th>No.</th>
<th>Organisms</th>
<th>No. of isolates</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>P. aeruginosa</em></td>
<td>23</td>
<td>23.5%</td>
</tr>
<tr>
<td>2</td>
<td><em>Penicillium</em> spp.</td>
<td>13</td>
<td>13.3%</td>
</tr>
<tr>
<td>3</td>
<td><em>Candida</em> spp.</td>
<td>9</td>
<td>9.2%</td>
</tr>
<tr>
<td>4</td>
<td>Coagulase negative</td>
<td>9</td>
<td>9.2%</td>
</tr>
<tr>
<td></td>
<td><em>staphylococci</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><em>S. marcescens</em></td>
<td>6</td>
<td>6.1%</td>
</tr>
<tr>
<td>6</td>
<td><em>Aspergillus flavus</em></td>
<td>5</td>
<td>5.1%</td>
</tr>
<tr>
<td>7</td>
<td><em>Bacillus</em></td>
<td>5</td>
<td>5.1%</td>
</tr>
<tr>
<td>8</td>
<td><em>S. liquefaciens</em></td>
<td>4</td>
<td>4.1%</td>
</tr>
<tr>
<td>9</td>
<td><em>P. fluorescens</em></td>
<td>4</td>
<td>4.1%</td>
</tr>
<tr>
<td>10</td>
<td><em>E. cloacae</em></td>
<td>4</td>
<td>4.1%</td>
</tr>
<tr>
<td>11</td>
<td><em>Aspergillus niger</em></td>
<td>4</td>
<td>4.1%</td>
</tr>
<tr>
<td>12</td>
<td><em>C. lutolusa</em></td>
<td>3</td>
<td>3.1%</td>
</tr>
<tr>
<td>13</td>
<td><em>C. indolgenes</em></td>
<td>3</td>
<td>3.1%</td>
</tr>
<tr>
<td>14</td>
<td><em>Stenotrophomonas</em></td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td><em>maltophilia</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><em>S. odorifera</em></td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>16</td>
<td><em>E. aerogenes</em></td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>17</td>
<td><em>K. pneumoniae</em></td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>98</td>
<td>100%</td>
</tr>
</tbody>
</table>

### Conclusion

Twelve disinfecting solutions for soft hydrogel contact lenses were examined for growth of microbes after lenses were removed from the eyes and immersed overnight in the disinfecting solutions. Forty percent (40%) of the solutions grew some microbes, with polyhexanide containing solutions showing highest growth (65%). The least growth (5% and 5% respectively) came from polyhexamethylene and polyaminopropyl biguanides. Because of the small and unequal number of samples investigated, it is statistically difficult to state which is the best disinfecting solution.

The small number of samples used in this study limits the outcome of the investigation. Further work using larger samples and looking for parasites like *Acanthamoeba* is necessary. However, it is of importance that multipurpose solutions which clean, disinfect and rinse contact lenses and their cases be used for all contact lenses.19,21,24 The lenses...
should be stored dry in their cases after disinfection. Before removing the lenses from the eyes, the user should wash his/her hands thoroughly in soapy water. If a multipurpose solution containing hydrogen peroxide is used for disinfecting the lenses, the lenses should be rinsed several times in saline solution to get rid of the hydrogen peroxide which is toxic to the eyes. It should be borne in mind by all contact lens users that the disinfecting solutions do not sterilise contact lenses and lens cases, but only reduce the microbial load on them. The reduction is only possible if the organisms to be reduced are susceptible to formulations in the disinfecting solutions. Currently, the performance of disinfecting solutions for all types of contact lenses is being re-visited and various formulations are being suggested.

CONFLICT OF INTEREST
The authors reported no conflict of interest.

ACKNOWLEDGEMENTS
The authors are grateful to the Department of Microbiology & Immunology for providing the media and the reagents used for the study and for their cooperation throughout the duration of the work.

References


**Myelomatous Pleural Effusion**

Case report and review of the literature

*Khalil Al-Farsi, Ibrahim Al-Haddabi, Nafla Al-Riyami, Rashid Al-Sukaiti, Salam Al-Kindi*

**ABSTRACT:** Plasma cell myeloma is an uncommon disease which, besides primarily involving the bone marrow, has a tendency to involve other organs thus presenting with different clinical manifestations. While pleural effusions are infrequent in this disease, true myelomatous pleural effusions are extremely rare. We report the case of a middle-aged Omani man with relapsed plasma cell myeloma who developed bilateral pleural effusions. The diagnosis of myelomatous pleural effusion was made by finding many abnormal plasma cells as well as a high level of a monoclonal protein (IgG κ) in the pleural fluid. In spite of a good initial response to therapy, the patient had progressive disease and died 6 months later with bacterial sepsis. We present a review of the literature that indicates the rarity of such a manifestation and its association with poor prognosis and short survival.

**Keywords:** Multiple myeloma; Plasma cells; Pleural effusion; Case report; Oman

**MULTIPLE MYELOMA (NOW KNOWN AS PLASMA CELL MYELOMA)** is a malignant disease caused by a proliferation of clonal plasma cells associated with a monoclonal protein or light chain in the serum and/or urine. Patients with plasma cell myeloma commonly present with hypercalcaemia, renal insufficiency, anaemia and/or bony lesions. However, the disease can present with a wide variety of clinical manifestations as a result of the involvement of various organ systems, due to either direct infiltration by plasma cells or the deposition of monoclonal proteins or light chains. Pleural effusions are seen in a minority of patients with myeloma. However, effusions directly related to infiltration of the pleura by plasma cells, i.e. myelomatous pleural effusions (MPE), are extremely rare. In this paper, we report a case of an Omani patient with relapsed myeloma who developed a true myelomatous pleural effusion. We also present a review of the relevant literature.

**Case Report**

A 55 year-old man was diagnosed with Durie-Salmon stage IIIA IgG kappa plasma cell myeloma in 2004. He was treated for three months with a combination of thalidomide and steroids-based therapy and achieved a partial response. He was subsequently lost to follow-up and presented again in 2007 with progressive disease with severe anaemia and multiple lytic lesions. He was then treated with four cycles of bortezomib, thalidomide and dexamethasone and achieved complete remission. This was followed by melphalan-based...
high dose chemotherapy and autologous stem cell transplantation (ASCT) in April 2008. His disease progressed a year after the transplant and he was treated with lenalidomide and dexamethasone. After five months of therapy, the treatment was interrupted as he developed severe cytopenias. He presented in January 2010 with shortness of breath and dry cough. His temperature was 38.5 °C, pulse was 124/min, respiratory rate was 22 breaths/min, blood pressure was 140/68 mmHg and oxygen saturation 91% on room air. A chest examination revealed decreased breath sounds in both infra-scapular areas with dullness to percussion on both sides. A complete blood count (CBC) revealed a white blood cell (WBC) count of 2.2 x 10^9/L, absolute neutrophil count of 0.5 x 10^9/L, Hb of 8.7 g/dl and platelet count of 36 x 10^9/L. The peripheral blood film showed rouleaux formation and confirmed the thrombocytopenia and neutropenia noted on the CBC. There were no circulating plasma cells or other abnormal cells. Blood chemistry tests showed albumin of 26 g/L, total protein 89 g/L, glucose 5.7 mmol/L, lactate dehydrogenase (LDH) 301 U/L, β2 microglobulin 12.4 mg/L and C-reactive protein 121 mg/L. Serum calcium, creatinine, uric acid, thyroid stimulating hormone (TSH) and liver enzymes were normal. Serologies for HIV, hepatitis B and hepatitis C were negative. Serum protein electrophoresis and immunofixation showed a monoclonal IgG κ of 30.9 g/L with normal levels of uninvolved immunoglobulins. The most recent 24-hour urine test showed a total protein of only 0.13 g/24hour. The chest X-ray showed bilateral pleural effusions. A computed tomography (CT) scan of the chest confirmed the presence of bilateral pleural effusions [Figure 1]. It also showed multiple rib, sternal and thoracic vertebral osseous lytic lesions. There were also multiple sub-centimetre mediastinal lymph nodes. There was no evidence of pulmonary embolism. An echocardiography showed no significant abnormalities. The left ventricular ejection fraction was 70%. A thoracocentesis was performed and about 1 L of pleural fluid was drained from the right side. Analysis showed glucose of 6.0 mmol/L, protein of 50 g/L and LDH of 172 U/L. The cytological examination revealed many abnormal plasma cells that constituted around 20% of the total nucleated cell in the pleural aspirate [Figure 2]. Although flow cytometry suggested that these cells were positive for CD38, the results were of poor...
quality due to the suboptimal quality of the sample and therefore difficult to interpret, especially with regards to light chain restriction. However, protein electrophoresis and immunofixation on the pleural fluid showed 16.7 g/L of IgG κ monoclonal protein [Figures 3 and 4]. A Gram stain, acid fast bacilli (AFB) stain and cultures (bacterial, fungal and TB cultures) were all negative. He was treated with high dose dexamethasone followed by one cycle of a combination of liposomal doxorubicin, bortezomib and dexamethasone. The pleural effusion resolved completely. However, the disease started to progress systemically over the following month, and his performance status deteriorated. He developed refractory cytopenias and became transfusion dependent. The effusions recurred bilaterally within 4 months. He was managed with palliative supportive care and died due to Escherichia coli sepsis in the setting of progressive disease in July 2010. A post-mortem examination was not performed.

Discussion

Although plasma cell myeloma is mostly a bone marrow based disease, it can produce a variety of clinical presentations through the involvement of different extramedullary sites. One of these manifestations is pleural effusion. Pleural effusions, caused by several aetiologies, are reported to occur in 6% of patients with myeloma during the course of their disease. Myelomatous pleural effusions are rare and only about 80 cases have been reported in English medical literature.

Pleural effusions in patients with myeloma often results from non-malignant causes, some of which are treatable. The most common cause is congestive cardiac failure due to amyloidosis. Heart failure can also result from hyperviscosity and from cardiomyopathy related to the use of anthracyclines, commonly used in the treatment of myeloma in the past. Other causes include pulmonary embolism, infections, nephrotic syndrome and chronic renal failure. In addition, secondary neoplasms occurring in patients with myeloma, like carcinomas of the breast and lung and mesothelioma, can cause malignant pleural effusions. A detailed systematic approach to investigating pleural effusions, as demonstrated in our case report, is therefore important to exclude these alternative diagnoses.
Myelomatous Pleural Effusion
Case report and review of the literature

Our patient had normal cardiac and renal functions and no evidence of pulmonary embolism or nephrotic syndrome. In addition, there was no evidence of any infective aetiology and no evidence of secondary malignancies.

A true myelomatous pleural effusion is rare and occurs in less than 1% of patients with myeloma. It is usually a sign of advanced disease, although there are a few reports of it being the initial presenting feature of myeloma in some patients. There are about 80 cases reported in English medical literature. Older reports indicate that most effusions are due to IgA myeloma. However, more recent reports indicate that the majority occur in patients with IgG myeloma, which is the most common type of myeloma, as was the case in our patient. These recent reviews also indicate that it has an equal gender distribution, is commonly haemorrhagic, more commonly affects the left side and that these patients usually have poor prognostic disease markers. Our patient had bilateral effusions at a late stage of his relapsed/refractory disease.

The pathogenesis of myelomatous pleural effusion is not well understood, but several possible mechanisms have been proposed. These include: 1) direct extension of the disease to the pleura from adjacent skeletal or lung parenchymal tumors; 2) direct infiltration or implantation of tumour deposits on the pleura, and 3) lymphatic obstruction from mediastinal lymph node infiltration. Extension from a mediastinal extramedullary plasmacytoma has also been suggested as one possible mechanism. It is possible that the myelomatous pleural effusion in our patient resulted from extension of his disease from the many lesions in his ribs, sternum and thoracic vertebrae. Whether he had direct infiltration of the pleura is hard to prove as he did not have a pleural biopsy and small areas of involvement might be missed on CT scans.

Diagnostic criteria have been suggested to confirm the myelomatous nature of pleural effusions. The criteria include: 1) detection of atypical plasma cells in the pleural fluid; 2) demonstration of a monoclonal protein on pleural fluid electrophoresis, and 3) histological confirmation using pleural biopsy specimens or autopsy. Our patient had an exudative effusion that had a high level of monoclonal IgG κ as well as many abnormal plasma cells. A pleural biopsy was not done because of his poor general condition and severe thrombocytopenia at that time. In fact, one could argue that a pleural biopsy is not an integral part of the diagnosis. Pleural biopsies are not always done in these patients and when done are not always diagnostic or helpful. The risk associated with the procedure as well as the patchy nature of disease involvement make it less attractive and less reliable as a diagnostic tool.

Despite the proposed criteria, the diagnosis of myelomatous pleural effusions can be challenging. Reactive plasma cells may be seen in effusions secondary to cardiac surgery, tuberculosis, viral infections, connective tissue diseases, Hodgkin’s lymphoma and carcinomatosis. In addition, malignant plasma cells have a wide spectrum of appearances in fluid specimens and may be missed.

Figure 3: Protein electrophoresis on (A) serum and (B) pleural fluid, both showing a dense monoclonal band in the slow gamma region.

Figure 4: Immunofixation on pleural fluid showing an IgG κ monoclonal band.
as being of plasmacytic origin, especially if low in number. Furthermore, due to \textit{in vivo} and \textit{in vitro} degeneration and changes during sample processing, the morphology can be significantly altered leading to further difficulties in recognising these cells as malignant plasma cells.\textsuperscript{7} The characteristic clock-faced condensed chromatic pattern is absent in these cases. Instead, the nuclei of these cells are round to oval or pleomorphic and have a coarse and irregular chromatin pattern with prominent nucleoli. These malignant cells also have dense cytoplasm with absent or inconspicuous perinuclear hof.\textsuperscript{19,17} Pleural biopsies might not be feasible and are not always diagnostic. It has been suggested that flow cytometric studies should be used to supplement the diagnosis.\textsuperscript{7} It has been shown, however, that in some instances flow cytometry might not be helpful due to poor specimen quality causing non-specific light-chain staining.\textsuperscript{17,19} It has also been suggested that cytogenetic analysis be done on the pleural aspirate to support the diagnosis as an abnormal cytogenetic karyotype in the pleural fluid can provide unequivocal evidence of malignancy;\textsuperscript{7} however, this is not always possible. The diagnosis in most of the reported cases relied mainly on finding abnormal plasma cells and a monoclonal protein in the pleural fluid.

The lack of alternative diagnosis and the presence of malignant-appearing plasma cells in the pleural fluid support the diagnosis of myelomatous pleural effusion in our patient. In addition, the lack of circulating plasma cells in his peripheral blood, while there were many in his pleural fluid, argues strongly against the monoclonal protein in his pleural fluid being the result of contamination with peripheral blood. Flow cytometry was attempted, but the suboptimal quality of the sample precluded interpretation of the results. The pleural fluid was not subjected to cytogenetic analysis in our patient. Such analysis is not necessary for routine diagnosis.\textsuperscript{7} In addition, cytogenetic studies in myeloma patients can be difficult because few mitoses are often obtained.\textsuperscript{18,20} Overall, with the clinical presentation and the findings on pleural fluid analysis, there is no doubt that our patient had a true myelomatous pleural effusion.

The diagnosis of myelomatous pleural effusion carries a poor prognosis despite aggressive treatment. The literature suggests that the median survival of these patients is about 4 months. Several treatments have been tried including different combinations of systemic chemotherapy,\textsuperscript{7,12,21} as well as intra-pleural injections of different agents like adriamycin and interferon.\textsuperscript{19,20,22,23} Despite some reported responses, the majority of these were transient and recurrences were common. There seems to be no added benefit from salvage chemotherapy followed by high dose therapy and ASCT in these patients.\textsuperscript{7} There appears to be some hope, however, with the use of novel agents. Bortezomib, a novel proteasome inhibitor which has been shown to overcome some of the poor prognostic factors in myeloma, has proven to be safe and effective in patients with relapsed/refractory myeloma, especially if combined with other novel agents like liposomal doxorubicin.\textsuperscript{21,24} Some have reported encouraging responses to systemic as well as intra-pleural bortezomib.\textsuperscript{22,23,25,26} Our patient was exposed to all available novel drugs including thalidomide, lenalidomide and bortezomib and did have a good response to systemic treatment with bortezomib, liposomal doxorubicin and dexamethasone. As his effusions resolved, no intra-pleural therapy was given. Unfortunately, the response was transient and he was not able to tolerate further therapy. He eventually died within 6 months of developing the myelomatous pleural effusion.

**Conclusion**

Pleural effusions in patients with multiple myeloma result from different aetiologies, each requiring a different type of treatment. Due to the important therapeutic and prognostic implications of finding a myelomatous pleural effusion, diagnostic thoracocentesis with careful cytological examination and protein electrophoresis with immunofixation should be performed whenever possible. Supplemental studies with flow cytometry and cytogenetics should also be considered.

**References**


**Abstract:** We describe a case of a 38-year-old Sri Lankan female who was referred to the surgeon on call with a picture of acute abdomen. She presented with a three-day history of fever, headache, abdominal pain, and diarrhoea; however, the physical examination was not consistent with acute abdomen. Her platelet count was 22 x 10^9/L. A diagnosis of dengue haemorrhagic fever (DHF) was made and dengue serology was positive. Dengue epidemics have been associated with a variety of gastrointestinal symptoms and signs, including acute abdomen. Acute abdomen in patients with DHF makes the diagnosis and management challenging.

**Keywords:** Dengue; Haemorrhagic fever; Acute abdomen; Case report; Oman

Dengue virus is a mosquito-borne flavivirus and the most prevalent arbovirus in tropical and subtropical regions of the world.1 The 2005 World Health Assembly resolution WHA58,3 on the revision of the International Health Regulations (IHR) has included dengue as an example of a disease that may constitute a public health emergency of international concern with implications for health security due to disruption and rapid epidemic spread beyond national borders.2 Acute abdomen is an uncommon presentation of dengue haemorrhagic fever (DHF). It is important to take DHF into consideration when making a differential diagnosis for patients with acute abdomen, a history of travel to dengue endemic areas and thrombocytopenia. Reaching the right diagnosis may help in preventing unnecessary surgical interventions for patients with DHF.

**Case report**

A 38-year-old Sri Lankan lady presented with a three-day history of fever associated with abdominal pain, vomiting, and diarrhoea. She also gave a history of headache. These symptoms had started on the day she arrived in Oman from Sri Lanka. She denied any history of skin rashes, urinary symptoms or contact with sick people. She had been working in Oman for the previous four years and had visited her home country, Sri Lanka, for four weeks coming back to Oman three days prior to admission to hospital.

Clinical examination showed a sick looking and mildly dehydrated woman. There was no evidence of jaundice, lymphadenopathy or skin rash. She was febrile and hypotensive, but she was not tachypneic or tachycardic. An abdominal examination revealed a generalised abdominal tenderness mainly in the right hypochondrium, but there was no guarding or rigidity. Other systemic examinations were unremarkable. Initial investigations showed haemoglobin of 14.2 g/dl; haematocrit count of

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Dengue Haemorrhagic Fever Presenting as Acute Abdomen

39.9%; platelet count 22 x10^9/L; white blood cell count 11.5 x10^9/L with neutrophils of 2.4 x10^9/L and lymphocytes of 4.8 x10^9/L; mildly raised alanine transaminase (ALT) of 86 IU/L, and alkaline phosphatase of 184 IU/L. Urea and electrolytes, coagulation profile and amylase were normal. An abdominal ultrasonography showed free fluid in the abdomen with a slightly thickened gall bladder wall, but no evidence of gall bladder calculi. The patient was referred to the surgical team with an initial diagnosis of acute cholecystitis. She was kept nil by mouth and was started on intravenous fluids and ceftriaxone injections. On the second day of admission, the patient continued to have severe abdominal pain and a clinically detected guarding abdomen. An urgent computed tomography (CT) scan of the chest and abdomen with oral and intravenous contrast was done. It showed bilateral pleural effusion with right lower lobe collapse and segmental atelectasis, and abdominal and pelvic ascites, but the gall bladder was normal. In view of the CT findings, acute cholecystitis was ruled out and an alternative diagnosis was considered. Malaria screening was negative. The blood film revealed very mild leukocytosis with reactive lymphocytes and a mild neutrophil left shift; the platelets were markedly reduced and showed occasional large forms. The features of the blood film were compatible with a viral infection; in view of the recent travel history to a dengue endemic country, dengue haemorrhagic fever (DHF) was suspected.

The patient was managed conservatively and made a remarkable improvement clinically with a gradual increase in the platelet count. She was sent home on the fifth day after her admission, symptom free and with a platelet count of 224x10^9/L. Dengue serology was done on admission and was immunoglobulin M (IgM) positive; it was repeated two months later and the result was equivocal. Polymerase chain reaction (PCR) for dengue virus was requested on admission, but it was not done due to technical reasons in the laboratory. It was, however, done with the repeated serology two months after the initial presentation and was negative.

Discussion

Dengue virus infection is the most common cause of arboviral disease in the world. The estimated annual occurrence of dengue fever is 100 million cases of dengue fever with 250,000 cases of DHF, and a mortality rate of 25,000 per year. In the last 50 years, the incidence has increased 30-fold with geographic expansion to new countries and, in the present decade, from urban to rural settings. Dengue is endemic in most tropical and subtropical parts of the world. Some 1.8 billion (more than 70%) of the populations at risk for dengue worldwide live in member states of the World Health Organization’s (WHO) South-East Asia and Western Pacific regions which bear nearly 75% of the current global disease burden due to dengue. Dengue is transmitted by the mosquito vectors *Aedes aegypti* and *Aedes albopictus*. Dengue infection is caused by any of 4 different serotypes of the virus (DEN-1, DEN-2, DEN-3, and DEN-4). The incubation period is 4–7 days after an infective mosquito bite. The recent emergence of DHF in the Indian subcontinent has been well documented in Sri Lanka. The four dengue virus (DENV) serotypes have been co-circulating in Sri Lanka for >30 years. Over this period, a new genotype of DENV-1 has replaced the old genotype. Moreover, new clades of DENV-3 genotype III viruses have replaced older clades. The emergence of new clades of DENV-3 in 1989 and 2000 coincided with abrupt increases in the number of reported dengue cases, implicating this serotype in severe epidemics. From 1980 to 1997, most reported dengue cases were in children. Recent epidemics have been characterised by many cases in both adults and children. Changes in local transmission dynamics and genetic changes in DENV-3 are probably responsible for the increasing emergence of severe dengue epidemics in Sri Lanka. There is no published data on dengue fever from Oman apart from one case report.

The clinical manifestations of dengue range from asymptomatic infection, self-limited dengue fever to DHF with shock syndrome. The risk of severe disease is much higher in sequential rather than primary dengue infection. The most common symptoms of dengue virus infection are fever, headache, retro-orbital pain, photophobia, backache, severe myalgia and arthralgias. Other signs and symptoms include generalised maculopapular rash, lymphadenopathy, positive tourniquet test, petechiae and other haemorrhagic manifestations. The WHO has set criteria for
Case Report

Hanaa Al-Araimi, Amal Al-Jabri, Arshad Mehmoud and Seif Al-Abri

2. World Health Organization. Revision of the International Health Regulations. World Health...
Dengue Haemorrhagic Fever Presenting as Acute Abdomen


Leishmaniasis are a group of zoonotic diseases caused by a haemoflagellate protozoan of the genus *Leishmania*. The parasites are present in the macrophages of a wide variety of vertebrates. They are transmitted from the animal reservoir by the bite of female sand flies of the *Phlebotomus* species. There are several species of *Leishmania* that can infect human and result in a spectrum of diseases known as leishmaniasis. Depending on the mode of presentation there are three main types: cutaneous leishmaniasis, which is often self-limiting, mucosal leishmaniasis and visceral leishmaniasis. Visceral leishmaniasis affects mainly the mononuclear phagocytic system of the bone marrow, liver and spleen and is caused mainly by *Leishmania donovani* and *Leishmania infantum* species. It shows a wide geographical spread in more than 88 countries all over the world.

Clinically, typical cases of visceral leishmaniasis are found primarily in children. It's features include fever, anaemia, hepatosplenomegaly, adenomegaly, hypergammaglobulinaemia, and pancytopenia, but it can also manifest itself atypically, mostly in patients infected with HIV and geriatric immunocompetent patients.

The definitive diagnosis of visceral leishmaniasis is achieved by identification of the organism in a bone marrow biopsy. The characteristic *Leishmania* amastigotes are round to ovoid in shape and can be identified after routine haematoxylin-

**CASE REPORT**

**Visceral Leishmaniasis with an Unusual Presentation in an HIV Positive Patient**

Nazar M.T. Jawhar

**ABSTRACT:** Visceral leishmaniasis is a disease caused by a haemoflagellate protozoan of the genus *Leishmania*. It has a wide geographical spread. Classic cases are found primarily in children and present with typical features that include fever, anaemia, hepatosplenomegaly, hypergammaglobulinaemia, and pancytopenia. The diagnosis is usually achieved by bone marrow smears, culture and serology, however, it can manifest itself atypically, mostly in patients infected with HIV and geriatric immunocompetent patients. We report an unusual case of visceral leishmaniasis diagnosed in a 27 year-old HIV-infected male who presented with abdominal discomfort and diarrhoea of four weeks duration associated with nausea and vomiting, but with no typical symptoms or signs of visceral leishmaniasis. The diagnosis was established through the identification of the *Leishmania* organism in duodenal and colonic biopsies and confirmed by subsequent bone marrow smears.

**Keywords:** Visceral leishmaniasis; HIV; Duodenal biopsy; Case report; Iraq
Visceral Leishmaniasis with an Unusual Presentation in HIV Positive Patient

eosin or Giemsa staining. Other diagnostic tools include isolation of promastigotes by Novy-McNeal-Nicolle (NNN) culture and serological tests to detect antileishmanial antibodies, but the latter have low sensitivity. Histopathological identification of leishmania organisms in tissue sections is quite easy and very sensitive; however, the diagnosis of leishmaniasis in paraffin sections may be difficult in some conditions, such as when the parasites are present in unusual sites which is frequently observed in visceral leishmaniasis that develops in immunocompromised patients. This is a presentation of an unusual case of visceral leishmaniasis diagnosed in an HIV-infected patient, with atypical clinical features, who was unexpectedly diagnosed through the identification of the Leishmania organism in an unusual site.

Case report

The patient was a 27 year-old Yemeni male, diagnosed with HIV infection 8 years previously, who presented with abdominal discomfort and diarrhoea of four weeks duration associated with nausea and vomiting, but no fever or anorexia. The diarrhoea (5–6 times a day) was watery and accompanied by mucus, but with no blood. On physical examination, the patient was conscious, oriented, afebrile and not pale. His vital signs were stable. His chest was clear and abdominal examination showed mild subumbilical tenderness, but no abdominal mass or organ enlargement was detected. No lymphadenopathy was present. The patient was not receiving any antiretroviral therapy.

Laboratory investigations showed leukocytes $10.88 \times 10^3/\mu l$, 83% neutrophils, 8.4% lymphocytes and 8.4% monocytes. The haemoglobin level was 136 g/l, erythrocytes sedimentation rate 16 mm/hour. Urine examination showed mild proteinuria and his serum creatinine was mildly elevated at 2.1 mg/dl. Stool samples were negative for Cryptosporidium and Clostridium difficile toxin and repeated stool culture revealed no pathogens. His CD4 cell count was 210 cells/mm3. An abdominal ultrasound showed no abnormalities. An upper GIT endoscopy showed normal oesophageal and gastric mucosa; however, the mucosa of the second part of the duodenum showed congestion with a peculiar whitish nodular appearance [Figure 1]. A colonoscopy showed normal colonic mucosa. Multiple biopsies were taken from the oesophagus, stomach, duodenum and colon for histopathological examination to exclude microscopic lesions and opportunistic infections.

The histopathological examination demonstrated widening of the duodenal villi with infiltration of duodenal and rectal mucosa by a large number of macrophages filled with intracytoplasmic Leishmania amastigote parasites (Donovan bodies) [Figure 2]. Gastric and oesophageal biopsies showed no significant pathologic changes. The case was diagnosed as visceral leishmaniasis. Subsequent bone marrow aspirate (showing Leishman–Donovan bodies) confirmed the diagnosis [Figure 3].

The patient was treated with sodium stibogluconate (20 mg/kg/day), but he was lost to follow-up after 1 week of therapy.

Figure 1: Upper GIT endoscopy revealing whitish nodular appearance of the duodenal mucosa.

Figure 2: Duodenal biopsy showing many macrophages with abundant intracytoplasmic leishmaniae.
Discussion

Although it affects mainly immunocompetent individuals, *Leishmania* is considered an opportunistic pathogen in immunosuppressed patients particularly those with AIDS. On the other hand, HIV infection increases the risk of developing visceral leishmaniasis by 100–1,000 times in endemic areas. In fact, some studies showed that visceral leishmaniasis is the fourth most common opportunistic parasitic disease in HIV-positive individuals after pneumocystosis, toxoplasmosis, and cryptosporidiosis. Indeed, both HIV and leishmaniasis result in a cumulative deficiency of the cellular immune response since both agents damage similar immune resources thus promoting chronicity and, when untreated, result in death. The first case of leishmania/HIV co-infections was diagnosed in 1985 and almost all cases of *Leishmania* co-infection with HIV have been described in patients with HIV-1. According to data from the World Health Organization, HIV-*Leishmania* co-infection is widely distributed. The most common areas are southern European countries (like Spain), and Brazil, India, Bangladesh and Nepal. The real impact of HIV-*Leishmania* co-infection is probably underestimated owing to constraints in the surveillance and reporting of cases.

The majority of leishmaniasis cases in HIV-positive patients appear in the advanced stages of the disease. In about 80% of patients, the number of CD4 lymphocytes is less than 200/mm3 while in c. 20 % of patient. In the current case, the number was low (210 cells/mm3). Leishmaniasis has different characteristics in patients with AIDS compared with immunocompetent patients. Classic visceral leishmaniasis in immunocompetent individuals is found primarily in children, but in recent years an increasing number of adult cases have been observed mostly in HIV patients. In the latter, the location is more likely to be atypical such as gastrointestinal tract, larynx, lungs, kidneys, pancreas and testes. Organomegaly, which is one of the typical clinical features of classical visceral leishmaniasis in immunocompetent individuals, is usually absent in HIV positive adults as in our case. Also cytopenia is more frequent in immunosuppressed individuals along with negative serology and higher relapse rate after therapy. The gastrointestinal involvement and overt malabsorption in visceral leishmaniasis is reported more frequently in those with concomitant HIV infection. Lesions have been seen from the oesophagus to the rectum; however, the duodenum is the most common site. The exact pathogenesis of the diarrhoea and malabsorption is not clear, but it has been suggested that these symptoms in enteropathic visceral leishmaniasis may be a combination of the mechanical occlusion of the mucosa by parasites, bacterial overgrowth, partial villous atrophy, competition between the host and the parasite for nutrients, altered motility, bile salt deconjugation and lymphatic blockade. Endoscopic examination of these patients is usually performed because of diarrhoea and epigastralgia. The findings are variable and may be unremarkable, showing non-specific inflammation, or an atrophic mucosal pattern. In the current case, the mucosa of the second part of the duodenum showed congestion with a peculiar whitish nodular appearance, a rare and unusual finding also reported by others. The colonoscopy showed a normal colonic mucosal pattern. Histopathological examination of intestinal (duodenal and colonic) biopsies shows intact architecture and abundant macrophages with intracytoplasmic *Leishmania* amastigotes (Donovan bodies). Some cases may show duodenal villous atrophy.

Conclusion

In conclusion, clinicians should be alert about the
possibility of leishmaniasis in HIV positive patients presenting with diarrhoea, particularly in patients from endemic areas. Also pathologists should pay attention to the possible finding of Leishmania amastigotes in biopsies from intestinal mucosa in HIV infected patients.

References


Patient positioning for surgical procedures has long been associated with intraoperative complications; this is especially true for surgery in the prone position. Reported complications resulting from the prone position are usually related to neurovascular injuries, eyes and ears. Other reported complications are related to loss of airway, monitors and catheters or to venous air embolisms. Ventilatory and haemodynamic changes have also been reported in the prone position, as well as pressure necrosis of the skin. To the author’s knowledge lip necrosis has not been reported before in English medical literature as a complication of the prone position.

Case report

A 16 year-old female, a known case of right thoracic scoliosis (idiopathic type) was admitted to the Orthopedic Department at College of Medicine, King Saud University, Riyadh, Saudi Arabia, for elective surgical correction and spinal fusion for the scoliotic curve. During the procedure, the patient was placed in a prone position as is usual for posterior surgical correction in scoliosis surgeries. During the operation, gel pads were placed under the chest and another one against both iliac crests with a pillow under both feet to relax the knees which were also supported by separate gel pads. The face was supported with a gel pad too, but it was placed on the operating table not on a horseshoe head support. The endotracheal tube was fixed and maintained by tape over an airway protector to protect the lips and teeth as well as the tongue. The procedure was done under the continuous control of the motor evoked potential and sensory evoked potential. These give stimulation through the cortex and transmit the signals through the spinal cord for certain muscles to contract in upper limb as well as the lower limbs. In this way, the status of spinal cord conductivity and affection during the corrective surgery of scoliosis is checked. The time taken for the procedure was four hours.

After the extubation we noticed that the patient had a swelling in the left side of the lower lip. There was no wound on the lips. The eyes, cheeks, chin, ears, and other bony prominent areas were not affected. After discussing the case thoroughly
with the anaesthetist, we thought that the cause of this problem was a direct pressure from the endotracheal tube which was pushed against the lip by the gel pad support for the face. The swelling in the lower lip was observed for few days without any spontaneous improvement. Six days later, an area of the swollen lower lip became black and necrotic [Figures 1 and 2].

The patient was seen by the plastic surgeon who continued the observation and dressings for the necrotic part of the lower lip for ten more days, but no improvement was noticed. The plastic surgeon therefore then decided to take the patient for advancement lip flap surgery of the lower lip. This was done successfully fifteen days after the original surgery. The dressing for the lip and the flap were changed daily. The patient was followed up by the plastic surgeon in his clinic. Three months later, the patient had recovered well with complete healing of the lower lip with a very minimal scar [Figure 3a & 3b].

Discussion

Pressure necrosis of the skin is a well-known complication for patients who undergo lengthy surgical procedures under general anaesthesia. The condition occurs more frequently in patients undergoing surgical procedures in the prone position.5,6

It is crucial that both the surgeon and the anaesthetist are aware of the risks and the need for careful positioning of the face, eyes, ears, breasts, genitalia, and other dependent areas to prevent pressure sores or skin necrosis.5,8 Other areas that also need care include the iliac crests, the chin, eyelids, the nose, and the tongue.9,10

The case reported here had a lower lip necrosis secondary to direct pressure of the endotracheal tube which had been pushed by the gel pad against the lower lip as a result of improper head positioning.

Previously, a horse shoe (c-shape) head support which has free space around the lower part of the face was routinely used. With this device there would not be any risk of pressure around the mouth and lower part of the face. It was not used in this case because of the anesthetist’s preference for the use of a gel pad. This unfortunate complication is rare and could be avoided by following the strict precautions of prone head positioning and the use of the proper devices as well as continuous checkups by the attending anaesthetist.

Many devices have been described to be used to protect the face during prone position other than the well known horse shoe head support. In 2007, Mollmann et al. described a foam-cushion face mask and a see-through operating table as a new setup for face protection and increase safety in the prone position.11

No previous case of direct pressure necrosis of the lip has been reported secondary to prone positioning. However, lip injury has been reported in a single case due to allergic contact dermatitis to the face, including the lips of a patient, who had become sensitised to the material of the flexible polyurethane foam applied to support the face during surgery.12
Conclusion

In conclusion, lip necrosis can occur if the head of the patient is improperly positioned for scoliosis surgery. Both the anaesthetist and the surgeon should work together to create proper positioning for the patient during the surgical procedure and always use the appropriate equipment for the patient's safety. The author recommends the use of a horse shoe head support in all cases undergoing surgery in the prone position and in scoliosis corrective surgeries in particular.

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References


Figure 3a and 3b: Two views for the lip three months after plastic surgery.
Reconstruction of Exenterated Orbit using Combined Surgical and Prosthetic Approach

D R Prithviraj, Anish Gupta, Sumit Khare, *Pooja Garg, Malesh Pujari

ABSTRACT: Reconstruction of an exenterated orbit remains a challenge. Orbital prostheses are nowadays made of silicone elastomers. A major limitation with silicone orbital prostheses is their relatively short life span. This case report describes the treatment of a patient with an exenterated orbit using a combined surgical and prosthetic approach. The upper and lower eyelids were reconstructed surgically using a deltopectoral flap. A sectional eye prosthesis was made and placed in the modified bottle-neck shaped defect to restore the patient’s appearance and confidence.

Keywords: Exenteration; Ocular prosthesis; Maxillofacial prosthesis; Psychology; Silicone elastomers; Case report; India

Orbital exenteration is a radical procedure consisting of removal of the orbital contents, including orbital fat, conjunctival sac, globe, and a part or whole of the eyelids. Orbital defects are injurious to a person’s self-concept and sense of body image. Treatment should be provided as soon as possible to raise morale and ease the mind of the afflicted person.

Orbital prostheses are made of silicone elastomers, acrylic resin, or a combination of these. Most maxillofacial prostheses perform well initially, but deterioration, associated with either degradation of mechanical properties or changes in appearance, commonly occurs subsequently. This deterioration limits the service life of extraoral prostheses, and refabrication of these prostheses is time consuming, labour intensive, and costly.

Moreover, extraoral prostheses are exposed to mucosa and skin secretions; subsequently, multilayer biofilm formation can occur on the silicone surfaces. Problems such as black stains on the surface of prostheses, offensive odours, and tissue infection can arise from microbial colonisation. Karakoca et al. reported a mean life span of 14.5 to 14.7 months for a patient’s first and second implant-retained extraoral prostheses, respectively. The primary reasons for making a new prosthesis were discoloration, tear of the prosthesis, and mechanical failures of the acrylic resin substructure or retentive elements. Jebreil reported that adhesive-retained orbital prostheses last for 6–9 months and need to be refabricated subsequently.

Problems with silicone orbital prostheses can be avoided by reconstructing the upper and lower eyelids surgically and then rehabilitating with custom-made ocular prostheses. This clinical report describes the management of a patient with an orbital defect by a
A 24 year-old woman, who had undergone a right orbital exenteration for orbital meningioma, presented to the Department of Prosthodontics and Implantology, at the Government Dental College and Research Institute (GDCRI), Bangalore, India, for rehabilitation of an orbital defect [Figure 1]. It was decided to reconstruct the eyelids surgically in collaboration with the department of Plastic Surgery, Victoria Hospital, Bangalore.

A deltopectoral flap from the second and third intercostal region was raised and then rotated into the exenterated orbit and sutured to the free skin margins. After 3 weeks, the pedicle was separated from the intercostal region. Four weeks later the flap was divided to construct the upper and lower eyelids. After 6 months, the patient presented to the Department with reconstructed upper and lower eyelids [Figure 2]. Although plastic surgery resulted in marked improvement, yet the resultant eyelids were thick, tense, and scarred. Moreover, the modified orbital defect was bottle-neck shaped. The palpebral aperture was 15 mm whereas the cavity inside was approximately 32 mm; hence, it was virtually impossible to fabricate a single piece eye prosthesis. This necessitated a unique treatment modality for the rehabilitation of the modified exenterated orbit.

Separate impressions were made of the superior and inferior surfaces of the defect using irreversible hydrocolloid material (Hydrogum, Zhermack SpA, Italy). After that, irreversible hydrocolloid was injected directly into the remaining socket using an ocular impression tray. Multiple parts of the impression were assembled outside to pour a two-piece dental stone cast. Three pieces of wax template were fabricated to be assembled in a specific spatial configuration in the reconstructed orbit and processed using heat cure acrylic (Trevalon, India). A notch was made in the middle piece for orientation of the fourth piece. After placing the multiple pieces of eye prosthesis in the modified orbit, an impression for the fourth piece was made according to the Allen and Webster technique. The irreversible hydrocolloid material was injected into the remaining socket through the attached hollow stem of the impression tray.

Using this impression and a small plastic tumbler, an irreversible hydrocolloid mould was prepared, which was cut using a sharp blade to remove the impression. The mould space was subsequently filled with molten inlay wax. Once the wax was hard, it was removed from the mould, and the external surface was smoothed for a try-in on the patient's face. The wax form and its corneal prominence were modified wherever necessary to duplicate the shape of the natural eye. After a try-in the wax template was processed using white acrylic. The acrylic shell was removed and trimmed for about 1–2mm on the external surface.

During iris orientation patient was asked to gaze straight ahead. The distance from the pupil of the normal eye to the midline was used in establishing the horizontal position of the prosthetic pupil's centre. Its vertical position was determined by the canthus relationships. Marked coordinates of the pupil were used to circumscribe the diameter of the iris. Iris and scleral painting were carried out using acrylic colors and mono-poly. As the palpebral aperture of the reconstructed eyelids was larger than that of the natural eye, it was camouflaged during scleral painting. Subsequently, using the same plaster mould, the eye shell was packed with

**Figure 1:** Orbital defect following exenteration.

**Figure 2:** Reconstructed upper and lower eyelids.
Reconstruction of Exenterated Orbit using Combined Surgical and Prosthetic Approach

transparent acrylic to give a natural appearance. Later, it was removed from the mould, trimmed, finished and polished. The prosthesis was placed into the ocular defect and critically evaluated [Figure 3]. Spectacles were used to camouflage the scarred tissue [Figure 4]. At the time of writing, the prosthesis had been in service for 9 months without complications.

Discussion

This case report describes the treatment of a patient with exenterated orbit using a combined surgical and prosthetic approach. Upper and lower eyelids were reconstructed surgically using a deltopectoral flap from the second and third intercostal region to avoid the fabrication of a silicone prosthesis.

Silicones have been used for over 50 years in the field of maxillofacial prosthetics, with desirable material properties including flexibility, biocompatibility, ability to accept intrinsic and extrinsic colorants, chemical and physical inertness and mouldability. A major limitation with silicone orbital prostheses is their relatively short life span (on average 1.5 to 2 years). The main reasons for the refabrication of orbital prostheses are discoloration, problems with the attachment of the acrylic resin clip carrier to the silicone, rupture or deterioration of the silicone material and a poor fit. Moreover, meticulous hygiene is mandatory to prevent peri-implant problems, including inflammation of the skin in the implant retained orbital prosthesis.

The resultant eyelids were thick, tense, and scarred and the modified orbital defect was bottle-neck shaped. A sectional eye prosthesis was fabricated to overcome this limitation. The impression was made with irreversible hydrocolloid which helped in retrievability of the impression from undercut area. Heat cure polymethyl methacrylate was used for fabrication of the prosthesis which has better biocompatibility. Multiple pieces of eye prosthesis were fabricated to be assembled in a specific spatial configuration in the reconstructed exenterated orbit. The prosthesis, although static, helped restore the patient’s appearance and confidence. In the absence of recurrent orbital meningioma, this prosthesis can be a definitive treatment for the patient.

Conclusion

Reconstruction of the exenterated orbit remains a challenge. Patients in this situation can be treated by reconstructing the upper and lower eyelids surgically and then rehabilitation with custom-made ocular prostheses.

ACKNOWLEDGEMENT

The authors would like to thank the patient for granting consent for her case and photographs to be published.

References


Acquired Pure Red Cell Aplasia caused by Parvovirus B19 Infection following a Renal Transplant

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Abstract: We report a young Omani male who developed severe and persistent anaemia after a kidney transplantation while being on immunosuppression therapy, standard practice to prevent rejection of the transplanted kidney. His bone marrow aspirate showed the classic morphological changes of pure red cell aplasia (PRCA), induced by parvovirus B19 infection which is the presence of giant proerythroblasts with viral inclusions. The virus was also demonstrated by polymerase chain reaction in the blood along with IgM antibodies to parvovirus B19. He responded dramatically to high dose immunoglobulin with a normalisation of his haemoglobin level in two weeks and remained normal until seven months later. Parvovirus B19 induced PRCA can be cured. This aetiology must be kept in mind especially when a chronic anaemia, refractory to treatment, is accompanied by a reticulocytopenia. The latter reflects the lysis of the proerythroblasts, preventing maturation of the erythroid cells causing anaemia. Early recognition and prompt treatment spares the patient unnecessary exposure to blood transfusions, erythropoietin and renal disease caused by the virus. Parvovirus B19 infection following kidney transplantation is reported in the literature, but not in the Omani population. To the best of our knowledge, this is the first such report in Oman.

Keywords: Red cell aplasia, pure; human parvovirus B19; kidney transplantation; Immunosuppression; Case report; Oman

Parvovirus, a single stranded DNA virus with tropism for the erythroid progenitor cells1 is known to cause lytic destruction of the proerythroblasts leading to a mild anaemia in the immunocompetent person.2 It is the only known member of the Parvoviridae family to be pathogenic to humans.3 Infections occur worldwide and especially in the spring and winter months. It is so common in the Northern European community that by the age of 50 years about 80% of this population will have been infected.4

Although it is believed that the virus infects only erythroid progenitors, the viral capsid antigen has been demonstrated inside giant granulocytes in the bone marrow in patients with pancytopenia following bone marrow
transplantation.\textsuperscript{5} Viral growth can also be maintained in fetal liver cell cultures.\textsuperscript{2} In children, parvovirus B19 infection causes a transient anaemia associated with an erythematous rash called the fifth disease or \textit{Erythema infectiosum}. Occasionally, in immunocompetent adults, a symmetric polyarthropathy mimicking rheumatoid arthritis occurs.\textsuperscript{3} The tropism to erythroid progenitors in the bone marrow is well known to cause a transient aplastic crisis (TAC) in individuals with an underlying haemolytic anaemia and \textit{Hydrops fetalis} in intrauterine infections.\textsuperscript{6}

In immunocompromised patients, the inability to generate an immune response leads to a state of persistent anaemia, reticulocytopenia caused by lytic destruction of proerythroblasts giving rise to an acquired pure red cell aplasia (PRCA). Following allogeneic stem cell transplants (ASCT), this infection is known to occur most commonly in the first year post transplant as the immune suppression is at a maximum during this period.\textsuperscript{7-11} The standard treatment for these patients is intravenous (IV) gammaglobulin (IVIG). This replaces the neutralising antibodies which the patient does not possess; however, it is unknown whether the virus is always eliminated completely by this treatment.

Case Report

An Omani man aged 30 had end stage renal disease caused by pyelonephritis of the right kidney. He was on haemodialysis for three years following which he had a kidney transplant from a live donor. He had a course of antilymphocyte globulin (ALG), commenced intraoperatively and was on tacrolimus, mycophenolate mofetil and prednisolone as a means of immunosuppression. No information was available regarding the donor’s parvovirus status as the transplant was done in another country. Three months later he was referred to our clinic for investigation of tiredness on exertion and anaemia with a haemoglobin of 5 g/dL. On presentation, his renal and liver functions were normal. He was afebrile, cheerful and, apart from being very pale, was clinically well.

He received a transfusion of two units of packed red blood cells. Despite this his anaemia persisted at an Hb of 6.9 g/dL. The doses of immunosuppressive drugs (tacrolimus and mycophenolate mofetil) were reduced. Other laboratory investigations were as follows; red cell count - 2.93 x 10\(^9\)/L (4.5–6.6); white blood cells - 4.0 X 10\(^9\)/L (4–11); platelets - 353 x 10\(^9\)/L; absolute reticulocyte count- 3 x10\(^9\)/L; haptoglobin Level - 1817 mg/L (360 – 1950mg/L); lactate dehydrogenase level - 322 (95–190 IU/L); folate Level - 30.7 (4.8–30.5 nmol/L); vitamin B12 – 130 (139–651 pmol/L); iron profile – normal; direct and indirect antibody tests – no antibodies detected; antibodies for parvovirus B19 – positive; IgM antibodies and polymerase chain reaction (PCR) parvovirus - positive. Figure 1 shows the bone marrow aspirate, Figure 2 shows bone marrow trephine biopsy with giant proerythroblast with a megakaryocyte at the left hand end of the row, and Figure 3 positive glycophorin stain for giant
Acquired pure red cell aplasia caused by parvovirus B19 infection following a renal transplant

The investigations show the absence of an aetiology of haemolytic anaemia (immune mediated and non immune), iron deficiency, vitamin B12 or folate deficiency for the anaemia in this patient. The persisting anaemia, with a reticulocytopenia, no evidence of myelodysplasia, haemolysis, nutritional deficiency, the morphological evidence of parvovirus B19 infection, of giantoblasts containing viral inclusion bodies and the absence of late normoblasts in the bone marrow confirmed the diagnosis of parvovirus B19 by morphology. Positive staining of giant proerythroblasts with the glycophorin stain, established the large cells as being erythroid in nature. Further confirmation was made by the presence of the anti parvovirus B19 immunoglobulin M (IgM) and positive polymerase chain reaction (PCR) for a high load of parvovirus B19.

The cornerstone of treatment for this disease is passive transfusion of IVIG to enrich the humoral immunity of the patient supported with packed red blood cell transfusions. In the immune competent host, 0.4g/kg/day of IVIG is given for 3 days. In the immunocompromised host, prolonged treatment with IVIG reduces the viral levels to undetectable levels by repeated PCR. A higher dose of 1g/kg/day is used for 5 days in these patients and when necessary for a longer period. Patients generally respond after two weeks of treatment. Some patients may require more than one course of immunoglobulin therapy and some may benefit from alteration of their immunosuppressive therapy. Other immunomodulatory approaches such as rituximab, steroids, (ALG), cyclophosphamide, and methotrexate have also been used in chronic PRCA. This is especially the case if it present as the primary haematological disorder, with no obvious cause, or in association with other disease such as lymphoproliferative disorders, connective tissue diseases, thymoma, solid tumours, pregnancy, or following bone marrow transplantation, but rarely in patients with parvovirus B19 infection.

Our patient was treated with 1g of IVIG /kg / day for 5 days and packed red blood cells. His haemoglobin levels recovered in two weeks. He was completely well with a normal complete blood count (CBC) seven months later, at time of writing.

Discussion

In immunocompetent persons with normal red cell life spans, parvovirus B19 infections cause a 5–10 day erythropoietic aplasia, but do not cause significant anaemia as their red cell life span is 120 days. However, in patients with haemolytic anaemias whose red cell life spans are shortened, for example 15 days in hereditary spherocytosis, a transient decompensated erythropoiesis leads to a severe anaemia. In immunocompromised patients, such as our patient, the infection can persist leading to chronic anaemia. Congenital immunodeficient states, human immunodeficiency virus (HIV) infections, post organ transplants, lymphoproliferative disorders are some of the other known immunodeficient states associated with PRCA caused by parvovirus B19.

The diagnosis rests on the presence of a persistent anaemia, with normal other blood cell counts, a reticulocytopenia, giant proerythroblasts (gigantoproerythroblasts) with prominent eosinophilic viral inclusions in the bone marrow, serum anti parvoviral IgM/IgG and positive PCR for parvoviral DNA. The neutralising antibodies are able to clear the infection usually by 5th to 10th day of infection. It is proposed that with the rising titres the virus is cleared and the giant proerythroblasts are replaced by regenerating erythroid cells.

Parvoviridae are difficult to culture, but can be grown from the bone marrow. In the immunocompromised host, parvoviral antibodies maybe difficult to demonstrate, although the presence of anti parvo viral IgG
makes persistent infection improbable. In PRCA caused by other aetiological causes like thymoma, large granular lymphocytic leukaemia, systemic lupus erythematosus and rheumatoid arthritis, gigantoproerythroblasts are not seen. Parvoviral infections are also associated with glomerulonephritis and a nephrotic syndrome such as protein-losing kidney disease.

### Conclusion

In isolated persistent anaemia in immunocompromised adults, accompanied by a reticulocytopenia and no other aetiological evidence for the anaemia, a parvovirus B19 induced PRCA should be excluded, particularly as there is no vaccine for protecting those at risk.

### References

A 22-year-old man from South India presented with migraine with aura and depression. Neurologically, he demonstrated cognitive impairment, pseudobulbar affect and bilateral pyramidal signs. The magnetic resonance imaging (MRI) scan of his brain [Figure 1] showed increased FLAIR and T2 signals in the bilateral anterior temporal and frontal white matter, basal ganglia and external capsule. The clinical features and the MRI finding of bilateral white matter lesions in the anterior temporal pole and external capsule, in the absence of hypertension and optic nerve and spinal cord lesions, were diagnostic of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).1-3

Figure 1: Magnetic resonance imaging (MRI) scan of brain demonstrating increased signal in A) FLAIR image of the white matter in the anterior temporal region, B) frontal region, and C) T2 weighted image of the external capsule and basal ganglia.

CADASIL - Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Ramachandiran Nandhagopal
CADASIL is a rare inherited neurological disorder that clinically manifests with migraine with aura, depression, stroke-like episodes before the age of 60 years, cognitive impairment and behavioral disturbances.1-4 The characteristic lesions, which can be seen on an MRI scan, involve white matter of temporal pole and external capsule1-3 and the lesion load is often highest in the frontal white matter.1-3 Although a positive family history might provide diagnostic support, it is not required in making the diagnosis.4 CADASIL is associated with notch 3 gene mutation and de novo mutation accounts for the sporadic cases;4 however, genetic analysis was not available in our centre in India where the patient was seen. Brain MRI scanning aids in the diagnosis of CADASIL in young subjects with a phenotypic manifestation of migraine with aura, depression, stroke and cognitive disturbance, but lacking conventional vascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, obesity, smoking and alcohol consumption. The characteristic lesion distribution differentiates these cases from acquired white matter conditions such as multiple sclerosis.

References

A 28-year-old woman presented to the Ophthalmology Clinic at the Armed Forces Hospital, Muscat, Oman, with severe pain, redness, photophobia and decrease in visual acuity of her left eye of 1 day’s duration. She gave a history of a pterygium excision with intraoperative topical mitomycin-C application (0.1 mg/ml for 5 minutes) in the same eye two years before. There was no other systemic or local disease. She underwent a detailed ophthalmic and systemic evaluation and laboratory examination. The best corrected visual acuity in her right eye was -0.25 sph/-0.50 cyl /90 = 6/6 and in the left eye -0.25 sph/-1 cyl 140 = 6/12. Her left eye showed conjunctival and ciliary congestion. There was a linear ulcer on the cornea about 2 mm from the nasal limbus with a scar immediately temporal to it. There was no surrounding infiltration, but the nasal 4–5 mm of cornea was thin between 6 and 11 o’clock [Figures 1a and 1b] The adjacent sclera was normal. The intraocular pressure and fundus of both the eyes was normal. Scrapings and swabs from the ulcer base were sent for microbiological evaluation. The left eye was treated with prophylactic antibiotic drops and artificial tears. The ulcer responded to treatment in a period of 4 weeks, leaving a thin nasal cornea with peripheral limbal vascularisation [Figure 2].

Pterygium is an epithelial hyperplasia accompanied by a fibrovascular growth originating at the corneo-conjunctival junction, from where the modified limbic cells migrate and surpass

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the cornea. It is an active process associated with cell growth, remodelling of the connective tissue, angiogenesis and inflammation, triggered by ultraviolet irradiation. Different investigators have recently emphasised the importance of the limbus and its stem cells in the pathogenesis of the pterygium.\textsuperscript{1,2} Surgery as a treatment for pterygium has been known since 1,000 B.C and has been directed towards excision, prevention of recurrence, and restoration of ocular surface integrity. The recurrence rate has, in the past, been estimated as high as 30–70%, despite adoption of different evolutionary techniques.\textsuperscript{1,2,3} Although irradiation therapy and antimetabolite use have diminished the recurrence rate to 5–12%, complications like secondary glaucoma, cataracts, uveitis, corneal perforation, scleritis, scleral necrosis and secondary endophthalmitis can occur.\textsuperscript{1-5} Mitomycin, isolated from \textit{Streptomyces caesipitosus}, is an extremely toxic, non cell-specific alkylating antibiotic with antineoplastic properties that selectively inhibits the synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein, and prevents cellular division.\textsuperscript{1-3} The DNA damage mimics that of ionising radiation and has a radiomimetic effect. The drug has been used in the eye since 1963 for its anti-fibroblast proliferating action, in pterygium and glaucoma surgeries and recently in refractive procedures, both for the management of certain complications and to improve vision after surgery.\textsuperscript{1-5} However, in susceptible individuals, it causes keratocyte depletion leading to delayed wound healing, irrespective of the technique of application.\textsuperscript{1,5} Complications occur either immediately after surgery, or up to 20 years later, and are related to drug concentration, contact time and predisposing ocular factors, highlighting the fact that such patients need long term follow-up.\textsuperscript{3,4,5}

References

Sir,

The Editorial Article by Lamk Al-Lamki “UN Millennium Development Goals and Oman: Kudos to Oman on its 40th National Day” published in the December 2010 issue of SQUMJ depicts comprehensively how Oman has fared in relation to the Millennium Development Goals (MDG’s) benchmarks. Indeed, Al-Lamki’s article has also provided a well articulated discussion of Oman’s development and progress in the health field in the last 40 years that has exceeded all expectations. There is no doubt that Oman has made impressive gains in achieving health-related targets and evidence for that was carefully provided in the article. In this regard, I would like to comment on three important points that were especially mentioned in that article.

The first point is related to the problem of undernourished children in Oman. As mentioned in Al-Lamki’s article, the first national survey that was carried out in Oman to assess the rate of protein energy malnutrition (PEM) was conducted in 1999, and it was found that 17.9% of children below five years of age were underweight. Following that, another study on the risk factors associated with PEM was conducted in three regions in Oman in 2004. This study indicated that the most important risk factors of PEM among young infants and children were related to feeding practices such as bottle feeding, improper hygiene and lack of nutrition awareness among mothers. As a result of these studies, a national programme for combating PEM was implemented through primary health care institutions and community-based activities. A national PEM reporting and monitoring system was also established and integrated into the Ministry of Health’s regular statistics. Through this system, the PEM incidence among children who attend the Ministry of Health facilities is reported on a monthly basis and feeding patterns of children are being accessed and reported. In 2008, the second national protein energy malnutrition survey was conducted to monitor the trend in PEM, and assess whether it still persisted as a public health problem or not, in order to guide efforts to eliminate PEM in future years. Now comes the good news: the recently published survey results showed that 8.6% of children below five years of age were underweight. This figure is less than half of that reported in 1999 which means a great success has been achieved in the battle against PEM in Oman.

My second point relates to the future health challenges in Oman that were very well identified in the article. It is quite clear that, if health improvement is to have its full impact on reducing poverty as per MDG1, there is a need to address the growing burden of non-communicable diseases that are leading to a “double burden” of ill-health in Oman. Unfortunately, these diseases are not included among the Millennium Development Goals, Targets, or Indicators; nonetheless, we should not forget them. Also, we should not forget the “nutrition transition” change process whereby people in Oman began to adopt the unhealthy eating habits common in richer countries and then suffer the ensuing health consequences. Further, we should not forget the need for universal access to reproductive and sexual health services as well as the impact of globalisation on the worldwide spread of infectious diseases. Moreover, as a means of improving the quality of life of the people, Oman needs continuing investment in the fight against road
traffic accidents, tobacco and drug addiction. Success in these battles depends on effective health awareness interventions throughout peoples’ lives. This can only be achieved by extensive cooperation with local civil society organisations, mainstream and traditional media, religious and traditional leaders, and the communities themselves. In other words, Oman needs strategies that deliver interventions to hard-to-reach populations, strategies that build social and grassroots support, and strategies that enhance accountability. Unless urgent investments are made in the Omani health system, the current rates of progress towards the MDGs will not be sufficient to meet the currently prevalent health problems in Oman.

The third and last point is my support of Prof. Al-Lamki in his emphasis on health advocacy to educate the people of Oman about improving their health and that of their families. As Prof. Al-Lamki stated in his article, all health professionals, and not just the Ministry of Health alone, have a major responsibility to act as advocates for public health at all levels. I suggest, besides the current efforts, that health advocacy should be carried out using mass and multi-media and community mobilisation. Through such vehicles, health advocacy may be carried out within an institution or through public social societies, patients’ associations and even through the private sector. This is very important because advocacy is the only way to enable individuals to take more responsibility and control for the decisions that affect their health and to lessen their dependency on the public health system.

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References
Sir,

I would like to congratulate you on your timely editorial in the February issue of SQUMJ\(^1\) which has strangely coincided with a clinical review by Davies \(et \ al\). recently published in the British Medical Journal.\(^2\) According to Davies \(et \ al\.), an estimated 30% of imaging may be unnecessary. Some of the most relevant issues have been brought by Prof. Lamki including the massive increase in the number of procedures performed, and the need to educate both physicians and patients.

The arguments in favour of imaging are growing as it is non-invasive compared to surgical procedures and thus increases patient satisfaction, etc. Medical imaging and nuclear medicine is also the most sought after specialty in Oman, India and even Western countries for postgraduate studies. This development is at the expense of bedside clinical examination which is becoming a forgotten art at the expense of technology and high radiation exposure. We do not hear any more of McBurney and Murphy in morning meetings, but only that (computed tomography) CT abdomen ruled out appendicitis and so on.

This wake-up call is necessary not only for Oman, but also for the rest of the world, as the risks of radiation exposure are underestimated by both patients and physicians.

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References
Woman-Centered Care in Pregnancy and Childbirth

Editors: Sara G. Shields and Lucy M. Candib
Publisher: Radcliffe Publishing, Oxford & New York, 2010
Orders: www.radcliffe-oxford.com

They work with many women from a variety of social, cultural, and economic situations who face both normal situations and challenges from the inception of their pregnancies onwards.

The authors justify their title, Woman-Centered care as a necessary reaction, first, to technology centered care where the pressure of modern technology which forces institutions to use more machines to reduce labour costs. Second, the title is also in reaction to physician controlled care in pregnancy and child birth and their preoccupation with malpractice suits leading to a leap in interventions. For those clinicians who were trained without all these gadgets and trends these are understandably good arguments.

Family-centered care is another approach to labour and delivery which happens to a large extent in Asian and Middle Eastern countries, but is not possible for women who are single, lesbian, or drug users etc, in a western population. In family-centered care, men can exert emotional control over the lives of women and children and one of the examples being a husband denying a woman an epidural anesthaesia for pain relief.

The authors also present how care is becoming fetal-centered with the advancing technology of ultrasound and fetal monitoring in labour and how fetocentric care can obscure the needs of the pregnant woman.

This book is written to promote the practice of maternity care in the context of the woman- where she comes from, where her partner comes from and...
how the baby fits into that context. There are a lot of case vignettes and narratives that makes the book interesting to read.

The authors have divided the book into seven sections. Part one addresses the magnitude of the problem. Other six chapters detail the normal process of pregnancy and its problems, women experiencing miscarriage, fetal anomalies, preterm labour, cesarean sections, etc. There are also chapters on the cultural issues that arise when caring for immigrant women, on prevention and health promotion and on the importance of woman centeredness in family planning and contraception.

The final chapter focuses on team work and wise stewardship of resources and the worldwide increase in cesarean sections and the efforts to reverse it. The goal of the authors is to combine practical, woman-centered, evidence-based perspectives that trainees and fully-fledged clinicians can apply in clinical practice in order to strengthen the healing relationship, make it easier to provide good pregnancy and child birth care and lead to women’s self empowerment.

On the whole, this book is a very interesting read for patients, physicians and anyone interested in the care of women without the overuse of technology. It is a heavy volume to carry, but nevertheless worth reading.

**REVIEWERS**

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The worth of a book is to be measured by what you can carry away from it
James Bryce

Life would be much simpler for General Practitioners (GPs) if patients presented with a diagnosis. Unfortunately, patients present with symptoms that are frequently vague, sometimes multiple and often obscure” is an often repeated statement in the book. It is this situation which first prompted the authors to write this book which has become so popular that it is already in its fourth edition.

There is a gap between how medicine is taught and practised. The focus in teaching on the biomechanical model together with the current advances in technology are replacing the crucial tasks of history taking and examination with more and more investigations. The importance of symptoms in making decisions about diagnosis is being whittled away.

This book is a pleasure to read because of its contents and the way they are presented, each symptom described in brief and to the point sections of bulleted points. It helps to make sense of 100 or so symptoms with which patients commonly present to the family physician (FP). It is written by two GPs in UK and primarily targeted at GPs at all levels of training and experience, as a source of rapid reference.

Each chapter in the book addresses a symptom under the headings of: GP Overview, Differential Diagnosis (further subdivided into Common, Occasional and Rare), Ready Reckoner, Possible Investigations (categorised into Likely, Possible and Small print), Top Tips and Red Flags. Each symptom chapter could be reviewed in less than five minutes.

To test this book, we tried it out in a real life situation. A 37 year-old lady presented to a FP with a history of three episodes of dizziness since that morning; they were self limiting and lasted for about 3–5 minutes each. She was worried because she had been operated on for coarctation of the aorta 12 years ago, had then had angioplasty 6 years later and an ablation done last year. She was being followed up by the cardiologist. On examination she was apparently healthy, not distressed,
haemodynamically stable with a pulse of 68, regular, normal volume and blood pressure of 130/70 mmHg. The systemic exam was non-contributory. The FP was faced with the challenge of a familiar symptom in an unfamiliar territory. Referring to the book, I found a chapter on dizziness and had a quick glance at the list of differential diagnosis to identify possible reasons such as viral illnesses, postural hypotension and arrhythmias. A review of the section on red flags excluded any urgent condition. The patient was discharged with advice to follow up after three days or sooner, and that if the symptoms worsened she should go to the Emergency Department.

The above example demonstrates the usefulness of this book and justifies the “Highly Commended” recommendation by the British Medical Association Book Awards in both 2004 (2nd edition) and 2008 (3rd edition).

What I would like to see in the future edition of this book is, first, that it be available in electronic format and, second, that it would give the likelihood ratios of various symptoms so that it becomes a more ‘evidence-based’ book.

In summary, this is a book worth having available at the point of care for health professionals, including doctors, nurses, undergraduates and postgraduates, to help them make sense of common symptoms. With the help of the authors’ opinions in combination with our own experience we should then, as health care professionals, be able to make better clinical decisions.

REVIEWER
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A

Simplified by the title, the book is aimed at medical students and practising doctors, and focuses on their communication with patients. Chapter titles include: How doctors talk to patients and why, Different types of patient, Ways of looking at the consultation and Useful strategies and skills.

Generally, the book is an easy read. As it is not aimed at communication studies’ students or practitioners, it contains very little reference to communication theory. The author draws primarily on experience (his own and others) and uses these examples to illustrate concepts. Some of the more valuable aspects include:

• Balancing the patients’ concerns and perceptions with those of the doctor. In several instances, the author sketches situations, and illustrates how differences between concerns and perceptions have a negative impact on health care delivery. The author then offers solutions to the problem.

• History taking. The author considers the standard model of history taking as “Victorian, patronising and, in most hands, communicatively disastrous,” and provides other approaches to achieve the desired result.

• Listening, especially active listening, and avoiding the too-quick reaction of “putting communication into a straitjacket in order to maximise pattern recognition.”

• The weaknesses of reliance on patient pamphlets and handouts, and the related confusion of information diffusion and effective communication.

• Considerations of language. The author deals with problems of jargon, and also considers other, more common vocabulary misconceptions (such as the use of the word “risk”), that impact negatively on patient-doctor communication.

I do, however, have some criticisms of the book. I would like to see:

• A brief chapter summary at the end of each chapter, although there is an overall summary of the text at the end.

• A far greater acknowledgment of the impact of 21st century technology in patient-doctor communication. Although there are references to the Internet, there are several missed opportunities for guidance on the more problematic areas. For example, the chapter entitled Useful strategies and skills ends with a discussion of telephonic communication, but does not mention the use
of email, text messaging, and other new forms of communication currently facing doctors. In addition, while reference is made to patients accessing information on the Internet, the model is still firmly that there are two experts: “one on medical matters and the other on their own mind and body.” Medical communication is still viewed as a one-way flow from doctor to patient.

• At least one chapter devoted to communication between doctors, or a change in book title. The title of the book does not mention patients, but the book is focused on communication between doctors and patients.

Overall, The Doctor’s Communication Handbook is a useful text for medical students and practising doctors.

REVIEWER
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Gastrointestinal Endocrinology
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There are two types of endocrine tissue, one gathered in glands – this is classical endocrinology. The other is dispersed endocrine cells spread throughout particular tissues – the diffuse endocrine system. The latter, although less well recognised is the larger and, arguably the more important. Hormones are actually even wider than this – hormones being released from many cells not normally thought as endocrine (paracrine and neurocrine). The gut is controlled by both diffuse endocrine cells and non-endocrine cells producing “hormones”. The endocrine cells are mostly in the mucosa and integrate with the submucous neural plexus as well as sensing what has been eaten. From the physicians viewpoint there are two main conditions of interest – gastrointestinal endocrine tumours and dysfunctional regulation of digestion. Endocrine tumours are important because they are eminently treatable. Our understanding of digestive regulation is less well developed but shows the tight integration of the body as several gut hormones have powerful effects on how we think and behave.

Treatment of Obesity
Prof. Steve Bloom  
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The treatment of obesity is easy – eat less food. Obesity clinics are frustrating as it is rare for patients to successfully lose weight and they often blame their physician. Obviously low calorie, high fibre foods eaten with restraint and plenty of exercise are the key. Equally obviously it often doesn't work. With chronic conditions we need safe medication (e.g. hypertension, hypercholesterolaemia, chronic lymphatic leukaemia etc are all handled with chronic medication). Can we treat obesity with a pill? Approaching 130 new obesity treatments have been tested in human trials and only one remains on the market throughout the world – orlistat (Xenical, Alli), an agent which blocks lipase with such significant GI consequences that only 1% of patients are still taking it at the end of a year. Is there no successful approach? Bariatric bypass surgery works well, producing lifelong major weight loss, improving physical activity, halving heart disease and halving cancer and often curing diabetes. The increased release of satiety hormones in mainly responsible and we propose to mimic their increase medically.

Changing Classification of Neurological Diseases
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The naming of disease does not stand still. At first merely providing a description of symptoms or the most obvious physical manifestations, nomenclature later adopted the style of the medical eponym or acronym. Famous figures were remembered through diseases named after them. Many of these designations attracted rival claims for priority in having provided the first account of that disease, but as clinical neurology became more sophisticated and laboratory methods were introduced, the descriptive phenotypes broadened and overlap between apparently different conditions came to be recognised. The beginnings of mechanism-based disease classifications began to emerge. That process has continued with the recognition of a genetic basis for many common disorders, the identification of their environmental triggers, and the characterisation of molecular pathways involved in the pathogenesis of these complex phenotypes. Generic principles such as aberrant protein folding, immune-based disorders and the failure of ion-channel activity have changed the classification of neurological disease. This is not just a matter of naming: the future of neurology may be less colourful in terms of hagiography but it will be more realistic and useful in terms of mechanism-based disease classification and therapeutics.
**Neuromyelitis Optica**
Prof. Alastair Compston  
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The disease that Eugene Devic described in 1894 was largely forgotten as knowledge on the aetiology, pathogenesis and phenotype of more common demyelinating diseases flourished in the 20th century. Although cases were often misdiagnosed, the distinguishing features of neuromyelitis optica have been increasingly recognised and emphasised over the last 10 years. Some patients respond to plasma exchange; antibody and complement deposition are demonstrated in tissue samples; a serum immunoglobulin biomarker for the condition has been described; and aquaporin 4 identified as the target antigen. With improved recognition attention has been drawn to the fact that neuromyelitis optica has a geographical distribution that differs from that of typical multiple sclerosis. This has led to debate on the relationship between these two disorders, the true and the false distinguishing features, and the status of transitional cases. As a result, the phenotype and features of neuromyelitis optica have broadened. Now neuromyelitis optica is a disorder of astrocytes with complex secondary pathological effects, originating from autoimmunity against aquaporin 4, in which lesions usually but not exclusively involve the optic nerves and spinal cord, and with treatments directed at reducing antibody production sometimes altering the otherwise poor natural history.

**Non Cirrhotic Portal Hypertension**  
Prof. Elwyn Elias  
British Society of Gastroenterology, Liver Unit, Queen Elizabeth Hospital, UK. Email: elwyn.elias@bhh.nhs.uk.

Portal hypertension is most commonly associated with cirrhosis of the liver. In this lecture we will briefly review the range of other conditions that can similarly lead to bleeding from oesophageal varices, ascites and even hepatic encephalopathy. Vascular conditions may interfere with the flow of blood into or its exit from the liver. We will discuss occlusion of the portal vein at extra- and intra-hepatic levels, sinusoids and hepatic vein. In addition hepatic problems may induce vascular changes in the pulmonary circulation which have a profound effect on gas exchange and right heart function.

**Intrahepatic cholestasis**  
Prof. Elwyn Elias  
British Society of Gastroenterology, Liver Unit, Queen Elizabeth Hospital, UK. Email: elwyn.elias@bhh.nhs.uk.

Cholestasis may result from purely intrahepatic problems involving hepatocytic function, canaliculare secretion, canalicular obstruction and ductular obstruction. Intrahepatic cholestasis may be caused by a variety of factors including inherited genetic mutations, metabolic, endocrine, toxic and pharmacological agents. We will review the symptoms and signs of cholestasis as well as approaches to its treatment.

**Oral Diseases: Systemic disease diagnosis from oral signs**  
Prof. Farida Fortune  
Clinical and Diagnostic Oral Sciences, Barts & The London School of Medicine and Dentistry. Email: f.fortune@qmul.ac.uk.

Most diseases (approximately 95%) can be diagnosed by careful consideration of Oral symptoms and signs. These are commonly neglected in the diagnostic hierarchy. The presentation will allow delegates to develop structured methods for examination of the head and neck. It will also give a clinical overview to assist in increasing the diagnostic accuracy within the general medical environment.

**Behcets Disease**  
Prof. Farida Fortune  
Clinical and Diagnostic Oral Sciences, Barts & The London School of Medicine and Dentistry. Email: f.fortune@qmul.ac.uk.

Behcet’s Syndrome (BS) is an immune related disease which is markedly prevalent in areas surrounding the old silk trading routes in the Middle East, including Oman, Qatar, and Central Asia. It is a multi-systemic disease characterised by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. BS is often associated with other major organ involvement, vasculitis and thrombotic activity. Uveitis is the main cause of blindness while the central nervous system involvement can lead to stroke or death especially in young people. BS is a debilitating chronic disease which severely affects patients’ quality of life (Fortune, 2003, Mumcu et al., 2009b). Patients most frequently present with recurrent oral ulceration as the initial sign of the disease. Because of this observation, it is thought that the oral environment may play a very important role in its etiology and pathogenesis. To date the consensus is that the disease is triggered by a profound inflammatory response to an undefined environmental factor in a genetically susceptible host but as yet the etiology remains poorly understood (Lehner, 1999). Diagnosis is based on clinical criteria, dependent on the presence of recurrent oral ulcerations, plus any two of recurrent genital ulcerations, ocular or skin lesions, and a positive pathergy test. Diagnosis is difficult but once diagnosed treatment options lead to good quality of life. The presentation will discuss issues of specific clinical symptoms and signs associated with diagnostic pathways. And current treatment options. Whilst clinical activity is associated with considerable morbidity, specific indicators for onset of disease activity are not known. T cells, neutrophils and inflammatory cytokines and chemokines are all believed to play important roles. Recent research associated with disease will be explored.
Individualisation of Cancer Care: Reality or Pipedream?

Dr. Charlie Gourley
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Cancer is a complex disease which historically has been largely treated according to the assumed tissue of origin of the tumour. It has always been known that cancers from a particular site may vary considerably in their histology and treatments sometimes take account of this. Recent research however has demonstrated the considerable molecular heterogeneity of tumours with apparently identical histology. Novel treatments are now being developed to target particular molecular or pathway defects and the necessity of individualisation of care is clear in this cases. What is less clear is how we should progress the stratified medical agenda in tumours with clearly different molecular make-up but without such obvious molecular targets. We will discuss various aspects of individualisation of cancer care; success stories to date, areas of imminent progress, difficult areas where progress is possible, mechanisms to speed up the discovery phase for molecular therapies and how to create molecular tests which are accessible to non-specialist centres.

The BRCA1 and BRCA2 Genes in Ovarian Cancer: So much more than markers of hereditary risk

Dr. Charlie Gourley
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Since the mid-1990s it has been clear that mutations in the BRCA1 and BRCA2 genes predispose female carriers to breast, ovarian and other cancers. Now we know that germline BRCA1/2 mutation carriers who develop ovarian cancer have a different disease course to non BRCA1/2 mutation carriers. They are more likely to: have a seious histology; respond to multiple lines of platinum-based chemotherapy; develop visceral metastases. Despite the propensity for visceral metastases their median survival is approximately twice that of comparable non-BRCA1/2 germline mutation carriers. The recognition of this discrete molecular entity has partly been driven by the development of a new class of anti-cancer agents known as poly (ADP-Ribose) polymerase (PARP) inhibitors. Early phase clinical trials have demonstrated exciting efficacy of these agents. As an extension of this, researchers have sought other ovarian cancer patients who have the ‘BRCAAness’ phenotype without carrying a BRCA1/2 germline mutation (other mechanisms include somatic mutation, epigenetic inactivation or mutation of other pathway members). There is now preliminary evidence that these patients may also benefit from PARP inhibition. The hope is that being able to identify this molecular subtype will allow use of PARP inhibitors and improve the outcome for these ovarian cancer patients.

Lupus: A story of failure and success

Prof. Graham Hughes
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Despite the advances in recognition and treatment of lupus, pitfalls and obstacles persist in the management of this complex disease. Examples of failure at the individual level include the development of strokes or M.I. in under-treated APS (Hughes Syndrome) patients, the treatment- resistance of some cases of severe lupus skin disease, the failure at present to protect against congenital heart block. At a more general level, there remains the problem of under-recognition and under treatment on the one hand, with, perversely, overtreatment and iatrogenic Cushings on the other. It is also apparent that lupus rivals diabetes in its risk of late atherosclerotic disease and that known risk factors such as high cholesterol and positive aPL are inadequately addressed. On the bonus side, the outcome of lupus pregnancy has been drastically improved, and the development of renal failure reduced. New drugs such as Mofetil and Rituximab are already extensively used and, at last, major pharmaceutical firms are keen on developing new agents for lupus. Another major ‘advance’ has been the more conservative approach to steroid and cyclophosphamide treatment, and the wider use of milder agents such as hydroxychloroquine. International co-operation in lupus research is good, and developments in lupus are having an impact on many other diseases. Perhaps the single most important change in lupus has come from the recognition of the importance of APS. Many features such as stroke, migraine, atypical M.S., seizures and M.I. previously ascribed to ‘vasculitis’ and treated with steroids and cyclophosphamide, are recognised as more likely due to APS and treated more appropriately with anti-thrombotic agents.

Tuesday : A clinician’s tale

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In 1983, a detailed clinical description of a new syndrome was published. This pro-thrombotic syndrome was initially called the antiphospholipid syndrome and subsequently the antiphospholipid syndrome (APS) or Hughes Syndrome. Almost uniquely, it results in arterial as well as venous thrombosis and is marked by the presence of circulating antiphospholipid antibodies. Clinical features are protein, ranging from peripheral deep vein thrombosis (DVT) to involvement of internal organs such as the liver, kidneys and adrenals. Likewise arterial thrombosis can result in life-threatening infarction of organs such as the heart. The nervous system is frequently affected, with migraine, memory loss, balance disorders, stroke and atypical multiple sclerosis being prominent. Other features include recurrent miscarriage, thrombocytopenia and livedo reticularis. More recent observations have included ischaemic bone fractures, renal and celiac artery stenosis and a possible tendency to accelerated atherosclerosis. The condition is seen in lupus patients, but, significantly, occurs without associated lupus (‘primary’ APS) – indeed increasing clinical recognition of Hughes Syndrome suggests that this condition will overtake lupus in prevalence. Treatment at present is by anticoagulation. The mechanisms for thrombosis are being worked out; it has been suggested that in some situations (e.g., in pregnancy loss), an inflammatory component as well as thrombosis may play a part.
Pathogenesis and Management of Osteoporosis

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Osteoporosis is a common disease characterised by reduced bone mineral density (BMD), and an increased risk of fragility fractures. It has been estimated that about 30% of women and 12% of men will suffer fractures related to the presence of osteoporosis at some point in life. Genetic factors play an important role in regulating susceptibility to osteoporosis and account for up to 80% of the variance in peak bone mass. However, many other factors such as diet, exercise, sex hormone deficiency, co-existing diseases and drug treatment such as corticosteroid therapy interact to modulate the risk of developing osteoporosis. Although low bone density is a major risk factor for the development of fractures, the majority of fractures occur in patients who do not have osteoporosis, as defined on the basis of low BMD, illustrating the importance of falls as a risk factor for the occurrence of fractures. The most useful tool for assessing patients at risk of osteoporosis is dual energy x-ray absorptiometry (DXA) and individuals with a BMD T-score of -2.5 or less at the spine or hip on DXA examination are considered to have osteoporosis. Measurements of BMD are important not only for diagnosis but also in targeting therapies since most of the pharmacological treatments for osteoporosis have undergone clinical trials in patients with osteoporosis as defined by DXA. Optimal management of osteoporosis requires a multidisciplinary approach. Lifestyle modifications such as increasing dietary calcium and vitamin D intake; taking regular exercise, stopping smoking and limiting alcohol intake to within recommended levels are beneficial in osteoporotic patients and those at risk of the disease. Drug treatments for osteoporosis can be divided into two broad groups depending on whether they inhibit osteoclast activity (antiresorptive drugs) or stimulate bone formation (anabolic drugs). The most widely used drugs in the treatment of osteoporosis are bisphosphonates which are antiresorptive. These agents typically reduced the risk of vertebral fractures by about 50% and non vertebral fractures by 25-30%. The most widely used anabolic drug is the 1-34 fragment of parathyroid hormone (Teriparatide) which stimulates new bone formation. This agent reduces the risk of vertebral fractures by about 65% and non vertebral fractures by 50%. It is particularly effective in corticosteroid induced osteoporosis and seems to be superior to the bisphosphonate alendronic acid in this situation. Although the treatments currently available are effective, none are completely effective in preventing fractures emphasising the importance of combining drug treatment for osteoporosis with falls prevention to reduce the risk of fractures.

Vitamin D Metabolism, Osteomalacia and Rickets

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Osteomalacia is a bone disease characterised by reduced mineralisation of bone, which in most cases is due to vitamin D deficiency. When osteomalacia occurs in the growing skeleton it is known as rickets. Muslim women and elderly housebound individuals are at increased risk of osteomalacia, since vitamin D is mostly derived from exposure to sunlight. Osteomalacia and rickets occur because of deficiency of the active metabolite of vitamin D (1,25(OH)2D). The most common cause is deficiency of the precursor cholecalciferol which is synthesised in the skin from 7-dehydrocholesterol under the influence of UV light or obtained from the diet. Cholecalciferol is converted in the liver to 25(OH)D and then in the kidney to (1,25(OH)2D) which is biologically active. When vitamin deficiency occurs, intestinal calcium absorption is reduced, stimulating production of parathyroid hormone which stimulates bone resorption and promotes renal phosphate wasting resulting in defective mineralisation of bone. Osteomalacia and rickets may also occur in patients with renal failure, as the result of drug treatment (bisphosphonates, fluoride, aluminium); inherited defects in vitamin D metabolism (vitamin D resistant rickets); inherited defects in phosphate metabolism (hypophosphataemic rickets) and acquired defects in phosphate metabolism (tumour induced osteomalacia). Major advances have been made in understanding the pathophysiology of hypophosphataemic rickets over recent years leading to identification of the PHEX, DMP1, MEPE and FGF23 genes as key regulators of mineralisation and phosphate homeostasis. Osteomalacia and rickets due to vitamin D deficiency can be treated with vitamin D supplements whereas active vitamin D metabolites and/or phosphate supplements are required for hypophosphataemic rickets.
Pulmonary Sarcoidosis: One diagnosis, two different presentations

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Even 140 years after the initial description, the etiology of sarcoidosis, a multisystem disorder, remains elusive, the diagnostic tests remain largely nonspecific and treatment produces inconsistent results.

Case One: A 69 year-old Omani female with hypertension, diabetes mellitus, depression and blindness was referred for evaluation of bilateral opacities on a chest radiograph. She had a three-month history of dry cough, exertional breathlessness, chest discomfort and weight loss. She denied any history of fever, night sweats, haemoptysis or recent travel. Clinical examination revealed a few small lymph nodes in the axillae. Basic blood tests, including serum calcium, were normal. The serum angiotensin converting enzyme (SACE) level was also normal. The sputum smear was negative for acid fast bacilli (AFB) by direct smear. The Mantoux test was negative. The chest radiograph showed bilateral paracypheral infiltrates. A computed tomography (CT) of the chest revealed bilateral extensive perihilar airspace consolidation with significant mediastinal lymph nodes. Spirometry results were as follows: forced expiratory volume 1 (FEV1) - 0.66 L (37%), forced vital capacity (FVC) - 1.01L (47%), FEV1/FVC - 65%. A bronchoscopy showed hyperaemic mucosa with diffuse granular changes and a few nodular lesions. An endobronchial biopsy revealed features of non-caseating granuloma confirming a diagnosis of sarcoidosis.

Case Two: A 42 year-old Omani female presented with a dry cough, generalised itching and extreme tiredness of 6 months duration. On examination, there were well demarcated hyperpigmented brown nodular skin lesions over the breast, abdomen, lower back and both thighs. Some showed central ulceration with healing and post-inflammatory hypopigmented and hyperpigmented patches and superficial mild depressed scars. Routine blood tests, including serum calcium and SACE level, were normal. The Mantoux test was positive, 24 mm. The chest radiograph and computed tomography (CT) scan revealed bilateral hilar and mediastinal lymphadenopathy. Pulmonary function test results were as follows: FEV1 - 1.87 L (78%), FVC - 2.29 L (81%), FEV1/FVC - 82%, carbon monoxide diffusing capacity (DLCO) - 75%, and carbon monoxide transfer coefficient (KCO) - 96%. The bronchoscopy did not show any abnormality; the bronchoalveolar lavage and sputum were negative for AFB by stain and culture. Skin lesions were biopsied, as well as a mediastinoscopy and mediastinal lymph node biopsy. Both skin and lymph node biopsies showed non-caseating granulomas suggestive of sarcoidosis.

Both the patients received prednisolone leading to symptomatic and radiological improvement. Since the Mantoux test was positive, the second patient received anti tuberculosis treatment prior to the initiation of steroids.

Despite advances in the knowledge of the immunopathogenesis of sarcoidosis, no single aetiologic agent or genetic locus has been clearly identified in the development of the disease.1 The disease varies in incidence and presentation among geographical regions.2 Any organ can be involved, the most commonly affected sites being the lungs (approximately 90% of patients), lymph nodes, skin, eyes, and the liver. Cutaneous involvement is common presenting as macular, nodular, maculopapular, ulcerative or plaque like lesions; it can also present as verrucous, ichthyosiform, hypomelanotic, or psoriasiform lesions.3 They can be divided into specific lesions and nonspecific lesions based on the characteristics and histology,4 the classic specific and nonspecific lesions being Lupus pernio and Erythema nodosum respectively. Spontaneous remission is common in sarcoidosis so not all patients require treatment. Generally, treatment is indicated when there are debilitating symptoms or evidence of significant or progressive end-organ damage. Glucocorticoids are the commonest treatment agents for pulmonary sarcoidosis. Refractory disease may require other agents such as immunosuppressive, cytotoxic, antimalarial drugs or anti-tumour necrosis factor (TNF) antibodies.
A 21 year-old boy, previously well, presented at Sultan Qaboos University Hospital, Oman, with a 2-month history of low grade fever, malaise, weight loss of about 3–4 kg, and haemoptysis. There was no history of shortness of breath, palpitation, recent travel, or contact with patients suspected to have tuberculosis or HIV. The physical examination was unremarkable apart from a dull percussion note between the loins and the ribs. Vital signs were temperature 38 ºC, pulse rate 128 bpm, respiratory rate 14/min, blood pressure 97/50 mmHg. A blood investigation revealed mild anaemia with an Hb of 9 g/dl, normochromic normocytic, and white cell count at diagnosis, immunophenotype, chromosomal aberrations, speed of treatment response, minimal residual disease, are all very important factors in determining the prognosis of the diseases. An eight year-old Omani girl was admitted to Sultan Qaboos University Hospital (SQUH) referred from a peripheral hospital with fever and poor school performance of more than one month's duration. The child had developed convulsions, septic shock and was ventilated and was therefore transferred to SQUH as a suspected case of leukaemia. In SQUH she was labelled as T-Cell leukaemia with central nervous system (CNS) involvement and was completely aphasic. Despite repeated magnetic resonance imaging (MRI) brain scans that confirmed white matter changes and demyelination initially and widely extended on repeated imaging, her cerebrospinal fluid (CSF) was repeatedly clear. After successful induction with a POG 9404 T3 protocol, she had a severe episode of febrile neutropenia that rapidly progressed to septic shock, deteriorating neurological status and respiratory distress. She had recurrent episodes of febrile neutropenia, sepsis with ELBS E.Coli, coagulase negative Staphylococcus and Candida. Her condition deteriorated with severe mucositis and respiratory distress which needed an emergency tracheostomy and later she was put on mechanical ventilation. She remained in very critical situation for 4 weeks and she was labelled as DNR (Do Not Resuscitate) status. Her chemotherapy was withheld for two and a half months due to her grave clinical condition. Of interest, she maintained her remission status on a repeat bone marrow aspiration; however; she had extensive haemophagocytosis (secondary haemophagocytic lymphohistiocytosis (HLH)) that needed to be treated with partial induction for 6 weeks (HLH 2004). After all these stormy events child ended up in a devastating state with severe weight loss (skin on bones), aphasia, and inability to walk. With extensive nursing support and physiotherapy, she improved remarkably, started to gain weight, her speech recovered and the tracheostomy was closed. Her MRI brain scan was almost normal. After one year of an uneventful course of maintenance chemotherapy, she suddenly developed facial palsy. Other CNS examinations were normal and the CSF was still clear. Unfortunately, her bone marrow showed 80% blasts of the initial phenotype confirming a combined bone marrow and CNS relapse. The brain images were obviously normal. She was started on UK ALL relapse protocol and planned for early bone marrow transplantation. During the induction phase she had another episode of febrile neutropenia, herpes simplex virus lesions that further deteriorated and progressed to septic shock. After a long severe prolonged course she expired. Everyone has got only one life; however, in our case she was labelled as DNR once and all the treating team members lost hope that she would survive. Such a courageous young girl made it through and came out of this tragedy learning again how to talk and walk.

This case was presented at the Sultan Qaboos University Clinical-Pathological Conference on 5th May 2010 with the title "You Only Live Twice"
Dehydrogenase (LDH) was minimally elevated to 698 U/L (up to 248 IU/L). Serum and urine β-human chorionic gonadotropin (HCG) were within the normal limits. An ultrasound scan of the testis was unremarkable, and a computed tomography scan of chest [Figure 1a] showed a large ill-defined lobulated anterior mediastinal mass in the superior mediastinum, extending into the left hemithorax. The mass was seen displacing the mediastinal vascular structures to the right and posteriorly, with significant compression of the left main pulmonary artery and possible infiltration of the main pulmonary artery. The left upper lobe bronchus was collapsed with loss of volume of the left upper lobe. The liver was found to be enlarged and showed numerous focal lesions predominantly in the right lobe with central necrosis and thick enhancing rims [Figure 1b]. A biopsy revealed an extensively necrotic poorly differentiated malignant neoplasm with the immunohistochemical profiles in keeping with mixed germ cell tumor. The patient was treated with combination chemotherapy consisting of bleomycin, etoposide and cisplatin (BEP). The tumour marker response is shown in Figure 2. Because of a lack of marker normalisation after three cycles of the combination chemotherapy, the treatment was changed to a combination of vinblastine, ifosfamide and cisplatin, of which he received four cycles. The treatment was further changed to third line chemotherapy consisting of gemcitabine and oxaliplatin because of lack of marker remission. Owing to no further marker decline, the patient was referred for a positron emission tomography (PET) scan, which revealed increased uptake in the mediastinum, but not in the liver. The patient underwent thoracotomy with resection of the residual mass lesion, the histopathology of which showed mainly necrosis. Following the thoracotomy, the alpha-fetoprotein (AFP) dropped to normal limits, and the patient has been in continuous complete remission since March 2008.

This case was presented at the Sultan Qaboos University Clinical-Pathological Conference in 15th April 2009 with the title “Between the Loins and the Ribs”.

Figure 1: Computed tomography (CT) scan of chest (1a) and the upper abdomen (1b), showing disease in the mediastinum and the liver before treatment. Figure 1c shows the CT scan following thoracotomy, resection of the residual mass.

Figure 2: Alpha-fetoprotein (AFP) levels in response to treatment and over time. The X-axis shows time in weeks, and the Y-axis shows the level of AFP on a logarithmic scale. BEP = bleomycin, etoposide and cisplatin; VeIP = vinblastine, ifosfamide and cisplatin; GemOx = gemcitabine and oxaliplatin.
ABSTRACTS HISTOPATHOLOGY SESSIONS

Fine Needle Aspiration Cytology of Pancreaticobiliary Tract

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Fine needle aspiration (FNA) is the method of choice for the diagnosis of pancreatic mass/cystic lesions. FNA may be performed percutaneously or under endoscopic ultrasound (EUS) guidance. Clinical and radiological examinations are not reliable methods to distinguish benign/inflammatory pancreatic disease from a carcinoma. FNA provides an accurate preoperative diagnosis for optimal and timely patient management. Most solid neoplasms are at an advanced stage at the time of detection and are mostly high grade adenocarcinomas which are readily diagnosed on cytology. Even if the tumour is unresectable, a tissue diagnosis is essential for the initiation of an appropriate treatment protocol. Low grade carcinomas can prove to be a challenge and are often differentiated from reactive ducts by certain features. Benign acinar cells can be differentiated similarly. Pancreatic endocrine neoplasms can likewise be distinguished by features peculiar to them. Cysts of the pancreas include congenital, developmental, inflammatory and neoplastic lesions. The cytology of pseudocysts are well characterised. Cystic neoplasms include serous cystadenomas, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, solid pseudopapillary neoplasms and cystic neuroendocrine tumours. Accurate preoperative diagnosis is critical, since this will determine the type of intervention needed, but clinical and imaging criteria are not consistently reliable. The use of FNA with cyst fluid analysis for amylase and tumour markers such as carcinoembryonic antigen (CEA), has improved the preoperative diagnosis of these lesions. The main diagnostic dilemmas in cytology specimens are distinguishing nonneoplastic from neoplastic lesions (particularly mucinous lesions) and benign neoplasms from borderline or malignant neoplasms. Cytology alone can distinguish mucinous from nonmucinous lesions and diagnose specific entities, such as solid-pseudo papillary tumours, cystic pancreatic endocrine tumours and carcinomas when the cell sample is sufficient, but lacks sensitivity due to sampling problems.

Molecular Pathology Targeted Therapeutics Leading the Paradigm Shift for Pathology

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The availability of an expanding armamentarium of antibodies and small molecule inhibitors has transformed the way we practice oncology. By targeting key oncogenic genes and pathways, many solid tumours can now be therapeutically addressed in a more focused and clinically efficient manner. This revolution in oncology treatment has also deeply transformed the way we practice pathology. Indeed, correct stratification of patients often depends on the immunophenotype or genotype profile of a single tissue-based biomarker. In our experience, the introduction of molecular testing in a traditional molecular histopathology operation multiplies the overall volume of tests by several fold, leading to substantial revenue gains. This also has a repercussion in the overall volume of testing in pathology departments. In our setting, the volume of molecular diagnostics after the validation of tests for targeted therapeutics amounts to an additional 10–20% increase in the overall testing volume. Targeted therapeutics is invariable changing the way we look at the taxonomy of cancer. We are currently witnessing the dawn of what appears to be a targeted therapeutics-oriented diagnostic paradigm in tumour pathology. The presentation provides several examples to this effect, showing both current and future trends that have a significant impact in the classification and characterisation of diseases.
has to do with the specific weight of pathology in overall diagnostic and therapeutic decision-making and, as a consequence, the way pathology and pathologists are perceived by the medical community, by our patients and by the industry. From the 1960s to perhaps the end of the 20th century, surgical pathology established itself as a central and fundamental discipline in clinical medicine. However, from a phenotypic-clinical framework of diagnosis, we are shifting into a phenotypic-molecular-clinical dimension. As a result of this shift, the process leading from morphological surgical pathology to therapeutic decision-making includes an area of expanding molecular diagnostic complexity. Increasingly so, surgical pathology departments understand that maintaining professional relevance requires not only passive knowledge of these techniques (i.e., when or how to order them), but active molecular diagnostic skills for molecular assay validation and interpretation to maintain key diagnostic relevance. Interestingly, the development of therapeutic pathology is also broadening the scope of pathology practice and, in particular, the role of pathologists in the pharmaceutical and the diagnostic industry. Therefore, it is the time for surgical pathology to embrace molecular pathology by integrating it, when indicated, into daily clinical practice at sign out. To do so, we should revisit and ensure its teaching in our residency programs—all of this building on the role of molecular pathologists certified by professional organisations as invaluable bridges between pathologists’ roles as responsible diagnosticians and as clinical scientists. In essence, the systematic embracement of molecular pathology will allow pathology departments to regain a central role at the core of the diagnostic and therapeutic endeavour.

Molecular Pathology—ErbB2 Testing: FISH (fluorescence in situ hybridisation), CISH (chromagen in situ hybridisation), SISH (silver in situ hybridisation) and HIC (immunohistochemistry) - What is their relevance?

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A better understanding of “molecular markers” in recent years has allowed the characterisation of a group of drugs, primarily antibodies and small molecule inhibitors, developed against a specific target based on its important function in cancer. These treatments are “personalised”, i.e. the target analysis will indicate the patient’s likely chance of response (Personalised Medicine 2009; 6:465–8). Of these, the use of the antibody trastuzumab or the small molecule inhibitor lapatinib, targeting Her-2 for the treatment of breast cancer, is arguably the best established example to date. Which is the most accurate manner of analysing Her-2 status prior to treatment is still a matter of some controversy. A few years ago, we and others proposed a cost-effective manner of analysing Her-2 using IHC and complemented by FISH in selected cases (Modern Pathology 2003; 16:79–85 and Human Pathology 2003; 34:362–8). More recently, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) Guidelines have tried to present a homogeneous approach to Her-2 testing (Journal of Clinical Oncology 2007; 118–45), although authoritative opinions against this approach have been voiced (Journal of Clinical Oncology 2009; 1323–33). We shall review this body of evidence, which will be complemented with other more recent technical approaches that may be relevant in years to come. Finally, the increasingly important issue of Her-2 testing in gastric cancer will also be reviewed.

Molecular Pathology: A hospital-based platform for translation research

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Formalin fixed and paraffin embedded tissue (FFPE) collections in pathology departments are the largest resource for retrospective biomedical research studies. Based on the literature analysis of FFPE related research, as well as our own technical validation, we present the Translational Research Arrays (TRARESA), a tissue microarray centered, hospital based, translational research conceptual framework for both validation and/or discovery of novel biomarkers. TRARESA incorporates the analysis of protein, DNA and RNA in the same samples, correlating with clinical and pathological parameters from each case, and allowing a) the confirmation of new biomarkers, disease hypotheses and drug targets, and b) the postulation of novel hypotheses on disease mechanisms and drug targets based on known biomarkers. While presenting TRARESA, we illustrate the use of such a comprehensive approach. The conceptualisation of the role of FFPE-based studies in translational research allows the utilisation of this commodity, and adds to the hypothesis-generating armamentarium of existing high throughput technologies.

Immunohistochemistry: Basic aspects

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The process of implementing immuno-histochemical tests in the diagnostic laboratory has been greatly simplified by the availability of standardised re-agents, instruments, and assay protocol from commercial manufacturers. However, researchers and diagnosticians who wish to develop new immuno-histochemical assays, or explore new applications for existing tests, must carefully consider the methods of tissue preparation and the reaction conditions for each assay step in order to obtain clear, specific antigen signals and to minimise non-specific reactions.
Fine Needle Aspiration Cytology of the Thyroid

Prof. Kusum Kapila
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Fine needle aspiration (FNA) is an important widely used investigative procedure for both palpable and ultrasonographically detected thyroid nodules. FNA is a reliable triage method for identifying patients requiring surgery. The direct smear technique is highly sensitive and specific. A trained cytopathologist is skilled in recognising the different types of non-neoplastic and neoplastic cells in these FNAs. The main diagnostic categories of fine needle aspiration of the thyroid are benign and functional and include the thyrotoxic goitre, nodular goitre, hyperplastic nodules, thyroiditis, acutely suppurative thyroiditis, subacute thyroiditis (de Quervain's disease) and chronic lymphocytic thyroiditis (Hashimoto's disease). Tumours of the thyroid such as follicular adenoma/carcinoma, papillary carcinoma, medullary carcinoma and lymphoma infiltrating the thyroid and metastatic tumour also can be diagnosed by FNA. The rapid international spread of Klebsiella pneumonia strains that are carbapenem resistant is a major concern. Treatment options are severely limited and are a great challenge for infection control. Recently two cases of NDM-1 K. pneumoniae have been identified in Oman; this mandates urgent actions/measures to limit the spread of this strain and any other resistant bacteria.

Emergence of Resistance among Gram Negative Pathogens

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Antimicrobial resistance is one of the world's most pressing public health problems of today. Multiresistant Gram-negative infections are not only the cause of infections for hospitalised patients, but also for people in the community. Mechanisms of resistance are variable and options for treatment are limited. Clinical diagnostic laboratories are of variable capabilities and may not always be able to identify isolates with novel mechanisms of resistance which may lead to delays in diagnosis. The versatility with which these pathogens are able to produce resistance is quite impressive and extremely intimidating and challenging to the medical community. The emergence of extended-spectrum beta-lactamases (ESBLs) as a mode of resistance and their presence on transferrable plasmids has increased their presence within the Enterobacteriaceae species and allowed for easy transfer between patients and between patients and health care workers. Over 800 ESBLs have been identified in the Lahey database todate and many unidentified genes still exist. The explanation of the emergence of this resistance is not clearly identified; however, the wide misuse of antimicrobials in medicine and agriculture have most likely resulted in pressure selection of bacteria resistant to the microbiologic activity of these agents. In addition, poor compliance of health care workers with infection control measures may also play a role in the spread of these pathogens in the health care setting.
Primary Immunodeficiency in Oman - Experience at Sultan Qaboos University Hospital
Dr. Salim Al-Tamimi
Clinical Immunology & Allergy, Sultan Qaboos University Hospital, Muscat, Oman

Primary immunodeficiency diseases (PIDs) are considered to be rare but they are expected to be more common in Middle Eastern countries. The prevalence and characteristics of PIDs are unknown in Oman. Sultan Qaboos University Hospital is the national referral center for PIDs in Oman. Patients are referred for evaluation and management when suspected to have underlying immunodeficiency. They are diagnosed and classified according to the clinical and laboratory criteria of PID reported by the International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases Classification Committee. Between July 2005 and July 2010 there were a total of 90 patients, 55 males and 35 females who were diagnosed to have PID with an estimated prevalence of 1:30,000 in the country. The most common form of immunodeficiency was phagocytic disorders (42%) followed by predominantly antibody disorders (18%), other well defined PID syndromes (13%), combined immunodeficiency (12%), complement deficiencies (6%), unclassified PIDs (6%), and immune dysregulation syndromes (3%). The age of onset of symptoms varied from the first month of life up to 12 years of age with a mean of 20.1 months and a median of 9 months. The age of diagnosis ranged from the first week of life up to 16 years of age with a mean of 35.5 months and a median of 24 months. Consanguinity was present in 81% of patients. A family history of PID was present with a mean of 20.1 months and a median of 9 months. The age of diagnosis ranged from the first month of life up to 12 years of age with a mean of 35.5 months and a median of 24 months. The outcome of the study will also be used in advocacy regarding the impact of the future introduction of a rotavirus vaccine in Oman.
Laboratory Diagnosis and Genetic Characterisation of Measles Virus
Dr. Rupa M. Varghese
Specialist, Central Public Health Laboratories, Ministry of Health, Muscat, Oman

Measles is one of the most easily transmitted diseases. Transmission is primarily through large droplet spreads or direct contact with nasal or throat secretions from an infected person. Measles is a vaccine preventable disease, but it remains a major cause of death in infants in developing countries. The WHO Eastern Mediterranean region (EMRO) is in the elimination phase of the measles virus. In this phase, it is well established that surveillance based on only clinical recognition of cases is inaccurate. Laboratory confirmation of each and every suspected case is critical for effective surveillance. Detection of measles specific IgM is the standard test for the rapid laboratory diagnosis for measles. Isolation of the measles virus involves a high quality specimen collected in the window 0–5 days after rash onset. Vero/hSLAM cell lines have been approved for the isolation of measles virus in the Global Laboratory Network. However, expansion of measles surveillance to include the molecular characterisation of the measles virus will help facilitate measles control during this global phase of measles eradication. In 2007, the Omani Central Public Health Laboratories, which is a designated WHO Regional Reference Laboratory, established molecular characterisation of the measles virus by sequencing. Molecular characterisation of measles viruses is an important component of measles surveillance as it provides a method for identifying the geographical origin and tracing the transmission pathways of a virus. It also provides a valuable tool for measuring the effectiveness of measles control and elimination programmes, and also provides information that can be used to document the interruption of transmission of endemic measles. The sequence of the 450 nucleotides that code for the COOH-terminal 150 amino acids of the nucleoprotein (N) is the minimum amount of data required for determining the genotype of a measles virus. Sequence data can be obtained from a viral isolate or by amplification of measles sequences directly from ribonucleic acid (RNA) extracted from a clinical specimen. The circulating measles genotypes in Oman and neighbouring EMRO countries will be discussed. Currently, there are 8 clades (A–H) and 23 genotypes within these clades of the measles virus.

Cytomegalovirus Infection and Disease after Solid Organ and Bone Marrow Transplantation: An overview
Dr. Hanani Al-Kindi
Clinical Virologist, Central Public Health Laboratories, Ministry of Health, Muscat, Oman

Cytomegalovirus (CMV) is a well known cause of morbidity and mortality in immunocompromised patients. It is the most important pathogen affecting transplant recipients, which causes both direct effects, including tissue injury and clinical disease, and a variety of indirect effects. The impact of these CMV-induced effects on the organ transplant itself is great. There is a strong relationship between CMV and organ rejection and this relationship appears to be bidirectional. The prevention of CMV infection is of great importance either using the prophylaxis or the preemptive treatment approach. Treatment of clinical CMV disease usually requires administration of intravenous ganciclovir for two to four weeks. Clearance of viraemia should be documented before intravenous therapy is ceased.

Methicillin-Resistant Staphylococcus Aureus (MRSA) Management in Health Care Settings: Current guidelines
Dr. Martin J Gill
Consultant Medical Microbiologist, University Hospitals Birmingham, UK

The current approach to managing MRSA in healthcare settings in many countries has resulted from a combination of history, scientific evidence and patient/political pressure. This talk will compare and review the basis for existing guidelines that are used in different health care settings. It will review the success of approaches to MRSA control and provide some insights into how organisational influences might help achieve successful control.

Management of Health Care Workers Infected with HIV, HCV, HBV
Dr. Alya Al-Lawati
Specialist Microbiologist, Al Nahda Hospital, Muscat, Oman

In July 1990, the Centre for Disease Control and Prevention (CDC) reported the first case of possible transmission of HIV to a patient from an infected health care worker (HCW). Fear of transmission was rampant and several recommendations were published. The latest updated recommendations were from the Society of Healthcare Epidemiology of America (SHEA) regarding the management of health care providers infected with HIV, hepatitis B and C (HBV and HCV) were published early 2010. The society recommends that the HCW should not be prohibited from health care practice on the basis of a blood borne pathogen infection. The types of procedures done by HCW are divided into 3 categories according to the risk of transmission. For each pathogen, the recommendations are graduated according to the relative viral load level of the infected provider. However it is emphasised that because of the complexity of these cases each case will be slightly different and cases should be considered independently. The guidelines also reflect the importance of patient safety as well as provider privacy and medical confidentiality, all of which are absolutely essential. The presentation will cover the details on overall management of HCWs infected with blood borne viruses based on SHEA guidelines.
Measles Outbreak in Dhofar March–April 2009: Cross-border importation
Dr. Idris Al-Obaidani
Department of Communicable Disease Surveillance & Control, Ministry of Health, Muscat, Oman

The index case of the current outbreak was a 24-year-old woman (non-Omani) who reported, on 23rd March 2009, to Harwib Health Centre in the Dhofar region of Southern Oman with high-grade fever. She was immediately referred to Sultan Qaboos Hospital in Salalah, the capital city of the region. She was admitted and kept in isolation with a provisional diagnosis of viral fever. She gave history of visiting Al-Haul village in Yemen from 12–19 March. She developed a rash after admission which was then classified as a drug-induced rash and hence neither was a blood sample taken nor was the case notified as required under the Fever & Rash surveillance order.

Field Investigation: Action taken: Genotype identification and classification of the cases. Recommendation: Active case-finding: House-to-house survey will be conducted in the neighbouring villages in the border area after assessing feasibility. Mop-up immunisation campaign: The need for the immunisation of the population in the border area is being assessed.

Infective Endocarditis in the Era of Multi-Drug Resistant (MDR) Organisms
Dr. Zakariya Al-Muharrmi
Department of Microbiology & Immunology, Sultan Qaboos University Hospital, Muscat, Oman

The prevalence rate of infective endocarditis is increasing as a result of aging, intravenous (IV) drug users and increased rate of line related bacteremia. In January 2010, the American Heart Association declared that the rate of implantable device infections was increasing which increased the risk of in-hospital death by more than two-fold. Currently Staphylococci are the most common aetiological organism responsible for these infections and these organisms are becoming more resistant. The WHO has identified antimicrobial resistance as one of the three greatest threats to human health. At the same time, infectious disease experts have announced that multi-drug resistant organisms (MDRo) are responsible for >25% of serious infections in developing countries, with some of these bacteria not being susceptible to any licensed antibacterial agent. Some antimicrobial resistance mechanisms are difficult to detect with routine microbiological testing leading to inappropriate treatment. Biofilm formation by MDRO (mainly Staphylococci, Acinetobacter and Pseudomonas) increases the difficulty of management of infective endocarditis. Clear understanding of biofilm development, antibiotic pharmacokinetics, antimicrobial resistance mechanisms, institution of infection control measures and antibiotic stewardship are the mainstay of controlling this growing problem.

Diagnostic Approach to Primary Immunodeficiency
Dr. Salim Al-Tamimi
Clinical Immunology & Allergy, Sultan Qaboos University Hospital, Muscat, Oman

Host immune defense is accomplished by innate immunity and adaptive immunity; both of these are essential in order to fight infections and prevent autoimmune diseases. Innate immunity includes naturally occurring barriers, mucociliary clearance, peristalsis, secretions, cells and protein enzymes that do not involve the production of immunologic memory for their function. Adaptive immune responses are both humoral and cellular and depend on immunologic memory for antigen recognition. Patients who are immunodeficient present mainly with recurrent or severe infections. Immunodeficiency can be separated into primary and secondary states and the type of infection suggests the particular component of the system involved. Examples that can cause secondary immunodeficiency are HIV, drugs (e.g. cytotoxic agents, steroids) protein losing states. Primary immunodeficiency results from absence or malfunction of bone marrow precursor stem cells, various blood cells, and soluble molecules that make up the immune system which can lead to compromise of the host defense system. Over the last two decades, many genes have been discovered that are responsible for disease status in the immune system. These genes either fail to produce specific proteins (immunoglobulins in X-linked agammaglobulinemia) or produce altered proteins (truncated common gamma chain of the interleukin-2 receptor in X-linked severe combined immunodeficiency), and enzyme deficiency, as seen in adenosine deaminase deficiency. Conventionally, immunodeficiency is classified into four major host defense mechanisms (B-cell immunity, T-cell immunity, phagocytic cells, and complement pathways). Immunodeficiency usually presents with unusual severe or recurrent infections, the following are the most warning signs of primary immunodeficiency: 1) a family history of immunodeficiency disease; 2) two new ear infections within 1 year; 3) two serious sinus infections within 1 year; 4) two months on antibiotics with little effect; 5) two pneumonias within 1 year; 6) two deep-seated infections, such as meningitis, sepsis or osteomyelitis; 7) need for IV antibiotics to clear infections; 8) recurrent deep skin or organ abscesses; 9) failure to thrive; 10) persistent thrush in mouth or fungal infection on skin. When an immunodeficiency is suspected, the following screening tests should be performed and may be tailored according to the clinical information with respect to the immune system arm likely to be involved: antibody mediated immunity; quantitative immunoglobulins (IgG, A, M, E); isohaemagglutinins; functional antibodies e.g. diphtheria/tetanus titers, T-cell immunity; total lymphocyte count; T and B cells numbers; lymphocyte proliferation assay; lateral chest X-ray; HIV, neutrophil, cell count and differential nitro blue tetrazolium test (NBT); dihydrorhodamine 1,2,3 test; complement, total haemolytic complement test, C3 and C4 concentration. Further specialised functional immunological tests may be required to establish an accurate diagnosis; these tests are not available in all laboratories, for example phagocytic assays and cytotoxic assays. Genetic studies are more commonly used now.

Update on Zygomycosis
Dr. Saleh Al-Azri
Senior Consultant Medical Microbiology, Central Public Health Laboratories, Ministry of Health, Muscat, Oman

Zygomycosis is one of the most rapidly progressing forms of mould infections, which usually begins in the nose and paranasal sinuses. This infection produces angioinvasive disease with tissue necrosis and is prone to dissemination. Diabetes and immuno-suppression
are major risk factors. Recent reports showed an increased incidence of zygomycosis. The presentation and diagnosis are usually challenging and the treatment is even more so. Zygomycetes are resistant to most commonly used antifungal medications, but high dose liposomal amphotericin followed by posaconazole are considered in most cases. The clinical outcome is closely related to the patient’s overall health and control of the underlying diseases.

**Prosthetic Joint Infections**

Dr. Fatma M. Al-Rashdi
Specialist, Khoula Hospital, Muscat, Oman

Since its development in the late 1960s, total hip and knee replacement has increased from an infrequent procedure to one that is commonly performed. The success of these procedures is hampered in part by the development of joint infections. The rate of infection in most centers ranges between 0.5 to 1.0 % for hip replacements, 0.5 to 2 % for knee replacements, and less than 1 % for shoulder replacements. Prosthetic joint infections can be classified according to the time of onset (early, delayed and late) or the pathogenic mechanism causing infection. Any microorganism can cause prosthetic joint infection and the distribution of organisms varies with the time from implantation and source of infection. Diagnosis of prosthetic joint infections always requires obtaining samples of joint fluid or tissue. Treatment usually involves both medical and surgical measures. The type and timing of such therapies is dependent upon the cause and timing of the infection and the condition of the host.

**Molecular Epidemiology of Tuberculosis in Oman**

Dr. J. P. N. Singh
Specialist Bacteriologist, National TB Reference Laboratory, Central Public Health Laboratories, Ministry of Health, Muscat, Oman

Tuberculosis continues to be a major cause of morbidity and mortality throughout the world with 8.8 million new cases and 1.6 million deaths in 2005 (WHO fact sheet, 2007). Rapid detection, adequate treatment, and contact tracing to arrest further transmission are the key factors in the control of this infectious disease. Various developments in DNA technology and molecular biology have led to methods to trace tuberculosis transmission routes by the differentiation of clinical isolates based on polymorphism in genomic DNA of Mycobacterium tuberculosis. This presentation gives a brief introduction to molecular epidemiology and its applications, and then focuses on the molecular characterisation of Omani M. tuberculosis isolates by spoligotyping, a study performed by our laboratory. We identified 265 different spoligotypes among the 786 M. tuberculosis isolates. The designation of the spoligotype was attributed by comparison of the pattern to those contained in a SpolDB4 database. Out of these, 124 spoligotypes (containing 573 isolates) showed matching with SpolDB4 database, while 141 spoligotypes (containing 213 isolates) were not found in SpolDB4 database and an ST number could not be assigned for them. Most unidentified spoligotypes were orphan (n = 109), however, 104 clustered spoligotypes (without ST numbers) were roughly assembled into the Unknown group 1 to 32. Over all clustering was observed in 77.2% (n = 607) isolates, whereas 22.8% (n = 179) clinical isolates harboured unique profiles. This study gives an outline of the M. tuberculosis strains circulating in Oman, and describes the distribution of the major phylogenetic families. It contributes towards a better understanding of the current trend of TB epidemiology in a low-incidence Middle Eastern country.
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