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Lively Life

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"Do not go where the path may lead, go instead where there is no path and leave a trail."
Ralph Waldo Emerson

Vivacitas, vivacious, and lively life is possible, if only one were to nourish and cherish to maintain a healthy life style. “Cogito ergo sum” (I think, therefore, I am) wrote Rene Descartes. We are here because we are able to think. Think of your life, your dependents and the comforts of a healthy life. Health is the best wealth. What is health? Health could be simply be compassionate.\[1\] While we claim that science and technology of today have made human life easier and more comfortable, why is mankind not happy commensurate with this technological revolution? Why is there so much strife? Why is mankind unhappy? Do these external developments like industrialisation, technological comforts etc., make man happier?

Development - External
How I wish they did? Since the first industrial revolution starting in 1802 in England all our technological developments have only made some of us filthy rich and all our developments like the roads, skyscrapers, planes, interplanetary travel, agricultural revolution, hi-tech reductionist medical non-science, information technology, our distorted western model of education, political systems of oligarchy, monarchy, plutocracy, communism, dictatorships of all hues and color, and the latest DE monocracy where a cunning minority holds the vast majority to ransom, and what have you, have all been external developments which have and can make mankind rich and powerful externally but not necessarily make humankind happy. The industrial revolution did not make man happy as predicted by William Wordsworth in his poem of 1802 Life is too much with us:

Life is too much with us:
The world is too much with us; late and soon,
Getting and spending, we lay waste our powers;
Little we see in Nature that is ours;
We have given our hearts away, a sordid boon!
This Sea that bares her bosom to the moon,
The winds that will be howling at all hours,
And are up-gathered now like sleeping flowers,
For this, for everything, we are out of tune;
It moves us not. --Great God! I'd rather be
A Pagan sucked in a creed outworn;
So might I, standing on this pleasant lea,
Have glimpses that would make me less forlorn;
Have sight of Proteus rising from the sea;
Or hear old Triton blow his wreathèd horn.

Development - Internal
Happiness is an internal feeling and is a state of mind. It is not a goal but a continuous journey. If one is happy here and now s/he will be happy always. Triumph and disaster, the two imposters, do not bother such a happy human being. He could walk with the Kings but still keep his common touch, he could mix with the crowd but retain his virtue, he can fill the unforgiving minute with sixty seconds worth of distance run, thus will he be the richest and he shall inherit this world. Such a happy person is so rich within (might not be on the Forbes list, though) and has been having phenomenal development within himself, he has been internally engineering himself to greater heights of glory and peace. Thus is born the happy man!

New science of man
Science is change. Newer developments in science have uprooted all the conventional scientific thinking

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1Editor in Chief; 2Cardiologist & Former Vice Chancellor (Retd), 3Former Visiting Professor of Cardiology, 4Affiliate Professor of Human Health
Happiness is robbed by our “I” concept. There is no “I” germ, we live in symbiosis with us. Even the gene in our organelle, the cell battery, does not belong to us but belongs to the germ, E. coli. Now we come to the crux of happiness. Happiness is robbed by our “I” concept. There is no “I” in real human physiology. It is always “We” concept. “I” starts the word illness while “We” starts the word wellness and happiness. When we develop internally to understand the above truth (philosophy), we become happy. Happiness, therefore, is living for others. Health is health. With a fully internally engineered man, health is simply defined as “enthusiasm to work and enthusiasm to be compassionate.”

Human being thus gets some meaning for life. When once one gets a meaning for life, it becomes enjoyable and purposeful resulting in good health. Life becomes vivacious-vivacitas. Poets have always brought forward profound truth which later turns out to be scientifically correct. See what Ralph Waldo Emerson had to say about life:

“The purpose of life is not to be happy. It is to be useful, to be honourable, to be compassionate, and to have it make some difference that you have lived and lived well.”

Ralph Waldo Emerson

A fully developed human being using the best internal engineering is a happy man. Even if one gets angry for a minute, sixty seconds worth of happiness simply vanishes into the thin air! Fully developed man lives on positive thoughts and keeps the company of like-minded people. Let this world develop to that level of greatness, My Lord. The externally developed world encourages the rich to become richer and makes the poor, poorer. Until and unless the last human being is fed enough, this world will have NO PEACE! Have a heart!

“I cannot remember the books I’ve read any more than the meals I have eaten; even so, they have made me.”

Ralph Waldo Emerson

“Is it so bad, then, to be misunderstood? Pythagoras was misunderstood, and Socrates, and Jesus, and Luther, and Copernicus, and Galileo, and Newton, and every pure and wise spirit that ever took flesh. To be great is to be misunderstood.”

Ralph Waldo Emerson, Self-Reliance

REFERENCES


Review Article

The Application of Adjuvant Radiotherapy to Palliative Treatment of Osteosarcoma

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ABSTRACT

Osteosarcoma, the most common form of childhood cancer, is an aggressive malignant neoplasm arising from bones and surrounding tissues. Due to its aggression, strong invasion and early spread to lungs, the prognosis is grim. Although the application of adjuvant chemotherapy and neoadjuvant chemotherapy improves the survival rates of patients, large doses of chemotherapy drugs bring with them toxic side effects. Primary and secondary drug resistance of tumor cells limits further application of chemotherapy. Radiotherapy, as an adjuvant treatment, regained attention, owing to discovery of sensitizing drugs and advances made in radiotherapy equipment. This review article provides an overview of fundamental principles of and technical advancement in as well as experience in radiotherapy treatments both from home and abroad.

INTRODUCTION

Osteosarcoma, a malignant neoplasm arising from mesenchymal tissues, features spindle stroma cells that produce osteoid tissues and is an aggressive primary malignant neoplasm arising from bones and surrounding tissues, the most common form of childhood cancer[1,2]. Incidence rates for osteosarcoma are estimated to be 2 - 3 cases per 100,000 in the general population. It is slightly more common in males than in females. Osteosarcoma comprises 0.2% of all malignancies[3]. It originates more frequently from metaphysis enjoying rich blood supply, with 42% occurring in the femur (75% of all the cases in the femur occur in the distal femur), 19% in the tibia (80% of all the cases in the tibia occur in the proximal tibia), and 10% in the humerus. About 16% of all cases occur in the pelvis, skull, jaw and other regions[4].

The causes of osteosarcoma are not known. Since the study about applying molecular biology technology to tumor etiology, until now it is reckoned that the occurrence of osteosarcoma is the result of environmental factors, like ionizing radiation, alkylating agents, viral infection, and genetic factors like patients’ age, gender, ethnicity and even heights for example[5,6]. A study shows that around 3% of osteosarcoma cases occur due to exposure to excessive amount of ionizing radiation[7]. The use of large doses of anticancer drugs and radiation can also induce the occurrence of osteosarcoma[8]. Even epidemiological surveys found that people who are tall are more likely to have osteosarcoma than those who are short and babies with fetal macrosomia have greater risk of having osteosarcoma than newborns with normal birth weights. This also confirms that osteosarcoma often occurs in fast-growing long bone metaphysis[9,10].

Due to its aggression, strong invasion and early spread to lungs, the prognosis is grim. In the 1970s, treatment of osteosarcoma was limited to mere surgical excision or amputations with the five-year survival rate registering only 20%[11]. Because of the application of adjuvant chemotherapy and neoadjuvant chemotherapy, limb-sparing surgery gradually replaces amputation, resulting in marked improvement in survival rates. At present, osteosarcoma patients at an early stage and without metastases, treated by surgery and adjuvant chemotherapy, see three-year disease-free survival rates up to 60%[12,13], five-year disease-free rates up to 57% and five-year survival of 66%[14,15]. Though chemotherapy plays a pivotal role in the treatment of osteosarcoma, chemotherapy...
drugs cause severe drop in granular leucocytes and / or platelets. Large doses bring severe toxic side effects such as ototoxicity with cisplatin, cardiotoxicity by doxorubicin and adverse effects on nervous system by ifosfamide[16,17]. In addition, primary and secondary drug resistance of tumor cells cannot be ignored. The overall response rate to the treatment is around 60%[18]. What’s more, it is hard to remove tumors in some cases from the skull base, pelvis etc. Therefore, immunotherapy, gene therapy etc., become hot areas and even radiation therapy, as an adjuvant method, regains attention, owing to discovering of sensitizing drugs and advancement made in radiotherapy apparatus.

1. BASIC PRINCIPLES AND TECHNOLOGICAL ADVANCES OF RADIATION THERAPY

In radiation therapy of tumors, high-energy photons, including X-ray and γ-ray, or charged particles, mainly comprising of electrons are utilized to kill tumor cells. In clinical area, mostly-used X-ray and electron beam are emitted from linear accelerators. However, weak in infiltration and less popular, electron beam is mainly utilized in the treatment of superficial tumors. Strong in infiltration, X-ray is mainly utilized in the treatment of deep tumors. The reason why radiotherapy works in treatment of cancers is that radioactive ray itself possesses radiant energy. Radiation can induce cancer in a natural environment. Meanwhile, it is used as an effective means to kill tumor cells—by using ionizing radiation to do damages to cellular DNA in direct and indirect ways, cell structure and cell activity are transformed—eventually causing the death of tumor cells. Besides causing direct damage to the DNA and breaking the DNA double-strand, ionizing radiation causes indirect damage to the DNA. This is also considered as one of the important mechanisms to kill tumor cells. Indirect damage is done mainly by the large amount of free radicals, produced from cells under the impact of ionizing radiation, which results in irreversible damage to the DNA and some important biological macromolecules in cells. Thus it leads to cellular death[19].

There is no doubt that ionizing radiation not only damages tumor cells but can also target normal cells. Normal cells also suffer from damages at different levels. If the biological difference between tumor cells and normal cells is taken into consideration, then radiotherapy has trivial impacts on surrounding normal cells when utilized to kill tumor cells. Firstly, tumor cells are worse at repairing themselves than normal ones, based on the fact that normal cells, after exposure to appropriate doses of radiation, are capable of repairing damaged DNA and other biological macromolecules. However, the self-repairing ability of tumor cells is another story. Secondly, as a result of fast multiplication of tumor cells and the radiation-sensitive division stage at which most cells are, tumor tissues are more sensitive than normal ones. Taking the above mentioned points into consideration, adequate radiotherapy only affects tumors and their surrounding tissues, rather than the whole body, though certain normal cells are damaged in that process but can recover in time[19,20].

The progress made in computer technology, radiation physics, radiobiology and radiation therapy equipment serves as a contributor to theoretical and technical breakthroughs achieved in radiation oncology[21]. Change was made in radiotherapy equipment from conventional medical two-dimensional linear accelerator to three-dimensional radiation therapy system. For instance, after applying 3D-CRT and IMRT, promising results were obtained[22,23]. Thus, in recent years the center of general interest in clinical treatment is placed in 3D-CRT. In the mid-1990s, the development of digital imaging technology accelerating the advent of CT and MRI makes it possible to accurately identify and describe the spatial shape of the solid tumors in human bodies. 3D-CRT helped transition from the past two dimensional model in the radiation therapy to the three dimensional model. Radiation field generated in the process of radiation therapy can change the shape of the tumor, so that high-dose distribution shape in three dimensions is consistent with the lesions. In this way, this significantly increases the total exposure of the target and at the same time minimizes the exposure of normal tissues and organs near the tumor, hence reducing complications of normal tissue. This above-mentioned technique is frequently applied to the treatment of prostate cancer and breast cancer with phenomenal results attained[24,25]. Among the 40 cases where lung cancer patients received 3D-CRT, 31 out of which were diagnosed with primary lung cancer and nine metastatic lung cancers (1 out of the 9 was diagnosed as osteosarcoma with spread to the lungs). Nagata, according to the previous treatment, pointed out that these 40 patients enjoyed good results with the treatment[26]. Recent years have witnessed the evolution from 3D-CRT to IMRT, the hot radiotherapy technique in the 21st century. IMRT not only requires radiation field to be consistent with the three-dimension of tumors but also emit radiation with different intensity. Moreover, IMRT possesses multi-field irradiation technique. All these merits of IMRT lead to the conclusion of a suitable dose distribution for three-dimension target areas, which increases effective dose and decreases peripheral dose. Therefore, under the premise of protecting normal organs, by applying IMRT, tumor cells are easier to be killed and can better control tumors for improvements in survival rates[27].
2. THE APPLICATION OF RADIOTHERAPY TO PALLIATIVE TREATMENT OF OSTEOSARCOMA

Osteosarcoma has long been considered to be insensitive to radiotherapy. As compared with other tumors, a fairly large amount of radiative rays are required for favorable outcome in the treatment of osteosarcoma. Though it is reported that radiation doses less than 60 Gy only briefly inhibit tumor and slightly higher dose (80 Gy) causes greater damage to the surrounding normal tissues, radiotherapy still plays an active role in the treatment. For example, radiotherapy acts as an efficient way of raising survival rates and quality of life, in conditions where the osteosarcoma is in the skull base or other unresectable parts, patients are suffering from recurrence, metastases or other symptoms that make them candidates for limited palliative treatment, rather than surgery. Furthermore, radiotherapy, adjuvant systemic chemotherapy or surgical treatment effectively reduce local recurrence rate, eventually increasing survival rate.

2.1 Control of Primary Lesion

In the treatment of osteosarcoma, the treatment of the primary lesion is the key to the survival rate of patients. As to osteosarcoma at an early stage without metastases, surgery and adjuvant chemotherapy can increase the five-year survival rate of patients to more than 60%. However, how to enhance survival rates and quality of life becomes an urgent dilemma, for tumors that may grow in such parts of the body where it is hard to remove by surgery such as pelvis, skull base, spine, etc. or patients may refuse amputations and other maiming surgery. Since last century, the approach of radiotherapy combined with chemotherapy has been tried with patients whose lesions cannot be removed by surgeries and pertinent experience was obtained. In the 1980s, there were experiments where the approach of radiotherapy combined with chemotherapy had been tried with osteosarcoma patients, resulting in significant inhibition of tumor activity in most patients. The case is different in the following study. Kuhl et al and other researchers adopted local irradiation with fairly large dose of radiation rays in the range of 97.5 - 100 Gy and then chemotherapy was given to three patients with osteosarcoma in the femur and tibia. One or two years later, all patients suffered from tumor recurrence. It was concluded that although local irradiation with fairly large doses of radiation rays caused no severe complications, radiotherapy failed to replace surgery and was only applicable to individual cases. In 2003, Cooperative Osteosarcoma Study Group COSS with multi-national membership statistically analyzed 67 cases of patients with osteosarcoma in pelvis. Out of 67 cases, thirty cases had no surgery. Out of these 30 cases, 11 patients accepted radiotherapy treatment of primary lesions. It was found that the five-year survival rate of patients treated by radiation registered 16%, exceeding that of patients without radiotherapy. This indicates that though most researches consider that osteosarcoma has low sensitivity to radiation, radiotherapy works in actual clinical practice. It is also useful in patients with osteosarcoma in limbs which cannot undergo surgery for various reasons. According to Russian researchers, chemotherapy including cisplatin and doxorubicin combined with radiotherapy of large doses greatly reduced local recurrence rate and did little damage to limbs. This research suggests that local recurrence was related to radiation doses, because patients with greater exposure to radiation enjoyed lower recurrence rate than those with less exposure. Mahajan and colleagues, after treating 39 osteosarcoma patients suffering from metastasis with multi-radiation therapy combined with chemotherapy, noticed that 72% of them were greatly improved and came to the conclusion that this combined treatment was more effective for patients unsuitable for surgery.

As for patients who are suitable for surgery radiotherapy before and after surgery is conducive to reducing tumor recurrence rate and increasing survival rate. As early as in the 1960s or 1970s, it was reckoned that pre-surgical radiotherapy increased success rate of limb-sparing surgery and reduced local recurrence in case of patients with osteosarcoma in limbs. This point was verified by following researchers. Eiber and his colleagues at the University of California in the USA conducted regional chemotherapy by injecting doxorubicin into arteries and at the same time regional radiotherapy with 35 - 46 Gy of radiations, followed by surgeries. The result implied that their treatment assured low local recurrence rate and high limb-sparing rate with the exception of a few patients who suffered from complications and thus had amputations. Wanebo and other co-workers came to a similar conclusion that local recurrence rate of tumors reached only 1.5% and the five-year survival rate was 59%. Researchers at the University of Istanbul, Turkey adopted radiotherapy in combination with adjuvant chemotherapy and then surgery in 46 cases with osteosarcoma in limbs, diagnosed from 1987 to 2002. Excellent results were obtained. What’s more, radiation after surgery was also considered as conducive to increasing the survival rate. It was reported by German scholars that after removing lesions in patients with osteosarcoma in the spine, those exposed to radiation had higher survival rate than those who were not.

Furthermore, intra-operative radiation therapy has been widely applied on a certain scale. Intra-operative radiation therapy is applying therapeutic levels of
radiation to grafts with tumor cells, while the area is exposed during surgery. This method is better than usual limb-sparing surgery theoretically. The first reason is that re-implanted bones are consistent with original anatomical defects, thus avoiding the nuances between the prosthesis and the patient’s own structure. Hence, limb structure and function are maximally recovered. The second reason is that re-implantation of patients’ own bones eliminates rejection and spread of disease, caused by implanting other alien biological materials. Even some scholars hold the opinion that cancer tumor dies of exposure to radiation, after being re-implanted, activated the body’s immune response thus inhibiting tumor cell growth[45,46]. Anacak and colleagues adopted intra-operative radiation therapy to malignant bone patients, eight of whom were diagnosed with osteosarcoma. During surgery, involved soft tissue was excised and involved grafts exposed to radiation of 50 Gy before re-implantation. Based on a 22-months follow-up, all re-implanted grafts survived without regional recurrence[47].

2.2 Prevention and Treatment of Lung Metastasis

The lung is the most common site for metastases of osteosarcoma, in 15 - 20% of patients who were found to have lung metastases during conventional examination and diagnosed with osteosarcoma in the early stages. Even in the process of formal adjuvant chemotherapy, 30 - 50% of patients still suffered from lung metastases or recurrence. Current research suggests that lung metastases is the main reason for the failure of treatment and death[48]. Therefore, it is anticipated that radiation therapy plays a great role in preventing and treating lung metastases in osteosarcoma. In the 1960s, Lougheed and colleagues first proposed the concept of prophylactic lung irradiation (PLI) and thought that in the course of chemotherapy treatment if normal lung tissue was selectively exposed to radiation this could prevent or delay lung metastases in osteosarcoma. This concept was supported by Newton and other people in the following decades[49]. According to 1988 report from The French Osteosarcoma Research Group, after adopting preventive radiotherapy (systematic chemotherapy and 20 Gy radiation) to the lungs of 41 patients with osteosarcoma in their lower limbs, the five-year survival rate reached 58%, which was higher than that of patients treated differently[50]. Though this treatment increased survival rates, there emerged lung injuries caused by radiation, mainly manifesting symptoms of restrictive ventilatory dysfunction and lung infection that was hard to control. One patient died of pneumocystis carinii pneumonia. Scholars hold different opinions about preventive lung radiotherapy. American ones state that it brings no benefits to lung metastases but rather damages normal lung tissue[51]. Presently, surgical resection and adjuvant chemotherapy are mainly adopted in the treatment of osteosarcoma with pulmonary metastases[52,53]. However, there are case reports claiming promising effect of radiotherapy. Shibamoto and other scholars from Japan reported that after conducting lobectomy several times, the patient with osteosarcoma in distal femur, who endured pulmonary metastases, still suffered from two pulmonary metastases. But the two gradually shrank and disappeared after being exposed to 60 Gy and 64 Gy of radiation respectively. The 43-month follow-up indicated a satisfactory outcome[54]. Lung metastases of osteosarcoma occurs most commonly in the lung parenchyma, but also occasionally in the bronchial tissue. Moqulkoc et al., for the first time, adopted radiation therapy within the lumen to one osteosarcoma patient suffering from bronchial metastasis. Good results were achieved[55]. Therefore, radiotherapy is also considered good treatment for osteosarcoma patients with pulmonary metastases.

2.3 Treatment of Bone Metastases

Normally bone metastases appear late in osteosarcoma patients and when diagnosed, 0.5% of patients have already suffered from distant bone metastases[56]. According to Harris, it is reported that eventually bone metastasis occurred among around 10% of osteosarcoma patients[57]. Bone metastases become the second major factor affecting the survival rate of patients, following lung metastasis[58].

Bone metastases often result in severe and persistent pain, seriously affecting patients’ quality of life. In recent years, many a hospital applied 153Sm-EDTMP, radionuclide, to treat bone pain, caused by advanced multiple bone metastases, with a satisfactory outcome. Half-life of Samarium is 46.6 hours. The three β rays it releases results in tumor necrosis and inhibition of secretion of chemical substances that cause pain. The affinity between EDTMP (ethylene diamine tetracarboxylic acid) and bone lesions is 16 times higher than that between EDTMP and normal bones. Thanks to its feature mentioned above, it plays a crucial role in inhibiting the osteoclast activity, slowing the destructive speed of bone lesions and reducing the loss of calcium salts in the body[59]. Consequently, 153Sm-EDTMP is widely applied to treatments to all types of malignant tumors with bone metastases. In the treatment of osteosarcoma, Bruland and other professionals were pioneers in applying 153Sm-EDTMP to severe pain torturing osteosarcoma patients in the terminal stages. Although it failed to obviously extend the lives of patients, the treatments and quality of life of patients were greatly improved[60]. Mahajan and others tried to conduct chemotherapy combined with in vitro radiation as well as 153Sm-
EDTMP treatment to 39 patients, in whose body 119 areas were exposed to radiation of an average dose of 30 Gy and 153 Sm-EDTMP 1 mCi/kg. At the end of this treatment, 29 areas with pain out of 38 were improved at different levels, making it 76% efficient[38].

Sm-EDTM, though achieves good therapeutic effect, brings about side effects such as bone marrow suppression and decrease in peripheral blood cells. Presently, a dose, greater than 1 mCi/kg, may be considered difficult to restore the hematopoietic dysfunction. Normally 0.5 - 1 mCi/kg is recommended as a suitable dose. As for its application in the treatment of osteosarcoma, some scholars have put forward as a suitable dose. As for its application in the treatment of osteosarcoma, some scholars have put forward

Presently, a dose, greater than 1 mCi/kg, may be observed in the process of osteosarcoma patients with bone metastasis, used as a suitable dose. As for its application in the treatment of osteosarcoma, some scholars have put forward

3. ADVERSE REACTIONS AFTER RADIATION THERAPY

Radiation therapy is effective as an adjuvant means in the treatment of osteosarcoma. Unfortunately, in proceeding with this treatment, patients suffered from a number of local and systemic reactions[62]. Skin was most prone to radio-dermatitis during radiotherapy[63]. The general symptoms of the skin in irradiated region are erythema, pigmentation and when worse, blisters, ulcers, and erosion. Surgical patients suffer from such complications as there is no healing or delayed wound healing. It was reported that 17% of patients exposed to radiation after surgery suffered from delayed healing of wounds and thus required surgery, while the figure was higher (reaching 35%) among those exposed to radiation before surgery. To make it worse, large dose of radiation leads to tissue edema and fibrosis of organs, thus causing limb contractures, muscle atrophy, pathological fracture and other long-term adverse effects. All these seriously affect the functional recovery of patients with osteosarcoma after accepting limb salvage surgery. Different from early adverse reactions in skin, what patients suffer after exposure to radiation after surgery mainly is fibrosis in the irradiated field and further ankylosis, eventually severely affecting limb function[64].

4. PROSPECT

Osteosarcoma is the most common form of childhood cancer and one of the most malignant bone tumors. Human beings have been fighting this disease for over a century. Although limb-sparing surgery combined with adjuvant chemotherapy raises the five-year survival rate of osteosarcoma patients who are at an early stage without metastases to 60%, as for those at early stage suffering from metastases, post-surgical recurrence or tumors in unresectable parts, the only feasible treatment is palliative in combination with chemotherapy and radiotherapy. What is pleasing is the result of higher survival rates and better quality of life. As time is flying, a substantial amount of clinical experience shows that radiotherapy treatment, as an adjuvant measure, is effective. Owing to the discovery of sensitizing drugs and advances made in radiotherapy apparatus, radiotherapy plays a greater vital role in palliative treatment of osteosarcoma patients.

CONCLUSION

Though most researchers consider that osteosarcoma has low sensitivity to radiation, in actual clinical practice, radiotherapy works!

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ABSTRACT

Objectives: To show the results of a limited surgical protocol in treating complex fracture-dislocation of the elbow with terrible triad, including replacement of the unfixable comminuted fractured head of radius, fixation of type II or III Regan & Morrey fracture coronoid and repair of the lateral collateral ligament (LCL) and lateral ulnar collateral ligament (LUCL). We also aimed to demonstrate that the medial collateral ligament (MCL) repair is dispensable.

Design: Retrospective study

Setting: Department of Orthopedics, Al-Jahra Hospital, Kuwait

Subjects: Twenty patients with complex fracture-dislocation of the elbow joint

Intervention: Surgical protocol of replacement of comminuted unfixable fractured head of radius, fixation of coronoid process, repair of LCL, LUCL injuries and short elbow immobilization in a plaster splint followed by intensive physiotherapy

Main Outcome Measure: Broberg and Morrey score on four parameters (motion, strength, stability and pain) was calculated, and clinical and radiological complications were assessed

Results: Sixteen patients (80%) were very satisfied, two satisfied and two disappointed. The average cumulative Broberg and Morrey score was 86 / 100 (range, 58 - 100). No patients developed re-dislocation post-surgically. Radiological results showed two cases of heterotopic ossification. No case had secondary post-traumatic osteoarthrosis or prosthesis breakage or loosening.

Conclusion: Operative management as described above can achieve elbow stability, functional range of motion and minimal complications without the need to repair the MCL, or to use hinged external fixator, or cross-pinning.

INTRODUCTION

Radial head fracture is the most common fracture of the elbow. Although they sometimes occur in isolation, many of these fractures are associated with elbow dislocation and terrible triad of coronoid fractures, disruption of the medial collateral ligament (MCL), lateral collateral ligament (LCL) and avulsion of the common flexor-pronator origin and common extensor-supinator origin creating very unstable situation at the elbow joint. Significant number of the radial head fractures associated with elbow dislocation are comminuted fractures with fracture fragments more than three or four pieces and even when the fracture fragments are three pieces they are often associated with fracture of the radial neck making their fixation a very difficult or unattainable task[1-13].

Numerous biomechanical studies have demonstrated the importance of the radial head as an axial and valgus stabilizer of the forearm and elbow respectively, particularly in the setting of associated coronoid and ligamentous injuries[4,7,4,13].
Excision of the fragments of the head of radius which can not be fixed in case of associated elbow dislocation will lead to chronic and recurrent elbow instability which will compromise the function of the whole upper limb with chronic elbow pain and development of secondary osteo-arthritis [16-23].

An efficient management of the elbow fracture-dislocation whenever the comminuted fracture of head of radius is unfixable is to maintain and preserve the elbow lateral column stability by replacing the radial head by a prosthesis with ligamentous repair and fixation of the coronoid fracture when it is of considerable size (Regan and Morrey Type II and III) [24-34].

SUBJECTS AND METHODS

From July 2005 to October 2008, we operated upon 20 patients with fracture-dislocation elbow.

There were 16 male and four female patients with a male to female ratio of 4:1 and the average age at the time of trauma was 40 years (range, 34 – 66 years). The mechanism of injury was a fall from height (high velocity fall) in seven patients, falling from a standing height in five patients, and involvement in road traffic accident (high-energy trauma) in eight patients. The mean time to surgery was two days (range, 1 – 4 days). The mean follow-up was for 30 months (range, 18 – 54 months).

All the patients had a posterior or a postero-lateral elbow dislocation associated with comminuted, non-fixable fracture of the radial head. A type I coronoid fracture according to Reagan and Morrey was associated in eleven patients and type II in only one patient (Fig. 1a, b, and 2a, b). All patients, (after clinical and radiological assessment using X-rays), had closed manipulation of their dislocated elbow in the emergency room under sedation and were described to have unstable reduction with redislocation of the elbows in more than 30° flexion. These patients’ elbows were further investigated using CT scan and kept immobilized in a plaster of Paris (POP) slab in more than 90° flexion of the elbow. Three of those patients were found redislocated in the POP slab, on the 3rd day of injury and admission.

Surgical Technique

Preoperative prophylactic antibiotic (one gram of ceftriaxone) was routinely given with the induction of anesthesia. All the patients were positioned supine with their elbows supported on a side table with a group of towels and the tourniquet inflated in the upper arm.

Surgical Approach

Dorso-lateral Kocher’s approach with radial head access between the ancones and extensor carpi ulnaris...
muscule was used in all cases. Blunt retractors were then used genitally to gain exposure of the radial head and neck. Careful retraction on the fully pronated forearm preserves the posterior intersosseous nerve.

The entire radial head fragments were removed. Fourteen patients had four fragments and six patients had five fragments. These fragments were reassembled on table to provide a template for the size of the prosthesis. The intramedullary canal of the radius was shaped to accept the stem of the implant using a cannulated lag screw.

The top of the intramedullary canal must be slightly counter-bored with a burr to obtain clearance for the bearing head. A trial implant that best replicates the size of the assembled head was inserted into the prepared canal and the joint reduced. Good contact of the trial head with the capitellum and smooth elbow and rotation on the forearm.

The trial implant was then removed and the medullary canal of the proximal radius was thoroughly irrigated with saline solution. The canal was gently filled with PMMA bone cement using the finger packing method. The implant was then inserted into the canal using gentle impaction with a blunt instrument. Excess cement was thoroughly removed. Solar radial head prosthesis (Stryker, Howmedica Osteonics) comes in three sizes, but we used the medium, 15 mm implant in 18 cases and the medium 12 mm implant in two cases.

After intra-operative X-ray confirmation of the position of the radial head prosthesis, the annular ligament was closed using absorbable sutures.

The LCL, the lateral ulnar collateral ligament (LUCL) and the common extensor-supinator origin were found avulsed with bald lateral epicondyle and repaired using No. 1 absorbable sutures passed through drill holes on the lateral epicondyle in 14 patients and in six patients only the LUCL was found torn and needed a direct suturing repair using 2/0 absorbable sutures. In one patient the coronoid fracture (type II Regan and Morrey) was fixed by a cannulated lag screw.

After release of the tourniquet, hemostasis, and closure of the wound in layers, the stability of the elbow joint was examined. Thirteen patients (65%) had an unstable elbow, which re-dislocated with flexion in the range of 30° - 45°. Twelve elbows were re-located and the reduction was confirmed by AP and lateral X-rays and maintained immobilized with the elbow in 90° or more flexion for 2 - 3 weeks. In one patient cross-pinning was done with pins removed after two weeks and followed with severely limited range of elbow motion (Fig. 3a, 3b, 4).

**Post-Operative Care**

After surgery, all patients had a posterior plaster slab for one week for those with stable elbow reduction and for 2 - 3 weeks, for those with unstable reduction. Rehabilitation only started after removal plaster splint which was supervised by a physiotherapist. Active motion was encouraged for elbow flexion and extension and forearm rotation.

Mobilization against resistance began six weeks after surgery. All patients received heterotopic ossification prophylaxis with indomethacin (25 mg, three times per day) for a period of three weeks.

**Follow-up**

Each patient was seen two, four and six weeks after surgery and then every three months during the first year and every six months thereafter until the end of the follow-up period. During every follow-up visit, the range of elbow motion and forearm rotation was measured and recorded using a goniometer. Plain
radiographs were taken at each review (AP and lateral views). AP views were performed in pronation and supination. The radial head prosthesis was considered stable when the contact with the capitellum was total in all positions. The prosthesis size is satisfactory when the upper level of the implant is at or within one mm from the level of the coronoid process in the X-ray views indicating the absence of impingement of the capitellum by the metal implant.

Statistical Analysis

The differences in the four sections of Broberg and Morrey scoring system (motion, strength, stability and pain) and also the clinical and radiological complications were analyzed in the view of using post-operative short period of elbow immobilization, with setting the level of significance at p < 0.05.

RESULTS

Sixteen patients (80%) were very satisfied and two (10%) were satisfied. Two patients (10%) were disappointed and both developed heterotopic ossification. The first one had 40° flexion deformity and the second one had 30° flexion deformity of his elbow and weak grip strength and both of them were obliged to change their type of work from being heavy manual workers to some kind of lighter job. Regarding the range of motion, the average elbow flexion was 130° (range, 110 - 140°). Average extension was 18° (range, 0 - 30). Average pronation was 70° (range, 40 - 80°). This was translated to a mean of 37 / 40 on the Broberg and Morrey Scale (Table 1)[12, 15]. Average supination was 70° (range, 50 - 80°).

Regarding the stability, nobody had instability or redislocation after the plaster splint was removed and none of them also had any sense of lack of strength or sense of instability in their elbows after the combined procedure of radial head replacement and lateral soft tissue repair. At the last follow-up, the average stability in Broberg and Morrey score was 5 / 5.

The average strength in Broberg and Morrey score was 13.5 / 20; grip strength averaged 75% of the non-injured side.

The average pain score was 32 / 35. Three patients complained of a mild pain in their elbow on using their upper limbs to carry heavy objects. Therefore, the average cumulative Broberg and Morrey score was 86 / 100 (range, 58 - 100).

The follow-up radiographs demonstrated good congruity of both the humero-ulnar and the radiocapitellar joints. The implant was considered stable in pronation and supination X-rays in all cases.

In no patient the radiographs showed the radiological signs of aseptic or septic loosening or capitellar erosion or overstuffing and subluxation of the implant.

One of our patient developed posterior interosseous nerve injury during surgery for which a dynamic cock-up splint was used by the patient for ten weeks when the nerve recovered with full active extension of his thumb and other fingers. In none of our patients we had deep or superficial wound infections.

All our patients returned to their original work except two patients. The other five patients in our series, who were heavy manual workers also returned to the same kind of heavy physical work.

At the latest follow-up, none of our patients developed post-traumatic secondary osteo-arthritis in their injured elbow joints. Two of our patients (10%) developed heterotopic ossification despite our routine of giving all the patients indomethacin for three weeks
post-operatively and both of these patients were disappointed with the result of surgery.

DISCUSSION

Posterior and postero-lateral elbow dislocation usually occurs as a result of a rearward fall on an outstretched, supinated upper limb. Several lesions can result from this mechanism. In the frontal plane the MCL is torn. A radial head fracture can occur either by a severe valgus compression and / or by radio-capitellar abutment during elbow dislocation. In the sagittal plane, the anterior displacement of the trochlea leads to coronoid fractures and / or major capsular detachment. In the transverse plane, tearing of the humero-ulnar part of the LCL leads to rotational instability of the humero-ulnar joint. It is the association of frontal, sagittal and transverse lesions that yields major elbow instability, the so called Hotchkiss’ “terrible triad”[36-40].

Treatment of complex fracture dislocations of the elbow tends to be mostly unstable after closed reduction and even with prolonged immobilization, re-dislocation commonly occur in plaster with poor results of elbow chronic instability and recurrent dislocation especially when the soft tissue injury is severe. Open reduction and rigid fixation of fractured radial head should improve stability and allow early active movements, but unfortunately this can be difficult or impossible to achieve with comminution of the radial head, commonly encountered in elbow complex fracture-dislocation. Ring et al showed that results for fixation of radial head fractures with greater than three parts were less predictable. In those patients with Mason type III injuries, 13 of 14 fractures with greater than three parts treated with open reduction and internal fixation had poor or unsatisfactory results. The authors concluded that those fractures with greater than three head fragments should be excised and possibly replaced[36-38].

Partial excision of displaced, unfixable fragments of the radial head can be carried out with the remaining intact part retained for stability. However, the elbow will still tend to be unstable and a raw cancellous surface will remain with the probable formation of dense adhesions leading to restriction of forearm rotation. Excision of the intact part of the head will only worsen the instability, but radial head replacement in this situation often restores stability and allows early active motion. Scar tissue cannot adhere to the smooth surface of the radial head implant and restrict movement.

Ring et al recently reported on 11 patients with comminuted fracture radial head associated with type II Regan-Morrey coronoid fractures. Seven elbows re-dislocated in a splint after manipulative reduction. Five, including all four treated with resection of the radial head redislocated after operative treatment. The authors concluded that elbow dislocation associated with fractures of the radial head and coronoid process are especially prone to recurrent subluxation, instability and post-traumatic arthritis. In this series we have 12 (60%) patients with associated coronoid fractures with only one case with Regan-Morrey type II fracture which has been fixed with a cannulated screw. We do not believe that Regan-Morrey type I needs any surgical intervention (like Morrey) and we feel that such fractures of the coronoid process are not significant in terms of humero-ulnar stability, and they are usually detached with the capsule and non-repairable. The fracture of the very tip of the coronoid is a herald of posterior elbow dislocation and not a focus of surgical fixation[33-39].

Treatment of a dislocation of elbow with an associated fracture of the radial head is much more challenging than treatment of simple dislocation. Not only was there probably more energy involved in the traumatic event but also failure to restore the contact compression of the radial head against the capitellum. This may severely compromise the ability of the lateral and medial collateral ligament complexes to heal with proper physiological tension. Treatment of a fracture-dislocation of the elbow with excision of the radial head without prosthetic replacement can lead to problems.

Josefsson et al reviewed the results of treatment of twenty-three patients who had a combined fracture of the radial head and dislocation of the ulno-humeral joint. By an average of fourteen years postoperatively, severe arthrosis had developed in twelve out of nineteen patients who had excision of the radial head without replacement. Broberg and Morrey noted arthrosis in twenty-two (92%) of twenty-four patients an average of ten years after fracture-dislocation of the elbow treated without repair or replacement of the radial head. Although only seven patients had moderate or severe arthrosis, more severe radiographic changes were associated with longer duration of follow-up. Four patients in the series of Jossefsson et al and two patients in the series of Broberg and Morrey had a re-dislocation within the first two months after the injury, even though many patients in both series had been managed with immobilization in a cast or splint. The re-dislocation was associated with concomitant fracture of the coronoid process in all of the patients in the series by Jossefsson et al. Persistent instability, loss of motion, heterotopic ossification, and post-traumatic arthrosis have been well documented, following fractures of the radial head associated with dislocation[11,14,16,35]. Data from Beingessner et al suggests that radial head replacement is insufficient to restore postero-lateral stability in the setting of an LUCL injury and the LUCL must be repaired. In all
the patients from this series we found that the LUCL was torn and repaired and in 14 cases the entire LCL with LUCL component were found avulsed and torn and were associated with avulsion of the common extensor muscles origin and repaired by suturing through drill holes in the epicondyle. According to Beingessner and others if the elbow is still unstable after radial head replacement, coronoid fracture fixation and repair of the LUCL, the MCL should be explored and repaired or a dynamic hinged external fixator should be placed across the elbow joint or even to transfix the humero-ulnar joint by cross-pins for short periods of 7-14 days to provide stability as the soft tissue injuries heal[25-31].

According to the results of our study we believe that the medial ligament repair is always technically difficult and the repair is weak. It is actually unnecessary, even in case of instability after radial head replacement and fixation of the coronoid process if type II is associated with repair of LUCL, LCL and lateral soft tissue. There is also no indication to use hinged external fixator which is difficult to apply and is always cumbersome to the patient or to transfix the elbow by pins which may injure the articular joint and increase the rate of post-surgery elbow stiffness. All what is needed as our results indicated is to immobilize the elbow in 90° or more flexion in plaster splint for short time of two or three weeks after which the rehabilitation program can be started promptly after soft tissue injuries to heal after which rehabilitation program can be started promptly without complications of chronic instability or joint stiffness.

We also conclude that the medium-term results of replacement of the comminuted and non-repairable fractured head radius using a metal prosthesis are satisfactory and without complications of synovitis, instability, capitellar erosion, breakage or loosening of the prosthesis.

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Clinical Significance of HIF-1α, MMP-2, and E-cadherin Expression in Rectal Carcinoma

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ABSTRACT

Objectives: To investigate the clinical significance of aberrant hypoxia inducible factor-1α (HIF-1α), matrix metalloproteinase-2 (MMP-2), and E-cadherin expression in rectal adenocarcinoma

Design: Prospective study

Setting: Chongqing Medical University, Chinese Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Provincial Key Laboratory of Pediatrics, Chongqing, China

Subjects: A total of 88 rectal adenocarcinoma tissues and 12 normal mucosa specimens were included in the study. The expression of HIF-1α, MMP-2 and E-cadherin protein were detected by using immunohistochemistry. Clinico-pathological factors associated with expression of HIF-1α, MMP-2, and E-cadherin were analyzed using the χ² test. Survival curves were plotted according to the Kaplan-Meier method.

Main Outcome Measure: HIF-1α, MMP-2, and E-cadherin protein expression

Results: HIF-1α, MMP-2, and E-cadherin proteins were expressed in 65.9%, 71.6%, and 28.4% of rectal cancer tissues, respectively. However, HIF-1α and MMP-2 proteins were not expressed, but E-cadherin protein was strongly expressed in 12 normal tissue samples. Altered HIF-1α and MMP-2 protein expression was associated with lymph node and distant metastases and Duke’s classification, while loss of E-cadherin protein expression was associated with tumor de-differentiation and lymph node and distant metastases. Combining these three markers together, the association was even more significant. Kaplan-Meier curve analysis showed that HIF-1α and MMP-2 protein expression but loss of E-cadherin protein expression significantly contributed to poor overall patient survival.

Conclusions: Altered HIF-1α, MMP-2, and E-cadherin protein expression significantly contributed to the progression of rectal carcinoma and poorer patient survival.

KEY WORDS: cancer metastasis, e-cadherin, hypoxia-inducible factor 1 alpha (HIF-1α), matrix metalloproteinase-2 (MMP-2)

INTRODUCTION

Colorectal cancer is a significant health problem for both males and females, accounting for an estimated 1.2 million new cancer cases and 600,000 cancer-related deaths annually worldwide. Although genetic analysis has shown that colon and rectal cancers are essentially the same cancer[1], the 5-year survival of rectal cancer patients is less than that of colon cancer patients[2]. Moreover, approximately 28% of cancer and 5% of adenomatous polyps occur in the rectum, which may also indicate that the etiology of rectal cancer is different from colon cancer[3]. Clinically, invasion and metastasis of rectal cancer affect the prognosis and leads to cancer-related death[4]. The 5-year survival rate of patients with disease spreading to distant sites is only approximately 19%[5]. Thus, novel approaches are urgently needed to control tumor progression and develop novel treatment options for rectal cancer.

To this end, invasion and metastasis of rectal cancer frequently occur, and the underlying mechanisms, like in all other cancers, remain to be defined. Multiple mechanisms and steps are involved in tumor invasion and metastasis. For example, hypoxia is a characteristic feature of the microenvironment of solid tumors, which plays an important role in neoplastic development and metastasis[6]. Previous studies have demonstrated that
hypoxia promotes tumor invasion and metastasis. Hypoxia inducible factor-1α (HIF-1α) plays a regulatory role in tumor invasion by modulation of angiogenesis and the extracellular environment[8]. The α-subunit (HIF-1α) and the constitutively expressed β-subunit form a heterodimer, which together act as a transcription factor. Thus, HIF-1α is the key component of hypoxic response by transcriptional regulation of multiple genes related to angiogenesis, energy metabolism, invasion, and metastasis[9]. HIF-1α is degraded rapidly in normoxic conditions but is stabilized and activated during hypoxia. In addition, HIF-1α has been shown to be overexpressed in more than 70% of solid tumors[8] and is associated with tumor progression and poor prognosis[9]. With rapid growth of solid tumors, cancer cells are in a hypoxic microenvironment, which in turn promotes tumor cells to lose adhesion, affix to the extracellular matrix (ECM), degrade the ECM, and invade into adjacent tissues[10]. This series of events will promote epithelial-mesenchymal transition (EMT)[11]. During invasion, tumor cells produce proteases that degrade the ECM and basement membrane (BM). Among proteases, matrix metalloproteinase-2 (MMP-2) can degrade the ECM and plays a critical role in tumor invasion[12]. In addition, HIF-1α can downregulate E-cadherin but upregulate MMP-2 to enhance tumor invasion[13,14]. Previous studies have shown that MMP-2 protein is highly expressed in colorectal cancer tissues compared to normal tissues and is associated with lymph node and liver metastases of colorectal cancer[15-17]. E-cadherin is a calcium-dependent cell-cell adhesion glycoprotein; loss of E-cadherin function or expression has been implicated in cancer progression and metastasis[18].

In this study, we analyzed the protein expression of HIF-1α, MMP-2, and E-cadherin in rectal cancer tissue specimens using immunohistochemistry to determine their association with patient clinicopathological data.

**SUBJECTS AND METHODS**

**Tissue Specimens**

In this study, we recruited a total of 88 rectal adenocarcinoma patients from The First Affiliated Hospital of Chongqing Medical University between March 2008 and April 2010. The rectal carcinoma patients underwent a curative tumor resection and had received neither chemotherapy nor radiation therapy before surgery. Among them, 39 patients were male and 49 were female with a mean age of 54.8 years; 14 cases were well-differentiated adenocarcinoma, 60 cases were moderately differentiated adenocarcinoma, and 14 cases were poorly differentiated adenocarcinoma. In addition, we obtained 12 distant normal rectal tissues from some of these patients as normal controls. Our institute review board approved the current study, and an informed consent form was signed by each participant.

**Immunohistochemistry**

To detect protein expression of HIF-1α, MMP-2, and E-cadherin, we performed immunohistochemical staining with the standard streptavidin-peroxidase method and the S-P Histostain-Plus Kit (Beijing Zhongshan Biotechnology Co., Ltd., Beijing, China) according to the manufacturer’s instructions. Sections were subjected to routine deparaffinization and rehydration. Antigen retrieval was achieved by microwaving the sections in 0.01 M citrate buffer for 10 min and then cooling them to the room temperature for 30 min. Endogenous peroxidase activity was blocked by incubation of the sections in 3% hydrogen peroxide/methanol solution for 20 min, and any non-specific binding was blocked by incubation with 5% bovine serum albumin in phosphate-buffered saline (PBS) at room temperature (RT). After three PBS washes, the sections were incubated with the first antibody overnight at 4°C.

A murine monoclonal anti-human HIF-1α antibody (diluted 1:200, Clone H1apha67, Abcam, Boston, MA, USA), a rabbit polyclonal anti-MMP-2 antibody (diluted 1:100; BA0571, Boster Bio-engineering Ltd. Company, Wuhan, China), and a rabbit polyclonal anti-E-cadherin antibody (diluted 1:100; BA0475, Boster Bio-engineering Ltd. Company, Wuhan, China) were used as the primary antibodies. After incubation with IgG2b-conjugated horseradish peroxidase, the positive signal was developed with 3,3-diaminobenzidine tetrahydrochloride solution in Tris–HCl buffer (pH 7.6) containing 0.02% hydrogen peroxide. The sections were then counterstained with hematoxylin and mounted. Negative controls were incubated with PBS instead of the specific primary antibody.

**Review and score of immunostained tissue sections**

The immunostained tissue sections were independently reviewed and scored by two pathologists. According to the staining intensity and percentage of tumor cells stained by these three markers, each tissue section was categorized in a semiquantitative manner. The staining intensity in tumor cells was scored as follows: 0 (negative), 1 (weakly positive), 2 (moderately positive), and 3 (strongly positive). The percentage of positive tumor cells was scored as follows: 0 (< 5% positive cells), 1 (6 - 25% positive cells), 2 (26 - 50% positive cells), 3 (51 - 75% positive cells), and 4 (> 75% positive cells). A cumulative sum was then obtained by multiplying the intensity score and the percentage score to obtain a final staining score[19]: 0 (negative), + (1 - 4), ++ (5 - 8), and +++ (9 - 12). For statistical analysis, tumors with a final staining score less than or equal to 4 were defined as negative, while tumors with a score greater than or equal to 5 were defined as positive.
All statistical analyses were performed by using the SPSS 11.0 software package (version 11.0, SPSS Inc., Chicago, IL, USA). Clinicopathological factors associated with expression of HIF-1α, MMP-2, and E-cadherin were analyzed using the X² test. Survival curves were plotted according to the Kaplan-Meier method, and the p-value was determined by using the log-rank test. Differences with p < 0.05 were considered statistically significant.

**RESULTS**

**Expression of HIF-1α, MMP-2, and E-cadherin in rectal carcinoma tissue specimens**

In this study, we analyzed the expression of these three-tumor invasion and metastasis-related proteins in normal and rectal cancer tissue specimens. Our data showed that neither HIF-1α nor MMP-2 protein was expressed in 12 normal tissue samples (Fig. 1A & C), but E-cadherin protein was strongly expressed in these normal tissue samples (Fig. 1E). In contrast, HIF-1α protein was expressed in the cytoplasm of 65.9% (58 out of 88 cases) of tumor tissues (Fig. 1B), while MMP-2 protein was expressed in the cytoplasm of 71.6% (63 out of 88 cases) of peripheral tumor tissues (Fig. 1D). However, E-cadherin protein was just weakly or moderately expressed in the cytoplasm of 28.4% (25 out of 88 cases) of tumor tissues (Fig. 1F). The differences of these three protein expressions between normal and tumor tissues were statistically significant (p < 0.01).

**Association of HIF-1α, MMP-2, and E-cadherin expression with clinicopathological factors from rectal cancer patients**

Next, we associated the expression of these three proteins with clinicopathological data from the patients and found that altered expression of HIF-1α
and MMP-2 proteins was associated with lymph node and distant metastases and Duke’s classification (p < 0.05), while loss of E-cadherin protein expression was associated with tumor de-differentiation and lymph node and distant metastases. However, there was no association between their expressions and age or sex of the patients (p > 0.05; Table 1).

Since these three proteins are all related to tumor invasion and metastasis, aberrant expression of these proteins separately or in combination was associated with clinicopathological data from the patients. Our data showed that the rate of lymph node metastasis was significantly greater (66.7%) in patients with tumors expressing both HIF-1α and MMP-2 than in those patients (26.8%) with tumors expressing only one of these two proteins. Similarly, the rate of lymph node metastasis was significantly greater in patients with tumors positively expressing HIF-1α but without E-cadherin protein expression. However, there was no significant difference between lymph node metastasis and MMP-2 expression but loss of E-cadherin expression (p = 0.108; Table 2).

Furthermore, the rate of distant metastasis tended to be greater in rectal cancer patients with expression of both HIF-1α and MMP-2 (p < 0.01; Table 2) or expression of HIF-1α but loss of E-cadherin expression (p < 0.01; Table 2). In contrast, the combination of MMP-2 (+) and E-cadherin (-) did not increase the rate of distant metastasis (p = 0.066; Table 2). We also found an association of rectal cancer distant metastasis with the combination of HIF-1α (+), MMP-2 (+), and E-cadherin (-). In particular, out of the 20 cases with distant metastasis, 15 cases showed HIF-1α (+), MMP-2 (+), and E-cadherin (-) (p < 0.001; Table 2).

<table>
<thead>
<tr>
<th>Clinicopathological factors</th>
<th>N</th>
<th>HIF-1α (+) (%)</th>
<th>p-value</th>
<th>MMP-2 (+) (%)</th>
<th>p-value</th>
<th>E-cadherin (-) (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 55 years old</td>
<td>39</td>
<td>28 (71.8)</td>
<td>0.368</td>
<td>30 (76.9)</td>
<td>0.252</td>
<td>25 (64.1)</td>
<td>0.234</td>
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<tr>
<td>≥ 55 years old</td>
<td>49</td>
<td>30 (61.2)</td>
<td></td>
<td>32 (65.3)</td>
<td></td>
<td>38 (77.6)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>48</td>
<td>34 (70.8)</td>
<td>0.367</td>
<td>30 (62.5)</td>
<td>0.101</td>
<td>36 (75.0)</td>
<td>0.483</td>
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<tr>
<td>Female</td>
<td>40</td>
<td>24 (60.0)</td>
<td></td>
<td>32 (80.0)</td>
<td></td>
<td>27 (67.5)</td>
<td></td>
</tr>
<tr>
<td>Differentiation degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>14</td>
<td>10 (71.4)</td>
<td>0.434</td>
<td>9 (64.3)</td>
<td>0.146</td>
<td>5 (35.7)</td>
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<tr>
<td>Moderate</td>
<td>60</td>
<td>37 (61.7)</td>
<td></td>
<td>43 (71.7)</td>
<td></td>
<td>45 (75.0)</td>
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<tr>
<td>Poor</td>
<td>14</td>
<td>11 (78.57)</td>
<td></td>
<td>10 (71.4)</td>
<td></td>
<td>13 (92.9)</td>
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<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>20</td>
<td>18 (90.0)</td>
<td>0.014</td>
<td>18 (90.0)</td>
<td>0.048</td>
<td>19 (95.0)</td>
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<tr>
<td>Negative</td>
<td>68</td>
<td>40 (58.8)</td>
<td></td>
<td>44 (64.7)</td>
<td></td>
<td>44 (65.7)</td>
<td></td>
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<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>38</td>
<td>32 (84.2)</td>
<td>0.002</td>
<td>32 (84.2)</td>
<td>0.018</td>
<td>33 (86.8)</td>
<td>0.008</td>
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<td>Negative</td>
<td>50</td>
<td>26 (52.0)</td>
<td></td>
<td>30 (60.0)</td>
<td></td>
<td>30 (60.0)</td>
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<tr>
<td>Duke’s classification</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A, B</td>
<td>40</td>
<td>18 (45.0)</td>
<td>0.000</td>
<td>21 (52.5)</td>
<td>0.001</td>
<td>27 (67.5)</td>
<td>0.483</td>
</tr>
<tr>
<td>C, D</td>
<td>48</td>
<td>40 (83.3)</td>
<td></td>
<td>41 (85.4)</td>
<td></td>
<td>36 (75.0)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Association of the combined expression of HIF-1α, MMP-2, and E-cadherin with lymph node metastasis and distant metastasis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lymph node metastasis</th>
<th>Distant metastasis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>p-value</td>
</tr>
<tr>
<td>HIF-1α/MMP-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either HIF-1α (+) or MMP-2 (+)</td>
<td>30</td>
<td>11</td>
<td>0.001</td>
</tr>
<tr>
<td>Both HIF-1α (+) and MMP-2 (+)</td>
<td>13</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>HIF-1α/E-cadherin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either HIF-1α (+) or E-cadherin (-)</td>
<td>24</td>
<td>12</td>
<td>0.014</td>
</tr>
<tr>
<td>Both HIF-1α (+) and E-cadherin (-)</td>
<td>16</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>MMP-2/E-cadherin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either MMP-2 (+) or E-cadherin (-)</td>
<td>19</td>
<td>11</td>
<td>0.108</td>
</tr>
<tr>
<td>Both MMP-2 (+) and E-cadherin (-)</td>
<td>21</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>HIF-1α/MMP-2/E-cadherin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either HIF-1α (+), MMP-2 (+), or E-cadherin (-)</td>
<td>40</td>
<td>17</td>
<td>0.000</td>
</tr>
<tr>
<td>All HIF-1α (+), MMP-2 (+), and E-cadherin (-)</td>
<td>10</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>
Next, we associated the expression of these three proteins with patient survival using Kaplan-Meier curve analysis. Our data showed that the overall 5-year survival rate in HIF-1α (+) and MMP-2 (+) patients was significantly less than that in patients with single positive protein expression [HIF-1α (+) or MMP-2 (+); 39.3% Vs 77.8%, p = 0.011; Fig. 2A]. Similarly, the overall 5-year survival rate in patients with HIF-1α (+) and E-cadherin (-) expression was significantly less than that of patients with a single protein alteration [HIF-1α (+) or E-cadherin (-); 44.4% Vs 90%, p = 0.045; Fig. 2B]. Again, the overall 5-year survival rate was significantly less in patients with HIF-1α (+), MMP-2 (+), and E-cadherin (-) than that of patients with one or two alterations [HIF-1α (+), MMP-2 (+), or E-cadherin (-); 25% Vs 77.8%, p = 0.0046; Fig. 2C). In contrast, the overall 5-year survival rate was not statistically significant between patients with MMP-2 (+) and E-cadherin (-) and with a single alteration [MMP-2 (+) or E-cadherin (-); 48.5% Vs 69.2%, p = 0.162).

**DISCUSSION**

Tumor invasion and metastasis are complex processes. For example, initiation of tumor metastasis involves the acquisition of a motile phenotype in tumor cells to disrupt the integrity of the BM, which interacts directly with the ECM to eventually penetrate the lymph or blood vessel walls and form metastatic tumors[20]. Usually, after the diameter of a solid tumor exceeds 1 - 2 mm³, dispersion will not be able to satisfy the need for tumor cell survival and growth; thus, regional hypoxia results, which in turn induces a series of changes in gene transcription and protein expression in response to the hypoxic environment. Therefore, these events not only promote angiogenesis and change the ECM environment but also promote tumor invasion and metastasis. EMT induced by hypoxia is based on downregulation of E-cadherin expression and transformation of the ECM, the main features of which include the loss of interstitial characteristics and the acquisition of epithelial characteristics[21]. EMT has a close relationship with tumor cell invasion in situ and distant metastasis. All of these phenomena are associated with alteration of these three protein expressions.

Indeed, as one of the most important transcription factors mediating hypoxia-induced cellular responses, HIF-1 can promote tumor angiogenesis and glycolysis[22], thereby playing a critical role in adaptation of tumor cells to hypoxia[23,24]. Increasing evidence has implicated HIF-1α activity in tumor cell growth and metastasis. Previous studies have demonstrated HIF-1α overexpression in many types of cancer compared with the respective normal tissues, including colon, breast, gastric, lung, skin, ovarian, pancreatic, prostate, and renal cancer[25,26]. In the present study, we found that HIF-1α expression was significantly elevated in rectal carcinoma tissues compared to that of normal tissue and that HIF-1α
expression was associated with lymph node and distant metastases and tumor stages, which is consistent with the observations by Simiantonaki et al[27].

Furthermore, MMP-2 has been shown to be regulated by HIF-1α[28]. MMP-2 is a gelatinase (also called type IV collagenase), the main component of the BM and ECM[29,30]. Li et al[31] have demonstrated that exposure to hypoxic conditions significantly enhances MMP-2 expression in fibroblast-like synoviocytes and knockdown or inhibition of HIF-1α expression blocks hypoxia-mediated MMP-2 expression and cell migration and invasion. In addition, Jing et al[32] have reported that hypoxic conditions also suppress E-cadherin expression but enhance MMP-2 expression by favoring esophageal carcinoma cell migration and invasion via HIF-1α activation. Furthermore, elevated levels of MMP-2 have been found in breast, brain, ovarian, pancreatic, colorectal, bladder, prostate, and lung cancers and melanoma[33,34], and its expression and activity are often associated with tumor aggressiveness and a poor prognosis. Our current results showed that expression of both HIF-1α and MMP-2 proteins was highly associated with lymph node and distant metastases as compared to that of a single protein alone. Therefore, these proteins were able to predict poor prognosis and short survival rate in rectal carcinoma patients.

In addition, E-cadherin is a major component of the adherent junctions that maintain epithelial integrity and polarity. Loss of E-cadherin is a hallmark and functional requirement of EMT. Hypoxia induces EMT by HIF-dependent upregulation of transcription repressors of E-cadherin expression[35]. Many studies have shown that during cancer development, E-cadherin expression is mostly lost or reduced and that loss of its expression is associated with the degree of tumor de-differentiation, clinical pathological stage, and prognosis[36]. For example, Turashvili et al[37] have shown that loss of E-cadherin expression was found in 42.9% of breast cancer tissues and was associated with lymph node and distant metastasis, advanced TNM stages, and poor prognosis. Thus, E-cadherin is an independent predictor in breast cancer prognosis. Blechschmidt et al[38] have reported that loss of E-cadherin expression was found in 25% of original ovarian cancers and 22% of metastatic ovarian cancers in a retrospective study and that loss of E-cadherin protein expression was associated with ovarian cancer metastasis. Moreover, loss of E-cadherin expression has been associated with tumor invasion and metastasis in gastric cancer[39,40], pancreatic cancer[41], and bladder cancer[42]. Our current study confirmed these previous data. More importantly, the combined altered expression of HIF-1α, MMP-2, and E-cadherin was associated with rectal cancer clinicopathological data. We found that 21 out of 38 (70%) of rectal cancers with these three protein alterations had lymph node metastasis, and 17 out of 20 (85.0%) had distant metastasis. The overall 5-year survival rate in HIF-1α (+)/MMP-2 (+)/E-cadherin (-) patients was significantly less than that in patients with one or two alterations. Therefore, our current study demonstrated the usefulness of the combination of these three proteins to predict rectal carcinoma progression and patient survival. However, further studies will be needed to verify our current data and investigate whether the target of these genes could effectively control rectal carcinoma in the clinic.

ACKNOWLEDGMENT
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Conflict of Interest Statement: The authors disclose no conflicts of interest.

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expression increases during colorectal carcinogenesis. U, Kirkpatrick CJ. Hypoxia-inducible factor 1 alpha
Simiantonaki N, Taxeidis M, Jayasinghe C, Kurzik-Dumke U, Kirkpatrick CJ. Hypoxia-inducible factor 1 alpha
25. Koh MY, Spivak-Kroizman TR, Powis G. HIF-1alpha and cancer therapy. Recent Results Cancer Res 2010; 180:15-34.
ABSTRACT

Objectives: To investigate the prevalence of PER-1, PER-2, GES, IMP-1, VIM-2, OXA-23, and OXA-24 type beta-lactamases in carbapenem-resistant Acinetobacter baumannii isolates, in view of the fact that Beta-lactamase production is the most important mechanism of acquired beta-lactam resistance in Gram-negative pathogens.

Main Outcome Measure: Prevalence rate of beta-lactamase genes in carbapenem-resistant A. baumannii isolates

Results: GES beta-lactamase was found in 59 isolates (60.20%). PER-1 was found in eight isolates (8.16%). IMP-1 was found in five isolates (5.10%). OXA-24 was detected in two isolates (2.04%). No isolate possessed VIM-2, PER-2, or OXA-23 beta-lactamase genes.

Conclusion: This study indicates that the GES type beta-lactamases are the most prevalent among carbapenem-resistant A. baumannii isolates in our hospital. Screening for beta-lactamases and strict infection control for these isolates will help prevent further spread of resistance.
The isolates were obtained from clinical specimens such as tracheal aspirates, sputum, blood, urine, wound, and cerebrospinal fluid samples. The isolates were identified using conventional techniques (Gram-stained morphology, growth on MacConkey agar, lack of oxidase activity, lack of motility, resistance to penicillin and the oxidative-fermentative test)\(^6\) and/or the API 20NE identification system (BioMerieux, Marcy l’Etoile, France).

Antimicrobial susceptibility was determined via the disc diffusion technique in accordance with the guidelines established by the Clinical and Laboratory Standards Institute (CLSI)\(^7\). The following antibiotic discs (Bioanalyse, Turkey) were used: amikacin (30 µg), gentamicin (10 µg), tobramycin (10 µg), ceftazidime (30 µg), cefotaxime (30 µg), ceftiraxone (30 µg), cefepime (30 µg), ampicillin-sulbactam (10/10 µg), trimethoprim-sulfamethoxazole (1.25 /23.75 µg), ceftazidime (30 µg), cefotaxime (30 µg), ceftriaxone (30 µg), gentamicin (10 µg), tobramycin (10 µg), amikacin (30 µg), and colistin (10 µg).

### Molecular studies

All carbapenem-resistant isolates were subjected to polymerase chain reaction (PCR) assays for the detection of beta-lactamase genes. Total DNA was prepared as the template for PCR. Genomic DNA of the clinical isolates was extracted after 10 min of boiling followed by centrifugation. The primers used for amplification were designed by Sigma Genosys (Sigma Aldrich, Inc., St. Louis, MO, USA) and are listed in Table 1.

<table>
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<tr>
<th>Primer pairs</th>
<th>Sequence (5'-3')</th>
<th>Amplicon size (bp)</th>
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<tbody>
<tr>
<td>PER-1F</td>
<td>GCAAAGTGGCAGCAGCA</td>
<td>855</td>
</tr>
<tr>
<td>PER-1R</td>
<td>CACCGGATCCCGACGTC</td>
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<tr>
<td>PER-2F</td>
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<tr>
<td>OXA-23F</td>
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<tr>
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<tr>
<td>GES-D</td>
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PCR was used to detect IMP-1 and VIM-2. PCR was performed with 2 µl of heat-extracted DNA template, 20 pmol of each primer, a premix containing 1 U of Taq DNA polymerase, and other ingredients in a total volume of 20 µl. A thermal cycler (MyCycler; Bio-Rad, Philadelphia, PA, USA) was used under the following conditions: 94 ºC for 5 min, 25 cycles of 94 ºC for 30 s, 56 ºC for 30 s, and 72 ºC for 45 s, followed by 72 ºC for 7 min\(^1\). The PCR products were analysed by electrophoresis using 1.5% agarose. The PCR products of 780 bp (for VIM-2) and 488 bp (for IMP-1) were visualized by agarose gel electrophoresis.

The primers GES-C and GES-D were used under standard PCR conditions to amplify a 371-bp product. The PCR mixture comprised 20 pmol of each primer, 5 µl of Taq DNA reaction buffer, 3 µl of 25 mM MgCl\(_2\), 1 µl of dNTP mixture, 1.25 U of Taq DNA polymerase (Fermentas, Vilnius, Lithuania), 2 µl of DNA template, and distilled water to a final reaction volume of 50 µl. The PCR program for GES consisted of an initial denaturation step at 95 ºC for 2 min followed by 35 amplification cycles, each comprising a denaturation step at 95 ºC for 30 s, followed by an annealing step at 50 ºC for 1 min and an extension step at 72 ºC for 1 min. After completion of the 35 amplification cycles, an extension step was performed at 72 ºC for 5 min\(^6\). The PCR products were visualized by electrophoresis at 100 V for 45 min in a 0.8% agarose gel containing ethidium bromide. The amplicon size was verified by comparison with a 100-bp DNA ladder.

The PCR program for PER-1 and PER-2 consisted of an initial denaturation step at 96 ºC for 30 s followed by 30 cycles of DNA denaturation at 96 ºC for 40 s, primer annealing at 50 ºC for 30 s, and a primer extension step at 72 ºC for 30 s. A final extension step was carried out at 72 ºC for 10 min. The PCR mixture comprised 20 pmol of each primer, 2.5 µl of Taq DNA reaction buffer, 1.5 mM MgCl\(_2\), 10 µM of each dNTP, 1.25 U of Taq DNA polymerase, 2 µl of DNA template and distilled water to a final reaction volume of 25 µl. The expected PCR products of 855 bp (for PER-1) and 939 bp (for PER-2) were verified by agarose gel electrophoresis\(^9\).

OXA-23 and OXA-24 were amplified by pre-denaturation of the reaction mixture for 5 min at 95 ºC; this was followed by 35 cycles of 95 ºC for 20 s, 59 ºC for 40 s, and 72 ºC for 30 s, and a final elongation step for 5 min at 72 ºC\(^1\). The PCR mixture comprised 20 pmol of each primer, 2.5 µl of Taq DNA reaction buffer, 1.5 mM MgCl\(_2\), 10 µM of each dNTP, 1.25 U of Taq DNA polymerase (Fermentas), 2 µl of DNA template, and distilled water to a final reaction volume of 25 µl. The expected PCR products of 1058 bp (for OXA-23) and 825 bp (for OXA-24) were verified by agarose gel electrophoresis. A MYCycler (Bio-Rad) was used for all PCR cycles.

### RESULTS

Forty-eight (49.0%), 17 (17.3%), 17 (17.3%), seven (7.2%), seven (7.2%), and two (2.0%) isolates among the total of 98 were obtained from tracheal aspirates,
sputum, blood, urine, wound, and cerebrospinal fluid samples, respectively. The results of our antimicrobial susceptibility testing of the 98 isolates revealed that the prevalence of resistance to ceftriaxone, cefotaxime, ceftazidime, cefepime, tazobactam-piperacillin, and piperacillin (100.0%, 97.9%, 95.9%, 95.9%, 89.7%, and 86.7%, respectively) were high. Among the 98 isolates, 78.5%, 75.5%, and 64.2% were resistant to amikacin, gentamicin, and tobramycin, respectively, and 76.5%, 76.5%, 85.7%, and 80.6% were resistant to ampicillin-sulbactam, tetracycline, ciprofloxacin, and trimethoprim-sulfamethoxazole, respectively. All isolates were resistant to imipenem and meropenem. All isolates were susceptible to colistin (Table 2).

### Beta-lactamase genes

PCR for the detection of beta-lactamase genes was performed on all 98 isolates. GES, PER-1, IMP-1, OXA-24 genes were detected by PCR among 59 (60.20%), 8 (8.16%), 5 (5.10%), and 2 (2.04%) isolates of *A. baumannii*, respectively. Four isolates were positive for both IMP-1 and GES. Two isolates were positive for both PER-1 and GES. No isolate was positive for VIM-2, PER-2, or OXA-23. Examples of the PCR results are presented in Fig. 1 and 2.

### DISCUSSION

*A. baumannii* is recognised as an important opportunistic Gram-negative pathogen and is frequently associated with nosocomial outbreaks worldwide[10]. Multidrug resistance (MDR) is increasingly reported in these pathogens and is posing a threat to hospitalized patients due to the limitation of therapeutic options. The acquisition of MDR is related to environmental contamination and contact with transiently colonized health care providers. Carbapenems have been the drug of choice

### Table 2: Antimicrobial resistance of *A. baumannii* strains

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>98 (100.0)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>98 (100.0)</td>
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<tr>
<td>Ampicillin-sulbactam</td>
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<tr>
<td>Cefazidime</td>
<td>94 (95.9)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>96 (97.9)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>98 (100.0)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>94 (95.9)</td>
</tr>
<tr>
<td>Tazobactam-piperacillin</td>
<td>88 (89.7)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>77 (78.5)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>76 (75.5)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>63 (64.2)</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>85 (86.7)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>84 (85.7)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>79 (80.6)</td>
</tr>
<tr>
<td>Tetracyclin</td>
<td>75 (76.5)</td>
</tr>
<tr>
<td>Colistin</td>
<td>0 (00.0)</td>
</tr>
</tbody>
</table>

**Fig. 1:** PCR amplification of GES and PER-1.
M: DNA ladder 100bp; 1,2: PCR products GES (371bp); 3: Negative control; 4,5: PCR products PER-1 (855bp)

**Fig. 2:** PCR amplification of IMP-1 and OXA-24.
M: DNA ladder 100bp; 1: PCR products IMP-1(488 bp); 2 and 5: PCR products OXA-24(825bp) 3,4: Negative control

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A. baumannii is recognised as an important opportunistic Gram-negative pathogen and is frequently associated with nosocomial outbreaks worldwide[10]. Multidrug resistance (MDR) is increasingly reported in these pathogens and is posing a threat to hospitalized patients due to the limitation of therapeutic options. The acquisition of MDR is related to environmental contamination and contact with transiently colonized health care providers. Carbapenems have been the drug of choice
for treatment of infections caused by *A. baumannii*. However, in recent years, the number of isolates showing resistance to carbapenems has increased worldwide. This is mediated by the lack of drug penetration and/or carbapenem-hydrolyzing beta-lactamases and metallo-beta-lactamases[9,11]. In this study, the prevalence of the PER-1, PER-2, GES, IMP-1, VIM-2, OXA-23, and OXA-24 beta-lactamase genes were investigated in carbapenem-resistant *A. baumannii* isolates.

The OXA-type carbapenemases have been described in *A. baumannii*. Outbreaks of OXA-23-producing *Acinetobacter* have been reported in various regions of the world[10,11,12,13]. Numerous studies have reported that OXA-23 is the most frequent type of carbapenemase identified among the carbapenem resistant *A. baumannii*[10,11,13,14]. In contrast, OXA-23 was not detected in *A. baumannii* isolates, in our study. Sari *et al*[15] reported that among 450 multidrug resistant *A. baumannii*, OXA-24-like gene was detected in 23 isolates. Amudhan *et al*[16] reported that among 116 *A. baumannii*, OXA genes were detected in 106 isolates. In the same study, OXA-24-like gene was detected in two isolates. Similarly, in this study, two *A. baumannii* isolates were found to produce OXA-24.

Some *Acinetobacter* strains express class B metallo-beta-lactamases (MBLs), such as VIM and IMP, which hydrolyse a broad array of antimicrobial agents, including carbapenemases. MBLs pose a significant threat because they are often located on mobile genetic elements easily transferred among bacteria. Many variants exist, and both IMP and VIM have been found worldwide in a wide variety of bacterial species, including *Acinetobacter* spp.[16].

The VIM and IMP enzymes hydrolyse a broad spectrum of beta-lactams, including oxyiminocephalosporins and carbapenems[17]. VIM enzymes have been identified very rarely in *A. baumannii*, which is represented by only VIM-2 reported in Korea[17,18]. The IMP and VIM variants confer a high level of carbapenem resistance to *A. baumannii* isolates, as well as resistance to all beta-lactams, except aztreonam, because of their strong hydrolytic efficiency against these antibiotics[17]. Sung *et al*[19] reported that 15 of 16 *A. baumannii* with MBL genes harboured IMP-1, and only one of these isolates harboured VIM-2. In Karthika *et al*[19] study, while IMP-1 gene was detected in 23 (42%) isolates, VIM-2 was not detected in *A. baumannii* isolates. In Shahcheragh *et al*[20] study, the VIM-2 and IMP genes were not detected in *A. baumannii* isolates. Similarly, in this study, VIM-2 was not detected in any of the isolates. IMP-1 was detected in five isolates (5.10%).

PER-1 is an extended spectrum beta lactamase (ESBL) active against penicillins, cefotaxime, ceftazidime, and aztreonam, but has no significant activity against carbapenems. It is commonly detected in *Acinetobacter* spp. in Turkey[21]. About 78% of imipenem-resistant *Acinetobacter* spp. isolates in China were found to produce a PER-1-like enzyme[22]. The PER-1-producing isolates responsible for the outbreak were highly resistant to ampicillin, ampicillin-sulbactam, piperacillin, piperacillin-tazobactam, cephalotin, cefoxitin, cefoperazone, ceftazidime, cefotaxime, cefepime, and aztreonam; piperacillin resistance was presumably mediated by overexpression of chromosomal AmpC, because PER-1 shows poor activity with this substrate and good activity with other beta-lactams. Therapeutic management of infections due to MDR PER-1-producing *A. baumannii* isolates was problematic compared to that of non-producing strains[9]. PER-1 beta-lactamase was expressed by most *P. aeruginosa* and *Acinetobacter* spp. isolates in Turkey[22]. In this study, 8.16% of imipenem-resistant *Acinetobacter* spp. isolates were found to produce PER-1. No isolate was positive for PER-2.

Class A beta-lactamases that can hydrolyse carbapenems have been reported. Most of these enzymes also hydrolyse oxyimino-cephalosporins. From a clinical point of view, it is not practical to categorize these enzymes as ESBLs because carbapenems are regarded as the drug of choice for ESBL-producing organisms. GES enzymes pose a more difficult problem; GES-1 possesses hydrolytic activity similar to the classic class A ESBLs and is inhibited by beta-lactamase inhibitors, and is generally classified as an ESBL. However, some GES variants, such as GES-2 and GES-4, also exhibit hydrolytic activity against carbapenems[13].

ESBLs of the GES type have been reported with increasing frequency in Gram-negative rods. The GES-1 beta-lactamase possesses a hydrolysis profile similar to those of classical clavulanic acid-inhibited Ambler class A ESBLs, including penicillins and expanded-spectrum cephalosporins, but not cephamycins and carbapenems, which are also inhibited by clavulanic acid and tazobactam. Unlike most ESBLs, GES-1 does not possess hydrolytic activity toward aztreonam. GES-2 beta-lactamase also hydrolyses carbapenems and is less susceptible to inhibitors[21]. GES-2, GES-4, and GES-5 class A beta-lactamases show weak imipenem hydrolysis[4]. Among class A enzymes, GES enzymes, including GES-2, generally demonstrate lower affinities for beta-lactamase inhibitors. GES-2, which differs from GES-1 by a single Gly170Asn substitution located inside the omega loop of the catalytic site, additionally hydrolyses carbapenems, though at a low level[22]. GES-2 may confer resistance to imipenem, most likely when associated with a membrane impermeability-mediated
resistance mechanism\textsuperscript{[23]}]. Additionally, Bonnin et al\textsuperscript{[23]} reported that GES-14 was identified in carbapenem-resistant \textit{A. baumannii} isolates. Shahcheraghi et al\textsuperscript{[5]} reported that among 100 \textit{A. baumannii} isolates, GES-1 was detected in two isolates. In our study, GES was found in 59 (60.20\%) out of 98 imipenem-resistant isolates. The GES type beta-lactamases were the most prevalent in carbapenem-resistant \textit{A. baumannii} isolates in our hospital.

MBLs producing isolates are resistant to many antibiotics, signalling the need for the development of new, potent therapeutic agents with novel modes of action. Alternative, older, more toxic drugs, such as polymyxin B and colistin, are being used\textsuperscript{[24]} in our study, all isolates were susceptible to colistin.

Despite its reputation for relatively low virulence, MDR \textit{Acinetobacter} infection poses a formidable threat to patients. The cause of many outbreaks, this organism is increasingly endemic in the healthcare setting. Antimicrobial resistance is increasing, likely as a result of both the emergence of resistance in the context of antimicrobial pressure and the healthcare-associated transmission of drug-resistant strains. MDR \textit{Acinetobacter} infections have an extremely high crude mortality rate and occur most frequently in severely ill patients. Treatment options are limited. Carbapenems and colistin are the agents of choice for most drug-resistant infections. The roles of other agents and combination therapy remain unclear\textsuperscript{[10]}.

Antimicrobial resistance greatly limits the therapeutic options for patients who are infected with this organism, especially if isolates are resistant to the carbapenem class of antimicrobial agents. Because therapeutic options for MDR \textit{Acinetobacter} infection are limited, the development or discovery of new therapies, well-controlled clinical trials of existing antimicrobial regimens and combinations, and greater emphasis on the prevention of health care-associated transmission of MDR \textit{Acinetobacter} infection are essential. Further investigations of the efficacy and cost-effectiveness of various infection control strategies to prevent transmission of MDR \textit{Acinetobacter} infection are needed. This indicates the importance of laboratory detection of beta-lactamase-producing isolates for proper treatment of patients and for control of nosocomial spread of these strains.

**CONCLUSION**

Our data indicate that GES type beta-lactamases are the most prevalent among carbapenem-resistant \textit{A. baumannii} isolates in our hospital. Therefore, it is essential to rapidly screen for beta-lactamase genes in \textit{A. baumannii}. This would facilitate selection of appropriate therapies and initiation of effective infection control strategies to prevent further dissemination.

Besides, multi-facility \textit{A.baumannii} outbreaks can be also sustained by inter-hospital transfer of colonized patients. These outbreaks emphasize the need to adopt surveillance and infection control programmes to prevent colonization and infection by MDR \textit{A.baumannii} in the hospital setting. These programmes would include the study of global epidemiology of MDR \textit{A.baumannii} using molecular typing of bacterial isolates and characterization of antibiotic resistance in order to control the spread of \textit{A.baumannii} infections over a wide geographic region. Epidemiologic clarification of an outbreak caused by carbapenem-resistant \textit{Acinetobacter} species requires both genomic species identification and the detection of carbapenemase gene-associated genetic structures.

**REFERENCES**


Prevalence of Blood Borne Viruses in the Dialysis Unit, Mubarak Al-Kabeer Hospital, Kuwait

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1Virology Unit, Department of Pathology, Mubarak Al-Kabeer Hospital, Kuwait
2Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait
3Department of Nephrology, Mubarak Al-Kabeer Hospital, Kuwait

ABSTRACT

Objectives: Transmission of hepatitis B virus (HBV), hepatitis C virus (HCV) and human immune deficiency virus (HIV) does take place in dialysis units worldwide at different rates. The aim of this study was to identify the prevalence rates of HBV, HCV and HIV in the dialysis unit, Mubarak Al-Kabeer Hospital (MAKH), Kuwait.

Design: Retrospective study

Settings: Dialysis Unit and Virology Unit, MAKH, Kuwait

Subjects: In 2012, a total of 1369 samples from adult patients on dialysis at MAKH were screened.

Intervention: HBV, HCV and HIV were screened for HBV surface antigen (HBsAg) (ARCHITECT HBsAg Qualitative II 2011, Abbott), HCV antibodies (Anti-HCV) (ARCHITECT Reagent Kit 2011, Abbott) and HIV antigen and antibody (HIV Ag/Ab) (ARCHITECT HIV Ag/Ab Combo Reagent Kit 2011, Abbott), respectively

Main Outcome Measures: Prevalence rates of HBV, HCV and HIV in the dialysis unit, MAKH, Kuwait

Results: HBV, HCV and HIV prevalence among dialyzed patients in the MAKH dialysis unit was 1.2%, 6.3% and 0.1% respectively.

Conclusion: This study, to our knowledge, is the only study providing recent data on blood borne viruses (BBVs) among patients in a dialysis unit in Kuwait. A multicenter study is recommended to determine the national prevalence of BBVs in all the dialysis unit of Kuwait.

KEY WORDS: blood borne viruses, dialysis, Kuwait, prevalence

INTRODUCTION

The use of dialysis as a treatment modality for those with renal failure and the gap between end stage renal disease (ESRD) and the number of those who are treated with transplantation has increased over recent years[1,2]. At the same time, the risk for possible blood borne viruses (BBVs) transmission, in that setting, has also increased[1,2]. BBVs that maybe transmitted in a dialysis unit include Hepatitis B virus (HBV), Hepatitis C virus (HCV) and human immune deficiency virus (HIV)[1,3]. The risk of transmission of BBVs is directly related to the immune suppressive status of patients, asymptomatic presentation of these BBVs infections as well as the non-adherence to strict infection control procedures[1,3,4].

Transmission of HBV has been and is still taking place in dialysis units worldwide at different rates[1,2,5]. The risk of HBV transmission with positive antigen is around 30%[1]. HBV can be transmitted vertically by cross contamination from the dialysis machine to the patient or horizontally between patients or staff[1,3,4]. That is why HBV infected dialyzed patients have segregated dialysis machines, staff and place[1-3]. Transmission of HCV in dialysis units varies throughout the world[1,3]. The prevalence of HCV would range from 3.9% in Glasgow to 71% in Kuwait[1,3]. The risk of transmission is around 3%[1]. HCV can be transmitted horizontally by cross contamination between patients or staff[1,3,4]. With strict adherence to infection control measures, there is no need for segregated dialysis machines[1,3,4]. Transmission of HIV caused by sharing of dialysis machines is considered rare but must remain as a potential risk[1,3,4].

Due to the lack of recent data in Kuwait, we decided to investigate the prevalence of HBV, HCV and HIV, among dialyzed patients in the dialysis unit at the Mubarak Al-Kabeer Hospital (MAKH), Kuwait.

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MATERIAL AND METHODS

Between the first of January and 31st of December, 2012, a total of 1369 blood samples were received by the virology unit from adult patients on dialysis at MAKH in Kuwait. In the Virology Unit at the MAKH, HBV, HCV and HIV, screening for dialyzed patients is undertaken every three months.

HBV, HCV and HIV were screened for HBV surface antigen (HBsAg) by ARCHITECT HBsAg Qualitative II 2011 (Abbott), HCV antibodies (Anti-HCV) by Architect Reagent Kit 2011 (Abbott) and HIV antigen and antibody (HIV Ag/Ab) by Architect HIV Ag/Ab Combo Reagent Kit 2011 (Abbott), respectively. This was performed using Architect i1000 system (Abbott). A positive screening result was followed by a confirmation method. HBsAg was confirmed by measuring the total core antibody by Architect, Architect Anti-Hbc II Reagent Kit (Abbott). Anti-HCV was confirmed by INNO-LIA HCV Score (Innogenetics) and HIV Ag/Ab was confirmed by INNO-LIA HIV I/II Score (Innogenetics).

SPSS software (version 17.0 for Windows; SPSS, Chicago, IL, USA) was used for all statistical analyses. For categorical variables, \( \chi^2 \)-test or Fisher’s exact test was used.

RESULTS

A total of 1369 blood samples were collected over a one year period. Five hundred and eighty-eight samples (43%) were from female and 781 samples (57%) were from male patients. Seven hundred and forty four (54.3%) samples were received from Kuwaiti patients and 625 (45.7%) samples from non-Kuwaitis.

Out of the 1369 blood samples, 1346 (93.3%) were negative, six (0.4%) were indeterminate and 17 (1.2%) were confirmed positive for HBV. Out of the 781 (57%) male patients, 762 (97.6%) were negative, four (0.5%) were indeterminate and 15 (1.9%) were confirmed positive for HBV. Out of the 588 (43%) female patients, 584 (99.3%) were negative, two (0.3%) were indeterminate and two (0.3%) were confirmed positive for HBV. In addition, out of the 744 (54.3%) Kuwaiti patients, 736 (98.9%) were negative, five (0.6%) were indeterminate and four (0.5%) were confirmed positive for HBV. Out of the 625 (45.7%) non-Kuwaiti patients, 610 (97.6%) were negative, two (0.3%) were indeterminate and 13 (2.1%) were confirmed positive for HBV (Table 1).

Out of the 1,369 samples, 1277 (93.3%) were negative, six (0.4%) were indeterminate and 86 (6.3%) were confirmed positive for HCV. Out of the 781 (57%) male patients, 709 (90.8%) were negative, five (0.6%) were indeterminate and 67 (8.6%) were confirmed positive for HCV. Similarly, out of the 588 (43%) female patients, 568 (96.6%) were negative, one (0.2%) was indeterminate and 19 (3.2%) were confirmed positive for HCV. In addition, out of the 744 (54.3%) Kuwaiti patients, 708 (95.2%) were negative, one (0.1%) was indeterminate and 35 (4.7%) were confirmed positive for HCV. Finally, out of the 625 (45.7%) non-Kuwaiti patients, 569 (91%) were negative, five (0.8%) were indeterminate and 51 (8.2%) were confirmed positive for HCV (Table 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>HBV N (%)</th>
<th>HCV N (%)</th>
<th>HIV N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1346 (98.3)</td>
<td>1277 (93.3)</td>
<td>1362 (99.5)</td>
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<tr>
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<tr>
<td>Male</td>
<td>762 (97.6)</td>
<td>709 (90.8)</td>
<td>776 (99.4)</td>
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<tr>
<td>Female</td>
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<td>568 (96.6)</td>
<td>586 (99.7)</td>
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<td>Indeterminate</td>
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<td>5 (0.4)</td>
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<td>708 (95.2)</td>
<td>740 (99.5)</td>
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<tr>
<td>Non-Kuwaiti</td>
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<td>569 (91)</td>
<td>622 (99.5)</td>
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<td>Positive</td>
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<td>86 (6.3)</td>
<td>2 (0.1)</td>
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<td>Gender</td>
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<tr>
<td>Male</td>
<td>15 (1.9)</td>
<td>67 (8.6)</td>
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<td>Female</td>
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<tr>
<td>Non-Kuwaiti</td>
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<td>51 (8.2)</td>
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<tr>
<td>p-value</td>
<td>0.020</td>
<td>0.012</td>
<td>0.557</td>
</tr>
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</table>

HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus

Furthermore, out of the 1369 blood samples, 1362 (99.5%) were negative, five (0.4%) were indeterminate and two (0.1%) were confirmed positive for HIV. Out of the 781 (57%) male patients, 776 (99.4%) were negative, three (0.4%) were indeterminate and two (0.3%) were confirmed positive for HIV. Out of the 588 (43%) female patients, 586 (99.7%) were negative, two (0.3%) were indeterminate and no samples were confirmed positive for HIV. In addition, out of the 744 (54.3%) Kuwaiti patients, 740 (99.5%) were negative, two (0.3%) were indeterminate and no samples were confirmed positive for HIV. In addition, out of the 744 (54.3%) Kuwaiti patients, 740 (99.5%) were negative, two (0.3%) were indeterminate and no samples were confirmed positive for HIV. In addition, out of the 744 (54.3%) Kuwaiti patients, 740 (99.5%) were negative, two (0.3%) were indeterminate and no samples were confirmed positive for HIV. In addition, out of the 744 (54.3%) Kuwaiti patients, 740 (99.5%) were negative, two (0.3%) were indeterminate and there were no positive confirmed samples for HIV (Table 1).

DISCUSSION

Between first of January and 31st of December 2012, 1369 samples were received from the dialysis unit at Mubarak Al-Kabeer Hospital. These samples were screened for HBV, HCV and HIV. The calculated prevalence for HBV, HCV and HIV are 1.2%, 6.3% and 0.1%, respectively.
The last calculated prevalence for HCV in dialysis patients in Kuwait, to the best of our knowledge, was 71% in 1993[1,5]. This figure is considerably higher than our calculated prevalence of 6.3%. This decrease is most likely due to the higher standards and adherence to strict infection control policies in the dialysis units and the screening of transfused blood and blood products for BBVs.

The prevalence of HBV among males (1.9%) was significantly higher when compared to HBV prevalence among females (0.3%) (p-value = 0.018). Considering HBV mode of transmission, unprotected sexual habits and drug abuse by injection, were commonly seen in males than females in Kuwait, which might explain the significant difference in HBV prevalence between male and female patients. In addition, the prevalence of HBV among non-Kuwaitis (2.1%) was significantly higher when compared to HBV prevalence among Kuwaitis (0.5%, p-value = 0.020). This might be attributed to the fact that non-Kuwaitis are more likely to be dialyzed in centers outside Kuwait with compromised infection control standards. Therefore, the offer of HBV vaccine and the annual monitoring of antibody response are very important factors in controlling the transmission of HBV in dialysis units [1-4,6].

Furthermore, HCV prevalence among male patients (8.6%) is significantly higher when compared to female patients (3.2%, p-value = 0.001). Again, HCV mode of transmission including drug use by injection is usually associated with male individuals rather than females, which might explain the difference. In addition, HCV prevalence among non-Kuwaitis (8.2%) was significantly higher when compared to HCV prevalence among Kuwaitis (4.7%, p-value = 0.012). This is most likely due to the higher chance of non-Kuwaitis traveling outside to dialysis centers abroad, probably of compromised infection control standards.

In contrast, the prevalence for HIV in the dialysis unit was 0.1%, which is relatively low when compared with HBV and HCV. Therefore, screening for HIV is best when based on a risk assessment of individual patients and screening offered to those who are at a higher risk of acquiring the infection. However, the risk of transmission, although rare, must always be considered.

CONCLUSION
This study, to our knowledge, is the only study with recent data on BBVs prevalence in a dialysis unit in Kuwait. A multi-center study in Kuwait is recommended to determine the national prevalence of BBVs in all the dialysis units in Kuwait.

REFERENCES
Original Article

Patterns of Self-Medication with Over-the-Counter Pain Relievers (Acetaminophen, Ibuprofen, and Aspirin) among the Kuwaiti Population

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Department of Biomedical Science, College of Nursing, Public Authority for Applied Education and Training, Kuwait


ABSTRACT

Objectives: To estimate the prevalence of self-medication with over-the-counter pain relievers (OTCPR, like acetaminophen, ibuprofen, and aspirin) among Kuwaiti citizens above the age of 16 years and describe their patterns of use, perceived awareness of, and concerns about the drugs’ potential side effects

Design: A descriptive cross-sectional questionnaire-based survey

Setting: Selected population from the six Kuwaiti governorates

Subjects: The data were collected over a four-month period in 2012, from 850 subjects identified as Kuwaiti citizens. These subjects were recruited using stratified random sampling.

Results: Overall, a 67% response rate was obtained. In total, 68% (573) of the respondents reported use of OTCPR. Women, middle-aged or singles, and those with higher education used these drugs more than other subgroups (p < 0.05).

We found evidence of inappropriate use of these drugs, with 15% (88) of consumers using them almost daily. Not only were 81% of the consumers unaware of the potential side effects, but also more than 61% were not concerned about them. Women were more knowledgeable than men regarding the maximum dose (p = 0.036, OR = 1.49, CI = 1.03-2.17). Consumers with higher levels of education did not show distinct knowledge regarding the maximum allowed dose of the drugs (p = 0.252, OR = 1.71, CI = 0.68-4.25).

Conclusion: The results showed a high prevalence of self-medication with OTCPR among Kuwaiti citizens. The subjects showed unawareness and unconcern regarding potential complications. This demonstrates the need for educational interventions.

KEYWORDS: awareness of side effects, concern, over-the-counter pain relievers, patterns of use, prevalence

INTRODUCTION

Over-the-counter pain relievers (OTCPR) are analgesic drugs for which a prescription is not required. The two main types of OTCPR are available are acetaminophen (paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs), which include ibuprofen and aspirin. Although these drugs are some of the most widely used internationally, they are not fully understood by most consumers. They are reliable and effective when used appropriately, but are associated with many risks and potential side effects if used inappropriately. Sinclair et al [1] showed that OTCPR are not always used optimally, with evidence of drug interactions, excessive dosing, and instances of contraindicated use. In addition, Wilcox et al [2] have shown a striking prevalence of OTCPR use, particularly NSAIDs, among Americans. In their study, one-fourth of the users exceeded the recommended dosage, and there was a common misconception that OTCPR are safer than prescription pain relievers. Furthermore, their results showed that about half of the people interviewed were either unaware of the potential toxicity of these agents or were unconcerned about it. In Scotland, a study on the use of OTCPR identified the potential risks associated with the use of these drugs and emphasized that current measures related to pharmacovigilance, which refers to the detection, assessment, monitoring, and prevention

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of the adverse effects of non-prescribed medicines, should be continued and improved upon[3]. The wide use of OTCPR and the belief that they are safe subsequently led to a higher number of toxicities; thus, gastrointestinal (GI) toxicity associated with NSAIDs, both OTC and prescription drugs, continue to occur in conjunction with cardiovascular, hepatic, and renal complications[4]. Unlike NSAIDs, acetaminophen does not have adverse effects on the stomach. However, taking more than the recommended dose can cause liver damage, ranging from abnormalities in liver function blood tests to acute liver failure and even death. Recent data suggest that acetaminophen is the most common cause of acute liver failure in adults in the United States (US)[5].

Collectively, these studies indicate higher rates of OTCPR use and a lack of understanding regarding the toxicity of these drugs among a wide spectrum of populations. Published data on self-medication with OTCPR are limited in the Arabian Gulf countries as well as Kuwait, as compared to those of other countries.

Since the magnitude of this problem in Kuwait is not known, it is necessary to study the extent of the use of OTCPR as well as the factors involved in such use. It is also necessary to assess Kuwaiti citizens’ awareness of and concerns about the potential side effects of these drugs. Such information would enable the identification of the prevalence of and factors associated with self-medication with OTCPR, as well as demonstrate a need for planning interventions to promote the judicious use of these medications.

Objectives

The aim of this study was to estimate the prevalence and identify patterns of self-medication with OTCPR (acetaminophen, ibuprofen, and aspirin) among Kuwaiti citizens above the age of 16 years. In addition, we aimed to identify perceived knowledge, awareness, and concerns about OTCPR and their potential toxicity.

SUBJECTS AND METHODS

Design: A descriptive cross-sectional questionnaire-based survey

Sample

Sampling strategy: We recruited subjects using stratified random sampling. The inclusion criteria were being Kuwaiti citizens, being more than 16 years old, and agreeing to complete the questionnaire.

The samples were selected from the six Kuwaiti governorates, according to the ratio of the population of each governorate to the total adult Kuwaiti population. The distribution of male and female subjects in the sample was according to their actual representation in the population. The respondents were recruited in coffee shops, large malls, government buildings, and universities.

Sample size: The calculated sample size was 425 subjects. We used the equation, \( n = \frac{z^2 \cdot pq}{e^2} \) to calculate the sample size[6] where \( n = \) sample size, \( z = 1.96 \) at the 95% confidence level, \( e = \) precision desired (0.05), \( p = \) estimated variance in the population as a decimal (0.5 for 50 - 150), and \( q = 1 - p \). A tenth of the calculated \( n \) was re-added, assuming a response rate of 90%. The power used to determine the difference in population between groups at the 5% significance level was 0.85. To provide such power, we multiplied the calculated sample size by two, reaching a total sample size of 850 subjects.

Data collection

The data were collected using a questionnaire compiled on the basis of similar studies[2-3]. We translated the questionnaire into Arabic after taking into account the cultural relevance of the items; back-translation was conducted for the verification of some questions. We conducted a pilot study for the questionnaire, using 50 subjects who were selected randomly. A few changes were incorporated into the final version so as to clarify some questions for the respondents. The questionnaire was divided into three sections:

1. The first section collected data on age, gender, marital status, education, profession, smoking or alcohol use, and general health status.
2. In the second section, the respondents were asked about the use of an OTCPR in the previous three months without prescription. The question included a list specifying aspirin along with acetaminophen products: Panadol, paracetamol, acetaminophen, and Tylenol as well as ibuprofen products: Brufen, Advil, and Motrin. If a respondent answered “yes,” he or she was considered a consumer and would then be asked to complete the rest of the questionnaire, which examined his or her self-medication patterns (type of medicine used, reasons for use, frequency of use, and whether the respondent read the labels on the packages of OTCPR). We asked each respondent about the dosage of the drug and whether he or she had exceeded the maximum allowed dose. In instances where the respondent had not taken OTCPR within the last three months, he or she was asked to answer only the third section of the questionnaire.
3. In the third section, each respondent answered questions designed to assess awareness of the use of OTCPR. This included awareness of the potential side effects of OTCPR and toxic interactions with other medications. Furthermore, in this section, respondents’ attitudes towards OTCPRs were examined; they were specifically asked about their concerns regarding the risks of side effects, as well as opinions regarding the safety of these medications.
We countered information bias by avoiding leading questions and providing categories that subjects could choose from instead of asking them to report specific values. The data were collected over a four-month period, from June 2012 to October 2012.

Data analysis
We used Minitab statistical software, version 16, to analyze the data. The respondents were divided into two groups: consumers and non-consumers. Demographic variables were analyzed using Pearson’s chi-square test for categorical data. Odds ratios and confidence intervals were calculated for all significant differences. A p-value below 0.05 was considered statistically significant.

RESULTS
Over the study period, 850 subjects participated in the study, with a response rate of 67%. Out of the 850, ten were excluded because they were not identified as either consumers or non-consumers. Participants’ age ranged from 16 to 77 years (Mean: 29.65 ± 10.54 years), and women made up 62% (522) of the sample.

It was determined that 68% (573) of the respondents were consumers. Women made up more than 65% (376) of this subgroup. There was no statistical difference in mean age for consumers versus non-consumers. Table 1 shows the respondents’ demographic data, as well as a comparison between consumers and non-consumers.

A comparison of consumers’ and non-consumers’ demographic data showed that the consumer group consisted of more middle-aged individuals than the non-consumer group (18% [104] Vs 13% [36], p < 0.046) as well as women (66% [376] Vs 53% [146], p < 0.001), singles (46% [261] Vs 37% [102], p < 0.029), and those with university education (55% [317] Vs 42% [115], p < 0.001).

The most commonly used OTCPRs were acetaminophen products (98%), followed by ibuprofen (38%) and aspirin (14%). Table 2 shows that the most commonly reported medical reasons for using OTCPRs were headaches and migraines (76%).

Heavy users (i.e., those consuming OTCPR daily or several times per week) comprised 15% (88) of the consumer subgroup. We found that 16% (92) of the consumers consumed more than the dose recommended on the package instructions, in spite of their declaration that they know this recommended dose. The study also showed that 33% (190) of the consumers used more than one medication at a time.

### Table 1: Demographic data for all the respondents and a comparison between consumers and non-consumers

<table>
<thead>
<tr>
<th>Variables</th>
<th>All respondents</th>
<th>Consumers</th>
<th>Non-consumers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
<td>(% N = 850)</td>
<td>(% n = 573)</td>
<td>(% n = 277)</td>
</tr>
<tr>
<td>Young (16-39 years)</td>
<td>75</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>Middle-aged (40-59 years)</td>
<td>17</td>
<td>18*</td>
<td>13</td>
</tr>
<tr>
<td>Old (&gt; 60 years)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>62</td>
<td>66*</td>
<td>53</td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>43</td>
<td>46*</td>
<td>37</td>
</tr>
<tr>
<td>Married</td>
<td>50</td>
<td>49</td>
<td>53</td>
</tr>
<tr>
<td>Divorced</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Widowed</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than senior school</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Senior school</td>
<td>20</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Diploma</td>
<td>19</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>University</td>
<td>51</td>
<td>55*</td>
<td>42</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Professional</td>
<td>21</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Running private business</td>
<td>23</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Clerical</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Student</td>
<td>34</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Housewife</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Retired</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Smokers</td>
<td>18</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>

*p < 0.05
* respondents who had consumed OTCPRs within the last three months

### Table 2: Types of OTCPRs used and reasons for use

<table>
<thead>
<tr>
<th>Type of OTCPRs</th>
<th>Consumers*, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen products</td>
<td>65</td>
</tr>
<tr>
<td>Panadol</td>
<td>83</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>10</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>3</td>
</tr>
<tr>
<td>Tylenol</td>
<td>2</td>
</tr>
<tr>
<td>Ibuprofen products</td>
<td>26</td>
</tr>
<tr>
<td>Brufen</td>
<td>32</td>
</tr>
<tr>
<td>Advil</td>
<td>4</td>
</tr>
<tr>
<td>Motrin</td>
<td>3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>9</td>
</tr>
<tr>
<td>Headache and migraine</td>
<td>76</td>
</tr>
<tr>
<td>Flu and fever</td>
<td>53</td>
</tr>
<tr>
<td>Toothache</td>
<td>40</td>
</tr>
<tr>
<td>Menstruation</td>
<td>34</td>
</tr>
<tr>
<td>Back pain</td>
<td>23</td>
</tr>
<tr>
<td>Joint pains</td>
<td>20</td>
</tr>
<tr>
<td>Trauma</td>
<td>5</td>
</tr>
</tbody>
</table>

OTCPR: Over-the-counter pain reliever
* respondents who had consumed OTCPRs within the last three months
A total of 39% (227) consumers stated that they did not know the maximum dose of the OTCPRs used. When asked about reading the labels on the packages of OTCPRs, only 30% (171) stated that they always read it; 24% (138) stated that they never read it, and 46% (263) indicated that they sometimes read it.

When the consumers were asked about their opinions regarding the statement, “combining OTCPRs is perfectly safe,” 12% (71) agreed, 25% (142) were unsure, and 62% (345) disagreed.

Awareness

A total of 80% (461) of the consumers were not fully aware of the maximum allowed dose for a drug (p = 0.252, OR 1.71, CI 0.68 - 4.25). Awareness of and concerns about potential side effects.

Concern

More than 61% of the consumers described themselves as either not too concerned (40%) or not at all concerned (21%) about the potential side effects of OTCPRs. We tested the association between age, sex, and education on the one hand and the following on the other: daily consumption of OTCPR, knowledge of the maximum dose, opinions regarding safety implications when combining OTCPRs, and awareness of and concerns about potential side effects.

Table 3: Regression analysis of factors associated with daily drug intake, knowing the maximum dose, opinions about the safety of combining OTCPRs, and awareness of and concerns about potential side effects

<table>
<thead>
<tr>
<th>Factors associated with daily drug consumption</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 40-59 Vs 16-39 (y)</td>
<td>0.029</td>
<td>0.55</td>
<td>0.33 – 0.94</td>
</tr>
<tr>
<td>Women Vs Men</td>
<td>0.721</td>
<td>0.91</td>
<td>0.55 – 1.52</td>
</tr>
<tr>
<td>Educational level Vs Less than a diploma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>0.071</td>
<td>2.51</td>
<td>0.92 – 6.80</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>0.069</td>
<td>2.48</td>
<td>0.93 – 6.60</td>
</tr>
<tr>
<td>Knowing the maximum dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 40-59 Vs 16-39 (y)</td>
<td>0.031</td>
<td>1.66</td>
<td>1.05 – 2.64</td>
</tr>
<tr>
<td>Women Vs Men</td>
<td>0.036</td>
<td>1.49</td>
<td>1.03 – 2.17</td>
</tr>
<tr>
<td>Educational level Vs Less than a diploma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>0.252</td>
<td>1.71</td>
<td>0.68 – 4.25</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>0.081</td>
<td>2.23</td>
<td>0.90 – 5.52</td>
</tr>
<tr>
<td>It is safe to combine OTCPRs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 40-59 Vs 16-39 (y)</td>
<td>0.535</td>
<td>0.87</td>
<td>0.55 – 1.37</td>
</tr>
<tr>
<td>Women Vs Men</td>
<td>0.042</td>
<td>0.7</td>
<td>0.46 – 0.99</td>
</tr>
<tr>
<td>Educational level Vs Less than a diploma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>0.116</td>
<td>0.48</td>
<td>0.19 – 1.20</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>0.080</td>
<td>0.45</td>
<td>0.18 – 1.10</td>
</tr>
<tr>
<td>Full awareness of side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 40–59 Vs 16–39 (y)</td>
<td>0.005</td>
<td>1.8</td>
<td>1.2 – 2.7</td>
</tr>
<tr>
<td>Women Vs Men</td>
<td>0.439</td>
<td>1.14</td>
<td>0.81 – 1.61</td>
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<tr>
<td>Educational level Vs Less than a diploma</td>
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<td></td>
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<tr>
<td>University</td>
<td>0.019</td>
<td>2.65</td>
<td>1.18 – 5.99</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>0.053</td>
<td>2.21</td>
<td>0.99 – 4.93</td>
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<tr>
<td>Concerns about side effects</td>
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<td></td>
<td></td>
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<tr>
<td>Age 40–59 Vs 16–39 (y)</td>
<td>0.001</td>
<td>2.19</td>
<td>1.38 – 3.46</td>
</tr>
<tr>
<td>Women Vs Men</td>
<td>0.433</td>
<td>1.16</td>
<td>0.80 – 1.70</td>
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<td>Educational level Vs Less than a diploma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>0.024</td>
<td>0.34</td>
<td>0.13 – 0.87</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>0.222</td>
<td>0.56</td>
<td>0.23 – 1.41</td>
</tr>
</tbody>
</table>

OR = Odds ratio, CI = Confidence interval

Knowledge about the medication

A total of 39% (227) consumers stated that they did not know the maximum dose of the OTCPRs used. When asked about reading the labels on the packages of OTCPRs, only 30% (171) stated that they always read it; 24% (138) stated that they never read it, and 46% (263) indicated that they sometimes read it.

The consumers were asked about their opinions regarding the statement, “combining OTCPRs is perfectly safe.” 12% (71) agreed, 25% (142) were unsure, and 62% (345) disagreed.

Awareness

A total of 80% (461) of the consumers were not fully aware of the potential side effects of OTCPRs.

Concern

More than 61% of the consumers described themselves as either not too concerned (40%) or not at all concerned (21%) about the potential side effects of OTCPRs. We tested the association between age, sex, and education on the one hand and the following on the other: daily consumption of OTCPR, knowledge of the maximum dose, opinions regarding safety implications when combining OTCPRs, and awareness of and concerns about potential side effects.

Table 3 shows that participants in the middle-aged group (40 - 59 years) consumed OTCPRs more frequently (p = 0.029, OR 0.55, CI 0.32 –0.94). Women were more knowledgeable than men regarding the maximum dose (p = 0.036, OR 1.49, CI 1.03 - 2.17), and the percentage of women who disagreed with the statement, “combining OTCPRs is perfectly safe,” was higher than that of men (p = 0.042, OR 0.7, CI 0.46 - 0.99). The table also shows that consumers with higher levels of education were more aware of (p = 0.019, OR 2.65, CI 1.18 - 5.99) and concerned about (p = 0.024, OR 0.34, CI 0.13 - 0.87) potential side effects. However, they did not show distinct knowledge regarding the maximum allowed dose for a drug (p = 0.252, OR 1.71, CI 0.68 - 4.25).

DISCUSSION

Acetaminophen and NSAIDs are among the most widely used OTCPRs, and their use to relieve acute pain is extremely common in the general population [7]. Consumers often perceive OTCPRs as safe because these drugs are freely available for self-selection. Although they provide notable benefits, their use may pose significant health risks, owing to the potential side effects and drug interactions, especially when users are uninformed.
The aim of this study was to highlight this problem in Kuwait by assessing the prevalence of OTCPR use and providing evidence of consumption patterns. We also aimed to identify individuals’ perceived knowledge of these medicines as well as awareness and concerns (if any) regarding potential side effects.

The current study showed a high prevalence of OTCPR use among Kuwaiti citizens. The high frequency of OTCPR use is consistent with findings from similar studies. Wolf et al. interviewed 500 adult patients receiving care at outpatient general medical clinics in Atlanta and Chicago between September 2009 and March 2011. Over half of the patients reported some acetaminophen use, and 19% were “heavy users” (i.e., they had taken it every day or at least a couple of times a week during the previous six months). Moreover, in a study by Rolita and Freedman (2008) OTCPRs were the most popular self-treatment choice, with 20 - 30% of older adults using these products on any given day.

When comparing consumers’ and non-consumers’ demographic characteristics, we found that some subgroups were more likely to have recently used OTCPRs than others, specifically middle-aged people (40 - 59 years), women, singles, and those with university education.

The high prevalence of OTCPR use by middle-aged subjects is consistent with some studies, but not others. In our study, this high usage may be related to joint and back pains associated with osteoarthritis which is common among Middle Eastern patients; especially obese, middle aged women. The high percentage of women in the consumer group is consistent with the results of a survey by Neafsey and Shellman on non-prescription analgesic use in Scotland, as well as other studies in which women were found to be more likely to use non-prescription medication in general and, analgesics in particular.

Studies by Porteous et al. and Sihvo et al. support our findings in Kuwait, indicating that better-educated people are more likely to use OTCPRs. These findings can be examined further in future studies so as to determine whether an increase in the use of these drugs reflects job stress, more trust in medicines, or other factors. The higher percentage of OTCPR consumption by students may also require further clarification.

On examining the types of OTCPRs used by consumers in Kuwait, we found that almost all of the consumers used acetaminophen-based products, followed by ibuprofen and, lastly, aspirin. Out of the acetaminophen-based products, Panadol was the most frequently used, while out of the ibuprofen-based products, Brufen was the most frequently used. The main reasons cited for using OTCPRs in the current study were headaches and migraines. This is consistent with other studies in which acetaminophen was the most commonly used non-prescription analgesic, with headaches identified as the most frequently treated condition.

With regard to patterns of OTCPRs use, more than 60% of consumers reported using OTCPRs on an as-needed basis. However, in the current study, several indicators relating to the inappropriate use of OTCPRs were identified. A total of 15% of consumers could be regarded as heavy users. The use of more than one medication at a time was reported by more than thirty percent of the consumers, this in addition to exceeding the recommended dosage.

Those considered to be heavy users were mainly in the middle-age subgroup. Heavy consumption was not significantly related to gender or education level. The inappropriate use of OTCPRs carries an increased risk of unintentional overdosing. This high risk was recently highlighted by Wolf et al. among a significant number of adults using OTCPRs in the US.

Lack of knowledge regarding the use of OTCPRs was evident in this study. Statistical analysis showed that knowledge about these medications was not predicted by the subjects’ level of education. However, women had better knowledge of these medications than men did.

Our findings suggest that some individuals are placing themselves at risk due to their daily use of the drugs, while others tend to exceed the recommended dosage; worst of all are those who think that it is perfectly safe to combine two of these drugs. What is more worrisome is the fact that although we hypothesized that more highly educated people would have more knowledge of these medications, no correlation between education and knowledge regarding OTCPRs was found.

The study showed a considerable lack of awareness of and concern about potential side effects. This trend was also observed by Wilcox et al. where about half of the NSAID users in the two surveys admitted that they either did not know or were not concerned about the possible side effects of these OTC medications. In the current study, those with higher levels of education showed better awareness of and concern about potential side effects. Studies in diverse populations worldwide have also shown a high frequency of misperceptions regarding the toxicity of OTCPRs and under-reporting of the use thereof. Cham et al. found significant gaps in their patients’ knowledge regarding OTCPRs. More than 40% of their patients were unaware of toxic interactions or gastrointestinal side effects, while more than 60% were unaware of the relationship between these drugs and hepatic and renal disease, and more than 80% were unaware of the relationship between aspirin and adverse effects on asthma patients. This low level of awareness of the potential adverse effects of OTCPRs was alarming...
and, as stated by the researchers, indicated a need for patient education about OTCPRs.

In summary, our study suggests that OTCPRs are widely used and frequently taken inappropriately. Perceived awareness of and concern about the potential side effects of OTCPRs is lacking, and that these medications are generally believed to be safe; therefore, educational interventions targeting both patients and healthcare professionals are necessary.

Limitations

One of the limitations of the current study is the fact that teenagers were excluded from the study sample. Other studies\(^\text{[18]}\) have shown that teenagers tend to underestimate the hazards of exceeding the recommended dosage of OTCPRs such as acetaminophen, ibuprofen, and aspirin. Other limitations include the potential misinterpretation of questions and the inability to formulate additional questions based on responses. In addition, the information collected through the survey was not sufficient to unequivocally identify clinically significant cases inappropriately using OTCPRs. Such cases probably require a clinical review for validation.

CONCLUSION

Our survey showed a high prevalence of OTCPR (acetaminophen, ibuprofen, and aspirin) use and lack of awareness of and concern about the toxicity of these drugs among a wide spectrum of the Kuwaiti population. Thus, we strongly recommend educational interventions aimed at the general public as well as physicians. It is important for patients to understand the need to take OTCPRs as directed on the label, because of the significant risks posed by inappropriate use of the drugs. Our data should enhance clinicians' awareness of the use of non-prescription medication and assessment of individuals in the consulting room. Our study highlights the need to advise the public to consult pharmacists or primary care providers before using OTCPRs, as this can help prevent potential side effects. It is important for the public to understand what these drugs are indicated for, their potential side effects, and the risk of combining different medications.

Future research: This study will be followed up with another study which will be considered as an extension of the current one. We will focus more on comparisons regarding consumption on the basis of gender in university students. The two subgroups (according to gender) will be compared with respect to reason of using a particular OTCPR, asking for advice from a doctor / pharmacist regarding the use of OTCPRs, in addition to comparing patterns of use, as well as perceived awareness and concern about potential side effects.

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REFERENCE


Original Article

An Audit of Hypertension in Electronic Medical Records

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ABSTRACT

Objectives: To audit the documentation of medical care provided to hypertensive patients and to evaluate the management of hypertension in the department of internal medicine at the Ahmadi hospital, Kuwait

Design: Retrospective study

Setting: Outpatient clinics, Department of Internal Medicine, Ahmadi Hospital, Kuwait Oil Company, Kuwait

Subjects & Methods: An audit of electronic medical records (EMR) was carried out during 2012 on a representative sample of 150 patients, selected randomly using a simple randomization method. A re-auditing was done in 2013. McNemar’s test was used to compare data in 2013 with data in 2012.

Intervention(s): Auditing of EMR

Main Outcome Measure: Recorded data of hypertensive patients

Results: Age, gender, blood pressure recording, renal function tests, and lipid levels were accurately recorded (> 75%) in the computer system. History of pertinent symptoms and smoking were poorly recorded (< 1%). Fifty-five percent of the hypertensive patients were sufficiently controlled (BP < 140/90 mmHg). There were significant differences between 2012 and 2013 data with respect to documentation and recording of pertinent symptoms (p < 0.001) and renal function tests (p = 0.026).

Conclusion: Conducting an audit of EMR is essential to evaluate clinical performance and to determine what changes should be made to improve quality of care. There was significant improvement in documentation of pertinent symptoms in the second audit

KEYWORDS: blood pressure, medical audit, primary health care

INTRODUCTION

Hypertension is a major public health problem worldwide and is associated with high morbidity and mortality rates[1]. Evidence shows that the number of death and disability cases resulting from coronary artery disease (CAD) and cerebrovascular disease (CVD) are increasing rapidly in developing countries and are expected to rank as number one and four, respectively, as major causes of the global burden of disease by the year 2020[2,3].

Improvement in the management of hypertension has significantly decreased cardiovascular mortality in several developed countries[4]. Well organized care can improve the outcome of the hypertensive patients by early prevention of complications[2]. Because physicians have a direct role in treatment outcomes, physicians’ overestimation about hypertension management can contribute to inadequate blood pressure control. Thus, interventions for improving physicians’ awareness regarding the management of patients with hypertension are needed[5].

A clinical audit of electronic medical records (EMR) for hypertension was done twice at Ahmadi hospital under the supervision of the department of internal medicine to assess the quality of medical care given to hypertensive patients and to assess the improvement in patient care after the first auditing.

SUBJECTS AND METHOD

In this retrospective analysis, we investigated the process of care for patients with hypertension during 2012 and 2013. The target population consisted of staff members and their families working at Kuwait Oil Company (KOC), coming from different regions of the state of Kuwait. There was no specific clinic for hypertension.

One hundred and fifty patients were randomly selected with the help of the nurse in the internal medicine clinic at Ahmadi Hospital by collecting the medical record number (MRN) for any patient taking antihypertensive medication for a period of two months. Hypertensive patients usually attended the
clinic every three to four months for follow-up and were seen by internal medicine registrar or senior physicians.

The study was approved by the local Internal Medicine Committee.

The indicators for structure, process, and outcome of hypertension care were assessed using the scoring system based on the recommendations by World Health Organization (WHO)[4]. For every patient, the MRN number, age, sex and number of visits to the staff clinic for year 2012 were documented. The number of times the blood pressure measurement was taken in year 2012 was documented. The number of documentation of important symptoms, e.g., chest pain, palpitation, dizziness, and shortness of breath in year 2011 was taken. Smoking history documentation following investigations (serum urea, creatinine, serum potassium, and serum lipid profile) were checked whether or not they were ordered in that year.

SOB = shortness of breath
After one year, the whole cycle was repeated again in 2013, using the same patients’ medical records used in 2012. The means and percentage of variables were calculated using SPSS version 16. The McNemar’s test was used to compare data in 2012 with data in 2013. All tests were two sided and a p-value of < 0.05 was considered statistically significant.

RESULTS

One hundred and fifty hypertensive patients were included in the study. The patients’ mean age was 54.8 ± 9.9 years. All patients were Kuaitis except 10 and 53.3% were female. Table 1 shows the means and percentages of all the variables in 2012 and 2013. The age, gender, blood pressure recordings, renal function tests, and lipid levels were adequately recorded in the computer system. History of important symptoms and smoking history were poorly recorded. Out of the hypertensive patients, 56.4% were well controlled (BP < 140/90). The last serum creatinine, last serum urea, and last serum potassium were normal in 89.7%. The last serum lipid profile (total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (TG)) was normal in only 29.7% of patients in 2012, whereas it was normal in 40% of patients in 2013. Table 2 shows the results of McNemar’s test which was used to compare two related and dependent variables, as well as the p-values. There were significant differences between 2012 and 2013 with respect to documentation and recording of important symptoms (p < 0.001) and renal function tests in the computer (p = 0.026).

DISCUSSION

Analysis of data in this audit shows poor documentation of history of important symptoms (e.g., chest pain, palpitation, dizziness and shortness of breath), and documentation of smoking history. The factors which can contribute to these results are; 1) a new computer system (Meditec) and perhaps the doctors documented the history but forgot to save it, 2) a busy clinic and no time to write in the computer, 3) lack of knowledge of important symptoms which are essential to ask in any hypertensive patient, and 4) smoking history may have been documented several years back, but the doctor may have neglected to document it again. The lipid profile was poorly controlled and the factors which could have contributed to these result are; 1) poor compliance of patients for statins, 2) inadequate dose of statins, 3) unhealthy life style, and 4) poor knowledge of the doctor of the importance of primary prevention of hyperlipidemia. The last blood pressure reading was normal (< 140/90 mmHg) in 56% of patients, which is lower than in some studies which reported a range between 63% and 71.3% of patients with blood pressure < 140/90\[6-8\].
Other studies showed a lower rate (16 - 44%) of blood pressure control in patients with blood pressure < 140/90\textsuperscript{[2, 9, 10, 11]}. Our analysis showed that the blood pressure measurements increased from 96.7% in 2012 to 97.9% in 2013. Other study showed that the blood pressure recordings increased from 62% to 89% in the years 2004 to 2006\textsuperscript{[12, 13]}. There was a significant increase in performing renal function tests (from 75.3% in 2007 to 87.1%, \( p = 0.026 \)). Some studies showed yearly improvements in electrolyte testing, from 28% to 62\%.\textsuperscript{[14]} One of the limitations of this study is that our sample may not be representative of the whole country. Therefore, these results cannot be generalized to other clinics in Kuwait. We did not include in the auditing whether patients visited only the primary healthcare center or also secondary or tertiary healthcare centers. Another limitation could have been that only one reading for blood pressure was taken, which is the last reading, and this may not have been enough. Probably taking two to three readings and then taking the average would have been more conclusive. Electrocardiogram (ECG) results were not included in the auditing, because the computer Meditech system was new and in almost all patients it is hard to trace the ECG. Also, entering data from the Meditech computer system to the SPSS system may have exposed us to observer bias and inter-observer bias.

**CONCLUSION**

Conducting an audit of EMR is essential to evaluate clinical performance and to determine what changes should be made to improve quality of care. There was significant improvement in documentation of pertinent symptoms in the second audit.

**REFERENCES**

Case Report

Use of Bridging Plates for Tile Type C2 Pelvic Fracture: A Case Report

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ABSTRACT

The bony pelvis consists of the iliac wings, ischium, and pubis, which form an anatomic ring with the sacrum. Disruption of this ring is usually a result of high-energy trauma often requiring a multidisciplinary approach. We present a patient with a Tile C2 type of pelvic fracture that was treated using bridging plates. Acting as an extra-medullary splint, the bridging plate fixed the two main fragments, while the fracture zone is left virtually untouched. This novel application of bridging plates allowed limited exposure and disturbance to the surrounding neurovascular structures. Satisfactory position and good functional outcomes were achieved.

INTRODUCTION

Pelvic fracture is caused by high-energy trauma, and is often associated with visceral injury and hemorrhagic shock leading to high morbidity and mortality. Treatment of pelvic fracture requires a multidisciplinary approach and is often challenging[1]. Because early death associated with pelvic fracture is mainly due to hemorrhagic shock, multiple organ system failure, or sepsis[2,3], initial treatment focuses on maintenance of hemodynamic stability and prevention of infection. Associated injuries should be evaluated and treated appropriately. External fixation is frequently indicated in patients with unstable fractures.

After the patient’s condition is stabilized, open reduction and internal fixation is considered the definitive procedure. This can be technically demanding, depending on the complexity of the fracture and its anatomic location, which may be difficult to expose.

We report here the case of a patient with a Tile type C2 pelvic fracture who underwent a definitive fracture fixation using the bridging plate technique. Fixed to the two main fragments the bridging plating uses the plate as an extra-medullary splint. The use of these plates allows the complex fracture zone to be left relatively untouched, and at the same time ensures better stability, preserves vascularity, and permits controlled micro-motion that promotes rapid and abundant callus formation.

Traditionally, bridging plates have been used to manage long bone fractures, particularly those of the tibia. We report on the successful use of the bridging plate in the management of pelvic Tile type C2 fracture. Using the bridge plating technique, the fracture was successfully fixed with minimal injury to surrounding tissues. Satisfactory reduction and functional outcomes were achieved.

CASE REPORT

A 23-year old male was seen in the emergency room with the history of fall of a heavy object onto his lower abdomen and pelvis. He was initially treated at a local hospital where he was diagnosed with polytrauma involving pelvic fractures and injuries to multiple abdominal organs. After initial stabilization and abdominal surgery, he was referred to our department for the definitive management of the pelvic fracture.

The physical examination revealed multiple bruises in the groin region, scrotal swelling, and a positive pelvic compression test. The distance from the umbilicus to the anterior superior iliac spine was...
<3.5 cm longer on the right side than the left side. The right lower limb was shorter than the left by 3 cm. X-rays of the pelvis (Fig. 1, 2) and three-dimensional (3D) computed tomography (CT) reconstruction were performed to study the configuration of the fractures. They demonstrated multiple fractures of the right sacral promontory and iliac crest, bilateral pubis, and comminuted fracture of the bilateral ischium (Fig. 3, 4). According to the Young-Burgess classification system, this case would be classified as a complex mixed pattern of injuries involving both anterior-posterior compression and vertical stress. According to the Tile classification system, the fracture was defined as type C2, indicating a bilateral vertical and rotationally stable fracture.

On admission, the patient’s blood pressure was 60/40 mmHg, indicating hypovolemic shock. Therefore, large-bore intravenous lines were established and the patient was given a crystalloid solution infusion and blood transfusion. Hemodynamic stability was ensured and maintained. As a temporary measure, external fixation was used to fix the disrupted pelvic ring (Fig. 3, 4), and traction of the right leg was also maintained. The patient subsequently developed...
a high grade fever, pulmonary infection, pleural effusion, acute respiratory failure, multiple electrolyte imbalances, and hypoalbuminemia. He was managed in an intensive care unit for these problems. Two weeks later, his condition stabilized and a treatment plan that included definitive open reduction and internal fixation was decided upon.

Under general anesthesia, the patient was placed in supine position. Using an ilio-inguinal approach, the inner table of the ilium was exposed, with care being taken to avoid injury to the lateral cutaneous nerve. The periosteum was elevated, which revealed a vertical split fracture of the iliac body, with ~2 cm displacement. The fracture was reduced and fixed temporarily with two Kirschner wires. After a satisfactory reduction was ascertained by a C-arm fluoroscope, three locking plates were used to fix the fracture of the right sacroiliac joint; stabilization of the posterior pelvic ring was thereby established. Subsequent to fixation the provisional Kirschner wires were withdrawn.

The incision was extended medially to the pubic symphysis, and the distal pubic bone was exposed lateral to the pubic symphysis. After closed reduction of the fracture, a 14-hole reconstruction locking plate was bent into the form of an arc (\(\text{\textbullet}\)). One end of the plate was fixed medially to the anterior superior iliac spine with three screws. Then, without exposing the femoral sheath or the spermatic cord, a bridging plate was slid to the other end, bridging the fracture to the symphysis pubis. The other end of the plate was fixed medially to the pubic symphysis with two screws. Subsequently, the left anterior pelvic ring fracture was fixed in a similar fashion. Finally, the wound was closed with application of vacuum sealing drainage. The entire operation lasted about two hours with an estimated blood loss of about 1400 ml. The fixation of the right sacroiliac joint and the bilateral anterior pelvic rings led to blood losses of 1000 ml and 400 ml, respectively.

Three days after surgery, passive range of motion of the hip and knee was started. Two weeks postoperative, the patient was allowed to sit. Eight weeks after surgery, he began to walk with crutches.

According to the scoring system of Tornetta and Matta,\(^4\) the surgery achieved an excellent reduction with a postoperative displacement less than 4 mm. Based on outcome assessment criteria proposed by Majeed \textit{et al},\(^5\) the outcome was excellent (Fig. 5-8). No postoperative complication was observed.
DISCUSSION

The initial management of pelvic fracture consists of advanced trauma life support (ATLS) focused on prevention and treatment of hypovolemic shock. Garbuglia et al. \(^6\) demonstrated that 57% of the mortality after pelvic fracture was caused by hemorrhagic shock. They found that using Hoffmann's anterior external fixation frame combined with arteriography and embolization stabilized the pelvic ring and was associated with improved survival\(^6\). Bassam et al. \(^7\) concluded that in patients with hemodynamic instability caused by pelvic fracture, external fixation combined with angiographic embolization was essential to stop hemorrhage and improve outcome. In the present case, after the injury the patient received prompt external fixation, which was necessary to maintain pelvic and hemodynamic stability.

An unstable Tile type C pelvic fracture requires internal fixation, which can be technically demanding for the surgeon. It has been demonstrated that the reconstruction plate is superior to other methods of fixation\(^8,9\). Using the ilio-inguinal approach developed by Letournel and Judet\(^10\), the iliac wing, sacroiliac joints, anterior column of the acetabulum, superior pubic ramus, and pubic symphysis can be sufficiently accessed. However, it involves exposure of the multiple major neurovascular structures in the area, such as the femoral nerve and the femoral sheath enveloping the femoral nerve, artery, and vein. Intraoperative damage to this area carries significant risks that can lead to hemorrhage and nerve deficit\(^11\).

In the present case, we used reconstruction locking plates as bridging plates for the fixation of this unstable complex pelvic fracture. Using this novel technique, we ensured that the complex fracture region was left virtually untouched, yet bridged by the plate. This ensured that the already compromised vascularity of the comminuted fracture fragments was not jeopardized. Length, alignment, and rotation were restored, but an exact anatomical alignment was not attempted. With this technique the plates provided relative stability, and at the same time the preservation of natural fracture biology resulted in rapid callus formation and fracture consolidation.

The bridging plate technique is widely employed for managing long bone fractures with complex fragmentation when conventional plating or periosseous nailing is not possible. Its use in pelvic fracture however is a relatively new and novel concept. In the past Krappinger et al.\(^12\) published a small series of cases in which they employed minimally invasive posterior plate osteosynthesis for type C pelvic fractures, with good outcome. Similar results were obtained by Hao et al.\(^13\) with minimally invasive fixation of the posterior pelvic ring. In the present study, we had good results using this technique in the anterior pubic symphysis region. We believe that this report is the first on the use of this technique in this region.

The advantages of this technique are multifold. Firstly, the bridge plating technique uses the plate as an extra-medullary splint similar to the way an external fixator spans the fracture and holds the anterior pelvic ring together. Thus the exposure of important neurovascular structures such as the femoral nerve, iliac vessels, and the spermatic cord or the round ligament of the uterus, is avoided. As well as preventing the potential complications associated with exposure of these structures, the technique also avoids division of the inguinal ligament and thereby minimizes the chances of postoperative hernia. Secondly, the limited exposure requires less time, which may result in less bleeding and prevention of infection. Furthermore, it requires less soft tissue dissection and periosteal stripping. Therefore, the blood supply can be preserved, which enhances fracture healing. Finally, the implant can be easily removed without significant secondary damage.

Postoperative X-rays of the patient showed functional reduction of the pubic ramus. This was to be expected since an anatomic reduction was not pursued. For severe pelvic fractures, although precise reduction may perhaps enhance physiological function, it necessitates longer time in surgery, more bleeding and damage to the surrounding tissues, all of which increase the risk of infection. At the 3-month follow-up, no complications had occurred and the patient had a good functional outcome. No loosening of the plates or displacement was detected. We thus propose that bridging plates might be an attractive alternative for Tile type C2 pelvic fractures.

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Case Report

A Case of Scrub Typhus-Related Acute Lung Injury Confirmed by Surgical Lung Biopsy

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ABSTRACT

Scrub typhus is an acute febrile and zoonotic disease caused by Orientia tsutsugamushi. Although scrub typhus can involve various organs, severe pulmonary complications such as acute lung injury (ALI) have been rare since the introduction of effective antibiotic therapy. In addition, the reports that described the histopathology of lung injury due to scrub typhus were very scarce worldwide and most of them were obtained from autopsy. We report a case of severe lung injury due to scrub typhus whose histopathology was confirmed by surgical lung biopsy in a mechanical ventilator-dependent patient.

KEY WORDS: acute lung injury, lung biopsy, Orientia tsutsugamushi, scrub typhus

INTRODUCTION

Scrub typhus is a zoonotic disease caused by Orientia tsutsugamushi. It is one of the most common infectious diseases of rural southeastern Asia and western Pacific[1]. The pulmonary involvement of scrub typhus usually presents as mild interstitial pneumonitis[2]. Although acute lung injury (ALI) associated with scrub typhus has been clinically reported, its incidence is very low[3]. Moreover, reports that described the histopathology of severe lung injury by scrub typhus were very scarce worldwide.

CASE REPORT

A 56-year-old woman with diabetes mellitus was referred to our hospital to evaluate progressive dyspnea. She lived in the rural area of South Korea. She was a farmer. Two weeks ago, she had visited a private clinic with fever and myalgia. Scrub typhus was confirmed by eschar and increased titer of O.tsutsugamushi antibody. Clinical manifestations improved to a degree with the administration of doxycycline for seven days. On seventh day after treatment completion, she was referred to our hospital due to progressive dyspnea. Chest radiography showed bilateral airspace consolidation with reticulonodular densities. Doxycycline and piperacillin were administered empirically under the impression of newly developed pneumonia. Physical examination demonstrated multiple lymphadenopathy and necrotic eschar. Body temperature was elevated to 38.5 °C. The crackle was heard in both lower lungs. Chest CT scan showed multiple patchy ground glass opacities (GGO) and airspace consolidations (Fig. 1A and 1B). They were predominant in lower lung zones. Complete blood cell counts were as follows: WBC 8,900/mm3 (72.6% neutrophil, 17.9% lymphocyte, 1.2% eosinophil), hemoglobin 9.2 g/dl, platelet 156,000 / mm3. Hepatic and renal functions were normal. Urine analysis showed protein 1+, WBC 2 ~ 4 /HPF and RBC 2 ~ 4 /HPF. Arterial blood gas analysis (ABGA) showed that pH was 7.493, PaCO2 was 31.3 mmHg, PaO2 was 54.9 mmHg, and HCO3- was 28 mEq/l. No drugs or environmental / occupational exposure associated with sputum, urine and blood were negative. Serological tests for Streptococcus pneumoniae, Mycoplasma pneumoniae, Leptospira species and autoantibodies including antinuclear antibody were all negative. However, antibody for O. tsutsugamushi remained still strongly positive (1:2560). To evaluate progressive lung lesion, video-assisted thoracic surgery biopsy was performed on the second day of admission.

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Microscopically, acute and organizing stage of diffuse alveolar damage was noted (Fig. 2). Prominent eosinophilic hyaline membrane along edematous alveolar septa was noted. Intra-alveolar edema characterized by feathery proteinaceous exudate within alveolar space was also present. Interstitial fibroblast proliferation of alveolar septa and alveolar lining cell hyperplasia were present in some areas. However, no vasculitis, perivasculitis, granuloma or microorganisms including cytomegalovirus, EB病毒和adenovirus were identified. Based on these findings, ALI associated scrub typhus was the most probable diagnosis. Levofoxacin was substituted for doxycycline because there was a possibility of resistance to doxycycline for scrub typhus. Methylprednisolone (2 mg/kg/day) was started at the same time. The patient improved and finally survived. A 3-month follow-up CT showed resolution of the diffuse pulmonary consolidations and GGO with residual fibrosis and traction bronchiectasis (Fig. 1C and 1D).

**Discussion**

Scrub typhus occurs by the bite of chiggers infected with *O. tsutsugamushi* and is characterized by fever, headache, myalgia, rash, lymphadenopathy and eschar\(^4\). Respiratory, gastrointestinal, and neurologic symptoms may be present. Doxycycline is the drug of choice and relapse occurs rarely in patients treated for five days or longer\(^1\).

However, some strains of *O. tsutsugamushi* are resistant to doxycycline\(^4\). For these resistant strains, levofoxacin has been reported to be effective\(^5\). The incidence of scrub typhus has recently increased in Korea\(^6\). There is growing concern about the occurrence of resistant strains. Lung injury in our case could be caused by strains poorly responsive to doxycycline in that dyspnea progressed despite treatment with appropriate dose (200 mg/day) and duration (7 days).

There were few reports describing lung pathology associated with *O. tsutsugamush* worldwide. Though histopathology of involved organs is characterized by vasculitis and perivasculitis of small vessels caused...
by proliferation of *O. tsutsugamushi* in endothelial cells[7], Park et al reported a case of scrub typhus that shows diffuse alveolar damage in the organizing stage without evidence of vasculitis[8]. Immunofluorescent antibody staining and polymerase chain reaction for *O. tsutsugamushi* failed to demonstrate the organism in the lung tissue[8]. This indicates that other mechanisms may participate in the pathogenesis of lung injury associated with scrub typhus. In our case, we found diffuse alveolar damage without the evidence of vasculitis and perivasculitis on lung biopsy.

CONCLUSION

In summary, since severe lung injury can be developed by scrub typhus despite antibiotics known to be effective like doxycycline, close observation after completion of treatment is required. In addition, severe lung injury seems to be able to develop without vasculitis or perivasculitis.

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Case Report

Genito-perineal Raphe Cyst in an Infant: A Case Report and Review of Literature

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ABSTRACT

Canaliform genitoperineal raphe cyst is an unusual entity. A three-month-old infant presented with a cordlike white swelling of one week duration. Surgical excision resulted in satisfactory recovery. Microbiology of cyst fluid confirmed bacteroides infection. Management and clinical presentation is discussed along with review of literature.

KEY WORDS: canaliform, cyst, genitoperineal raphe, infants

INTRODUCTION

Genito-perineal raphe cysts are rare congenital malformations usually presenting as asymptomatic cystic structures along line of fusion of the genito-urethral folds and urethral plate[1-4]. Glans penis remains the most common site although cyst has been reported along ventral aspect of the penis without any urethral communication. Among the reported cases canaliform genitoperineal raphe cysts have rarely been reported in infants especially in pediatric urology literature[1,3-5]. Since this cyst can result in parental anxiety apart from getting infected, awareness among treating physicians, especially, pediatric urologist is warranted so as to avoid confusion in diagnosis and thus optimizing the management of this rare entity.

CASE REPORT

A three-month-old male full-term infant presented with swelling in genitoperineal raphe for the last 10 days. The swelling was progressively increasing in size. Therefore, the parents opted for medical consultation. There were no associated inflammatory or gastrointestinal symptoms. There was no history suggestive of any trauma or predisposing factors nor was the swelling associated with any discharge. Clinical examination showed a canal like cyst along the scrotal genito-perineal raphe extending from peno-scrotal junction till the perineum (Fig. 1). The laboratory investigations showed slight leukocytosis with white blood cell count of 13,000. On perineal examination anal opening appeared normal. Since the lesion was progressively increasing in size, the child underwent surgical excision. Microbiological analysis of cyst fluid confirmed presence of bacteroides. The postoperative recovery was uneventful. During follow-up over the last three weeks, the child is doing well.

DISCUSSION

A genito-perineal raphe cyst (also called genitoperineal raphe cyst, parameatal raphe cyst) is an uncommon condition usually under-reported because of its asymptomatic nature[1,5,6]. This uncommon entity is reported with same incidence in pediatric and adult age group. Among reported cases only handful of such cases have been reported in infancy[1,2,4-6]. Since canaliform cyst remains an extremely rare entity, we present this case report and review the pertinent literature.

The embryological development of genito-perineal raphe cyst although unclear has been explained on basis of two different theories[1,4-6]. It is either attributed to presence of embryological epidermal remnants after fusion of urethral folds or to abnormal development of paraurethral duct. The presence of canaliform genitoperineal raphe cyst in the present case and reported cases in the literature support the former theory which is further supported by presence of variety of epithelial linings.

Histologically, as experienced in the present case the genito-perineal raphe cysts is characterized by the
The clinical course of genito-perineal raphe cyst is highly variable. Although rare, spontaneous regression has been reported in a few cases[1,2,3,4]. Most of the cases remain asymptomatic justifying appropriate clinical diagnosis and regular follow up as mainstay of treatment. As experienced in few reported cases, patients, usually adults can present with inflammatory signs secondary to cyst infection[1,2,6]. The present case appears unusual as the canaliform type of genito-perineal raphe cyst is rare and has the potential for future infection owing to growth of bacteroides as found on microbiological examination[1,2,5].

CONCLUSION

Genito-perineal genitoperineal raphe cyst remains an uncommon clinical entity which is often under-reported owing to its asymptomatic clinical course. An awareness of clinical presentation is warranted among treating physicians, especially dermatologists and pediatric urologists to execute topical applications and surgical intervention only when it is indicated thus avoiding undue morbidity and alleviating parental anxiety.

REFERENCES

Case Report

Anterior Bronchogenic Cyst Mimicking Thymoma in Patients with Myasthenia Gravis

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ABSTRACT

Bronchogenic cysts are extremely rare in the thymus. A 74-year-old man was found to have ocular-type myasthenia gravis. Chest computed tomography showed a tumor in the anterior mediastinum. A thymoma was suspected, and thymectomy was performed. Postoperative specimen showed dilated cyst wall lined by pseudostratified ciliated epithelium. A bronchogenic cyst was diagnosed. Although relatively rare, bronchogenic cysts should be included in the differential diagnosis of tumors in the anterior mediastinum in patients with myasthenia gravis.

KEY WORDS: anterior mediastinum, bronchogenic cyst, myasthenia gravis, thymectomy, thymoma

INTRODUCTION

Thymoma is the most common primary tumor of the anterior mediastinum. It usually occurs in middle-aged adults. Approximately 35-40% of patients with thymoma have myasthenia gravis (MG), and 10-23% of MG patients have thymoma[1]. However, bronchogenic cysts are rare mediastinal tumors and occur relatively rarely in the anterior mediastinum. Herein, we report the case of a patient with MG having bronchogenic cyst in the anterior mediastinum mimicking thymoma.

CASE REPORT

A 74-year-old male patient was admitted to our hospital because of progressive muscle weakness and headache. Ocular-type MG was diagnosed in this patient, and he was treated with pyridostigmine and followed up on an outpatient basis for half a year. He had been experiencing drooping of both eyelids for two weeks before admission. After admission, double vision and fatigue developed, and he had difficulty in opening both eyes and turning in bed without support. He had no fever, dyspnea, dysphagia, and family history of any medical illness. Physical examination and laboratory tests showed no abnormalities. Thoracic computed tomography showed a 1.7 × 1.3 cm mass within the hyperplasia of the thymus in the anterior mediastinum (Fig. 1). A clinical diagnosis of MG with thymoma was made based on the medical history and imaging findings. He underwent thymectomy through a sternotomy incision. The specimen measured 12 x 8 x 3 cm and contained a 2 x 1.5 x 1 cm unilocular cyst with a thin wall in the thymus. Histological analysis showed that the wall of the dilated cyst was lined by pseudostratified ciliated epithelium (Fig. 2). The lesion was diagnosed as a bronchogenic cyst occurring in the thymus. The patient was discharged on the 12th postoperative day. He received clinical follow-up without any complications and was free of symptoms with oral pyridostigmine therapy.

DISCUSSION

Anterior mediastinal cystic lesions of the thymus account for 1% of all mediastinal masses[2]. Bronchogenic cysts occurring in the thymus are rare. Harry et al[3] reported two extremely rare cases in which preoperative imaging did not indicate bronchogenic cysts. These cysts typically occur in the middle or posterior mediastinum near the tracheal carina. Atypical locations such as the neck, intradural sites, and subdiaphragmatic spaces have also been reported[3]. Two theories exist about the origin of ectopic bronchogenic cysts. One is budding of the

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tracheal primordia during development. The other is an abnormal migration of the tracheobronchial epithelium to the ectopic region\[^4\]. Bronchogenic cysts are pure cystic mediastinal masses. Computed tomography usually shows a single, smooth, round, or elliptical mass with homogenous low attenuation\[^5\]. However, thymomas usually present as sharply demarcated round or oval soft tissue masses in the region of the thymus and show mild-to-moderate contrast enhancement\[^2\]. When any suspicious lesion of the thymus is detected on computed tomography, it should be surgically removed to exclude the possibility of malignancy even if the lesion does not have the classic imaging appearance of a bronchogenic cyst. Regardless of the location, bronchogenic cysts should be considered in the differential diagnosis of mediastinal masses.

CONCLUSION
Bronchogenic cysts are uncommon in the anterior mediastinum, especially within the thymus. Surgeons should consider the possibility of bronchogenic cysts in the differential diagnosis of any mediastinal mass, regardless of its location.

REFERENCES
Case Report

Vitreous Hemorrhage as a Complication of HELLP Syndrome

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ABSTRACT

Hypertensive disorders during pregnancy often affect the eyes. Sometimes the eye symptoms precede other systemic changes necessary for a correct diagnosis. In the last trimester of pregnancy with mild pre-eclampsia a woman developed spontaneous vitreous hemorrhage. She was later diagnosed as having HELLP syndrome, a recently described disorder comprising of hemolysis, elevated liver enzymes, and a low platelet count. We believe this rare complication of pregnancy to be the cause of the intraocular bleeding.

KEYWORDS: elevated liver enzymes, pre-eclampsia, thrombocytopenia

INTRODUCTION

The hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome may be considered a severe variant of pre-eclampsia / eclampsia¹ or a separate disorder with features that overlap pre-eclampsia / eclampsia²⁻³. The HELLP syndrome may cause hepatic rupture, disseminated intravascular coagulation (DIC), acute tubular necrosis (ATN), pulmonary edema, adult respiratory distress syndrome, and hemorrhage⁴. The incidence of maternal mortality in the HELLP syndrome has been reported at 1% to 4% whereas perinatal mortality has been estimated at 10% to 20%. The few reported cases of ophthalmic manifestations in the HELLP syndrome do not describe major persistent visual loss. Patients with the HELLP syndrome are typically multiparous white women with a mean age of 25 years. Symptoms develop during the second or third trimester. HELLP occurs antepartum in 69% to 80% of cases, the remainder occurring between 48 hours to 7 days after delivery⁵. Although visual disturbances occur in 20% to 25% of patients with severe pre-eclampsia and eclampsia⁶⁻⁸, most patients demonstrate complete resolution within several weeks. The reported risk of recurrent HELLP syndrome in future pregnancies is between 3% and 27%, with the risk of recurrent eclampsia or pre-eclampsia being approximately 20%. The precise pathogenesis of the HELLP syndrome has not yet been determined. However, the prevailing theory⁹ is that endothelial injury leads to fibrin deposition, causing activated platelets to release vasoconstrictive substances, leading to further platelet aggregation and consumption at sites of endothelial damage. This leads to the microangiopathic hemolytic changes seen with this syndrome. To date, prompt delivery is the only intervention known to improve its clinical course.

CASE REPORT

A previously healthy 29-year-old woman was diagnosed with pre-eclampsia at 33 weeks of gestation. Her blood pressure was 170/92 mmHg with a hemoglobin 14.5 g/dl, hematocrit of 43.5%, platelet count of 118,000/mm³, proteinuria ++, creatinine 0.8 mg/dl, serum aspartate transaminase (SGOT) of 280 IU, serum glutamic pyruvic transaminase (SGPT) of 313 IU and lactic dehydrogenase (LDH) of 927 IU. Her past medical history was negative. She was placed on bed rest and treated with antihypertensives in the form of α-methyl dopa 250 mg QID, betamethasone 12 mg intramuscularly on admission and 12 mg dose repeated intramuscularly after 24 hours for foetal lung maturity. On the third day after diagnosis, her blood pressure increased to 188/96 mmHg and she reported severe epigastric pain, nausea, and vomiting.
followed by gross hematuria. Increased facial and extremity edema was noted. At that point, she first reported blurred vision in both eyes. A laboratory workup revealed platelets 90,000/ml (150,000 - 400,000/ml), SGOT 1497 U/l (12 - 30 U/l), SGPT 1723 U/l (5 - 32 U/l), and lactate dehydrogenase (LDH) 2419 U/l (85 - 200 U/l). Based on these clinical and laboratory findings the HELLP syndrome was diagnosed. The patient was transfused with platelets, fresh-frozen plasma, and packed red blood cells and taken up for emergency cesarean section. On the first postoperative day, she was treated with intravenous furosemide 20 mg and labetolol 10 mg intravenously with a peak blood pressure of 170/116 mmHg. She was placed on a protocol of labetolol, alfa -methyl dopa and nifedepine retard to maintain the systolic blood pressure at less than 150 mmHg. The patient’s metabolic parameters gradually returned to normal. Both mother and child improved except that she was drowsy and confused but still reported persistent blurred vision in both eyes and an inability to recognize family members. An ophthalmic consult was requested.

On ocular examination, the Snellen visual acuity was 20/30 in the right eye and 20/100 in the left. The intraocular pressures and anterior segment examinations were normal in both eyes. A fundus examination of the right eye showed it to be entirely normal (Fig. 1). A fundus examination of the left eye revealed one globular preretal hemorrhage of seven to eight, disc diameters in size, straddling the infra-temporal arcade (Fig. 2). A small amount of breakthrough vitreous hemorrhage obscured much of the detail of the posterior pole findings, though the retina was otherwise grossly intact and appeared normal. Blood pressure readings were normal in the following 10 days. Over the next two weeks the vitreous hemorrhage gradually resolved, though there was still a preretal hemorrhage in the fundus, presumably overlying the source of the initial bleed.

The patient returned for follow-up ophthalmic examination one month after delivery. The Snellen visual acuity in the left eye was then 20/30. Fundus examination of the left eye showed that nearly all the preretal hemorrhage had been reabsorbed. A tiny fibrotic scar was noted over a small branch arteriole in the fundus, which was previously obscured by the overlying blood, and which probably represented the healed focus of the previous hemorrhage.

**DISCUSSION**

From 4% to 12% of patients with pre-eclampsia or eclampsia develop the HELLP syndrome. Incomplete expression occurs in 50% of HELLP syndrome patients and does not carry the same risks as complete expression. The latter group tends to have a more severe disease process as manifested by an increased risk of postpartum hemorrhage and more complicated recovery\[10\]. The diagnosis of HELLP syndrome in 15% of patients without underlying pre-eclampsia is often delayed, leading to increased morbidity and mortality in this subgroup.

Although visual scintillations, visual perceptual impairments, and visual loss are well-recognized manifestations of pre-eclampsia / eclampsia they are usually transient. The main cause of posterior reversible encephalopathy syndrome (PRES) is acute elevation of blood pressure above the upper limit of cerebral blood flow autoregulation[11]. Severe hypertension is not mandatory for PRES to develop, and previously normotensive individuals can have signs of encephalopathy at blood pressures as low as 160/100 mmHg. The pathophysiology of PRES is also thought to be related to endothelial dysfunction, especially in cases without severe hypertension. The relatively selective involvement of the posterior cerebral areas may reflect a major susceptibility of this region because of a lesser degree of adrenergic innervation supporting circulatory autoregulation.
Among the few reported cases of visual complications in patients with the HELLP syndrome, none had permanent visual deficits. Burke et al.\(^ {12} \) described a case associated with bilateral serous retinal detachments, unilateral vitreous hemorrhage, and dural venous sinus thrombosis, but with complete recovery in all respects. In a series of 442 patients, there are two reported cases of acute cortical blindness in patients with pre-eclampsia and HELLP syndrome with full visual recovery 3 - 7 days postpartum. Sedrowicz et al.\(^ {13} \) reported retinal edema with hemorrhages showing spontaneous resolution after delivery. Gonzalvo et al.\(^ {14} \) described a patient with the HELLP syndrome who had a central retinal vein occlusion 10 days after delivery. The patient with the HELLP syndrome who had a central retinal vein occlusion 10 days after delivery. The visual symptoms and ophtalmoscopic findings spontaneously resolved after two months. Washita et al.\(^ {15} \) reported a case of the HELLP syndrome with an intracerebral hematoma and associated diffuse cerebral edema. The patient developed DIC, hepatic hematoma, and cerebral infarction after developing cerebral hemorrhage. Fifteen days after evacuation of the hematoma, no focal neurologic deficits were noted. However, after experiencing a hypertensive crisis and a convulsive seizure, the patient entered an irreversible coma with fixed and dilated pupils. In the HELLP syndrome, Barton et al.\(^ {16} \) observed in women with severe pre-eclampsia or eclampsia, that severe hypertension is often only transient or entirely absent.

Corticosteroids\(^ {17} \), plasmapheresis and expectant management are all therapeutic modalities undergoing investigation for treatment of the HELLP syndrome. We believe that our patient suffered from unrecognized thrombocytopenia secondary to HELLP syndrome and hence intraocular hemorrhage as a consequence of HELLP syndrome at the time of her initial visual complaint. Although the retinal hemorrhage was probably a result of this clotting abnormality, an unrecognized transient episode of hypertension related to pre-eclampsia may have also contributed to the rupture of the susceptible site in a peripheral retinal vessel.

**CONCLUSION**

The key to successful management of HELLP syndrome and associated devastating visual and systemic complications is its early detection by clinical judgement and laboratory warning signs. A multidisciplinary approach with rapid and consistent targeted symptomatic therapy to save the women at risk is essential considering the poor maternal and fetal outcomes.

**REFERENCES**

Phenytoin Therapy for Refractory Ischemic Ventricular Tachycardia

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ABSTRACT

Phenytoin is an antiepileptic drug with some antiarrhythmic properties that are seldom used for refractory ventricular tachycardia in the coronary care units. We present a case of refractory ischemic ventricular tachycardia that failed to respond to multiple attempts of direct current cardioversion and parenteral treatment modalities. This case describes the usefulness of phenytoin in life-threatening ventricular tachyarrhythmia when it is refractory to the recommended standard line of treatment and commonly used antiarrhythmic medications.

KEY WORDS: antiarrhythmic, polymorphic ventricular tachycardia, refractory

INTRODUCTION

The usage of phenytoin by physicians has been always challenged by the availability and the easy access of antiarrhythmic medications in the coronary care unit (CCU)1. Nevertheless, the treatment of resistant ventricular tachycardia (VT) in the context of ischemia has always been challenging. We present a case of refractory ischemic VT that failed multiple attempts of direct current cardioversions and parenteral treatment modalities.

CLINICAL REPORT

A 51-year-old male, chronic heavy smoker and type-2 diabetes mellitus (T2DM) patient presented with central chest pain associated with sweating and a sense of nausea. There was no prior history of similar illness or anginal episodes. On physical examination, his vitals were stable with unremarkable cardiovascular and chest abnormalities. The cardiac enzymes were elevated suggestive of myocardial injury with peak CK-MB isoenzyme of 80 IU/l (N: 0 - 10 IU/l) and Troponin I (TnI) of 170 µg/l (N: 0 - 1.5 µg/l). The serum potassium level was 4.2 mmol/l (N: 3.9 - 5 mmol/l) and magnesium level was 0.69 mmol/l (N: 0.60 - 0.90 mmol/l). The electrocardiogram (ECG) demonstrated normal sinus rhythm with interventricular conduction delay and non-specific ST segment depression as well as T wave inversion in lead I, aVL and V5 - 6 (Fig. 1). A non-ST elevation myocardial infarction (NSTEMI) treatment was initiated with intravenous (IV) heparin, metoprolol tablet 25 mg twice daily and aspirin 81 mg daily. The transthoracic echocardiogram demonstrated severe hypokinesia of the lateral wall with a mildly depressed LV systolic function (EF = 45%). The next day, he developed palpitation with a wide-complex ventricular tachycardia suggestive of monomorphic VT current shocks at 200 joules under sedation, which was successful in interrupting the arrhythmia but failed to maintain normal baseline rhythm. Therefore, he received boluses of IV magnesium sulphate 2 gm and a bolus of amiodarone 300 mg IV over 5 minutes, which was unsuccessful in restoring the baseline rhythm. Therefore, he received boluses of IV magnesium sulphate 2 gm and a bolus of amiodarone 300 mg IV over 5 minutes, which was unsuccessful in restoring the baseline rhythm. Then he was given a lidocaine IV bolus followed by four IV mexilitine boluses of 50 mg over 4-minutes duration each followed by in-between short periods of interruption to normal baseline rhythm. Nevertheless, his hemodynamics remained stable. Finally, his ventricular tachyarrhythmia responded to an IV loading dose of phenytoin 300 mg followed by infusion 50 mg per hour for 24 hours. The patient reverted to sinus rhythm after one minute of the bolus...
dose and he was continued afterward on maintenance therapy of oral phenytoin tablet of 100 mg three times daily. His hospital stay was uncomplicated by any further episode of monomorphic VT. His baseline and subsequent EKG after the event did not demonstrate long-QT or short-QT interval (The QT interval was 339 ms and QTc was 456 ms), and there was no Brugada syndrome configuration (Fig. 1).

DISCUSSION

In acute coronary syndrome the American College of Cardiology and the American Heart Association (ACC / AHA) guidelines recommend the usage of intravenous lidocaine and beta blockers for the treatment of polymorphic VT specifically associated with acute myocardial ischemia[5], plus an early revascularization strategy is advised in such situations[5]. Phenytoin is a Class IB agent which blocks the sodium channels affecting the refractory period as well as shortening the action potential duration in the His-Purkinje fibers[3,4]. It has been shown previously that phenytoin plays an important role in ventricular arrhythmia treatment and prophylaxis[3]. The early report was in animal-tested models with successful treatment of ectopic VT[6]. The usage of phenytoin was recommended for treating arrhythmias due to digoxin toxicity and other forms of inducible VT and ventricular fibrillation (VF)[7,8].

During the course of this case IV amiodarone was used, which is another widely available agent and used for various supraventricular and ventricular arrhythmias. It has a class III antiarrhythmic effect mainly prolonging the action potential duration, sodium channel blocking and β-blocking effect[9]. Hence, it may have the ability to transform a poorly tolerated VT into a tolerable one in the acute setting, and with a rapid intravenous administration it blocks fast sodium channels in a use-dependent fashion[10-11]. Amiodarone has very characteristic pharmacokinetics with slow accumulation and dissipation from the body, and the repolarization changes after the loading dose usually begin to appear after the fourth day, and it becomes more pronounced after 7-10 days[12]. Mitchell et al reported that the effect of amiodarone on sinus node automaticity, atrial and AV nodal conduction will reach its maximum effect within two weeks, whereas the effect on ventricular repolarization and the QTc interval will reach maximum effect in 10 weeks after oral administration of the drug[13]. Therefore, the micro-electrical effect of amiodarone with chronic use may take few days to appear. Nevertheless, in the ARREST trial, amiodarone was successful in resolving electrical storm in 60% of the population, especially, when compared with placebo[14], and can be effective even when other agents have been ineffective.

Mexiletine and lidocaine are from the same class as the phenytoin (Class IB oral antiarrhythmic medication) with similar mechanism of action, primarily blocking fast sodium channels, reducing the action potential but with negligible effect on conductivity and they do not prolong the QT (QTc) intervals[15]. Another antiarrhythmic medication which
was not used in this case is bretylium; this can cause a transient heart rate acceleration followed by a later decrease, but, primarily it lengthens the duration of the action potential and refractory periods of the atrial, ventricular and Purkinje fibres with a net effect of lowering the heart rate\[16\]. Overall, bretylium usage in life-threatening ventricular tachyarrhythmias that are refractory to treatment with other antiarrhythmic drugs has a reputation of effective suppression\[17\].

Propranolide and quinidine has a similar electrophysiological effect except that propranolide has no anticholinergic effect; but, both slow the conduction and prolong the refractoriness. In a comparison between the different antiarrhythmic drugs, Nademanee et al investigated the efficacy of sympathetic blockade in electrical storm by comparing propranolol, esmolol, and left stellate ganglionic blockade to combined lidocaine, propranolide, and bretylium therapy. The study subjects were non-randomized and all had a recent ischemic insult with more than 20 episodes of VT within 24 hours or more than four episodes per hour. The sympathetic blockade provided a marked survival advantage (78% Vs 18% at one week, and 67% Vs 5% at one year). Despite the high doses of propranolol, heart failure was not an issue\[18\]. These authors and others have suggested that the combination of amiodarone and propranolol improves survival rates and should be the mainstay of therapy in managing electrical storm in comparison with other antiarrhythmic medications\[19\]. Furthermore, Levine et al reported in a multi-center trial of 273 patients who had electrical storm that was refractory to propranolide, lidocaine and bretylium therapy, and when amiodarone was given, 46% of the patients survived for 24 hours without another episode of VT, and another 12% responded after taking amiodarone plus another agent\[20\]. In our case, the interaction or cumulative effect between different antiarrhythmic medications cannot be ruled out, plus the short time-period between the different medications may have been contributing for pro-arrhythmia or facilitating the phenytoin effect.

Phenytoin has been described in the past as an effective therapy for VT in several case reports and clinical scenarios in adult and pediatric patients\[21-26\]. In all of these cases, phenytoin has been used as the last resort to establish normal baseline rhythm. In our case, we demonstrate successful treatment of refractory ischemic VT with phenytoin without immediate or early revascularization. Our patient did not respond to magnesium sulphate, lidocaine, amiodarone, and mexilitine, but showed an immediate response to phenytoin. The limited data and the lack of large-scale RCTs between the different antiarrhythmic medications in different clinical scenarios may influence the physician’s choice and preference of the treatment modality, pending further clinical studies.

CONCLUSION
Phenytoin is still an effective treatment option for ischemia-induced ventricular tachyarrhythmia that is refractory to standard line of treatment and commonly used antiarrhythmic medications.

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Case Report

Transient Coronary Insufficiency Mimicking Acute Inferior Myocardial Infarction Triggered by Burn Injury

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ABSTRACT

ST-segment elevation with typical symptoms often indicates cardiac ischemia. There are many conditions that have been reported which mimic ST-elevation myocardial infarction. In addition to these reported conditions, we present the case of a 75-year-old Caucasian female who had transient myocardial injury after burn injury that mimicked inferior myocardial infarction. The electrocardiogram showed inferior ST-elevation indicative of an inferior myocardial infarction. The patient was evaluated as a case of acute coronary syndrome. However, the coronary angiogram and troponin-T levels were normal. We review the literature and suggest that the possible mechanism may be a coronary arterial spasm induced by the severe pain and emotional stress caused by the burn injury.

KEY WORDS: coronary angiography, electrocardiography, ST-segment elevation myocardial infarction

INTRODUCTION

A rapid and accurate diagnosis of acute ST-segment elevation myocardial infarction (STEMI) is of crucial importance as early initiation of primary percutaneous coronary intervention (PCI) is beneficial for patients[1]. In general, plaque rupture or plaque erosion and subsequent platelet aggregation and thrombosis resulting in acute occlusion of a coronary artery is considered the main mechanism of STEMI[2]. However, PRAGUE studies showed that 2.6 percent of patients with suspected STEMI were found to have intact coronary arteries in diagnostic coronary angiography (CAG)[3].

Various conditions may present with an identical electrocardiographic pattern as STEMI in clinical practice[4]. We report the case of an unusual form of acute myocardial injury which is an example of non-obstructive coronary artery disease.

CASE REPORT

A 75-year-old Caucasian female was admitted to the Emergency Department (ED) of our university hospital with burn injury. She was burned by boiling water as a consequence of a syncopal episode. Her medical history included type-2 diabetes mellitus (DM), hyperlipidemia and hypertension. She did not report any medical history of cerebrovascular or cardiovascular disease or any other medical problems. She was only suffering from the lesions of burn. These lesions, which approximately covered seven percent of her body surface area, appeared on her left arm and upper abdomen. Only two percent of burned areas were first degree in severity and the rest was second degree. Her physical examination was normal except a doubtful positive Babinski on the right side.

Her blood tests on admission were normal except elevated C-reactive protein and lactate dehydrogenase (LDH) levels. Her troponin T level and chest X-ray were also normal. A cranial diffusion MRI showed cerebellar-cerebral atrophy and enlargement of third and lateral ventricles but no hemorrhage or stroke signs were seen.

An echocardiographic examination demonstrated a sclerotic aortic valve and mild aortic regurgitation with left ventricular hypertrophy and grade one diastolic dysfunction. Her left ventricular ejection fraction was 70%.

A 12-lead electrocardiogram (ECG) on admission showed a sinus rhythm with normal findings and a heart rate of 68 beats/min (Fig. 1a).

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Five hours after entering the ED, while she was eating her meal, she began complaining about a sudden fatigue, sweating and dizziness. However, she did not have any chest pain while eating. On physical examination, she had bradycardia (58 beats/min) and low blood pressure (70/40 mmHg) which increased to 100/70 mmHg after 150 ml of 0.9% NaCl infusion. The patient’s ECG showed sinus rhythm with a heart rate of 62 beats/min and 1-mm ST segment elevations in leads II, III and AVF (Fig. 1b).

The patient was evaluated as a case of acute coronary syndrome and managed conservatively. A PCI was planned within the next 30 minutes which revealed normal coronary arteries without any signs of atherosclerosis, thrombosis or spontaneous spasm (Fig. 2a, b). Also, her troponin T levels obtained before angiogram and 12 hours later were negative (< 0.014 ng/ml).

**DISCUSSION**

Many conditions can make temporary changes in the electrocardiogram. Pericarditis or myopericarditis are among the most frequently reported diseases presenting as STEMI[4]. Brugada syndrome, an inherited disease with ST-segment elevation in leads V1 to V3 with or without right bundle branch block on the ECG and no structural heart disease, has been misdiagnosed as STEMI[5]. A coronary aneurysm and aortic stenosis are known causes of myocardial infarction without atherosclerosis[6]. In addition, multiple case reports have documented cardiomyopathies, aortic dissection and subarachnoid hemorrhage as the underlying
causes in patients with ST-segment elevation on the 12-lead ECG. Widimsky and his colleagues reported normal acute coronary angiograms in 26 / 1004 (2.6%) of patients with suspected STEMI. In contrast, a diagnosis of acute myocardial infarction was made in a total of seven patients (0.7%) with normal angiograms, and these patients with suspected STEMI had a conclusive diagnosis of pericarditis, myocarditis, dilated cardiomyopathy, hypertension with left ventricular hypertrophy, pulmonary embolism or misinterpretation of the ECG[3]. In a report, describing a range of non-coronary diagnoses in 958 STEMI patients by Larson and colleagues, a false-positive ST-segment elevation was described in 6.2 percent of their patients[7].

Wittstein et al proposed the concept of “stress-induced myocardial stunning”, and a neurohumoral reaction to a sudden emotional stress (a syndrome also called apical LV ballooning, or Tako-Tsubo cardiomyopathy)[8]. One possible mechanism of this condition is an ischemia resulting from an epicardial coronary arterial spasm. Also, increased sympathetic tone from a mental stress can cause coronary arterial vasoconstriction in patients without coronary disease. Lacy et al have shown that during a mental stressor of simulated public speaking patients have a decrease in coronary artery diameter, which returned to baseline after five minutes. Furthermore, these changes were similar in patients with and without coronary artery disease[9]. Myocardial dysfunction from smoke inhalation and primarily from carbon monoxide (CO) toxicity have been described[10]. Possible mechanism of this condition is mitochondrial dysfunction in the cardiac muscle due to inadequate oxygenation. Our case did not have exposure to smoke. The patient had severe pain and emotional stress because of exposure to boiling water. This high stress condition might have increased the sympathetic tone of the coronary arteries which might lead to coronary arterial spasm. Transient myocardial injury that happened in our case who had a normal angiogram might be caused by prolonged ischemic phase due to vasospasm.

CONCLUSION
The possible mechanism of myocardial injury in our case may be a coronary arterial spasm induced by the severe pain and emotional stress due to burn injury. In this respect, our case is a unique example of a transient myocardial injury, mimicking acute inferior myocardial infarction triggered by burn injury. There are no previous reports describing this condition. It is important for clinicians to recognize this kind of condition that mimic a STEMI, because the possibility of receiving thrombolytic therapy without an accurate indication may lead to dramatic results.

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Prevalence of Joint Hypermobility in Kuwait

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Aim: To determine the prevalence of joint hypermobility (JH) among young Kuwaiti adults

Methods: This was a cross-sectional study of 390 randomly selected healthy undergraduate university students, aged 18-29 years from the Health Sciences Centre, Kuwait University, Safat, Kuwait. Beighton score at four peripheral sites bilaterally (knees, elbows, thumbs and fifth fingers) and forward flexion of the trunk were used to evaluate joint hypermobility. Any student who met four out of the nine criteria was considered hypermobile. Joint pain was documented in all subjects through personal interview.

Results: A total of 390 subjects (male : female ratio 1.0 : 0.9) were assessed. Of those, 87 (22.3%) were found to have JH: 60 (29.4%) males and 27 (14.5%) females, showing a significantly higher male predominance (P < 0.001). Beighton score was inversely correlated with age (r = -0.15, P = 0.003). A higher incidence of finger signs was noted in comparison to elbow-knee hyperextension and hands-to-floor. Knee joint, back, neck and shoulder pains, in descending order, were the commonest type of joint complaints, although not statistically significant (P > 0.05) in subjects with and without joint hypermobility. It was also observed that the left side, at all the sites, was slightly more hypermobile in comparison to the right side in hypermobile subjects.

Conclusions: The prevalence of joint hypermobility is not uncommon among young Kuwaiti adults, and was comparable to the data published in other Asian-Pacific regions. General practitioners should therefore be familiar with the condition and its clinical associations, while assessing musculoskeletal complaints.

Emergency Peripartum Hysterectomy: A 13-Year Review at a Tertiary Center in Kuwait

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J Obstet Gynaecol India 2014; 64:403-408. doi: 10.1007/s13224-014-0554-z

Objective: To determine the incidence, indications, risk factors, and complications of emergency peripartum hysterectomy (EPH) and to evaluate total versus subtotal hysterectomy for EPH.

Materials And Methods: This is a retrospective case series involving thorough examination of the files of all women who had EPH between January 2000 and December 2012 in the department of Obstetrics and Gynecology, Al-Jahra hospital, Kuwait after taking approval from the ethics committee. Incidence, indications, risk factors, type of hysterectomy, and complications of EPH were obtained from patient files.

Results: There were 63,337 deliveries of which 70.3 % were vaginal deliveries, and 29.6 % were by cesarean section (CS). Sixty-eight women underwent EPH representing an overall incidence of 1 case per 1,000 deliveries. The indications for EPH included abnormal placentation (77.4 %), uterine atony (14.5 %), and uterine rupture (8.1 %). There was one maternal death. Maternal morbidity occurred in 25 (40.3 %)
women. The most common complications were mild to severe coagulopathy (19.35 %) and injury to the urinary tract (17.74 %). Injury to the ureter was avoided by placing ureteric stents preoperatively. Our population was significant in having higher rate of CS deliveries (91.9 %), women with prior CS (83.87 %), and high parity (mean 5.8).

**Conclusion:** Abnormal placentation was the most common indication to perform EPH. The relative risk of EPH was 27 for CS deliveries as compared to vaginal deliveries. There was no significant difference between subtotal versus total hysterectomy with respect to age, parity, previous CS, operative time, blood transfusion, and intra and post operative complications.

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**Celiac Disease in Children: Is it a Problem in Kuwait?**

Al-Qabandi W1, Buhamrah E2, Al-Abdulrazzaq D1, Hamadi K2, Al Refaee F3

1Department of Pediatrics, Faculty of Medicine, Kuwait University, Kuwait
2Department of Pediatrics, Al Amiri Hospital, Kuwait
3Department of Pediatrics, Al Adan Hospital, Kuwait


**Background:** Celiac disease (CD) is a chronic inflammatory disease of the small intestine triggered by gluten ingestion. The objective of this study is to describe our experience with CD children in Kuwait.

**Methods:** The records of children with CD seen in the pediatric gastroenterology unit between February 1998 and December 2010 were retrospectively reviewed. Patients were referred because of symptoms or positive CD antibody screening of a high-risk group (type 1 diabetes and Down syndrome).

**Results:** Forty-seven patients were diagnosed: 53% were symptomatic and 47% were identified by screening. The median age at diagnosis was 66 (range 7-189) months. All cases were biopsy-proven except one. The symptomatic patients were significantly younger than those identified following screening (P<0.004). In the whole group, 66% were females and 77% were Kuwaitis; 9% had a positive family history of CD. The estimated cumulative incidence was 6.9/10(5). The median duration of symptoms before diagnosis was 8.5 (range 2-54) months. Failure to thrive was the most common presenting complaint (72%) followed by diarrhea (64%) and abdominal distension (56%). Atypical manifestations were seen in 60% of patients. Underweight and short stature were confirmed in 19% and 17% of patients, respectively. Overweight and obesity were detected in 14% and 6%, respectively. CD serology was based on a combination of antiretinitis and antigliadin antibodies. The median follow up was 24 (range 12-144) months. All patients were commenced on a gluten free diet, but good compliance was only achieved in 78%.

**Conclusion:** The low frequency of childhood CD in Kuwait could probably be attributed to either an underestimation of the atypical presentations or failure of proper screening. Also, adherence to a gluten free diet is a major problem in our population.

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**Sudden Cardiac Death Diagnosed with Dilated Cardiomyopathy in a Kuwaiti Family: A Case Report**

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E-mail: maisa.mahmoud@dasmaninstitute.org


**Background:** Dilated cardiomyopathy is myocardial disease characterized by dilatation and impaired contraction of the left ventricle or both left and right ventricle. The majority of these cases are secondary
to coronary artery disease, hypertension and valvular cardiomyopathy. Patients diagnosed with dilated cardiomyopathy are further clinically evaluated for evidence of familial history of the disease. Those families have shown to have genetic predisposition to dilated cardiomyopathy; thus, currently there is no available single genetic test that allows comprehensive testing of all causative genes. We report a Kuwaiti case of dilated cardiomyopathy that was diagnosed at young age. The patient clinical presentation pointed out to the fact that this was a familial disease. This case is the first reported in Kuwait clinically presented with familial dilated cardiomyopathy implying a genetic susceptibility factor to be further investigated within the at-risk family members.

Case Presentation: 23-year-old Arab ethnicity Kuwaiti male with strong family history of dilated cardiomyopathy was admitted witnessed with sudden cardiac death. The patient presented with sudden arrhythmic death and survived with permanent anoxic brain injury. Transthoracic echocardiography revealed dilated cardiomyopathy with severe global left ventricular systolic dysfunction. After thorough investigation, the patient shown to have strong family history of dilated cardiomyopathy.

Conclusion: Familial dilated cardiomyopathy is poorly documented in Kuwait. We present this case with future plan to study the genetic map of his family.

Molecular Characterization of a Population-Based Series of Endometrial Stromal Sarcomas in Kuwait

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5Centre for Translational and Applied Genomics, British Columbia Cancer Agency, Vancouver, BC V5Z 4E6, Canada
6Department of Laboratory Medicine and Pathology, University of Alberta and Royal Alexandra Hospital, Edmonton, AB T5H 3V9, Canada

Hum Pathol 2014; 45:2453-2462 doi: 10.1016/j.humpath.2014.08.012

Endometrial stromal sarcomas (ESSs) frequently harbor genetic fusions, including JAZF1-SUZ12 and equivalent fusions in low-grade ESS (LGESS) and YWHAE-NUTM2 in high-grade ESS (HGESS). This study aims to classify a population-based series of ESSs in Kuwait based on the 2014 World Health Organization classification system and to assess the diagnostic use of interferon-induced transmembrane protein 1 (IFITM1) immunomarker for ESSs. Twenty ESSs including 19 LGESSs and 1 HGESS treated during the period between 2002 and 2013 were identified, and the cases were reviewed and characterized using fluorescence in situ hybridization and immunohistochemical studies. Thirteen (81.3%) of 16 LGESSs with interpretable results showed JAZF1 and/or PHF1 genetic rearrangements by fluorescence in situ hybridization, and the only HGESS in the series showed YWHAE genetic rearrangement. All LGESSs with interpretable results showed positive immunostaining for CD10 compared with 11 (61%) of 18 that showed positive immunostaining for IFITM1; 4 of 7 IFITM1-negative LGESSs showed JAZF1 and/or PHF1 rearrangements. A series of uterine leiomyomas, leiomyosarcomas, adenosarcomas, and carcinosarcomas were included for comparison, and positive IFITM1 staining was found in 1 of 10 leiomyomas, 3 of 13 leiomyosarcomas, 3 of 4 adenosarcomas, and 3 of 8 carcinosarcomas, compared to 0 of 10 leiomyomas, 9 of 13 leiomyosarcomas, 3 of 4 adenosarcomas, and 5 of 8 carcinosarcomas that were positive for CD10. Our results demonstrated characteristic genetic rearrangements in a high percentage of LGESSs in this Middle Eastern population, and IFITM1 antibody appears to be less sensitive than CD10 for LGESS.
Genetic Association of APOB Polymorphisms with Variation in Serum Lipid Profile among the Kuwait Population

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1Department of Biological Sciences, Faculty of Science, Kuwait University, PO Box 5969, SAFAT, 13060 Kuwait City, Kuwait.


Background: Several studies have identified APOB as a candidate gene predisposing individuals to dyslipidemia. Polymorphisms including the signal peptide (rs11279109), codon 2488 XbaI (rs1042031), codon 3611 MspI (rs693), codon 4154 EcoRI (rs1801701) and the 3’ variable number of tandem repeats have been reported to be associated with dyslipidemia in several populations. With limited studies on Arabs, this study aimed to investigate the genetic association of APOB polymorphisms and assess the potential influence of minor and rare alleles on serum lipid levels in the Kuwaiti population.

Methods: A total of 795 Kuwaiti subjects, documented with phenotypic data and fasting serum lipid levels, were genotyped for the five polymorphisms using PCR, PCR-RFLP and gene fragment analysis. Genotype and allele association with variation in serum lipid levels as well as haplotypes were analyzed using chi-square test, univariate and logistic regression analysis.

Results: Analysis of the genotype and allele frequencies distribution revealed a significant positive association between the APOB signal peptide and 3611 MspI polymorphisms with increased levels of triglycerides (statistical power of 80%). Haplotyping analysis further supported the findings by showing that carriers of haplotypes (IX-M-E+M) had significantly lower mean (SD) TG levels (0.86 ± 0.07) as compared to non-carriers (1.01 ± 0.02). Significance was also observed with regards to positive family history of hypercholesterolemia.

Conclusion: The results imply a “protective role” for two alleles (rs11279109 and rs1801701) in which logistic regression analysis showed a significant half-fold decrease in the risk for heterozygotes of rs11279109 and an 8.8 fold decrease in the risk for homozygous M-M- of rs1801701 of having lower TG levels (<1.70 mmol/L) in individuals. This suggests that genetic interaction between various polymorphisms at different gene loci act in linkage disequilibrium to affect serum TG levels. Apo B genotyping may be a useful adjunct for the identification of individuals at risk of developing dyslipidemia in order to provide them with lifestyle modifications and/or pharmacological intervention to mitigate the effects of gene interaction and environmental influence.

Candida Kefyr as a Cause of Bloodstream Infection and Adjunctive Role of Biomarkers in Its Diagnosis

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3Unit of microbiology, Al-Amiri hospital, Kuwait


A rare case of bloodstream infection caused by Candida kefyr is described. The diagnosis was established by repeatedly isolating the yeast in blood cultures and by detecting C. kefyr-specific DNA in serum samples. Demonstration of elevated serum levels of β-D-glucan and Candida mannan also provided additional diagnostic evidence. The identity of the isolates was confirmed by PCR sequencing of the ITS region of rDNA. This is the first report of C. kefyr candidemia from Kuwait and the Middle East. The report highlights emerging clinical significance of rare Candida spp. in etiology of candidemia and reinforces the adjunctive role of biomarkers in diagnosis.
Species Spectrum and Antifungal Susceptibility Profile of Vaginal Isolates of Candida in Kuwait

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Electronic address: alfouzan.w@hsc.edu.kw
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³Department of Obstetrics and Gynecology, Farwania Hospital, Kuwait
⁴Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 760, 51007 Fintas, Kuwait


Objective: The study was undertaken to determine the prevalence of vulvovaginal candidiasis (VVC) among patients with vaginitis, frequency of different Candida species, and their susceptibility profile. Patients And Methods: Over six months period, high vaginal swabs were cultured on Sabouraud’s dextrose agar and isolates were identified by culture on CHROMagar Candida and Vitek2 yeast identification system or/and API 20C (BioMerieux, France). Antifungal susceptibility of the Candida isolates was determined by E-test against amphotericin B, fluconazole, fluconazole, voriconazole, posaconazole, and caspofungin. Results: One thousand hundred and fifty-two women were screened for the prevalence of Candida spp. Vaginal swab cultures of 231 (13.2%) women yielded Candida spp. The isolation rates of different species were as follows: Candida albicans (73.9%), Candida glabrata (19.8%), Candida kefir (1.94%), Candida tropicalis (0.96%), Candida parapsilosis (0.96%), Candida krusei (0.96%), Candida guilliermondii (0.96%), and Saccharomyces cerevisiae (0.52%). All strains of C. albicans and non-C. albicans were susceptible to most of the antifungal agents tested. Conclusion: The high frequency with which C. albicans was recovered and its azole susceptibility support the continued use of azole agents for empirical therapy of uncomplicated VVC. However, a larger controlled study is required to determine the role of non-C. albicans in recurrent VVC.

Demography and Clinical Course of Ulcerative Colitis in Arabs - A Study Based on the Montreal Classification

Siddique I¹, Alazmi W, Al-Ali J, Longenecker JC, Al-Fadli A, Hasan F, Memon A
¹Department of Medicine, Faculty of Medicine, Kuwait University, Safat, Kuwait


Objective: Ulcerative colitis (UC) is generally considered a disease of the Caucasian populations in developed countries, but its incidence is increasing rapidly in many developing countries, including the Middle East. The objective of this study was to determine the clinical epidemiology of UC in Arabs. Material And Methods: This cross-sectional medical record-based descriptive study collected sociodemographic and clinical information on 182 Arab patients with UC in Kuwait. Age at diagnosis, extent and severity of disease were determined according to the Montreal classification. results: Among the 182 patients, 91 (50.0%) were males. The median age at diagnosis was 28.5 years. Family history of UC was reported by 26 (14.3%) patients. The extent of the disease was limited to the rectum in 34 (18.7%) patients, left sided in 67 (36.8%) and pan colitis in 81 (44.5%). At the time of inclusion in the study, 127 (69.8%) patients were in clinical remission, 53 (29.1%) had mild-to-moderate disease and 2 (1.1%) had severe colitis. Younger age at diagnosis and non-smoking were associated with more extensive colitis. The majority of patients were treated with mesalamine, steroids and immunomodulators, while biologic therapy and surgery were needed in 5% and 4% of the patients, respectively. Conclusions: UC presents more commonly at younger age among Arabs in Kuwait. Extensive disease at presentation is associated with younger age at diagnosis and absence of tobacco smoking. There also appears to be less need for surgery and biologic therapy for the disease in this population.
Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2015; 47 (1): 71 - 81

5th Asian Football Confederation Medical Conference
Apr 2 - 4, 2015
India / New Delhi
Contact: Conference Secretariat, All India Football Federation
Phone: 011-91-11-2804-1430
Email: aiff@the-aiff.com

Airway Interventions & Management In Emergencies - Montreal
Apr 8, 2015
Canada / Quebec / Montreal
Contact: Janice Macisaac, Cme Manager, Canadian Association of Emergency Physicians
Phone: 613-523-3343 Ext. 20; Fax: 613-523-0190
Email: jmacisaac@caep.ca

Diagnosis to Treatment: Recognizing Obesity as a Disease
Apr 8 - 12, 2015
United States / Colorado / Denver
Contact: Asbp
Phone: 303-770-2526; Fax: 303-779-4834
Email: info@asbp.org

2015 Anxiety & Depression Conference
Apr 9 - 12, 2015
United States / Florida / Miami
Contact: Anxiety & Depression Association of America
Phone: 240-485-1032

2015 Australain Psychological Society (APS) College of Health Psychologists Conference
Apr 10 - 11, 2015
Australia / Sydney
Contact: Aps
Phone: 011-61-3-8662-3300; Fax: 011-61-3-9663-6177
Email: events@psychology.org.au

94th American Association of Plastic Surgeons (AAPS)
Annual Meeting
Apr 11 - 14, 2015
United States / Arizona / Scottsdale
Contact: Aaps
Phone: 978-927-8330, Fax: 978-524-8890

2015 British Neuroscience Association (BNA) Festival of Neuroscience
Apr 12 - 15, 2015
United Kingdom / Edinburgh
Contact: Bna
Phone: 011-44-20-8166-8713
Email: office@bna.org.uk

Clinical Training Course: Osteoporosis & Other Metabolic Bone Diseases
Apr 13 - 15, 2015
United Kingdom / Oxford
Contact: Janet Crompton, Course Organiser, Bone Research Society
Phone: 011-44-14-5354-9929; Fax: 011-44-14-5354-8919
Email: janet@janet-crompton.com

Mental Health Care in the Community: Dementia & Older Adult Mental Health
Apr 13, 2015
United Kingdom / Birmingham
Contact: Amy Partleton, Centre For Professional Development, University of Birmingham
Phone: 011-44-12-1414-2677
Email: a.partleton@bham.ac.uk

14th Asian Australasian Congress of Neurological Surgeons
Apr 15 - 18, 2015
South Korea / Jeju
Contact: Gabriel Heng, Apm, Kenes Asia
Phone: 011-65-295-6984; Fax: 011-65-292-4721
Email: info@aacns2015.com

2015 European Lung Cancer Conference
Apr 15 - 18, 2015
Switzerland / Geneva
Contact: European Society For Medical Oncology
Phone: 011-41-91-973-1900; Fax: 011-41-91-973-1902
Email: esmo@esmo.org

7th International Congress on Psychopharmacology/3rd International Symposium on Child & Adolescent Psychopharmacology
Apr 15 - 19, 2015
Turkey / Antalya
Contact: Gokcen Demirkaya, Project Coordinator, Valor Congress Organizations
Phone: 011-90-31-2491-8888; Fax: 011-90-31-2491-9989
Email: valor@valor.com.tr
7th World Cornea Congress
Apr 15, 2015
United States / California / San Diego
Contact: Gail Reggio, Executive Director, Cornea Society
Phone: 703-591-0196; Fax: 703-434-3000
Email: info@corneasociety.org

8th International Dip Symposium on Diabetes, Hypertension, Metabolic Syndrome & Pregnancy
Apr 15 - 18, 2015
Germany / Berlin
Contact: Dip Secretary, Comtecmed
Phone: 011-972-3-566-6166
Email: dip@comtecmed.com

2015 Canadian Association for Clinical Microbiology & Infectious Diseases (CACMID) Annual Conference
Apr 16 - 18, 2015
Canada / Prince Edward Island / Charlottetown
Contact: Dr. Matthew W. Gilmour, Secretary Treasurer, Cacmid
Phone: 204-787-4597; Fax: 204-787-4699
Email: matthew.gilmour@cacmid.ca

Apr 16 - 18, 2015
France / Paris
Contact: Sylke Anderson, Meeting Administrator, Icjr
Phone: 760-942-7859; Fax: 760-942-1140
Email: sanderson@icjr.net

2nd World Congress on Controversies in Pediatrics
Apr 16 - 19, 2015
Hungary / Budapest
Contact: Secretariat, Congressmed
Phone: 011-972-73-706-6950
Email: copedia@congressmed.com

36th Annual American College of Oral & Maxillofacial Surgeons (ACOMS) Scientific Conference & Exhibition
Apr 18 - 20, 2015
United States / Florida / Fort Lauderdale
Contact: ACOMS
Phone: 202-367-1182; Fax: 202-367-2182

Management of Gynaecology in the Community
Apr 20 - 22, 2015
United Kingdom / Birmingham
Contact: Amy Partleton, Centre for Professional Development, University of Birmingham
Phone: 011-44-12-1414-2677
Email: a.partleton@bham.ac.uk

2015 Canadian Society of Nephrology (CSN) Annual General Meeting
Apr 22 - 26, 2015
Canada / Quebec / Montreal
Contact: Stacey Pacheco, Coordinator, Csn Administrative Office
Phone: 514-643-4985
Email: coordinator@csnscn.ca

2015 British Maternal & Fetal Medicine Society (BMFMS) Annual Conference
Apr 23 - 24, 2015
United Kingdom / London
Contact: Society Administrator, Bmfms
Email: bmfms@rcog.org.uk

2015 International Congress of Korean Society of Surgery
Apr 24 - 26, 2015
South Korea / Seoul
Contact: Danny D. Jung, Manager, Ib Planning
Phone: 011-82-2-2273-7650; Fax: 011-82-2-2273-7651
Email: korl@ibmed.co.kr

Diagnosis & Management of Prolapse, Including Use of Pessaries & Follow-Up of the Pessary Patient
Apr 24, 2015
Canada / Alberta / Calgary
Contact: Laurie Simmonds, Cumming School of Medicine, University of Calgary
Phone: 403-210-6275
Email: lsimmond@ucalgary.ca

Imaging in Adult Congenital Heart Disease: Pearls for All Cardiac Providers
Apr 24 - 26, 2015
United States / Florida / Ponte Vedra Beach
Contact: Cvcm, Coordinator, Mayo Clinic
Phone: 800-283-6296 or 507-266-6703
Email: cvcme@mayo.edu

1st World Conference on Abdominal Wall Hernia Surgery
Apr 25 - 29, 2015
Italy / Milan
Contact: Organizing Secretariat, Aim Group International Milan
Phone: 011-39-2-56-6011; Fax: 011-39-2-5660-9045
Email: hernia2015@aimgroup.eu

4th Joint Meeting of European Calcified Tissue Society & International Bone & Mineral Society
Apr 25 - 28, 2015
Netherlands / Rotterdam
Contact: Kate Timms, Congress Secretariat, Bioscientifica
Phone: 011-44-14-5464-2240; Fax: 011-44-14-5464-2222
Email: katie.timms@bioscientifica.com
5th Annual Bit World Congress of Molecular & Cell Biology  
Apr 25 - 28, 2015  
China / Nanjing  
Contact: Judy, Bit Congress, Inc.  
Phone: 011-86-411-8479-9609 Ext. 856; Fax: 011-86-411-8479-9629  
Email: judy@cmcbcongress.com

2015 Transcatheter Cardiovascular Therapeutics Angioplasty Summit (TCTAP)  
Apr 28 - May 1, 2015  
South Korea / Seoul  
Contact: Summit Md  
Email: cvrf@summitmd.com

2015 Asian Pacific Society of Cardiology Congress 2015  
Apr 29 - May 2, 2015  
United Arab Emirates / Abu Dhabi  
Contact: MCI Middle East, Congress Secretariat, MCI Middle East  
Phone: 011-97-14-311-6300  
Fax: 011-97-14-311-6301  
Email: apscc2015@mci-group.com

Clinical Endocrinology for Primary Care  
Apr 30 - May 3, 2015  
United Kingdom / Cayman Islands  
Contact: Medical Education Resources, Inc.  
Phone: 800-421-3756 Or 303-798-9682; Fax: 303-798-5731  
Email: info@mer.org

Diabetes Update & Advances in Endocrinology & Metabolism  
Apr 30 - May 2, 2015  
United States / California / San Francisco  
Contact: Office of Continuing Medical Education, UCSF  
Phone: 415-476-4251; Fax: 415-476-0318  
Email: info@ocme.ucsf.edu

Geriatrics & Pain Management for Primary Care  
May 1 - 3, 2015  
United States / New Mexico / Santa Fe  
Contact: Leslie Burk, MCE Conferences, MCE Conferences Inc.  
Phone: 888-533-9031  
Fax: 858-777-5588  
Email: info@mceconferences.com

2015 Association for Research in Vision & Ophthalmology (ARVO) Annual Meeting  
May 3 - 7, 2015  
United States / Colorado / Denver  
Contact: ARVO  
Phone: 240-221-2900; Fax: 240-221-0370

2015 Annual International Conference on Public Health  
May 4 – 7, 2015  
Greece / Athens  
Contact: Gregory Papanikos, Mr, Athens Institute For Education and Research (ATINER)  
Phone: 011-30-210-363-4210  
Email: info@atiner.gr

7th International Pediatric Simulation Symposia & Workshops  
May 4 - 6, 2015  
Canada / British Columbia / Vancouver  
Contact: Tanguy Roelens, IPSS Corporate Relations Manager, International Pediatric Simulation Society  
Phone: 011-32-2-740-2254  
Email: tanguy.roelens@associationhq.com

Anesthesia Update Mediterranean Cruise  
May 4 - 16, 2015  
Italy / Venice  
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars  
Phone: 509-547-7065; Fax: 509-547-1265  
Email: coleen@nwas.com

11th International Symposium on Endovascular Therapeutics  
May 6 - 9, 2015  
Spain / Barcelona  
Contact: Site Secretariat  
Phone: 011-34-93-505-2503; Fax: 011-34-93-488-3703  
Email: secretariat@sitesymposium.org

48th Annual European Society for Paediatric Gastroenterology, Hepatology & Nutrition (ESPGHAN) Meeting  
May 6 - 9, 2015  
Netherlands / Amsterdam  
Contact: Lucy Church, Project Assistant, MCI Uk Ltd  
Phone: 011-44-845-180-0360  
Email: annualmeeting2015@espghan.org

74th Annual Society for Investigative Dermatology (SID) Meeting  
May 6 - 9, 2015  
United States / Georgia / Atlanta  
Contact: SID  
Phone: 216-579-9300; Fax: 216-579-9333  
Email: sid@sidnet.org
<table>
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<tr>
<th>Conference</th>
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<tr>
<td>2015 Arteriosclerosis, Thrombosis &amp; Vascular Biology</td>
<td>May 7 - 9, 2015</td>
<td>United States / California / San Francisco</td>
<td>Phone: 888-242-2453 (Us) Or 214-570-5935 Email: <a href="mailto:scientificconferences@heart.org">scientificconferences@heart.org</a></td>
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<tr>
<td>21st World Congress on Controversies in Obstetrics, Gynecology &amp; Infertility (COGI)</td>
<td>May 7 - 10, 2015</td>
<td>China / Guilin</td>
<td>Contact: Secretariat, Secretariat, Congressmed Phone: 011-972-73-706-6950; Fax: 011-972-73-706-6959 Email: <a href="mailto:cogi@congressmed.com">cogi@congressmed.com</a></td>
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<td>14th European Association for Palliative Care World Congress</td>
<td>May 8 - 10, 2015</td>
<td>Denmark / Copenhagen</td>
<td>Contact: Interplan Congress, Meeting &amp; Event Management Ag Phone: 011-49-89-5482-3462; Fax: 011-49-89-5482-3444 Email: <a href="mailto:eapc2015@interplan.de">eapc2015@interplan.de</a></td>
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<td>2015 Canadian Blood &amp; Marrow Transplant Group (CBMTG) Annual Conference</td>
<td>May 13 - 16, 2015</td>
<td>Canada / Quebec / Montreal</td>
<td>Contact: CBMTG Head Office Phone: 604-874-4944; Fax: 604-874-4378 Email: <a href="mailto:cbmtg@malachite-mgmt.com">cbmtg@malachite-mgmt.com</a></td>
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<tr>
<td>23rd Annual Symposium: New Developments in Prenatal Diagnosis &amp; Medical Genetics</td>
<td>May 13, 2015</td>
<td>Canada / Ontario / Toronto</td>
<td>Contact: Elizabeth Gan, CME Administrative Course Director, Dept. of Ob/Gyn, University of Toronto / Mount Sinai Hospital Phone: 416-586-4800 Ext. 2489, Fax: 416-586-5958 Email: <a href="mailto:egan@mtsinai.on.ca">egan@mtsinai.on.ca</a></td>
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<tr>
<td>2015 Advances in Rhinoplasty</td>
<td>May 14 - 17, 2015</td>
<td>United States / Illinois / Chicago</td>
<td>Contact: American Academy of Facial Plastic &amp; Reconstructive Surgery Phone: 703-299-9291; Fax: 703-299-8898 Email: <a href="mailto:info@aafprs.org">info@aafprs.org</a></td>
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<td>2015 Annual Meeting of Society of Biological Psychiatry (SOBP)</td>
<td>May 14 - 16, 2015</td>
<td>Canada / Ontario / Toronto</td>
<td>Contact: SOBP Phone: 904-953-2842 Email: <a href="mailto:maggie@sobp.org">maggie@sobp.org</a></td>
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<td>4th International Spinal Cord Society / Am Spinal Injury Assoc. Joint Sc. Meeting</td>
<td>May 14 - 16, 2015</td>
<td>Canada / Quebec / Montreal</td>
<td>Contact: Contendam Ltd Phone: 011-44-20-8748-8868 Email: <a href="mailto:info@iscosasias2015.org">info@iscosasias2015.org</a></td>
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<tr>
<td>5th International Congress on Neuropathic Pain</td>
<td>May 14 - 17, 2015</td>
<td>France / Nice</td>
<td>Contact: Raya Van Hugten, Apm, Kenes International Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140 Email: <a href="mailto:neuropathic@kenes.com">neuropathic@kenes.com</a></td>
</tr>
<tr>
<td>Medical CBT: Ten-minute Cognitive Behaviour Therapy Techniques for real doctors</td>
<td>May 15 - 16, 2015</td>
<td>Canada / Ontario / Ottawa</td>
<td>Contact: Greg Dubord, MD, CME Director, CBT Canada Phone: 877-466-8228 Email: <a href="mailto:registrar@cbt.ca">registrar@cbt.ca</a></td>
</tr>
<tr>
<td>10th Recent Advances in Neuropsychiatric, Psychological &amp; Social Sciences</td>
<td>May 19 - 22, 2015</td>
<td>Greece / Athens</td>
<td>Contact: John Kouros, Dr., Association of Psychology &amp; Psychiatry for Adults &amp; Children Phone: 011-30-210-684-2663, Fax: 011-30-210-684-2079 Email: <a href="mailto:congress@appac.gr">congress@appac.gr</a></td>
</tr>
<tr>
<td>2015 Association of Psychology &amp; Psychiatry for Adults &amp; Children (APPAC) Annual International Conference</td>
<td>May 19 - 22, 2015</td>
<td>Greece / Athens</td>
<td>Contact: Secretariat, APPAC Phone: 011-30-210-684-2663 Fax: 011-30-210-684-2079 Email: <a href="mailto:congress@appac.gr">congress@appac.gr</a></td>
</tr>
<tr>
<td>10th European Congress on Menopause and Andropause</td>
<td>May 20 - 22, 2015</td>
<td>Spain / Madrid</td>
<td>Contact: Stephane Talboom, K.I.T. Group GMBH Phone: 011-49-30-246-030; Fax: 011-49-30-2460-3310 Email: <a href="mailto:info@emas-online.org">info@emas-online.org</a></td>
</tr>
<tr>
<td>2015 Obstetric Anaesthesia</td>
<td>May 20 - 22, 2015</td>
<td>United Kingdom / Torquay</td>
<td>Contact: Obstetric Anaesthetists’ Association Phone: 011-44-20-7631-8883 Fax: 011-44-20-7631-4352</td>
</tr>
</tbody>
</table>
7th International Symposium on the Diabetic Foot  
May 20 - 23, 2015  
Netherlands / Den Hague  
Contact: Symposium Secretariat, Congress by Design  
Phone: 011-31-88-89-8101; Fax: 011-31-88-89-8109  
Email: isdf@congressbydesign.com

2015 Canadian Society for Transfusion Medicine (CSTM) Annual Conference  
May 21 - 24, 2015  
Canada / Manitoba / Winnipeg  
Phone: 905-415-3917; Fax: 905-415-0071  
Email: conference@transfusion.ca

Advances in QPCR & DPCR  
May 21 - 22, 2015  
Singapore / Singapore  
Contact: Paul Raggett, CEO, Select Biosciences South East Asia Pte. Ltd.  
Phone: 011-65-9186-3246  
Email: p.raggett@selectbio.com

6th Annual Bit World Congress of Neurotalk  
May 22 - 24, 2015  
China / Hangzhou  
Contact: Lucy, Bit Congress Inc.  
Phone: 011-86-411-8457-5669 Ext. 855; Fax: 011-86-411-8479-9629  
Email: lucy@bit-neurotalk.com

2015 Canadian Centre for Applied Research in Cancer Control (ARCC) Conference  
May 24 - 25, 2015  
Canada / Quebec / Montreal  
Contact: ARCC  
Phone: 416-971-9800 Ext. 2326  
Email: arcc@cancercare.on.ca

2015 Paris-Echo  
May 27 - 29, 2015  
France / Paris  
Contact: Overcome  
Phone: 011-33-1-4192-0120; Fax: 011-33-1-4641-0521  
Email: paris-echo@overcome.fr

Advances in Brain Cancer Research  
May 27 - 30, 2015  
United States / District of Columbia / Washington  
Contact: American Association for Cancer Research  
Phone: 215-440-9300; Fax: 215-440-9313  
Email: aacr@aacr.org

5th World Congress on ADHD: From Childhood To Adult Disorder  
May 28 - 31, 2015  
United Kingdom / Glasgow  
Contact: Congress and Exhibition Office, CPO Hanser Service  
Phone: 011-49-40-670-8820; Fax: 011-49-40-670-3283  
Email: info@adhd.org

Metabolic & Nutritional Issues in the ICU  
Jun 2 – 3, 2015  
Belgium / Brussels  
Contact: Dominique Szyke, Intensive Care Department, Erasme Hospital  
Phone: 011-32-2-555-3694  
Email: d.szyke@intensive.org

2015 International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) Annual Scientific Meeting  
Jun 3 - 6, 2015  
Germany / Berlin  
Contact: ISMICS  
Phone: 978-927-8330  
Fax: 978-524-8890

17th Annual Conference of the Int. Society for Bipolar Disorders  
Jun 3 - 6, 2015  
Canada / Ontario / Toronto  
Contact: Raquel Louis, APM, Kenes International  
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140  
Email: isbd@kenes.com

24th Asian & Oceanic Congress of Obstetrics & Gynaecology - AOCOG 2015  
Jun 3 - 6, 2015  
Malaysia / Kuching  
Contact: Marcus, Console Communications  
Email: info@aocog2015.com

2015 International College of Neuropsychopharmacology (CINP) Thematic Meeting: Stress, Inflammation & Depression: Focus on Novel Psychotropic Drug Targets  
Jun 4 - 6, 2015  
Ireland / Dublin  
Contact: Northern Networking Events  
Phone: 011-44-13-5524-4930  
Email: enquiries@northernnetworking.co.uk

NeuroGASTRO  
Jun 4 - 6, 2015  
Turkey / Istanbul  
Contact: Congress and Exhibition Office, CPO Hanser Service GmbH  
Phone: 011-49-40-670-8820; Fax: 011-49-40-670-3283  
Email: Neurogastro@cpo-hanser.de

Asia Pacific Medical & Legal Conference  
Jun 5 - 13, 2015  
China / Beijing  
Contact: Continuing Professional Education Pty Ltd  
Phone: 011-61-7-3254-3331; Fax: 011-61-7-3254-3332  
Email: info@educationcpe.com
<table>
<thead>
<tr>
<th>Event</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td><strong>Forthcoming Conferences and Meetings</strong></td>
<td></td>
</tr>
<tr>
<td><strong>March 2015</strong></td>
<td></td>
</tr>
<tr>
<td>12th World Congress of International <strong>Neuromodulation</strong> Society (INS)</td>
<td>Jun 6 - 11, 2015 &lt;br&gt; Canada / Quebec / Montreal &lt;br&gt; Contact: Tia Sofatzi, Executive Director, INS &lt;br&gt; Phone: 415-683-3237 &lt;br&gt; Fax: 415-683-3218 &lt;br&gt; Email: <a href="mailto:ins@neuromodulation.com">ins@neuromodulation.com</a></td>
</tr>
<tr>
<td>2015 European Congress of <strong>Ophthalmology</strong></td>
<td>Jun 6 - 9, 2015 &lt;br&gt; Austria / Vienna &lt;br&gt; Contact: Congress Secretariat, Congrex Sweden &lt;br&gt; Phone: 011-46-8-459-6600 &lt;br&gt; Fax: 011-46-8-661-9125</td>
</tr>
<tr>
<td>6th World Glaucoma Congress</td>
<td>Jun 6 - 9, 2015 &lt;br&gt; China / Hong Kong &lt;br&gt; Contact: Professional Congress Organizer, MCI Amsterdam &lt;br&gt; Phone: 011-31-20-679-3411 &lt;br&gt; Email: <a href="mailto:wgc-2015-info@mci-group.com">wgc-2015-info@mci-group.com</a></td>
</tr>
<tr>
<td>6th World Glaucoma Congress</td>
<td>Jun 6 - 9, 2015 &lt;br&gt; China / Hong Kong &lt;br&gt; Contact: Professional Congress Organizer, MCI Amsterdam &lt;br&gt; Phone: 011-31-20-679-3411 &lt;br&gt; Email: <a href="mailto:wgc-2015-info@mci-group.com">wgc-2015-info@mci-group.com</a></td>
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<tr>
<td>10th Biennial Congress of International Society of <strong>Arthroscopy</strong>, <strong>Knee Surgery</strong> &amp; Orthopaedic Sports Medicine (ISAKOS)</td>
<td>Jun 7 - 11, 2015 &lt;br&gt; France / Lyon &lt;br&gt; Contact: ISAKOS &lt;br&gt; Phone: 925-807-1197 &lt;br&gt; Fax: 925-807-1199</td>
</tr>
<tr>
<td>69th Canadian Society of <strong>Otolaryngology</strong> - <strong>Head &amp; Neck Surgery</strong></td>
<td>Jun 7 - 9, 2015 &lt;br&gt; Canada / Manitoba / Winnipeg &lt;br&gt; Contact: Donna Humphrey, General Manager, CSO Administrative Office &lt;br&gt; Phone: 519-846-0630, Fax: 519-846-9529 &lt;br&gt; Email: <a href="mailto:cso.hns@sympatico.ca">cso.hns@sympatico.ca</a></td>
</tr>
<tr>
<td><strong>Metabolism and Cancer</strong></td>
<td>Jun 7 - 10, 2015 &lt;br&gt; United States / Washington / Bellevue &lt;br&gt; Contact: American Association for Cancer Research &lt;br&gt; Phone: 215-440-9300; Fax: 215-440-9313 &lt;br&gt; Email: <a href="mailto:aacr@aacr.org">aacr@aacr.org</a></td>
</tr>
<tr>
<td><strong>2015 British Fertility Society (BFS) Study Week</strong></td>
<td>Jun 8 - 12, 2015 &lt;br&gt; United Kingdom / London &lt;br&gt; Contact: BFS Office &lt;br&gt; Email: <a href="mailto:bfs@bioscientifica.com">bfs@bioscientifica.com</a></td>
</tr>
<tr>
<td>23rd World Congress of <strong>Dermatology</strong> (WCD 2015)</td>
<td>Jun 8 - 13, 2015 &lt;br&gt; Canada / British Columbia / Vancouver &lt;br&gt; Contact: Secretariat WCD 2015 &lt;br&gt; Phone: 604-738-8600; Fax: 604-738-8697 &lt;br&gt; Email: <a href="mailto:info@derm2015.org">info@derm2015.org</a></td>
</tr>
<tr>
<td><strong>Central Nervous System</strong> <strong>I MRI</strong></td>
<td>Jun 8 - 12, 2015 &lt;br&gt; United Kingdom / London &lt;br&gt; Contact: Walter Rijsselaere, Erasmus Course on Magnetic Resonance Imaging &lt;br&gt; Phone: 011-32-2-477-5322 &lt;br&gt; Fax: 011-32-2-477-5362 &lt;br&gt; Email: <a href="mailto:walter.rijsselaere@uzbrussel.be">walter.rijsselaere@uzbrussel.be</a></td>
</tr>
<tr>
<td>40th International <strong>Urogynaecological Association</strong> (IUGA) Annual Meeting</td>
<td>Jun 9 - 13, 2015 &lt;br&gt; France / Nice &lt;br&gt; Contact: , IUGA Office &lt;br&gt; Phone: 202-733-3234; Fax: 202-733-3365</td>
</tr>
<tr>
<td>2015 Annual Congress of the European League against <strong>Rheumatism</strong></td>
<td>Jun 10 - 13, 2015 &lt;br&gt; Italy / Rome &lt;br&gt; Contact: Conference Organizer, Aim Group International Rome &lt;br&gt; Phone: 011-39-6-33-0531; Fax: 011-39-6-3305-3229 &lt;br&gt; Email: <a href="mailto:aimcongress@aimgroup.eu">aimcongress@aimgroup.eu</a></td>
</tr>
<tr>
<td>7th International Workshop on <strong>Breast Densitometry &amp; Cancer</strong> Risk Assessment</td>
<td>Jun 10 - 12, 2015 &lt;br&gt; United States / California / San Francisco &lt;br&gt; Contact: Office Of Continuing Medical Education, UCSF &lt;br&gt; Phone: 415-476-4251; Fax: 415-476-0318 &lt;br&gt; Email: <a href="mailto:info@ocme.ucsf.edu">info@ocme.ucsf.edu</a></td>
</tr>
<tr>
<td><strong>Management of DVT &amp; Pulmonary Embolism</strong> within Primary Care**</td>
<td>Jun 10, 2015 &lt;br&gt; United Kingdom &lt;br&gt; Contact: Tamara Ball, Centre For Professional Development, University of Birmingham &lt;br&gt; Phone: 011-44-12-1414-3281 &lt;br&gt; Email: <a href="mailto:t.c.ball@bham.ac.uk">t.c.ball@bham.ac.uk</a></td>
</tr>
</tbody>
</table>
2015 International Congress on Obesity Management
Jun 11 - 13, 2015
United Kingdom / London
Contact: Sophie Hoad, Senior Account Director, Knowledgepoint360
Phone: 011-44-14-2566-4349; Fax: 011-44-14-2566-4391
Email: obesity@kp360group.com

5th Asian Vaccine Conference
Jun 11 - 14, 2015
Vietnam / Hanoi
Contact: Gabriel Heng, APM, Kenes Asia
Phone: 011-65-6292-4710; Fax: 011-65-6292-4721
Email: asvac2015@kenes.com

2015 Otolarynology Update Eastern Caribbean Cruise
Jun 13 - 20, 2015
United States / Florida / Fort Lauderdale
Contact: Continuing Education, Continuing Education, Continuing Education
Phone: 800-422-0711
Email: registrar@continuingeducation.net

Leukaemia and Lymphoma
Switzerland / Ascona
Contact: Organising Secretariat, European School of Oncology Bellinzona
Phone: 011-41-91-820-0952; Fax: 011-41-91-820-0953
Email: dknupfer@eso.net

Neurology & Pain Management Cruise to France & Spain
Jun 13 - 20, 2015
United Kingdom / Southampton
Contact: Continuing Education, Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

12th World Congress of Biological Psychiatry
Jun 14 - 18, 2015
Greece / Athens
Contact: Inga-Kristina Schwartz, CPO Hanser Service
Phone: 011-49-40-670-8820; Fax: 011-49-40-670-3283
Email: wfsbp2015@cpo-hanser.de

Advances in Medicine: Endocrinology & Women’s Health | Exotic Asia Cruise
Jun 15 - 24, 2015
Singapore / Singapore
Contact: Dr. Martin Gerretsen, Director of CME, Sea Courses Cruises
Phone: 888-647-7327; Fax: 888-547-7337
Email: cruises@seacourses.com

Adult HERMES Summer School
Jun 17 - 20, 2015
Spain / Barcelona Respirology
Contact: European Respiratory Society
Phone: 011-41-21-213-0101; Fax: 011-41-21-213-0100

Breast Cancer Screening Conference
Jun 18 - 20, 2015
Ireland / Dublin
Contact: Francesca Marangoni, Organising Secretariat, European School of Oncology
Phone: 011-39-2-8546-4525; Fax: 011-39-2-8546-4545
Email: fmarangoni@eso.net

2015 Canadian Anesthesiologists’ Society (CAS) Annual Meeting
Jun 19 - 22, 2015
Canada / Ontario / Ottawa
Contact: Cas Events
Phone: 416-480-0602; Fax: 416-480-0320
Email: meetings@cas.ca

2015 International Society on Thrombosis & Haemostasis (ISTH) Congress
Jun 20 – 25, 2015
Canada / Ontario / Toronto
Contact: Isth Headquarters
Phone: 919-929-3807; Fax: 919-929-3935
Email: headquarters@isth.org

Anticancer Drug Action & Drug Resistance: From Cancer Biology to The Clinic
Jun 20 – 23, 2015
Italy / Florence
Contact: American Association for Cancer Research
Phone: 215-440-9300; Fax: 215-440-9313
Email: aacr@aacr.org

Primary Care & Women’s Health: Key Topics & Core Strategies Mediterranean Cruise
Jun 20 - 27, 2015
Italy / Venice
Contact: Continuing Education, Inc, Continuing Education, Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

14th World Congress in Fetal Medicine
Jun 21 - 25, 2015
Greece / Crete
Contact: The Fetal Medicine Foundation
Phone: 011-44-20-7034-3070; Fax: 011-44-20-7034-3071
Email: fmfeducation@fetalmedicine.com
<table>
<thead>
<tr>
<th>Conference/Meeting</th>
<th>Dates</th>
<th>Location</th>
<th>Contact Information</th>
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<tbody>
<tr>
<td>Frontiers of Cell Signaling</td>
<td>Jun 21 - 24, 2015</td>
<td>China / Shanghai</td>
<td>Abcam Plc; Phone: 647-799-3007; Fax: 647-799-3014</td>
</tr>
<tr>
<td>16th International Coeliac Disease Symposium</td>
<td>Jun 21 - 24, 2015</td>
<td>Czech Republic / Prague</td>
<td>Congress Secretariat, Guarant International; Phone: 011-420-284-001-444; Fax: 011-420-284-001-448</td>
</tr>
<tr>
<td>2015 International Society for Prosthetics &amp; Orthotics World Congress</td>
<td>Jun 22 - 25, 2015</td>
<td>France / Lyon</td>
<td>Secretariat, ISPO France; Email: <a href="mailto:secretariat@ispo-france.com">secretariat@ispo-france.com</a></td>
</tr>
<tr>
<td>5th International Regional Stress &amp; Behavior Neuroscience &amp; Biopsychiatry Conference</td>
<td>Jun 22-24, 2015</td>
<td>United States / Florida / Miami</td>
<td>Na Nutsa, Conference Secretary, International Stress and Behavior Society; Phone: 240-899-9571</td>
</tr>
<tr>
<td>2nd Annual Microbiology &amp; Infectious Diseases Asia Congress</td>
<td>Jun 23 - 24, 2015</td>
<td>Singapore / Singapore</td>
<td>Steph Punfield, Marketing Executive, Oxford Global; Phone: 011-44-18-6524-8555</td>
</tr>
<tr>
<td>Pediatric Emergency &amp; Critical Care Ultrasound</td>
<td>Jun 23 - 24, 2015</td>
<td>United States / Florida / St. Pete Beach</td>
<td>Gulfcoast Ultrasound Institute, Inc.; Phone: 727-363-4500; Fax: 727-363-0811</td>
</tr>
<tr>
<td>11th International Congress on Complications during Cardiovascular Intervention: Management &amp; Prevention</td>
<td>Jun 24 - 26, 2015</td>
<td>Switzerland / Lausanne</td>
<td>Congress Secretariat, E&amp;E PCO; Phone: 011-43-1-867-4944 ext. 0; Fax: 011-43-1-867-4944 ext. 9</td>
</tr>
<tr>
<td>11th International Symposium on Endovascular Therapeutics</td>
<td>Jun 24 – 27, 2015</td>
<td>Spain / Barcelona</td>
<td>SITE Secretariat; Phone: 011-34-93-505-2503; Fax: 011-34-93-488-3703</td>
</tr>
<tr>
<td>61st American Society for Artificial Internal Organs (ASAIO) Annual Conference</td>
<td>Jun 24 - 27, 2015</td>
<td>United States / Illinois / Chicago</td>
<td>Asaio; Phone: 561-999-8969; Fax: 561-999-8972</td>
</tr>
<tr>
<td>14th International Congress on Pediatric Pulmonology</td>
<td>Jun 25 - 28, 2015</td>
<td>Poland / Krakow</td>
<td>Anne Flore Bidart, Secretariat; Phone: 011-33-4-9703-8597; Fax: 011-33-4-9703-8598</td>
</tr>
<tr>
<td>2015 Congenital &amp; Structural Interventions Congress</td>
<td>Jun 25 - 27, 2015</td>
<td>Germany / Frankfurt</td>
<td>Denise Thom, Congresses, Meetings and Education, cm4u GmbH; Phone: 011-49-69-8999-0507; Fax: 011-49-69-2562-8658</td>
</tr>
</tbody>
</table>
2nd International Congress of Aesthetic Dermatology & Healthy Aging Medicine Brazil
Jun 25 - 27, 2015
Brazil / São Paulo
Contact: EuroMediCom
Phone: 011-33-1-5683-7800; Fax: 011-33-1-5683-7805

25th British Menopause Society (BMS) Annual Conference
Jun 25 - 26, 2015
United Kingdom / Wroughton
Contact: BMS
Phone: 011-44-16-2889-0199; Fax: 011-44-16-2847-4042
Email: admin@thebms.org.uk

Breast Ultrasound with the Masters
Jun 26 - 28, 2015
Singapore / Singapore
Contact: International Institute for Continuing Medical Education
Phone: 205-467-0290
Email: IICMEMAIL@gmail.com

27th International Symposium on Cerebral Blood Flow, Metabolism & Function / 12th International Conference on quantification of brain function with pet
Jun 27 - 30, 2015
Canada / British Columbia / Vancouver
Contact: Charlotte Boskila, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: brain@kenes.com

7th International Conference on Children’s Bone Health
Jun 27 - 30, 2015
Austria / Salzburg
Contact: Janet Crompton, Conference Organiser, European Calcified Tissue Society
Phone: 011-44-14-5354-9929; Fax: 011-44-14-5354-8919
Email: iccbh@ectsoc.org

4th Annual Global Healthcare Conference
Jun 29 - 30, 2015
Singapore / Singapore
Contact: Conference Secretariat, Global Science & Technology Forum
Phone: 011-65-6327-0166; Fax: 011-65-6327-0162
Email: secretariat@globalhc-conf.org

Hot Topics in Infection & Immunity in Children
Jun 29 - Jul 1, 2015
United Kingdom / Oxford
Contact: Department of Paediatrics, University of Oxford
Phone: 011-44-18-6585-7466
Email: iic@paediatrics.ox.ac.uk

8th Oswestry Shoulder & Elbow Course for Orthopaedic Trainees
Jul 1 - 2, 2015
United Kingdom / Oswestry
Contact: Orthopaedic Institute Ltd.
Phone: 011-44-16-9140-4661

ENT Imaging with the Masters
Jul 1 - 4, 2015
Singapore / Singapore
Contact: International Institute for Continuing Medical Education
Phone: 205-467-0290

Infection in Cardiac Surgery
Jul 2 - 3, 2015
United Kingdom / Windsor (UK)
Contact: , European Association for Cardio-Thoracic Surgery
Phone: 011-44-17-5383-2166
Fax: 011-44-17-5362-0407
Email: info@escmid.org

14th European Society of Clinical Microbiology & Infectious Diseases (ESCMID) Summer School
Jul 4 - 11, 2015
Turkey / Istanbul
Contact: European Society of Clinical Microbiology & Infectious Diseases
Phone: 011-41-61-508-0153
Fax: 011-41-61-508-0151
Email: info@escmid.org

11th Summer Academy of Dermatopathology
Jul 6 - 10, 2015
Austria / Graz
Contact: Dr. Lorenzo Cerroni, International Society of Dermatopathology
Phone: 011-43-316-385-2423; Fax: 011-43-316-385-14957
Email: lorenzo.cerroni@medunigraz.at

18th International Confederation for Plastic, Reconstructive & Aesthetic Surgery World Congress
Jul 6 - 10, 2015
Austria / Vienna
Contact: Mr. Nikos Antonopoulos, Congress Secretariat, ZITA Congress & Travel S.A.
Phone: 011-30-211-100-1782
Fax: 011-30-210-664-2116
Email: N.AN@ZITA-CONGRESS.GR

2015 Institute of Psychiatry, Psychology & Neuroscience (IPPN) Summer School
Jul 6 - 10, 2015
United Kingdom / London
Contact: Nikki Whitelock, IPPN, King’s College London
Phone: 011-44-20-7836-5454
Email: nikki.whitelock@kcl.ac.uk
95th British Association of Dermatologists (BAD) Annual Meeting
Jul 7 - 9, 2015
United Kingdom / Manchester
Contact: Conference & Event Services, British Association of Dermatologists
Phone: 011-44-20-7383-0266; Fax: 011-44-20-7388-5263
Email: conference@bad.org.uk

21st International Liver Transplantation Society (ILTS) Annual International Congress
Jul 8 - 11, 2015
United States / Illinois / Chicago
Contact: ILTS
Phone: 856-439-0500; Fax: 856-439-0525
Email: ilts@ilts.org

Hormone Advanced Practice Module: Re-establishing Hormonal Balance in the Hypothalamic, Pituitary, Adrenal, Thyroid & Gonadal Axis
Jul 9 - 11, 2015
United States / Illinois / Chicago
Contact: Valerie Blomberg, Marketing Assistant, Institute for Functional Medicine
Phone: 505-780-8706
Email: valerieblomberg@fxmed.com

5th Latin American Congress on Autoimmunity
Jul 10 - 12, 2015
Brazil / Maceio
Contact: Anna Varsanyi, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: calendar@kenes.com

Advanced Aortic & Mitral Valve Reconstructive Surgery
Jul 10 - 11, 2015
United Kingdom / Windsor (UK)
Contact: European Association for Cardio-Thoracic Surgery
Phone: 011-44-17-5383-2166; Fax: 011-44-17-5362-0407

Medical & Surgical Approaches to GI Disorders
Jul 13 - 17, 2015
United States / South Carolina / Kiawah Island
Contact: Continuing Medical Education, Georgia Regents University
Phone: 706-721-2329; Fax: 706-721-4642
Email: coned@gru.edu

Metabolic & Endocrine Disease Summit West
Jul 15 - 18, 2015
United States / Nevada / Las Vegas
Contact: Kathleen Wenzler, Conference Marketing Director, Global Academy for Medical Education, LLC
Phone: 973-206-8092; Fax: 201-822-6114
Email: k.wenzler@gLOBALacademycme.com

Radioactive Seed Localized Breast Surgery
Jul 24, 2015
United States / Minnesota / Rochester (MN)
Contact: Mayo School of Continuous Professional Development
Phone: 800-323-2688
Email: cme@mayo.edu

2015 Best Evidence ENT
Jul 25 - 28, 2015
United States / Wisconsin / Kohler
Contact: Diann Fiscus, Program Manager, Medical College of Wisconsin
Phone: 414-805-5609; Fax: 414-805-7936
Email: dfiscus@mcw.edu

20th World Congress on Heart Disease: International Academy of Cardiology Annual Scientific Sessions
Jul 25 - 27, 2015
Canada / British Columbia / Vancouver
Contact: Cardiology Online, Inc.
Phone: 310-657-8777; Fax: 310-659-4781
Email: klimedco@ucla.edu

6th International Stress & Behavior Society Regional Stress & Behavior Neuroscience & Biological Psychiatry Conference
Jul 25 – 26, 2015
Japan / Kobe
Contact: NA Nutsa, Conference Secretary, International Stress and Behavior Society
Phone: 240-899-9571
Email: isbs.congress@gmail.com

2015 International Spine Intervention Society (ISIS) Annual Meeting
Jul 28 - Aug 1, 2015
United States / Nevada / Las Vegas
Contact: ISIS
Phone: 415-457-4747; Fax: 415-457-3495
Email: registration@spinalinjection.org

9th International Master Course on Aging Skin (IMCAS) Asia
Jul 31 - Aug 2, 2015
Indonesia / Bali
Contact: IMCAS
Email: contact@imcas.com

Clinical Topics in Anesthesia Banff
Aug 3 - 7, 2015
Canada / Alberta / Banff
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Anesthesia Seminars
Phone: 509-547-7065; Fax: 509-547-1265
Email: coleen@nwas.com
Emergency Medicine Greek Isles Cruise
Aug 16 - 23, 2015
Italy / Venice
Contact: Continuing Education, Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

Palliative Medicine & End of Life Care: 2015 Update Including Related Topics in Neurology Eastern Mediterranean Cruise
Aug 21 - 31, 2015
Italy / Rome
Contact: Continuing Education, Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

31st International Conference on Pharmacopeidemiology & Therapeutic Risk Management
Aug 22 - 26, 2015
United States / Massachusetts / Boston
Contact: International Society for Pharmacopeidemiology
Phone: 301-718-6500
Fax: 301-656-0989
Email: ISPE@paimgmt.com

46th World Congress of Surgery
Aug 23 - 27, 2015
Thailand / Bangkok
Contact: Congress Secretariat, CDM-Thailand
Phone: 011-66-2-965-8909; Fax: 011-66-2-965-8919
Email: wcs2015@cdmthailand.com

International Conference on Parasitology
Aug 24 - 26, 2015
United States / Pennsylvania / Philadelphia
Contact: Nidhi Arora, Ms, OMICS Group
Phone: 650-353-9744; Fax: 650-618-1417
Email: parasitology@omicsgroup.com

2015 International Symposium on Auditory and Audiological Research (ISAAR)
Aug 26 - 28, 2015
Denmark / Nyborg
Contact: ISAAR
Email: isaar@isaar.eu

7th European Plastic Surgery Research Council Meeting
Aug 27 - 30, 2015
Germany / Hamburg
Contact: Sandra Gottschalg, Congress Management, Conventus Congressmanagement & Marketing GmbH
Phone: 011-49-36-4131-16350
Fax: 011-49-36-4131-16243

1st European Meeting on Bone Marrow Adiposity
Aug 28 - 29, 2015
France / Lille
Contact: Sciencesconf.org
Email: bma2015@sciencesconf.org

5th Conference of International Union Against Tuberculosis & Lung Disease Asia Pacific Region
Aug 31 - Sep 2, 2015
Australia / Sydney
Contact: Terri Growcott, Conference Manager
Phone: 011-61-2-9254-5000; Fax: 011-61-2-9251-3552
Email: info@aprunion2015.com

2015 European Society for Artificial Organs Congress
Sep 2 – 5, 2015
Belgium / Leuven
Contact: KU Leuven congressbureau
Email: congressbureau@kuleuven.be

2015 International Meeting on Respiratory Pathogens
Sep 2 - 4, 2015
Singapore / Singapore
Contact: Stella Chee, Executive Conference Administrator, ace:daytons-direct (international) Pte Ltd
Phone: 011-65-6379-5260
Fax: 011-65-6475-2077
Email: admin@acedaytons-direct.com

Workshop on Neurobiology of the Epilepsies
Sep 2 - 6, 2015
Turkey / Istanbul
Contact: Headquarters Staff, International League Against Epilepsy
Phone: 860-586-7547, 2015
Fax: 860-586-7550

2nd World Congress on NeuroTherapeutics: Dilemmas, Debates, Discussion
Sep 3 - 6, 2015
Czech Republic / Prague
Contact: Secretariat, CongressMed Ltd
Phone: 011-972-73-706-6954
Email: dddn@congressmed.com

5th International Conference on Health, Wellness & Society
Sep 3 - 4, 2015
Spain / Madrid
Contact: Raquel Jiménez, Conference Producer, Common Ground Publishing
Phone: 011-34-696-488-400
Fax: 217-328-0435
Email: informacion@salud-sociedad.com
WHO-Facts Sheet

1. Alcohol
2. Suicide
3. Malaria
4. Headache Disorders
5. Mental Health: Strengthening Our Response
6. Asbestos: Elimination of Asbestos-Related Diseases

Compiled and edited by
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1. ALCOHOL

Overview
Alcohol is a psychoactive substance with dependence-producing properties that has been widely used in many cultures for centuries. The harmful use of alcohol causes a large disease, social and economic burden in societies.

Alcohol impacts people and societies in many ways and it is determined by the volume of alcohol consumed, the pattern of drinking, and, on rare occasions, the quality of alcohol consumed. In 2012, about 3.3 million deaths, or 5.9 % of all global deaths, were attributable to alcohol consumption.

The harmful use of alcohol can also result in harm to other people, such as family members, friends, co-workers and strangers. Moreover, the harmful use of alcohol results in a significant health, social and economic burden on society at large.

KEY FACTS
- Worldwide, 3.3 million deaths every year result from harmful use of alcohol, this represent 5.9 % of all deaths.
- The harmful use of alcohol is a causal factor in more than 200 disease and injury conditions.
- Overall 5.1 % of the global burden of disease and injury is attributable to alcohol, as measured in disability-adjusted life years (DALYs).
- Alcohol consumption causes death and disability relatively early in life. In the age group 20 – 39 years approximately 25 % of the total deaths are alcohol-attributable.
- There is a causal relationship between harmful use of alcohol and a range of mental and behavioural disorders, other noncommunicable conditions as well as injuries.
- The latest causal relationships have been established between harmful drinking and incidence of infectious diseases such as tuberculosis as well as the course of HIV/AIDS.
- Beyond health consequences, the harmful use of alcohol brings significant social and economic losses to individuals and society at large.

Alcohol consumption is a causal factor in more than 200 disease and injury conditions. Drinking alcohol is associated with a risk of developing health problems such as mental and behavioural disorders, including alcohol dependence, major noncommunicable diseases such as liver cirrhosis, some cancers and cardiovascular diseases, as well as injuries resulting from violence and road clashes and collisions.

A significant proportion of the disease burden attributable to alcohol consumption arises from unintentional and intentional injuries, including those due to road traffic crashes, violence, and suicides, and fatal alcohol-related injuries tend to occur in relatively younger age groups. The latest causal relationships are those between harmful drinking and incidence of infectious diseases such as tuberculosis as well as the course of HIV/AIDS. Alcohol consumption by an expectant mother may cause fetal alcohol syndrome and pre-term birth complications.

Factors affecting alcohol consumption and alcohol-related harm
A variety of factors have been identified at the individual and the societal level, which affect the levels and patterns of alcohol consumption and the magnitude of alcohol-related problems in populations.
Environmental factors include economic development, culture, availability of alcohol, and the comprehensiveness and levels of implementation and enforcement of alcohol policies. For a given level or pattern of drinking, vulnerabilities within a society are likely to have similar differential effects as those between societies. Although there is no single risk factor that is dominant, the more vulnerabilities a person has, the more likely the person is to develop alcohol-related problems as a result of alcohol consumption.

The impact of alcohol consumption on chronic and acute health outcomes in populations is largely determined by 2 separate but related dimensions of drinking:
- the total volume of alcohol consumed, and
- the pattern of drinking.

The context of drinking plays an important role in occurrence of alcohol-related harm, particularly associated with health effects of alcohol intoxication, and, on rare occasions, also the quality of alcohol consumed. Alcohol consumption can have an impact not only on the incidence of diseases, injuries and other health conditions, but also on the course of disorders and their outcomes in individuals.

There are gender differences in alcohol-related mortality, morbidity, as well as levels and patterns of alcohol consumption. The percentage of alcohol-attributable deaths among men amount to 7.6 % of all global deaths compared to 4.0 % of all deaths among women. Total alcohol per capita consumption in 2010 among male and female drinkers worldwide was on average 21.2 litres for males and 8.9 litres of pure alcohol for females.

Ways to reduce the burden from harmful use of alcohol

The health, safety and socioeconomic problems attributable to alcohol can be effectively reduced and requires actions on the levels, patterns and contexts of alcohol consumption and the wider social determinants of health.

Countries have a responsibility for formulating, implementing, monitoring and evaluating public policies to reduce the harmful use of alcohol. Substantial scientific knowledge exists for policymakers on the effectiveness and cost-effectiveness of the following strategies:
- regulating the marketing of alcoholic beverages (in particular to younger people);
- regulating and restricting availability of alcohol;
- enacting appropriate drink-driving policies;
- reducing demand through taxation and pricing mechanisms;
- raising awareness of public health problems caused by harmful use of alcohol and ensuring support for effective alcohol policies;
- providing accessible and affordable treatment for people with alcohol-use disorders; and
- implementing screening and brief interventions programs for hazardous and harmful drinking in health services.
WHO response

WHO aims to reduce the health burden caused by the harmful use of alcohol and, thereby, to save lives, prevent injuries and diseases and improve the well-being of individuals, communities and society at large. It emphasizes the development, implementation and evaluation of cost-effective interventions for harmful use of alcohol as well as creating, compiling use and dependence, and related health and social consequences. The Global Information System on Alcohol and Health (GISAH) has been developed by WHO to dynamically present data on levels and health and social consequences and policy responses at all levels. Successful implementation of the strategy will require action by countries, effective global governance and appropriate engagement of all relevant stakeholders. By effectively working together, the negative health and social consequences of alcohol can be reduced.

The disability-adjusted life year (DALY) extends the concept of potential years of life lost due to premature death to include equivalent years of "healthy" life lost by virtue of being in states of poor health or disability.

2. SUICIDE

Overview

Suicide is a serious public health problem; however, suicides are preventable with timely, evidence-based and often low-cost interventions. For national responses to be effective, a comprehensive multisectoral suicide prevention strategy is needed. Every 40 seconds, a person dies by suicide somewhere in the world.

KEY FACTS
- Over 800,000 people die due to suicide every year.
- For every suicide there are many more people who attempt suicide every year. A prior suicide attempt is the single most important risk factor for suicide in the general population.
- Suicide is the second leading cause of death among 15 - 29-year-olds.
- 75% of global suicides occur in low- and middle-income countries.
- Ingestion of pesticide, hanging and firearms are among the most common methods of suicide globally.

Introduction

Every year, more than 800,000 people take their own life and there are many more people who attempt suicide. Every suicide is a tragedy that affects families, communities and entire countries and has long-lasting effects on the people left behind. Suicide occurs throughout the lifespan and was the second leading cause of death among 15 - 29-year-olds globally in 2012.

Suicide does not just occur in high-income countries, but is a global phenomenon in all regions of the world. In fact, 75% of global suicides occurred in low- and middle-income countries in 2012.

Who is at risk?

While the link between suicide and mental disorders (in particular, depression and alcohol use disorders) is well established in high-income countries, many suicides happen impulsively in moments of crisis with a breakdown in the ability to deal with life stresses, such as financial problems, relationship break-up or chronic pain and illness.

In addition, experiencing conflict, disaster, violence, abuse, or loss and a sense of isolation are strongly associated with suicidal behaviour. Suicide rates are also high amongst vulnerable groups who experience discrimination, such as refugees and migrants; indigenous peoples; lesbian, gay, bisexual, transgender, intersex (LGBTI) persons; and prisoners. By far the strongest risk factor for suicide is a previous suicide attempt.

Questions and answers on suicide

Q: Is suicide really a problem? How many people die by suicide every year?
A: Every year over 800,000 people die as a result of suicide. This is one death every 40 seconds. Beyond this, suicide has a ripple effect that impacts on societies, communities, friends and families who have lost a loved one to suicide. So, yes, suicide really is a serious public health problem.

Q: How many people attempt suicide every year?
A: There are indications that for each adult who died of suicide there were likely to be more than 20 others attempting suicide. However, as is the case for the rates of suicide and suicide attempts, there is wide variation in the attempt-to-death ratio and in the case fatality rate of suicide attempts by country, region, sex, age and method.

Q: Are suicides preventable?
A: Yes, suicides are preventable and effective interventions exist. First and foremost, early identification and treatment of depression and alcohol use disorders are key for the prevention of suicide at individual level, as well as follow-up contact with those who have attempted suicide and psychosocial
support in communities. Equally important are effective interventions at population level aiming to reduce access to the means of suicide, to adopt responsible reporting of suicide by the media, and to introduce alcohol policies to reduce the harmful use of alcohol. From the health systems perspective, it is imperative for health-care services to incorporate suicide prevention as a core component.

Methods of suicide
It is estimated that around 30% of global suicides are due to pesticide self-poisoning, most of which occur in rural agricultural areas in low- and middle-income countries. Other common methods of suicide are hanging and firearms.

Knowledge of the most commonly used suicide methods is important to devise prevention strategies which have shown to be effective, such as restriction of access to means of suicide.

Prevention and control
Suicides are preventable. There are a number of measures that can be taken at population, subpopulation and individual levels to prevent suicide and suicide attempts. These include:

- reducing access to the means of suicide (e.g. pesticides, firearms, certain medications);
- reporting by media in a responsible way;
- introducing alcohol policies to reduce the harmful use of alcohol;
- early identification, treatment and care of people with mental and substance use disorders, chronic pain and acute emotional distress;
- training of non-specialized health workers in the assessment and management of suicidal behaviour;
- follow-up care for people who attempted suicide and provision of community support.

Suicide is a complex issue and therefore, suicide prevention efforts require coordination and collaboration among multiple sectors of society, including the health sector and other sectors such as education, labour, agriculture, business, justice, law, defense, politics, and the media. These efforts must be comprehensive and integrated as no single approach alone can make an impact on an issue as complex as suicide.

Challenges and obstacles
Stigma and taboo: Stigma, particularly surrounding mental disorders and suicide, means many people thinking of taking their own life or who have attempted suicide are not seeking help and are therefore, not getting the help they need. The prevention of suicide has not been adequately addressed due to a lack of awareness of suicide as a major public health problem and the taboo in many societies to openly discuss it.

To date, only a few countries have included suicide prevention among their health priorities and only 28 countries report having a national suicide prevention strategy.

Raising community awareness and breaking down the taboo is important for countries to make progress in preventing suicide.

Data quality: Globally, the availability and quality of data on suicide and suicide attempts is poor. Only 60 Member States have good-quality vital registration data that can be used directly to estimate suicide rates. This problem of poor-quality mortality data is not unique to suicide, but given the sensitivity of suicide – and the illegality of suicidal behaviour in some countries – it is likely that under-reporting and misclassification are greater problems for suicide than for most other causes of death.

Improved surveillance and monitoring of suicide and suicide attempts is required for effective suicide prevention strategies. Cross-national differences in the patterns of suicide, and changes in the rates, characteristics and methods of suicide highlight the need for each country to improve the comprehensiveness, quality and timeliness of their suicide-related data. This includes vital registration of suicide, hospital-based registries of suicide attempts and nationally representative surveys collecting information about self-reported suicide attempts.

WHO response
WHO recognizes suicide as a public health priority. The first WHO World Suicide Report “Preventing suicide: a global imperative” published in 2014, aims to increase the awareness of the public health significance of suicide and suicide attempts and to make suicide prevention a high priority on the global public health agenda. It also aims to encourage and support countries to develop or strengthen comprehensive suicide prevention strategies in a multisectoral public health approach.

3. MALARIA

Overview
Malaria is caused by Plasmodium parasites. The parasites are spread to people through the bites of infected Anopheles mosquitoes, called “malaria vectors”, which bite mainly between dusk and dawn.

According to the latest estimates, released in December 2014, there were about 198 million cases of malaria in 2013 (with an uncertainty range of 124 million to 283 million) and an estimated 584,000 deaths.
(with an uncertainty range of 367,000 to 755,000). Malaria mortality rates have fallen by 47% globally since 2000, and by 54% in the WHO African Region.

Most deaths occur among children living in Africa where a child dies every minute from malaria. Malaria mortality rates among children in Africa have been reduced by an estimated 58% since 2000.

KEY FACTS
- Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes.
- In 2013, malaria caused an estimated 584,000 deaths (with an uncertainty range of 367,000 to 755,000), mostly among African children.
- Malaria is preventable and curable.
- Increased malaria prevention and control measures are dramatically reducing the malaria burden in many places.
- Non-immune travellers from malaria-free areas are very vulnerable to the disease when they get infected.
- There are four parasite species that cause malaria in humans:
  - *Plasmodium falciparum*
  - *Plasmodium vivax*
  - *Plasmodium malariae*
  - *Plasmodium ovale*.

*Plasmodium falciparum* and *Plasmodium vivax* are the most common. *Plasmodium falciparum* is the most deadly.

In recent years, some human cases of malaria have also occurred with *Plasmodium knowlesi* – a species that causes malaria among monkeys and occurs in certain forested areas of South-East Asia.

Transmission
Malaria is transmitted exclusively through the bites of *Anopheles* mosquitoes. The intensity of transmission depends on factors related to the parasite, the vector, the human host, and the environment.

About 20 different *Anopheles* species are locally important around the world. All of the important vector species bite at night. *Anopheles* mosquitoes breed in water and each species has its own breeding preference; for example some prefer shallow collections of fresh water, such as puddles, rice fields, and hoof prints. Transmission is more intense in places where the mosquito lifespan is longer (so that the parasite has time to complete its development inside the mosquito) and where it prefers to bite humans rather than other animals. For example, the long lifespan and strong human-biting habit of the African vector species is the main reason why about 90% of the world’s malaria deaths are in Africa.

Transmission also depends on climatic conditions that may affect the number and survival of mosquitoes, such as rainfall patterns, temperature and humidity. In many places, transmission is seasonal, with the peak during and just after the rainy season. Malaria epidemics can occur when climate and other conditions suddenly favour transmission in areas where people have little or no immunity to malaria. They can also occur when people with low immunity move into areas with intense malaria transmission, for instance to find work, or as refugees.

Human immunity is another important factor, especially among adults in areas of moderate or intense transmission conditions. Partial immunity is developed over years of exposure, and while it never provides complete protection, it does reduce the risk that malaria infection will cause severe disease. For this reason, most malaria deaths in Africa occur in young children, whereas in areas with less transmission and low immunity, all age groups are at risk.

Symptoms
Malaria is an acute febrile illness. In a non-immune individual, symptoms appear seven days or more (usually 10–15 days) after the infective mosquito bite. The first symptoms – fever, headache, chills and vomiting – may be mild and difficult to recognize as malaria. If not treated within 24 hours, *P. falciparum* malaria can progress to severe illness often leading to death. Children with severe malaria frequently develop one or more of the following symptoms: severe anaemia, respiratory distress in relation to metabolic acidosis, or cerebral malaria. In adults, multi-organ involvement is also frequent. In malaria endemic areas, persons may develop partial immunity, allowing asymptomatic infections to occur.

For both *P. vivax* and *P. ovale*, clinical relapses may occur weeks to months after the first infection, even if the patient has left the malarious area. These new episodes arise from dormant liver forms known as hypnozoites (absent in *P. falciparum* and *P. malariae*); special treatment – targeted at these liver stages – is required for a complete cure.

Who is at risk?
Approximately half of the world’s population is at risk of malaria. Most malaria cases and deaths occur in sub-Saharan Africa. However, Asia, Latin America, and to a lesser extent the Middle East and parts of Europe are also affected. In 2014, 97 countries and territories had ongoing malaria transmission.

Specific population risk groups include:
- young children in stable transmission areas who have not yet developed protective immunity against the most severe forms of the disease;
• non-immune pregnant women as malaria causes high rates of miscarriage and can lead to maternal death;
• semi-immune pregnant women in areas of high transmission. Malaria can result in miscarriage and low birth weight, especially during first and second pregnancies;
• semi-immune HIV-infected pregnant women in stable transmission areas, during all pregnancies. Women with malaria infection of the placenta also have a higher risk of passing HIV infection to their newborns;
• people with HIV/AIDS;
• international travellers from non-endemic areas because they lack immunity;
• immigrants from endemic areas and their children living in non-endemic areas and returning to their home countries to visit friends and relatives are similarly at risk because of waning or absent immunity.

Diagnosis and treatment
Early diagnosis and treatment of malaria reduces disease and prevents deaths. It also contributes to reducing malaria transmission.

The best available treatment, particularly for P. falciparum malaria, is artemisinin-based combination therapy (ACT).

WHO recommends that all cases of suspected malaria be confirmed using parasite-based diagnostic testing (either microscopy or rapid diagnostic test) before administering treatment. Results of parasitological confirmation can be available in 15 minutes or less. Treatment solely on the basis of symptoms should only be considered when a parasitological diagnosis is not possible.

Antimalarial drug resistance
Resistance to antimalarial medicines is a recurring problem. Resistance of P. falciparum to previous generations of medicines, such as chloroquine and sulfadoxine-pyrimethamine (SP), became widespread in the 1970s and 1980s, undermining malaria control efforts and reversing gains in child survival.

In recent years, parasitoresistance to artemisinins has been detected in five countries of the Greater Mekong subregion: Cambodia, Laos, Myanmar, Thailand and Viet Nam. While there are likely many factors that contribute to the emergence and spread of resistance, the use of oral artemisinins alone, as monotherapy, is thought to be an important driver. When treated with an oral artemisinin-based monotherapy, patients may discontinue treatment prematurely following the rapid disappearance of malaria symptoms. This results in incomplete treatment, and such patients still have persistent parasites in their blood. Without a second drug given as part of a combination (as is provided with an ACT), these resistant parasites survive and can be passed on to a mosquito and then another person.

If resistance to artemisinins develops and spreads to other large geographical areas, the public health consequences could be dire. Therefore, the WHO recommends routine monitoring of antimalarial drug resistance, and supports countries to strengthen their efforts in this important area of work.

More comprehensive recommendations are available in the "WHO Global Plan for Artemisinin Resistance Containment (GPARC)", which was released in 2011. For countries in the Greater Mekong subregion, WHO has issued a regional framework for action titled "Emergency response to artemisinin resistance in the Greater Mekong subregion" in 2013.

Prevention
Vector control is the main way to reduce malaria transmission at the community level. It is the only intervention that can reduce malaria transmission from very high levels to close to zero.

For individuals, personal protection against mosquito bites represents the first line of defence for malaria prevention. Two forms of vector control are effective in a wide range of circumstances.

Insecticide-treated mosquito nets (ITNs): Long-lasting insecticidal nets (LLINs) are the preferred form of ITNs for public health distribution programmes. WHO recommends coverage for all at-risk persons; and in most settings. The most cost effective way to achieve this is through provision of free LLINs, so that everyone sleeps under a LLIN every night.

Indoor spraying with residual insecticides: Indoor residual spraying (IRS) with insecticides is a powerful way to rapidly reduce malaria transmission. Its full potential is realized when at least 80% of houses in targeted areas are sprayed. Indoor spraying is effective for 3 - 6 months, depending on the insecticide used and the type of surface on which it is sprayed. DDT can be effective for 9 - 12 months in some cases. Longer-lasting forms of existing IRS insecticides, as well as new classes of insecticides for use in IRS programmes, are under development.

Antimalarial medicines can also be used to prevent malaria. For travellers, malaria can be prevented through chemoprophylaxis, which suppresses the blood stage of malaria infections, thereby preventing malaria disease. In addition, WHO recommends intermittent preventive treatment with sulfadoxine-pyrimethamine for pregnant women living in high transmission areas, at each scheduled antenatal visit after the first trimester. Similarly, for infants living
in high-transmission areas of Africa, 3 doses of intermittent preventive treatment with sulfadoxine-pyrimethamine is recommended delivered alongside routine vaccinations. In 2012, WHO recommended Seasonal Malaria Chemoprevention as an additional malaria prevention strategy for areas of the Sahel sub-Region of Africa. The strategy involves the administration of monthly courses of amodiaquine plus sulfadoxine-pyrimethamine to all children under five years of age during the high transmission season.

**Insecticide resistance**

Much of the success to date in controlling malaria is due to vector control. Vector control is highly dependent on the use of pyrethroids, which are the only class of insecticides currently recommended for ITNs or LLINs. In recent years, mosquito resistance to pyrethroids has emerged in many countries. In some areas, resistance to all 4 classes of insecticides used for public health has been detected. Fortunately, this resistance has only rarely been associated with decreased efficacy, and LLINs and IRS remain highly effective tools in almost all settings.

However, countries in sub-Saharan Africa and India are of significant concern. These countries are characterized by high levels of malaria transmission and widespread reports of insecticide resistance. The development of new, alternative insecticides is a high priority and several promising products are in the pipeline. Development of new insecticides for use on bed nets is a particular priority.

Detection of insecticide resistance should be an essential component of all national malaria control efforts to ensure that the most effective vector control methods are being used. The choice of insecticide for IRS should always be informed by recent, local data on the susceptibility target vectors.

In order to ensure a timely and coordinated global response to the threat of insecticide resistance, WHO has worked with a wide range of stakeholders to develop the “Global Plan for Insecticide Resistance Management in malaria vectors” (GPIRM), which was released in May 2012. The GPIRM puts forward a five-pillar strategy calling on the global malaria community to:

- plan and implement insecticide resistance management strategies in malaria-endemic countries;
- ensure proper and timely entomological and resistance monitoring, and effective data management;
- develop new and innovative vector control tools;
- fill gaps in knowledge on mechanisms of insecticide resistance and the impact of current insecticide resistance management approaches; and
- ensure that enabling mechanisms (advocacy as well as human and financial resources) are in place.

**Surveillance**

Tracking progress is a major challenge in malaria control. In 2012, malaria surveillance systems detected only around 14% of the estimated global number of cases. Stronger malaria surveillance systems are urgently needed to enable a timely and effective malaria response in endemic regions, to prevent outbreaks and resurgences, to track progress, and to hold governments and the global malaria community accountable.

**Elimination**

Malaria elimination is defined as interrupting local mosquito-borne malaria transmission in a defined geographical area, i.e. zero incidence of locally contracted cases. Malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of malaria infection caused by a specific agent; i.e. applies to a particular malaria parasite species.

On the basis of reported cases for 2013, 55 countries are on track to reduce their malaria case incidence rates by 75%, in line with World Health Assembly targets for 2015. Large-scale use of WHO-recommended strategies, currently available tools, strong national commitments, and coordinated efforts with partners, will enable more countries – particularly those where malaria transmission is low and unstable – to reduce their disease burden and progress towards elimination.

In recent years, four countries have been certified by the WHO Director-General as having eliminated malaria: United Arab Emirates (2007), Morocco (2010), Turkmenistan (2010), and Armenia (2011).

**Vaccines against malaria**

There are currently no licensed vaccines against malaria or any other human parasite. One research vaccine against *P. falciparum*, known as RTS, S/AS01, is most advanced. This vaccine has been evaluated in a large clinical trial in seven countries in Africa and has been submitted to the European Medicines Agency under art. 58 for regulatory review. A WHO recommendation for use will depend on the final results from the large clinical trial and a positive regulatory review. The recommendation as to whether or not this vaccine should be added to existing malaria control tools is expected in late 2015.

**WHO response**

The WHO Global Malaria Programme (GMP) is responsible for charting the course for malaria control and elimination through:
• setting, communicating and promoting the adoption of evidence-based norms, standards, policies, technical strategies, and guidelines;
• keeping independent score of global progress;
• developing approaches for capacity building, systems strengthening, and surveillance;
• identifying threats to malaria control and elimination as well as new areas for action.

GMP serves as the secretariat for the Malaria Policy Advisory Committee (MPAC), a group of 15 global malaria experts appointed following an open nomination process. The MPAC, which meets twice yearly, provides independent advice to WHO to develop policy recommendations for the control and elimination of malaria. The mandate of MPAC is to provide strategic advice and technical input, and extends to all aspects of malaria control and elimination, as part of a transparent, responsive and credible policy setting process.

WHO is also a co-founder and host of the Roll Back Malaria partnership, which is the global framework to implement coordinated action against malaria. The partnership mobilizes for action and resources and forges consensus among partners. It is comprised of over 500 partners, including malaria endemic countries, development partners, the private sector, nongovernmental and community-based organizations, foundations, and research and academic institutions.

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

4. HEADACHE DISORDERS

Overview
Headache disorders are among the most common disorders of the nervous system. Primary headache disorders, such as migraine, tension-type headache, cluster headache, and the so-called chronic daily headache syndrome, can cause substantial levels of disability. Headache can also occur as a symptom of a considerable number of other conditions. There are effective treatments for all types of headache.

KEY FACTS
• Headache disorders are among the most common disorders of the nervous system.
• It has been estimated that 47% of the adult population have headache at least once within last year in general.

Headache disorders are associated with personal and societal burdens of pain, disability, damaged quality of life and financial cost.
• A minority of people with headache disorders worldwide are diagnosed appropriately by a health-care provider.
• Headache has been underestimated, under-recognized and under-treated throughout the world.

What are headache disorders?
Headache disorders are among the most common disorders of the nervous system. Headache is a painful and disabling feature of a small number of primary headache disorders namely migraine, tension-type headache, and cluster headache. Headache can also be caused by or occur secondarily to a long list of other conditions, for example medication overuse headache.

How common are headache disorders?
Headaches are extremely common. Nearly everyone has a headache occasionally. When they occur repeatedly, they are a symptom of a headache disorder. The most common headache disorder is tension-type headache. In developed countries, tension-type headache affects one third of men and over one half of women. Recent studies suggest the same in developing countries. Less well recognized is the toll of headache disorders characterized by very frequent headache: up to one adult in 20 has a headache every – or nearly every – day.

Globally, it has been estimated that prevalence among adults of current headache disorder (symptomatic at least once within the last year) is 47%. Half to three quarters of the adults aged 18 - 65 years in the world have had headache in the last year and among those individuals, more than 10% have reported migraine. Headache on 15 or more days every month affects 1.7 - 4% of the world’s adult population. Despite regional variations, headache disorders are a worldwide problem, affecting people of all ages, races, income levels and geographical areas.

Migraine is also very common affecting at least one adult in every seven in the world. It occurs across all continents, but for reasons not yet known appears to be somewhat less common in the Far East. It is up to three times more common in women than men, a pattern seen everywhere. This difference is hormonally-driven. Migraine has been better studied than other headache disorders. Often starting at puberty, migraine most affects those aged between 35 and 45 years but can trouble much younger people, including children.

Headache disorders are painful and disabling. They can cause substantial personal suffering, impaired quality of life and high financial cost. Repeated
headache attacks – and often the constant fear of the next one – can affect family life, social life and employment. Despite this, many people – including many health care professionals – tend to perceive headache as a minor or trivial complaint. As a result, the physical, emotional, social and economic burdens of headaches are poorly acknowledged. For the vast majority of people suffering from headache, effective treatment requires no expensive equipment, tests or specialists. Headache disorders are mostly, and rightly, managed in primary health care. The essential components of effective management are awareness of the problem, correct diagnosis, avoidance of mismanagement, appropriate lifestyle modifications and informed use of cost-effective pharmaceutical remedies.

What is the burden due to headache disorders?

Not only is headache painful, but also disabling. In the Global Burden of Disease Study, updated in 2004, migraine on its own was found to account for 1.3% of years lost due to disability (YLD).

Headache disorders impose a recognizable burden on sufferers including sometimes substantial personal suffering, impaired quality of life and financial cost. Repeated headache attacks, and often the constant fear of the next one, damage family life, social life and employment. The long-term effort of coping with a chronic headache disorder may also predispose the individual to other illnesses. For example, depression is three times more common in people with migraine or severe headaches than in healthy individuals.

Types of headache disorders

Migraine, tension-type headache and medication-overuse headache are of public health importance as they are responsible for high population levels of disability and ill-health.

Migraine

- A primary headache disorder.
- Most often begins at puberty and most affects those aged between 35 and 45 years.
- It is caused by the activation of a mechanism deep in the brain that leads to release of pain-producing inflammatory substances around the nerves and blood vessels of the head.
- Migraine is recurrent, often life-long, and characterized by attacks.
- Attacks include features such as
  - headache of moderate or severe intensity;
  - nausea (the most characteristic);
  - one-sided and/or pulsating quality;
  - aggravated by routine physical activity;
  - with duration of hours to 2 - 3 days;
  - attack frequency is anywhere between once a year and once a week; and
  - in children, attacks tend to be of shorter duration and abdominal symptoms more prominent.

Tension-type headache (TTH)

- TTH is the most common primary headache disorder.
- Episodic TTH is reported by more than 70% of some populations; chronic TTH affects 1-3% of adults.
- TTH often begins during the teenage years, affecting three women to every two men.
- Its mechanism may be stress-related or associated with musculoskeletal problems in the neck.
- Episodic TTH attacks usually last a few hours, but can persist for several days.
- Chronic TTH can be unremitting and is much more disabling than episodic TTH.
- This headache is described as pressure or tightness, like a band around the head, sometimes spreading into or from the neck.

Cluster Headache (CH)

- A primary headache disorder.
- CH is relatively uncommon affecting fewer than 1 in 1000 adults, affecting six men to each woman.
- Most people developing CH are in their 20s or older.
- It is characterized by frequent recurring, brief but extremely severe headache associated with pain around the eye with tearing and redness, the nose runs or is blocked on the affected side and the eyelid may droop.
- CH has episodic and chronic forms.

Medication-overuse headache (MOH)

- MOH is caused by chronic and excessive use of medication to treat headache.
- MOH is the most common secondary headaches.
- It may affect up to 5% of some populations, women more than men.
- MOH is oppressive, persistent and often at its worst on awakening.

Social and economic burden of headache

Headache disorders are a public-health concern given the large amount of associated disability and financial costs to society. As headache disorders are most troublesome in the productive years (late teens to 50s), estimates of their financial cost to society – principally from lost working hours and reduced productivity – are massive. In the United Kingdom, for example, some 25 million working- or school-days are lost every year because of migraine alone; this financial cost is matched by TTH and chronic daily headache combined. Headache is high among causes of consulting medical practitioners as one-third of all neurological consultations were for headache, in one
survey. Yet, many of those troubled by headache do not receive effective care. For example, in the United States of America and the United Kingdom, only half of those identified with migraine had seen a doctor for headache-related reasons in the previous 12 months, and only two-thirds had been correctly diagnosed. Most were solely reliant on over-the-counter medications.

Treatment
Appropriate treatment of headache disorders requires professional training of health professionals, accurate diagnosis and recognition of the condition, appropriate treatment with cost-effective medications, simple lifestyle modifications, and patient education. The main classes of drugs to treat headache disorders include: analgesics, anti-emetics, anti-migraine medications, and prophylactic medications. However, a large number of people with headache disorders are not diagnosed and treated.

Barriers to effective care
Lack of knowledge among health-care providers is the principal clinical barrier. Worldwide, on average only four hours of undergraduate medical education are dedicated to instruction on headache disorders. The minority of individuals with headache disorders worldwide are professionally diagnosed; 40% for those with migraine and TTH, while for MOH it is only 10%

Poor awareness extends to the general public. Headache disorders are not perceived by the public as serious since they are mostly episodic, do not cause death, and are not contagious. The low consultation rates in developed countries may indicate that many sufferers are unaware that effective treatments exist.

Many governments, seeking to constrain health-care costs, do not acknowledge the substantial burden of headache on society. They might not recognize that the direct costs of treating headache are small in comparison with the huge indirect-cost savings that might be made (eg, by reducing lost working days) if resources were allocated to treat headache disorders appropriately.

WHO response
These evident burdens call for action. WHO recognizes this, and is a partner, with the non-governmental organization Lifting The Burden, in the Global Campaign against Headache. This initiative, begun in 2004 and aims not only to raise awareness of headache disorders, but also, to improve the quality of headache care and access to it worldwide. WHO published the Atlas of headache disorders in 2011 describing the burden due to headache disorders and resources available to reduce them.

5. MENTAL HEALTH: A STATE OF WELL-BEING

Overview
Mental health is defined as a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community.

It refers to a broad array of activities directly or indirectly related to the mental well-being component included in the WHO’s definition of health: “A state of complete physical, mental and social well-being, and not merely the absence of disease”. It is related to the promotion of well-being, the prevention of mental disorders, and the treatment and rehabilitation of people affected by mental disorders.

KEY FACTS
- Mental health is an integral part of health; indeed, there is no health without mental health.
- Mental health is more than the absence of mental disorders.
- Mental health is determined by socioeconomic, biological and environmental factors.
- Cost-effective public health and intersectoral strategies and interventions exist to promote, protect and restore mental health.

The positive dimension of mental health is stressed in WHO’s definition of health as contained in its constitution: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

10 Facts on Mental Health; Some Important Facts and Figures
Fact 1: Around 20% of the world’s children and adolescents have mental disorders or problems
About half of mental disorders begin before the age of 14. Similar types of disorders are being reported across cultures. Neuropsychiatric disorders are among the leading causes of worldwide disability in young people. Yet, regions of the world with the highest percentage of population under the age of 19 have the poorest level of mental health resources. Most low-and middle-income countries have only one child psychiatrist for every 1 to 4 million people.

Fact 2: Mental and substance use disorders are the leading cause of disability worldwide
About 23% of all years lost because of disability is caused by mental and substance use disorders.
Fact 3: About 800,000 people commit suicide every year

Over 800,000 people die due to suicide every year and suicide is the second leading cause of death in 15-29-year-olds. There are indications that for each adult who died of suicide there may have been more than 20 others attempting suicide. 75% of suicides occur in low- and middle-income countries. Mental disorders and harmful use of alcohol contribute to many suicides around the world. Early identification and effective management are key to ensuring that people receive the care they need.

Fact 4: War and disasters have a large impact on mental health and psychosocial well-being

Rates of mental disorder tend to double after emergencies.

Fact 5: Mental disorders are important risk factors for other diseases, as well as unintentional and intentional injury

Mental disorders increase the risk of getting ill from other diseases such as HIV, cardiovascular disease, diabetes, and vice-versa.

Fact 6: Stigma and discrimination against patients and families prevent people from seeking mental health care

Misunderstanding and stigma surrounding mental ill health are widespread. Despite the existence of effective treatments for mental disorders, there is a belief that they are untreatable or that people with mental disorders are difficult, not intelligent, or incapable of making decisions. This stigma can lead to abuse, rejection and isolation and exclude people from health care or support. Within the health system, people are too often treated in institutions which resemble human warehouses rather than places of healing.

Fact 7: Human rights violations of people with mental and psychosocial disability are routinely reported in most countries

These include physical restraint, seclusion and denial of basic needs and privacy. Few countries have a legal framework that adequately protects the rights of people with mental disorders.

Fact 8: Globally, there is huge inequity in the distribution of skilled human resources for mental health

Shortages of psychiatrists, psychiatric nurses, psychologists and social workers are among the main barriers to providing treatment and care in low- and middle-income countries. Low-income countries have 0.05 psychiatrists and 0.42 nurses per 100,000 people. The rate of psychiatrists in high income countries is 170 times greater and for nurses is 70 times greater.

Fact 9: There are five key barriers to increasing mental health services availability

In order to increase the availability of mental health services, there are 5 key barriers that need to be overcome: the absence of mental health from the public health agenda and the implications for funding; the current organization of mental health services; lack of integration within primary care; inadequate human resources for mental health; and lack of public mental health leadership.

Fact 10: Financial resources to increase services are relatively modest

Governments, donors and groups representing mental health service users and their families need to work together to increase mental health services, especially in low- and middle-income countries. The financial resources needed are relatively modest: US$ 2 per capita per year in low-income countries and US$ 3 - 4 in lower middle-income countries.

Mental health is an integral and essential component of health. The WHO constitution states: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." An important implication of this definition is that mental health is more than just the absence of mental disorders or disabilities.

Determinants of mental health

Multiple social, psychological, and biological factors determine the level of mental health of a person at any point of time. For example, persistent socio-economic pressures are recognized risks to mental health for individuals and communities. The clearest evidence is associated with indicators of poverty, including low levels of education.

Poor mental health is also associated with rapid social change, stressful work conditions, gender discrimination, social exclusion, unhealthy lifestyle, risks of violence, physical ill-health and human rights violations. There are also specific psychological and personality factors that make people vulnerable to mental disorders. Lastly, there are some biological causes of mental disorders including genetic factors which contribute to imbalances in chemicals in the brain.

Mental health promotion and protection

Mental health promotion involves actions to create living conditions and environments that support mental health and allow people to adopt and maintain
implement mental health policy, it is vital to not only increase the chances of more people experiencing better mental health.

A climate that respects and protects basic civil, political, socio-economic and cultural rights is fundamental to mental health promotion. Without the security and freedom provided by these rights, it is very difficult to maintain a high level of mental health.

National mental health policies should not be solely concerned with mental disorders, but should also recognize and address the broader issues which promote mental health. These include mainstreaming mental health promotion into policies and programmes in governmental and nongovernmental sectors. In addition to the health sector, it is essential to involve the education, labour, justice, transport, environment, housing, and welfare sectors as well.

Promoting mental health depends largely on intersectoral strategies. Specific ways to promote mental health include:

- early childhood interventions (e.g. home visits for pregnant women, pre-school psycho-social activities, combined nutritional and psycho-social help for disadvantaged populations);
- support to children (e.g. skills building programmes, child and youth development programmes);
- socio-economic empowerment of women (e.g. improving access to education and microcredit schemes);
- social support for elderly populations (e.g. befriending initiatives, community and day centres for the aged);
- programmes targeted at vulnerable groups, including minorities, indigenous people, migrants and people affected by conflicts and disasters (e.g. psycho-social interventions after disasters);
- mental health promotional activities in schools (e.g. programmes supporting ecological changes in schools and child-friendly schools);
- mental health interventions at work (e.g. stress prevention programmes);
- housing policies (e.g. housing improvement);
- violence prevention programmes (e.g. reducing availability of alcohol and access to arms);
- community development programmes (e.g. integrated rural development);
- poverty reduction and social protection for the poor;
- anti-discrimination laws and campaigns;
- promotion of the rights, opportunities and care of individuals with mental disorders.

**Mental health care and treatment**

In the context of national efforts to develop and implement mental health policy, it is vital to not only protect and promote the mental well-being of its citizens, but also address the needs of persons with defined mental disorders.

Knowledge of what to do about the escalating burden of mental disorders has improved substantially over the past decade. There is a growing body of evidence demonstrating both the efficacy and cost-effectiveness of key interventions for priority mental disorders in countries at different levels of economic development. Examples of interventions that are cost-effective, feasible, and affordable include:

- treatment of epilepsy with antiepileptic drugs;
- treatment of depression with (generically produced) antidepressant drugs and brief psychotherapy;
- treatment of psychosis with older antipsychotic drugs plus psychosocial support;
- taxation of alcoholic beverages and restriction of their availability and marketing.

A range of effective measures also exists for the prevention of suicide, prevention and treatment of mental disorders in children, prevention and treatment of dementia, and treatment of substance-use disorders. The Mental Health Gap Action Programme (mhGAP) has produced evidence based guidelines for non-specialists to enable them in identification and management of mental health priority conditions.

**WHO response**

WHO supports governments in the goal of strengthening and promoting mental health. WHO has evaluated evidence for promoting mental health and is working with governments to disseminate this information and to integrate effective strategies into policies and plans.

In 2013, the World Health Assembly approved a "Comprehensive Mental Health Action Plan for 2013-2020". The Plan is a commitment to take specific actions to improve mental health and to contribute to the attainment of a set of global targets. It’s overall goal is to promote mental well-being, prevent mental disorders, provide care, enhance recovery, promote human rights and reduce the mortality, morbidity and disability for persons with mental disorders. It focuses on four key objectives to:

- strengthen effective leadership and governance for mental health;
- provide comprehensive, integrated and responsive mental health and social care services in community-based settings;
- implement strategies for promotion and prevention in mental health; and
- strengthen information systems, evidence and research for mental health.

Particular emphasis is given in the Action Plan to...
the protection and promotion of human rights, the strengthening and empowering of civil society and to the central place of community-based care.

In order to achieve its objectives, the Action Plan proposes and requires clear actions for governments, international partners and for WHO. Ministries of health will need to take a leadership role and WHO will work with them and with international and national partners, including civil society, to implement the plan. As there is no action that fits all countries, each government will need to adapt the Action Plan to its specific national circumstances.

Implementation of the Action Plan will enable persons with mental disorders to:

- find it easier to access mental health and social care services;
- be offered treatment by appropriately skilled health workers in general health care settings, WHO Mental Health Gap Action Programme (mhGAP) and its evidence-based tools facilitate this process;
- participate in the reorganization, delivery and evaluation of services so that care and treatment becomes more responsive to their needs;
- gain greater access to government disability benefits, housing and livelihood programmes, and better participate in work and community life and civic affairs.

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6. ASBESTOS: ELIMINATION OF ASBESTOS-RELATED DISEASES

Eliminating asbestos-related diseases is particularly targeted at countries still using chrysotile asbestos, in addition to assistance in relation to exposures arising from historical use of all forms of asbestos.

KEY FACTS

- About 125 million people in the world are exposed to asbestos at the workplace.
- According to WHO estimates, more than 107,000 deaths each year due to lung cancer, mesothelioma and asbestosis resulting from exposure at work.

What is asbestos?

Asbestos is a group of naturally occurring fibrous minerals with current or historical commercial usefulness due to their extraordinary tensile strength, poor heat conduction, and relative resistance to chemical attack. For these reasons, asbestos is used for insulation in buildings and as an ingredient in a number of products, such as roofing shingles, water supply lines and fire blankets, as well as clutches and brake linings, gaskets and pads for automobiles.

The main forms of asbestos are chrysotile (white asbestos) and crocidolite (blue asbestos). Other forms are amosite, anthophylite, tremolite and actinolite.

Why is asbestos a problem?

All forms of asbestos are carcinogenic to humans. Exposure to asbestos, including chrysotile, causes cancer of the lung, larynx and ovaries, and also mesothelioma (a cancer of the pleural and peritoneal linings). Asbestos exposure is also responsible for other diseases such as asbestosis (fibrosis of the lungs), and plaques, thickening and effusion in the pleura.

Currently, about 125 million people in the world are exposed to asbestos at the workplace. Approximately half of the deaths from occupational cancer are estimated to be caused by asbestos. In addition, it is estimated that several thousand deaths annually can be attributed to exposure to asbestos in the home.

It has also been shown that co-exposure to tobacco smoke and asbestos fibres substantially increases the risk for lung cancer – and the heavier the smoking the greater the risk.

WHO response

The World Health Assembly Resolution 58.22 on cancer prevention urges Member States to pay special attention to cancers for which avoidable exposure is a factor, including exposure to chemicals at the workplace and in the environment.

WHO, in collaboration with the International Labour Organization and other intergovernmental organizations and civil society, works with countries towards elimination of asbestos-related diseases in the following ways:

- by recognizing that the most efficient way to eliminate asbestos-related diseases is to stop the use of all types of asbestos;
- by providing information about solutions for replacing asbestos with safer substitutes and developing economic and technological mechanisms to stimulate its replacement;
- by taking measures to prevent exposure to asbestos in place and during asbestos removal (abatement);
- by improving early diagnosis, treatment, and rehabilitation services for asbestos-related diseases;
- by establishing registries of people with past and/or current exposures to asbestos and organizing medical surveillance of exposed workers;
- by providing information on the hazards associated with asbestos-containing materials and products, and by raising awareness that waste containing asbestos should be treated as hazardous waste.