



# KMJ



## KUWAIT MEDICAL JOURNAL

The Official Journal of The Kuwait Medical Association

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## Editorial

## Health is Environmental?

Belle M Hegde

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*"Skepticism is the highest of duties; blind faith the one unpardonable sin."*

**Thomas Huxley**

We have been depending too much on reductionist science to believe that health and diseases are basically controlled by our genes. This myth has now been blown apart and our genes, if anything, have very little to do with our evolution and even our existence here. That apart, we now know that we can even change our genetic pattern, if needed, by our environment. Our life style changes, for, the better can change even our genetic pattern. This has been recently shown in the case of killer diseases of old age.

If one is healthy and well at a given point in time, it is just chance; if one, on the other hand, is ill and suffering, it is also chance! No science can predict either of those events with any degree of certainty! Doctors have been predicting the unpredictable future of patients for generations based on some phenotypic features called risk factors. A very large prospective study followed up for 25 long years has shown that there are no "risk factors" as far as human diseases are concerned. The said MRFIT study did further show that the so called risk factors could be controlled by drugs or surgery but the risk, if it is there, still works itself successfully!

With the onset of quantum wisdom, we have been now able to comprehend much more than what we could grasp with our five senses. Quantum world view opens a new vista in human physiology where we can get a wider holographic view of human life at a given point in time. The so called life style management also

gets a new meaning in quantum world view. In the old Einstein-Newtonian world view, life style changes are simply work, sleep, food, exercise, stress reduction, the physical environments like air, water, earth, weather *etc.*, in addition to the medical money spinners like hypertension, diabetes, obesity and what all else you have. Although this has made a dent in the morbidity pattern, they did not make a huge difference. In addition, the powerful drugs used to control the risk factors have brought in their wake, many adverse drug reactions, some of them being even fatal.

In the new world view, human mind assumes special significance. Reductionist science does not take the mind into considerations seriously, although some fringe studies did show some mental altered states like depression and frustration leading to serious illnesses. The main line medicine is yet to give importance to the mind, as it is not yet sure where the mind is? The Canadian neurosurgeon Wilder Penfield, in his elaborate reductionist studies, put the mind inside the brain, but later realised his folly and in 1971 admitted that the mind cannot be confined to a small organ like the brain. Mind is our consciousness - the canvas on which our thoughts are projected. Consciousness is fundamental and all else will have to arise from consciousness, wrote Max Planck! Matter and energy being the two faces of the same coin, the human body becomes an illusion of the human mind. In view of this new scientific awareness, the real environment for our healthy living or even for recovery from any illness should be the human mind.

A healthy mind is an insurance against diseases and is a tool in reversing disease processes, many of them like cancer keep incubating for very long times.

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‡Affiliate Professor of Human Health



Our mind is at work in every disease situation from common cold to cancer. In the latter case, the cancer cells, "aimless, jobless wandering cells" that have mutated to survive a hostile environment in our bodies urgently need a conducive environment to remodel and survive. Our reductionist idea of early cancer detection (a big business move for the cancer industry) is a fraud, as these wandering cells have gone far and wide long before the cancer can be clinically detected. Hence there is nothing called "early" cancer detection. Sometimes the secondaries come up before the primary cancer shows up! Now one can understand the significance of the need for a healthy mind to keep us physically also healthy. For the lay person, what should be the meaning of a healthy mind?

Healthy mind is a mind filled with "enthusiasm to work and enthusiasm to be compassionate." This all-encompassing definition covers all parts of health. The words are chosen carefully. Enthusiasm is not just wanting to do a thing, but a compulsive motivation to do that. Enthusiasm to work is the love for work - want to work and NOT have to work! Similarly, enthusiasm to be compassionate is a compulsive urge to be of some use to someone almost always, nay to be universally compassionate. If one follows these two mottos in life, there is no room for any negative thoughts in the mind like hatred, jealousy, superego, anger, pride, and greed (that too Wall Street greed)? The latter are the real risk factors for all major killer diseases!

In the true sense of the word, the real environment for the human wellness and illnesses is the human mind. Rest of the conventionally acclaimed risk factors are not the real environment although they do contribute to the final outcome. Genetics has given place to epigenetics. Human mind sits in the driving seat in human affairs, which can even alter the gene

penetrance. Charles Darwin and Gregory Mendel have been given an undeservedly exalted position in medical textbooks although the neo Darwinists still want to hang on to their coat strings, as there is money in genetic profiling, genetic engineering, stem cell research, dead body and cord blood preservation *etc.* Charles Darwin himself, in his old age and, before him, his own grandfather Erasmus Darwin and Lamarck had clearly said that the environment is more important than the genes in human evolution. The new science of evolutionary biology has strongly reiterated that truth.

Like people who search for the God inside mud and stone structures, these scientists have been searching for the real environment far outside this real environment of the human mind in BP, sugar, cholesterol, tummy girth, and what have you? Our future generation at least should have the benefit of this truth. We have to bring forth a generation of our youth with a healthy mind. In that direction, real education takes the cake. Today, education is aimed at making a wealthy career for the child. That is not education. The real education is to make a healthy mind out of every child and not just a wealthy career. If every child develops a healthy mind with enthusiasm to work and enthusiasm to be compassionate, all our society ills like terrorism, laziness, crime, rape *etc.* will vanish without any effort on our part. Can I hope that the powers that be would change the base of education policy, which would lay the foundation for a healthy mind in every child?

*"21<sup>st</sup> century illiterate is one who cannot unlearn the wrong things that he has learnt and relearn the right things."*

**Anon**

## Review Article

# Establishment of the Kuwait Medical School (1965 - 1976)

Mohammad Jamal<sup>1</sup>, Latifa Al Mufarrej<sup>2</sup>, Adel K Ayed<sup>3</sup>

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This is a study on the establishment of the Kuwait Medical School. It examines the planning needed to establish a medical school, focusing mostly on the work done by the 1973 planning committee of the Kuwait Medical Faculty.

It also gives an insight on the process of medical education, since the establishment of the Kuwait Medical School was

during a period when the process of medical education was revised.

The study concludes that the establishment of the Kuwait Medical School was a great achievement and a fine example of early global collaboration in medical education.

KEY WORDS : medical education, medical faculty Kuwait

## INTRODUCTION

In 1827, a French doctor from Napoleon's occupying army established the first modern medical school in the Middle East. It was Kasr Al-Aini Medical School in Cairo, Egypt. The American University of Beirut (AUB) Medical School was second to be opened in the Middle East in 1866, by an American Presbyterian. The third medical school in the region was opened in Baghdad in early forties of the last century. Those were the three main medical schools in the region at the time of the birth of the idea of the Kuwait Medical School establishment. There was no single such school in the Arabian Gulf region.

From the above, we can see the unique situation of the Kuwait Medical School, in which it was the first school in the Gulf region and the first in the Middle East to be founded by native hands. Kasr Al-Aini, the AUB and Baghdad medical schools were all established under the role of colonial governments.

Was the establishment of the Kuwait Medical School a pioneering work? Of what standard was the planning of the new school? And finally, how was the method of teaching chosen in the new school? These are the questions that will be answered in this article.

The subject of this article is very original; hence there was a great difficulty in finding secondary sources. Most of the newspapers' and magazines'

archives were destroyed by the Iraqi invasion. One of the few preserved was Al-Qabas newspaper archive, which consisted of about 30 pages on the Kuwait Medical School. Another secondary source was an article published in Aberdeen university review by Dr Ian Olson, the first Vice-Dean academic of the Kuwait Medical School and one of its founders. Identifying primary sources was also a very difficult task. There was no medical school archive, probably due to its destruction by the Iraqi invasion.

Professor Fuad Al-Ali was met, who thought that the only help would be by interviewing the founders of the medical faculty. He then introduced us to Professor Abdulmohsin Al-Abdulrazzaq, the founding dean of the Kuwait Medical School, who was very kind in providing us with the original reports and papers of the planning committee of the Kuwait medical faculty, which were kept in his residence. Dr Ian Olson was interviewed in Aberdeen.

Also, we identified two WHO reports, which were the first to discuss the possibility of founding a medical school in Kuwait.

This article is the first ever-comprehensive study on the establishment of the Kuwait Medical School. It should be useful, especially now a days, when there are talks among the officials in Kuwait to establish a second medical school in Kuwait.

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### **Brief history of modern medicine in Kuwait**

Kuwait has one of the most comprehensive health care systems and one of the most all-encompassing social in the world. The origin of the modern system of health care in Kuwait can be traced back to the early years of the twentieth century. However, it was not till the 1950s that the government introduced an extensive health care program and medical services.

The first clinic was opened on the thirtieth of October, 1904. The British mandatory in Kuwait inaugurated the clinic, which was called 'Dar Al-Eitemad'. It was the first clinic in the history of Kuwait. The doctor in charge was of Indian origin called 'Daud ur Rahman'. In 1905, he published the first medical report; the clinic was able to provide care for 3976 patients and conducted 181 surgical operations. This British clinic continued to provide health services in Kuwait, and controlled quarantines until 1951, when the health department of Kuwait took over supervision of quarantine procedures<sup>[1]</sup>.

The first hospital in Kuwait was built in 1914 by a group of American doctors. They gained the trust of the people and of Sheikh Mubarak, who was the ruler at that time. They soon understood the customs of the Kuwaiti people, and decided to build another hospital for women, which was opened in 1920, under the direction of Dr Elia Naurkaleferlie. Dr Mylrea supervised medical services for men<sup>[2]</sup>.

The government of Kuwait established its own health department in 1936, and was chaired by Sheikh Abdullah Al-Salim. The first government clinic was established in 1939 in the Sharq area. Amiri hospital, which was the first government hospital, was opened in 1949, with great celebration, as it was a symbol of Kuwait's entry into the modern era<sup>[1]</sup>.

### **The dream for a Kuwait medical school**

Health services in any civilized society are essential. Kuwait in the sixties was a rapidly progressive society with lots of ambitions to join the club of civilized countries, with the aid of its natural resources, mainly oil. Enthusiasm has led to the establishment of Kuwait University in 1966 with five colleges, but without the faculty of medicine. Although the idea of founding a medical school was in mind since the start of planning of the university in 1964, it was decided to postpone the medical faculty establishment due to the lack of proper hospital facilities and a suitable number of local physicians and surgeons<sup>[3]</sup>.

The dream of having a Kuwait Medical School was shared even at the highest level among government officials. In 1965, the WHO was consulted by Kuwait University planning committee to study the possibility of founding a medical school in Kuwait. The WHO

sent Dr Gabriel Rifka from the American University of Beirut. He made visits to hospitals and met with government officials from the Ministry of Health and the Ministry of Education during the period between the third to ninth of December 1965<sup>[4]</sup>.

He reported that the need for a medical school in a country like Kuwait, with a population of 468,000, will only be justified, if account is taken to the possibility that students from the Gulf region will be given the opportunity to study in the Kuwait Medical School. Also the number of Kuwaiti students who could apply to the medical school was insufficient. This relied on the experience of the WHO, that one fourth of the secondary school graduates study sciences and that one tenth of the later will study medicine. Thus, the estimated number of students applying to the medical school in the year 1970 was expected to be 50 - 75 only<sup>[4]</sup>.

Dr Rifka found that the medical facilities in Kuwait were of world class standard, although he thought that they were not suitable for teaching. He suggested the building of a teaching hospital in Al-Sabah complex or adaptation of the current Sabah hospital to suite teaching. A third suggestion made by him was the introduction of changes to the Mubarak hospital, which was under construction to make it suitable for teaching purposes<sup>[4]</sup>.

An interesting subject in Dr Rifka's report was the debate about the language to be used for teaching in the new medical school and in the Science College of Kuwait University, since the language of the College of Sciences should be the same as the language of the Medical School as pre-medical teaching would take place in the Science College. During the sixties, left wing nationalists were very influential in the Arab world. The Egypt nationalist government and Syrian nationalist government united under the name 'United Arab Republic'. The United Arab Republic committee on higher education visited Kuwait to help in planning the new university, and recommended the use of Arabic language in the science college. Many of the senior officials met by Dr Rifka were in favor of the use of Arabic language in the new medical school. On the other hand, Dr Rifka was strongly in favor of the use of English language for several reasons, three of which he stated in the report were firstly, most of the scientific and medical literatures are written in English. Secondly, teaching in English would be more attractive to students from the region. Thirdly, more post graduate opportunities would be available for Kuwait medical school graduates, if the teaching is in English language<sup>[4]</sup>.

Another concern by Dr Rifka was that post mortem examinations are rarely done in Kuwait, due to the

public view on donating bodies. It's the custom of Muslim societies to bury the dead as soon as possible. This would hinder teaching of anatomy in the medical school, so he recommended the preparation of the community through the media. Finally, Dr Rifka recommended another visit by the WHO consultants group on education and the formation of a national planning committee to study the project further and aid the work of the WHO. He concluded that a medical school cannot be established at that time due to several reasons; firstly, the university was at its infancy; secondly, the lack of Kuwaiti doctors; thirdly, the poor social conditions for expatriate staff; fourthly, the total dependence on expatriate personnel; fifthly, the lack of suitable applicants and lastly the inadequacy of hospital facilities for teaching<sup>[4]</sup>.

This report by Dr Rifka was the first ever study on the feasibility of founding a medical school in Kuwait. It was very comprehensive and included useful information about Kuwait health care facilities like the number of hospital beds, the number of doctors, the number of students in secondary schools and a list of the Health Ministry and the Education Ministry officials at that period. It was very clear from his report that the social situation at that time was not in favor of establishing a medical school. This shows how social and political factors may influence medical schools.

However, Kuwait society in the sixties was changing rapidly in all aspects. A WHO consultative group visited Kuwait again two years later to identify the areas of improvement. The group included officials from Birmingham University, Khartoum University, Cairo University and the American University of Beirut<sup>[5]</sup>.

The group made a series of visits and interviews in the period from 6/10/1968 to 14/10/1968, and produced a report after further discussion in the regional WHO office in Alexandria<sup>[6]</sup>. The group found that many factors had changed from the last visit. There was an increase in population from 468,000 in 1965 to 512,794 in 1976, so the annual increase was 20%<sup>[5]</sup>. Also, Kuwait became a regional center for patients from neighboring countries wanting better medical care, this clearly lead to a demand for more doctors<sup>[5]</sup>. The most important change encountered by the group was the establishment of the Kuwait University and its rapid development. This is very vital for the beginning of the medical school, since the pre-medical teaching will take place in the Science College. Regarding the suitability of applicants, the WHO group thought that the increase in population would mean that more students will be graduating and hence more will be applying. They also thought that the new school would attract students from the region.

The WHO group recommended the establishment of the faculty of medicine in Kuwait University, and suggested the year 1971 to be the first year of admission. They also recommended the constitution of a national planning committee and the appointment of a dean for the faculty<sup>[5]</sup>.

### **The medical school argument**

There were two opinions on the need of a medical school.

The founding dean Professor A Alabdulrazzaq speaks about that; "There were two opinions on the need for a medical school, one school of thought said; why should we waste money by building a medical school when it's cheaper to send students abroad. In fact, the first Kuwaiti rector Dr Hasan Al-Ebrahim was of that opinion. We answered that we have to start a medical school for several reasons; number one is that although initially Kuwaitis went to good medical schools in London and Aberdeen, they later on went in a huge number to Egypt where the standard of teaching was low. Number two; you cannot improve the health service without a medical school with undergraduates' education, and more important, postgraduate education. Number three; research is very important. If you don't have good research in the community, you are not able to attract good doctors. This was very apparent when the school opened and the research publication shot up into the sky<sup>[3]</sup>.

One group was of the opinion that it's more expensive to establish the medical school in Kuwait than to send students abroad. They argued that it is better for the health services to have Kuwaitis graduating from prestigious medical schools abroad. The university rector was on that side and the health minister Dr Abdulrahman Al-Awadi. To understand why they had this view, one should know that Kuwait society in the late sixties was very well off materially and a very rich society, thanks to oil discovery. Everything was bought and imported, including experts from various fields. It would be understandable that they preferred to send the students abroad since the government was able to do that. However, it was very difficult trying to find a place for a Kuwaiti student to study abroad. It was even impossible to get a place in a medical school in USA, Canada or UK. This was attributed to the inadequacy of the secondary education in Kuwait during the nineteen sixties<sup>[3]</sup>.

The debate was clearly on the side of those in favor of establishing the medical school. It is the natural desire for any country to train its own people to replace foreign staff. Founding a medical school will encourage Kuwaitis to train in medicine in their own homeland, since many who go abroad at a young age would face

social problems, which may interfere with their work. Also, every country has its own peculiar problems and studying abroad means that students would not get exposure to these problems. Furthermore, a medical school would raise the standards of health services by the provision of continuous education for doctors and by stimulating research and postgraduate teaching.

### Plans and committees

Soon after the 1968 visit by the WHO, a national committee was formed which consisted of representatives from the Ministry of Education, the Ministry of Health, the Kuwait Medical Association and the planning board. They recommended the establishment of the medical faculty but with caution<sup>[3]</sup>. On 29 December 1968, at the council of ministers meeting, the resolution '55/68' was passed to begin establishing the medical faculty<sup>[6]</sup>. In February 1969, the university council decided to execute the project and appointed a local committee to follow it up.

The local committee met and came up with a plan to build the medical school in Al-Sabah hospital complex. It recommended the adaptation of Al-Sabah hospital to suit teaching. Their recommendations were submitted to the university council in May 1969. A joint meeting was then held between the university officials and the Ministry of Health in September 1969 to cooperate the establishment of the new faculty. They decided to appoint two committees, a planning committee and an advisory academic committee to assist with the detailed planning of the medical school<sup>[6]</sup>.

The planning committee consisted of representatives from the university, the Ministry of Education and two doctors from the Ministry of Health. The university rector founded the advisory academic committee; it consisted of four medical schools' deans from the University of Alexandria, the University of Khartoum, the University of London and the University of Baghdad. The advisory academic committee also included six doctors from the Ministry of Health and a representative from the Kuwait University. Dr Abdulmohsin Al-Abdulrazzaq and Dr Abdulrazzaq Al-Abdulrazzaq were members of both committees<sup>[6]</sup>.

In February 1970, a series of joint meetings between the two committees were held. Those meetings resulted in the 1970 report on the establishment of the Kuwait Medical School. They formed a complete plan for establishing the new school with a teaching hospital in Al-Sabah hospitals complex. The total cost estimated was 12.5 million Kuwaiti Dinar (KD). They suggested the establishment of a dental school and a pharmacy school in the same area, and their cost were included in the previously mentioned estimate. The committees also suggested the formation of a joint

council between the university and the Ministry of Health to administrate the teaching hospital<sup>[6]</sup>.

Nothing was heard about the project till early 1973, when a new planning committee was formed to study the economic implications of the 1970 report recommendation, which was thought to be excessive in its request. This committee managed to cut the costs to two and a half million KD. However, this reduction affected the research facilities and relied on using Al-Sabah hospital for teaching, although it had many deficiencies. Finally, the university council decided to appoint Dr Abdulmohsin Al-Abdulrazzaq as Dean in 1973 and the Amiri decree was issued to establish the medical faculty of the Kuwait University. It seemed then that Kuwait seriously desired to open a medical faculty<sup>[3]</sup>.

In 1973, many changes happened since the WHO 1968 report. Hospitals were ready for teaching. There were several Kuwaiti consultants of good quality, and the number of Kuwaiti doctors increased (10 - 15 percent) of total doctors<sup>[7]</sup>. All in all, there was a strong enough base to start the medical school.

### The difficult task

"They chose me one day and told me to start the school the next day. There was nothing, no space, no programme and no staff. I told them it's not possible. More planning is needed." Professor Abdulmohsin Al-Abdulrazzaq the founding dean of Kuwait medical faculty, said<sup>[3]</sup>.

The 1973 committee started to work straight away. This committee consisted of the dean elect Dr Abdulmohsin Al-Abdulrazzaq, the dean of the science college, a representative of the Health Ministry, and some Kuwaiti and other Arab clinicians<sup>[7]</sup>. They held several meetings, which resulted in many reports.

Professor Abdulmohsin Al-Abdulrazzaq the founding dean remembers the start of planning; "We formed the core planning group, which comprised of all the senior Kuwaiti doctors, we also had the dean of the science college. You can see in the planning document that we hired a consultancy group to give a master plan for the medical school. We had to look into several activities going in parallel; one is development of the curriculum. Second is looking at building facilities. Third is finding staff. Lastly, planning the entry requirements for the students" <sup>[3]</sup>.

"It was a difficult task; they wanted a John Hopkins of the Middle East<sup>[3]</sup>. To that extent was the ambition. So they tried to recruit European and North American staff. One of the difficulties in achieving their aims was that they could not find someone in the western medical world to advise them on how to start their John Hopkins<sup>[3]</sup>. Britain at that time had not built a new medical school for seventy years. They were just

establishing Nottingham and Southampton medical schools<sup>[8]</sup>. In the USA the case was the same, USA had not built a new school since the nineteenth century<sup>[3]</sup>. Also in Kuwait's own region (the Gulf), there was no single medical school".

"There was hardly anybody there, who had an experience on how to establish a medical school. If I consult medical school's deans, they know how to run a school, but they have no idea on how to start it from scratch", Professor Abdulmohsin Al-Abdulrazzaq, the founding dean of the Kuwait medical school remembers<sup>[3]</sup>.

The committee stipulated that the earliest possible date for opening is 1976. They acquired a temporary building in Shuwaikh, and planned further from there. The committee then divided the work into four major areas: development of the curriculum, the medical school buildings, the staff recruitments and the entry requirements for the students.

The committee also hired a consultancy group "PA international" to establish a master plan for the development of the new faculty<sup>[3]</sup>.

### Developing a curriculum

Medical education at that time was in a state of turmoil, where some were searching about the efficiency of conventional system is in full swing. Also there were lots of so called 'medical education reformers', each with their own idea. There was a decision to be made on the choice between a conventional system and one of the new systems of medical teaching.

To complete the picture of the new methods of teachings, the committee formed a team to visit medical schools, which implement the integrated systems<sup>[10]</sup>.

The team visited three medical centers in the period between 15 - 26 September 1973; the McGill medical center in Montreal, Canada, which adopts the traditional departmental system of teaching; the McMaster medical center in Hamilton, Canada, where teaching depends on self-learning supervised by tutors; and the Case Western Reserve in Cleveland, USA; which represents integrated teaching<sup>[9]</sup>.

The team members were impressed by the problem oriented system in McMaster medical center. It was a revolutionary form of medical teaching, in which it was entirely based on self-education supervised by tutors. The students were taught how to develop problem solving ability by learning how to formulate data rationally, utilise learning resources to help solving the problem, and finally devise solutions relevant to this situation. The philosophy there was, that a doctor is continuously learning to adapt to changing health care needs. So it is better to train doctors to face the lifelong work in the medical school under supervision

by problem-solving-oriented teaching rather than loading them with excessive data while without sufficient instructions on how to utilise it.

However, the committee thought it was impossible to implement this system in Kuwait due to the cost. There was a cheaper version of that system implemented in Jordan and Addis Ababa medical schools. The person who directed that system was professor Howard from the Cambridge University<sup>[3]</sup>. The founding dean Dr Abdulmohsin Al-Abdulrazzaq visited Amman Medical School to take a closer look at what he called 'the developing world copy of McMaster's system', in the following paragraph he summarizes that visit and why the conventional method was adopted.

'When you are establishing the first medical school in a country, I don't believe you should try to experiment with new teaching methods. You can do that if you have the luxury, when you are building a second or a third medical school in a country. It's even more dangerous to experiment when you do not have the staff. If you took a closer look at the medical schools in the world at that time, the majority was adapting the conventional method of teaching; few started the modern methods of medical education like problem oriented and the integrated medical teaching. There are not many teachers who were familiar with modern systems. The so-called modern medical curriculum requires very mature and very capable students. Most of them should be PHD or Bsc students. In McMaster, I was meeting a PHD psychiatry student in a medical school. They were already established graduates with tremendous records. With such students, any system would work. Also, they had six hundred staff for fifty students in the class. In the traditional system, you would require a hundred only. It also requires a tremendous organization for teaching. So it was much more complex to run, than the traditional system. At that time, the WHO was going wild with medical education. There were lots of criticism about basic medical science teaching. They thought it was irrelevant to medical education. Addis Ababa adopted a cheaper version of McMaster system, which was invented and publicized by Prof. Howard. He was an excellent speaker and very enthusiastic about this system. He went to lots of medical conferences to speak about this system. But this cheaper version did not work. They gave it up in Addis Ababa. So Prof. Howard went to Jordan, where he was hired to implement the system in Amman medical school. I visited him there. I said to him; "Suppose I buy your idea, from where can I recruit the staff that knows how to run this system?" He answered there is no way that I can guarantee that. I was not impressed at all with the way the system was working there. It was very

different from what we saw in Canada. There was not a single research work taking place in Amman medical school laboratories<sup>[3]</sup>.

It was much safer for the committee to choose the conventional method of teaching to avoid experimenting with a new teaching method in an infant medical school. All the members<sup>[10]</sup> were impressed by the McMaster's teaching method, but they thought that it was very impractical to implement in Kuwait. It required more staff and more staff time for teaching. The committee also thought that this system does not leave enough time to staff for research. Even if they agreed on any of the new teaching methods, it will be a very hard task finding experienced staff. Also the committee members thought that to implement McMaster's system, you need to have fully mature students capable of self-independent learning, as well as efficient postgraduate courses; both of which were not present in Kuwait at the time<sup>[3]</sup>.

Finally, the committee adopted the conventional method of teaching, 'the departmental method'. Teaching was agreed to be for seven years and divided into three phases. The first was the premedical phase, which takes two years to complete and was conducted under the credit hour system and students had to obtain 61 credits to pass. It was taught by the faculty of science. The second phase was the pre-clinical phase, which takes two years to complete and was taught in the temporary medical school in Shuwaikh campus<sup>[10]</sup>. The final stage was clinical phase, which takes three years to complete, where students were trained in the wards and in the outpatient clinics of the Sabah hospital, which was used temporarily. Students were awarded the degrees of Bachelor of Medicine and Bachelor of Surgery after completing this phase<sup>[6]</sup>.

### **The medical school buildings and the teaching hospital**

The plan was to open the medical school in 1976. The medical school buildings and the teaching hospital were required to start the teaching. However, cost of these buildings was a center of conflict between the government of Kuwait and the faculty of medicine, taking many years to be solved.

In 1970, the planning committee for the medical school estimated the cost of the medical school and the teaching hospital to be 12.5 million KD. This was thought to be a very high price by the government. In 1973, the new committee lowered the price to two and a half million KD, after reducing the space required from 40,000 m<sup>2</sup> to 6,500 m<sup>2</sup> to add to the confusion, the committee in December 1973 concluded that at least 20,000 m<sup>2</sup> is needed, and the price estimate went up to 4,100,000 KD. Then a month later in January 1974,

the final estimate was 10 million KD<sup>[6]</sup>. The budget to achieve this was not given by the government. The medical faculty in a final attempt, asked to have Al-Sabah hospital converted as to a teaching hospital. This was rejected this time by the Ministry of Health.

It was agreed that the medical school would use Al-Sabah hospital temporarily for clinical teaching. The medical school building was temporarily situated in Al-Shuwaikh campus where pre-clinical teaching was taking place. Therefore, when the school opened in 1976, there was a lot of uncertainty.

The new medical school according to the plan was to consist of a pre-clinical building and a new teaching hospital with its clinical building, to fill the philosophy of the school. The dean insisted on a new teaching hospital but the Ministry of Health was strongly against that.

Dr Abdulmohsin Al-Abdulrazzaq the founding dean describes those events: 'First of all, we had a plan in which we build the hospital and the medical school in Al-Sabah hospital complex. Then as we reached the final stage in planning, the Ministry of Health refused the plan. Then we planned to have them in Al-Shuwaikh university campus, again by the time we reached the final stage, the government refused. At that moment, I was very upset, it wasted lots of time and I submitted my resignation as a result of that. It was in 1978, and then the government came to a compromise. The Minister of Health, Dr Abdulrahman Al-Awadi, wanted us at that time to use Sabah hospital permanently which I completely refused. The Sabah hospital at that time was a huge empire full of beurocrates. My final reply was; "Give us the Mubarak hospital (which was soon to be opened), and give me the budget to build the medical school next to it without any interference from anybody". The government accepted that<sup>[3]</sup>.

The dean fought hard for his case and at last the conflict was resolved. The new medical school was built on 43,000 m<sup>2</sup>, extending over five floors. The complete move from the temporary campus in Shuwaikh to the new medical school was in 1983, and to date, it is the site for the Kuwait Medical School.

As we can see, there was clearly a conflict, which delayed the completion of the medical school. The founding dean attributes the conflict to the differences in interests between medical schools and the Ministry of Health, since the medical school was to take care of the educational side, and the Ministry of Health to concentrate on the quality of services. "Every single joint recommendation we made was rejected by the ministry" said the founding dean<sup>[3]</sup>.

Dr Ian Olson, the first vice-dean undergraduates said; 'I never understood why there was that conflict.

Whether the Minister of Health did not like the medical work controlled by the university, in a way this is understandable. He did not want the services to be controlled by the medical school. I also got the feeling that he thought that it was better for Kuwaiti students to be trained abroad. But every move from the dean was blocked by the Minister. It slowed things extensively and it was a difficult situation. The Minister did not even want us to move to the Mubarak hospital although the Sabah hospital was wearing out<sup>[11]</sup>.

### CHOOSING THE STAFF AND THE STUDENTS

It was aimed to recruit high quality teachers from the United Kingdom and the United States. However lots of applications came from neighboring countries. The medical schools there were of low standards<sup>[3]</sup> and therefore, policy adopted by the Kuwait medical school planning committee was not to recruit teachers from regional medical schools. The reason for this attitude was due to the thought that a teacher practicing in a medical school of unacceptable quality is used to a standard, which is compromised, and it is difficult for him to fit into the standards desired by the Kuwait medical school.

The first choice for staff was Arab scientists and doctors in North America and the United Kingdom. For that, visits were made by the medical school planning committee. In their visits to the United States in 1975, they met with a group of prominent Arab medical scientists.

Then they visited Harvard, Rochester and Texas medical universities. In that visit, they managed to form an interview team to check on applicants applying from the United States and Canada. On their way back, they visited Canada and Nottingham medical schools.

The dean also reached an excellent agreement with the Lund University in Sweden, where teachers from Lund can teach in the Kuwait University without losing their position, and salary too paid by Lund. That was of great help to the infant Kuwait medical faculty<sup>[3]</sup>.

Another source of staff was Malta medical school. The school there was in crisis. Many of the teachers including the dean resigned due to the interference from the communist government. Some of the teachers were recruited by the Kuwait medical school including Professor Fenech, the resigned dean of Malta medical school, who became the professor of medicine in Kuwait<sup>[3]</sup>.

The Kuwait medical school managed to attract very well-known teaching staff. The department of physiology was chaired by Dr Nasr eldin Mahmood. Dr William G Armstrong from Britain organised the department of biochemistry and Dr Olav Thulesius for the department of pharmacology. Microbiology

was chaired by Vladimir Bezzak. Dr Ian Olson the vice dean undergraduates, chaired the anatomy and the pathology department. The department of medicine was chaired by Prof Frederick Fenech. Paediatrics was chaired by Dr Vilvaso Ayas from Malta. The department of obstetrics and gynaecology was chaired by Dr Hassan Hathout. The chairman of the surgical department was Dr George Abouna. Dr Richard Kurtz from the United States was the head of the community medicine department. The department of primary care was chaired by Swedish Dr Olof Lindquist. The department of psychiatry was chaired by Prof Fakhar Al-Eslam. Finally, the department of nuclear medicine was organised by Dr Hussain Abdel Dayem<sup>[12]</sup>.

Regarding students, their method of selection was based on secondary school leaving certificate marks, and interviews. The faculty accepted thirty students for the first batch; 15 of them were non-Kuwaitis. The maximum number which can be accepted in the school was 120 students, and the plan was to reach this with further development.

### Visits

Visits were the method of contact between the medical faculty planning committee and the western world. The visits were mainly to USA, Canada and the United Kingdom. A visit to North America in 1973 was already mentioned, which aimed to study the trends in modern medical education.

The planning committee formed a team to visit the United Kingdom during the period 1 - 12 July, 1974. This visit was arranged by the British council. The team visited several British medical schools including Dundee, Glasgow, Nottingham, Southampton and London<sup>[13]</sup>. Discussion topics were about medical education and the use of audio visual aids in medical teaching.

Another important visit was by the team to USA, Canada and UK during the period 3 - 17 July, 1975. The purpose of this visit was mainly staff recruitment and exploring the opportunity for postgraduate studies for Kuwaitis. During that visit, the dean met with Dr Ian Olson and invited him to visit Kuwait. Dr Olson was a founding member of the team which had established the first new United Kingdom medical school in the Twentieth century at Nottingham University in 1969; he had suggested that the course be run as integrated teaching of the pre-clinical and clinical aspects from year one and had implemented this concept as the Secretary to the Curriculum Committee and Chairman of the Multidisciplinary Laboratories and Audiovisual Services. Dr Olson visited Kuwait in May 1975 to advise further, and was offered the post of Academic Vice-Dean and Professor of Human Morphology and Experimental Pathology<sup>[9]</sup>.



There were also visits from the Western world to Kuwait. Professor Fuad Bashour, a prominent professor of cardiology from the Texas Medical School visited Kuwait on 17 April 1975. The outcome of his visit was the establishment of a cooperation program between the Kuwait Medical School and the Texas Medical School in which, Kuwait would receive assistance in its development program and in teaching staff. Also, it resulted in the formation of an American advisory medical council to represent the interests of the Kuwait medical faculty in America<sup>[14]</sup>.

Another visitor from USA was Dr Ali Nahas from Rochester medical school. In his visit, he submitted a report of the review of the medical school plan by several medical specialists from Rochester University. It also resulted in the recruitment of Dr Ali Nahas in the Kuwait Medical School and in the American advisory medical council<sup>[15]</sup>.

Two other important visits to the Kuwait Medical School were by Dr O'flanagan<sup>[16]</sup>, the dean of the Royal College of Surgeons medical school in Dublin and by Dr Hillman<sup>[17]</sup>, the post graduate dean of McGill University in Canada. Those two visits resulted in the provision of postgraduate training for Kuwaiti doctors in postgraduate programs in Canada and Ireland.

From these visits, we can see that the Western medical world was imported to Kuwait. With the input from Rochester, Texas, Lund<sup>[3]</sup>, McGill and Nottingham, the quality of the new medical school was assured to be high.

### **Postgraduate teaching**

Medical schools are not only involved in undergraduate teaching. The teaching of postgraduates is integral in medical school aims, since medical undergraduate courses do not produce a complete doctor.

In Kuwait, there was a clear need for postgraduate teaching. Firstly, to fulfill the aims of the establishment of the medical school and secondly, to train many doctors who graduated from regional medical schools of low standards.

Dr Abdulrazzaq Al-Abdulrazzaq and Dr Hassan Hathout were involved in organizing the postgraduate education in the new medical school. One of the difficulties faced was that hospitals in Kuwait were not university institutions. So the appointment of the clinical staff was done by the Ministry of Health and not by the medical school. This problem was solved when the medical school committee and the Ministry of Health agreed on the necessity that the medical school should appoint the clinical staff<sup>[18]</sup>.

Although the hospitals in Kuwait were not

teaching hospitals, they were considered to be of very high standard and deemed superior to many other teaching hospitals in the region. The Royal College of Surgeons, the Royal College of Physicians and the Royal College of Obstetricians considered Kuwait hospitals suitable for postgraduate specialty training<sup>[3]</sup>.

### **MEDICAL SCHOOL OPENING**

The medical school was officially opened on the 8<sup>th</sup> of November 1976, by the acting president of the University of Kuwait Mr Abdulwahab Al-Nafisi, at an opening ceremony attended by the rector, senior officials from the university and the Ministry of Health. Also, deans of medical schools from the Arab world, Europe and America were present on the occasion.

The first graduation in 1983, in the presence of H.E. Amir Sheikh Jaber Al-Ahmad Al-Sabah, coincided with the formal opening of the new building of the faculty of medicine in the Mubarak hospital complex.

### **CONCLUSION**

Establishing the Kuwait medical school was a pioneering work. It was the first in the Arabian Gulf region and the first in the Middle East with such quality and high standards. It was a great achievement not only for Kuwait but also for the region as a whole.

Medical schools require a huge input to establish. It is unlike other faculties in the university. Financial support is an essential requirement for any medical school. Political decisions are also important.

One of the interesting points in the establishment of the Kuwait medical school was choosing the teaching method. It was at a time where medical education was revised and new teaching methods were invented; mainly the integral teaching method and the problem based learning method. The Kuwait medical school adopted a conventional departmental method, which is the method of teaching in Kuwait for many years; however, in 2005, it was changed to an integrated curriculum.

We can see the link of Scotland in founding the school. The three founders were graduates from Scottish universities, Dr A Al-Abdulrazzaq and Dr Ian Olson, both were graduates of the Aberdeen medical school and Dr Abdullah Al-Refaeie, an Edinburgh university postgraduate.

Establishment of the Kuwait Medical School should be studied carefully by the educational authorities in Kuwait to provide them with guidance for the establishment of the second medical school in Kuwait; a subject, which has risen now since the current medical school is reaching its full capacity.

One of the difficulties in researching this subject is the lack of resources. The Iraqi invasion destroyed most of the archives. In this case, one can see the necessity of oral history.

In conclusion, the establishment of the Kuwait medical school was a great achievement for the Middle East and a fine example of early global collaboration in medical education.

#### ACKNOWLEDGMENTS

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**Ethical approval:** This article does not contain any study involving human participants or animals performed by any of the authors.

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## Original Article

# Medical Undergraduates Preference in Learning Style: A Single-Institute Experience from Bangladesh

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## ABSTRACT

**Objective(s):** Modern education should enable the learners' brain to think, contrasting the olden theory of just filling the bucket. Individualism in learning methods remains a major pedagogic concern in medical education, even today. Additionally, the trainees' own forte and flaw also adjunct in learning process significantly. We, therefore, assessed students' preference following sensory modalities of learning approach using visual, aural, read/write and kinesthetic (VARK) questionnaire.

**Design:** Descriptive, cross-sectional, questionnaire based survey

**Setting:** Holy Family Red Crescent Medical College, Dhaka, Bangladesh

**Subjects:** One hundred and eighty medical students of year 1 and 2

**Intervention(s):** The 16 item VARK 7.8 version was employed to collect data from respondents including certain socio-demographic information.

**Main outcome measure(s):** Recognizing students' choice of learning style

**Results:** Out of 180 respondents, 141 were females and 123 belonged to year 1. The responses were tallied and assessed for gender and level of study, according to learning style preference. More than half (55.6%) of the participants were found to have multimode learning preferences, in rank order as quad-modal (n = 47), bimodal (n = 30), and trimodal (n = 23). The hierarchy of single mode preferences (44.4%) were 46 aural, 26 kinesthetic, and 5 visual followed by 3 read/write. No significant association existed in sensory preferences with gender, academic background or year of study.

**Conclusion(s):** It became evident from this study, that majority of HFRCMC undergraduates preferred multimodal learning strategies. Hence, re-designing instructional methods in accordance with students' inclination is required to further potentiate learning.

KEYWORDS: learning style, medical education, sensory modality, VARK

## INTRODUCTION

It is essential for the teachers and students to be aware that individuals may and do have own preference of learning, just like having different personalities. Identification of learners' personal choice by the teachers will help students in attaining learning goals. Learning style is an innate character which influences individual learning, contrasting learning strategies, which are the learners chosen method<sup>[1]</sup>.

The learning style preference refers to a complex process of perceiving, processing, storing and retrieving effectively, what the students endeavor to learn<sup>[2,3]</sup>.

The proposition that students carry out to study and learn has emerged as a major pedagogical concern for the past few decades<sup>[4]</sup>.

Among a number of tools, the VARK instrument outlines the learning preferences based on the sensory modalities, like, visual (V), aural (A), read-write (R) and kinesthetic (K)<sup>[2]</sup>. Students with a V preference learn best by seeing drawings, pictures *etc.*, whereas A learners prefer to learn by listening to lectures and discussing material. Those with R modality learn through reading texts and finally, K style learners proceed with physical act of touching, manipulation of objects and so on<sup>[5]</sup>.

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We intended to determine the preferred learning style of our medical undergraduates, aiming to develop appropriate instructional tactics. Moreover, we intended to figure out if any significant variations in such preference was affected by variables like gender or study year. The rationale of this study was to assist us with outlining a lesson plan that tended to all learners and to recognize territories of further research.

## SUBJECTS AND METHODS

This cross-sectional, questionnaire based survey was conducted among the undergraduates of Holy Family Red Crescent Medical College (HFRCMC), Bangladesh. MBBS students of year 1 and 2, were included and consented, accordingly. Prior approval was obtained from institution ethics committee.

The 16 item VARK 7.8 version<sup>[6]</sup> was employed to collect the data from respondents after receiving copyright permission from the developers. The self-reported, newest version of VARK was selected due to its simplicity of use and free accessibility online. The next section of questionnaire was designed to record the demographic data.

The VARK questionnaire was administered in two classes consisting of 250 students, out of which 180 (72%) returned the form with other demographic data. The students were informed that there were no right or wrong answers. They were allowed to omit a question or to choose two or more options, if needed. The stepping stone method<sup>[7]</sup> was applied to comment on the respondent's particular preference.

The total number of student responses was matched for each of the four sensory modalities (V, A, R & K) and for all possible combinations of the modalities (e.g., VA, VAR, KR etc.). The scoring algorithm on the VARK website was then applied to identify each student modality preferences. Mean was calculated for quantitative variables, frequencies were determined for qualitative data, which were then analyzed with Pearson's Chi square and ANOVA. Value of  $p < 0.05$  was considered as significant while analyzing the data using SPSS v. 16. The responses were tallied and assessed for gender and level of study according to learning style preference.

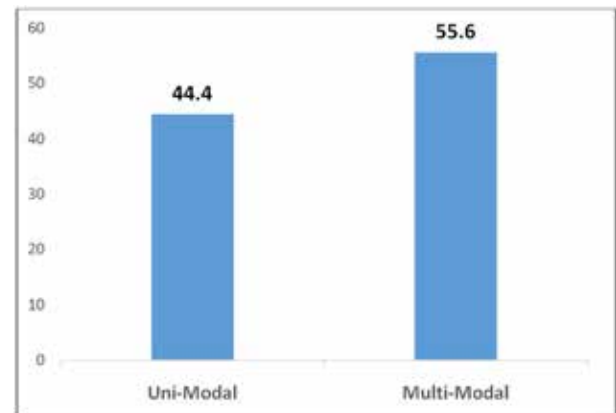
## RESULTS

Responses were assessed to know the learning-style preferences among 180 students who completed the questionnaire; characteristics of respondents are summarized in Table 1.

Fig 1 denotes more than half (55.6%) of the participants mentioned multimodal learning preferences and the rest (44.4%) were single modal.

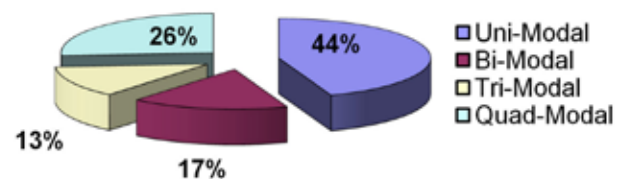
**Table 1:** Socio-demographic features of respondents; N = 180

Features	Respondents
Study year	123 - Year 1; 57 - Year 2
Mean Age	19.78 ± 0.91 SD
Gender	39 Male, 141 Female
Religion	165 Muslim, 14 Hindu, 1 Christian
Ethnicity	177 Bangladeshi, 3 Indian
Academic background	168 SSC/HSC, 12 O/A Level



**Fig 1:** Frequency distribution of learning style of the students (N = 180)

Out of 55.6% of the participants preferring multimode, quad-modal was ranked the highest, then the bimodal and lastly tri-modal (Fig 2).



**Fig 2:** Percentage of student respondents (N = 180) who preferred to use one, two, three or four sensory modalities to acquire information

Among the students who picked single mode preference (44.4%), most were categorized in aural (25.6%) mode, followed by kinesthetic group and very little responses in 'V' & 'R' class. Of the students having bi-modal learning style, AK was the dominant preference combination (11.7%) and ARK (4.4%) was highest among tri-modalists. Finally, quad modal learning style (VARK) was reported as the highest chosen preference (26.1%) over all other categories (Fig 3).

Fig 4 displays the learning choices in male and female respondents. Both the gender groups were almost similarly distributed in single and dual mode group. However, they indicated altered pictures in tri and quad modality, though statistically insignificant.

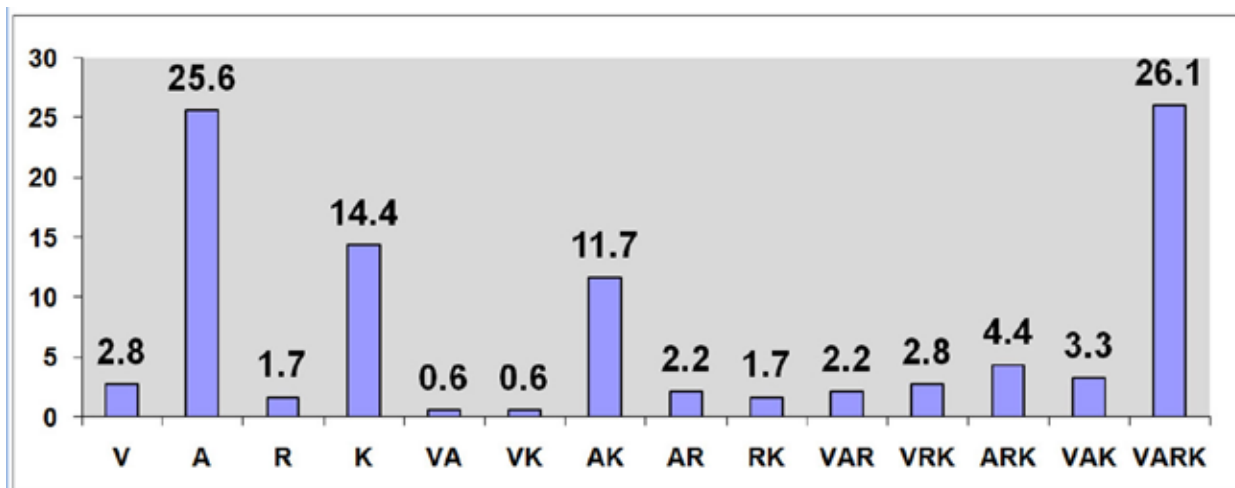


Fig 3: Prevalence (%) of dominant single and multiple learning styles among the study group

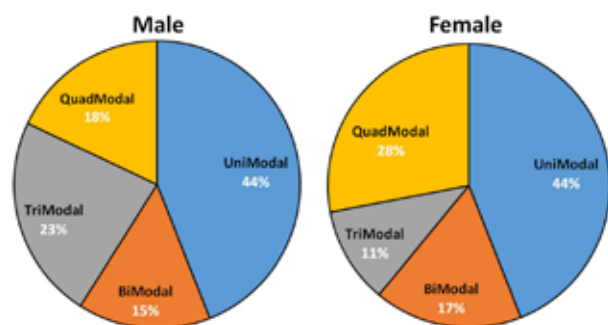


Fig 4: Learning style differences by gender

Pearson's chi square revealed no significant difference across other grouping variables like year of study, academic background, *etc.*

## DISCUSSION

The biggest challenge in teaching medicine is imparting boundless knowledge within a limited time frame and in a manner that students can retain, recall and effectively interpret. Moreover, university education inclined more towards deep learning and logical thinking compared to simple factual recall during school examinations<sup>[8]</sup>. These factors essentially called upon major changes in medical education, shifting from didactic teacher-centered approach to an interactive, student-centered learning. By and large, in Bangladesh, our current teaching curriculum of preclinical years are more emphasized on traditional lectures with few hours of laboratory/practical sessions. This instructional strategy does not target all four types of learners in an integrated way. Furthermore, here we are yet to practice the effective modern educational tools, like, Problem based learning (PBL), Self-directed learning (SDL), *etc.*

We aimed to draw an outline of the learning style preferences of Bangladeshi medical students. To our

knowledge, this study remains the pioneer of its kind reported from this part of the world. We believe, our findings would shed some light on this particular issue and facilitate teachers in designing appropriate classroom actions. Instead of direct modality titles (*i.e.*, V, A, R, and K), the VARK questionnaire asked for real-life scenario based answers. Therefore, it was unlikely for the participants to being biased or directed toward a particular sensory modality choice in this survey.

The assessed outcome observed in this investigation remains consistent with that of a much larger report ( $n = 20,254$ ) posted on the VARK website<sup>[9]</sup>. While the respondents in this study had slightly higher unimodal (44% vs. 36% on the website) and lower quad-modal (26% vs. 35.7% on the website) preferences, the bimodal preferences were analogous (17% vs. 15.4% on the website) and the tri-modal preferences were identical (13%).

Although, more than half of our respondents (55.6%) were found to be multimodal in their learning style, the percentage was well below the 68.9%, 68.7%, and 63.9% values reported by Ramirez<sup>[10]</sup>, Urval *et al*<sup>[11]</sup> and Baykan and Nacar<sup>[12]</sup>, respectively.

Interestingly, our men and women learners showed exactly the same percentage distribution of single (44%) and multi-mode (56%) preferences. Among the multimodal, females were predominantly quad-modal (28%) but the male participants were mainly tri-modal (23%). Choudhary<sup>[13]</sup> has described similar spreading pattern among selected Indian medical students.

Across the four unimodal VARK categories in our study, aural (25.6%) was the most preferred, followed by kinesthetic (14.4%). Similarly, a number of studies on undergraduate healthcare students from different countries affirmed this finding<sup>[14, 15]</sup>. By contrast, Murphy *et al*<sup>[16]</sup> reported that read-write (20.1%) and visual (14.5%) were the two dominant single learning

preferences. However, a recent study from Oman described the homogenous preference among single mode learners<sup>[17]</sup>.

Several authors have described about significant differences among gender on sensory preferences<sup>[13,18]</sup>. However, our study revealed no such association ( $p > 0.05$ ) alike the findings of Alkhasawneh *et al*<sup>[19]</sup> and Slater *et al*<sup>[20]</sup>. Here, we would like to indicate on the skewness of gender distribution among our participants (78.33% female), which might have influenced the finding. Almost similar pattern of gender ratio has been reported in studies from most of the medical colleges in Bangladesh<sup>[21,22]</sup>.

The medical degree program in Bangladesh is a traditional five year training with 1.5 years of preclinical study, two years para-clinical with limited patient contact, and 1.5 years of clinical study. We have assessed the students from pre and para-clinical cohort. However, the learners' modality preference was not influenced by their academic year or subject of study.

The elements of face to face communication includes: words, tone of voice and body language. A study from decades back reported that the words uttered are often not as significant as the verbal and non-verbal components used in lectures. The distribution of different elements was ranked as body language (55%), para-verbal (38%) and words (7%)<sup>[23]</sup>. Evidences displayed higher score by the learners when instruction matched their learning style instead of misalliance<sup>[24]</sup>. On the other hand, it has been argued that student's preferred style eventually could bring monotony and disengagement as well<sup>[25]</sup>. However, it is suggested to be mismatched occasionally to stimulate interest about the teaching strategy, but not to consider as a substitute of matching<sup>[13]</sup>. As a final point, the indication for medical teachers is to assort their presentation style to help out the medicos towards productive education.

### Limitations

Limitations of this study are, single institute and convenience sample. Hence, the inference could not be generalized to other settings in Bangladesh. In addition, this study might tend to have less variety in socio-demographic factors due to relatively homogenous study population. Further studies involving multiple centers with probability sampling technique are therefore, recommended.

### CONCLUSION

'How can we teach students, if we do not know how they learn?'- is the major concern raised by the individual learning style researchers. From this VARK survey, we can conclude that our medicos are diversified in their learning styles. Though varied, they were

mostly multimodal. This outcome should convince educators to adopt multiple modes of classroom presentation rather than one-way didactic lecturing. Moreover, there is a strong intuitive demand that teachers and course designers should consider students' learning styles, not only in identifying them but also encouraging learners to reflect on those and finally, planning teaching-learning interventions accordingly. Teachers who cater to the various needs of students through a range of teaching approaches could be rewarded with enhanced learning.

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## Original Article

# Diabetes Mellitus, Hypertension, Hyperlipidemia and Obesity do not Affect Tumor Expression of Estrogen and Progesterone Receptors in Saudi Breast Cancer Patients

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## ABSTRACT

**Objective:** To evaluate the relationship between estrogen and progesterone receptor status and the presence of diabetes mellitus, hypertension, obesity or dyslipidemia

**Design:** Retrospective study

**Setting:** Department of Oncology, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia

**Subjects:** A hundred and twelve Saudi patients diagnosed with breast cancer, admitted to King Khalid University Hospital (KKUH) between 2000 and 2006

**Intervention:** Fine needle or true cut biopsy

**Main outcome measure:** Association between tumor receptor status and the presence of comorbidity

**Results:** There was no relationship between estrogen

receptors and progesterone receptors expression and the presence of diabetes mellitus, dyslipidemia, hypertension or obesity. Hypertension was associated with HER2/neu positivity ( $p = 0.045$ , OR = 2.817, CI 95% (1.023 - 7.754)). Hypertensive patients were also found to present with earlier clinical T-stages ( $p = 0.045$ ).

**Conclusion:** Expression of estrogen and progesterone receptors was not affected by the presence of diabetes mellitus, dyslipidemia, hypertension or obesity. However, our findings suggest that hypertension is related to HER2/neu positivity. Hypertensives were also more likely to present with earlier clinical T stages than non-hypertensives.

KEY WORDS: breast cancer, estrogen receptor, metabolic syndrome X, ErbB-2 receptor, TNM stage

## INTRODUCTION

Breast cancer is the most common type of cancer in females, and is the fifth leading cause of cancer related deaths worldwide<sup>[1]</sup>. The issue is particularly pressing in Saudi Arabia, where it is ranked as the most commonly diagnosed type of cancer, accounting for 15% of all cancer incidences<sup>[2]</sup>. It is the most common cancer in Saudi female patients with a prevalence of 28.8%<sup>[2]</sup>.

Different risk factors have been linked to the development of the disease, such as age, family history, use of contraceptives, early menarche, and late menopause<sup>[3]</sup>. The rising prevalence of metabolic diseases in Saudi Arabia is alarming. In 2014, the WHO reported that the average body mass index (BMI) in Saudi women was found to be 28.7, and the prevalence of obesity was 41.4%<sup>[4]</sup>. The prevalence of raised blood

pressure was 21.8% and the prevalence of raised blood glucose was 18.3%<sup>[4]</sup>. Dyslipidemia was reported to be prevalent in between 25 to 44% of Saudis, depending on the type of dyslipidemia<sup>[5]</sup>.

A case-control study conducted in 2013 suggests that obesity might be a risk factor for developing breast cancer<sup>[3,6]</sup>. Another case-control study shows that hypertension might impact the risk for developing breast cancer, potentially affected by menopausal status<sup>[7,8]</sup>. Diabetes significantly increased the risk for developing breast cancer<sup>[7,9,10,11]</sup>. Also, low levels of high density lipoprotein cholesterol (HDL-C) might increase the risk of breast cancer development<sup>[12]</sup>.

Breast cancer is classified based on multiple characteristics including pathologic, histologic and molecular features. Molecular features are further subtyped by immunohistochemical detection of

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hormonal receptors including estrogen, progesterone and the human epidermal growth factor receptor (HER2/neu). Estrogen and progesterone positive breast cancers are associated with benign outcomes and respond well to Tamoxifen and aromatase inhibitors<sup>[13-15]</sup>. HER2 positive tumors, on the other hand, are biologically aggressive but still manageable with targeted monoclonal antibody therapy against the receptors<sup>[16,17]</sup>.

In light of this, studying the development of hormone receptors in breast cancer and their associated risk factors is essential to the management of the disease. However, more research is needed to link hormone receptor status in breast cancer with different comorbidities (hypertension, diabetes mellitus, dyslipidemia and obesity). This study aimed to assess the relationship between estrogen and progesterone receptor status and the presence of diabetes mellitus, hypertension, obesity or dyslipidemia at diagnosis.

## SUBJECTS AND METHODS

A hundred and twelve Saudi patients diagnosed with breast cancer, admitted to King Khalid University Hospital (KKUH) between 2000 and 2006, were available for this retrospective cross-sectional secondary data analysis study. Data was obtained from the oncology department at KKUH. They underwent either breast conserving surgery with axillary lymph node dissection or modified radical mastectomy after neoadjuvant chemotherapy and radiotherapy. The inclusion criterion was histopathologically confirmed breast cancer. Exclusion criteria were: (1) male sex, and (2) incompleteness of the above listed treatment regimen. A hundred and ten patients met the criteria. Formal consent to conduct this study was obtained from the Institutional Review Board Committee (IRB).

### Clinical variables

Clinical features recorded for this study included; age, presence of comorbidities, body mass index, menopausal status, tumor hormone receptor status, TNM staging, and tumor grade.

Comorbidities considered for the study were diabetes mellitus, hypertension, dyslipidemia and obesity. Diabetes Mellitus was defined as fasting blood glucose  $\geq 126$  mg/dL. Hypertension was defined as a blood pressure reading over 140/90 mmHg, measured on 2 different occasions. Dyslipidemia was defined as elevated total cholesterol ( $> 240$  mg/dL), high levels of low-density lipoprotein cholesterol (LDL-C) ( $>160$  mg/dL), or low levels of high-density lipoprotein cholesterol (HDL-C) ( $<40$  mg/dL). Obesity was defined as a BMI  $\geq 30$ .

Tumor estrogen and progesterone receptor statuses were evaluated at the time of presentation using immunohistochemical analysis with antibodies against the estrogen receptors (Dako, Glostrup, Denmark) and progesterone receptors (BioGenex, San Ramon, CA, USA). A cutoff value of 1% for both receptors was considered positive, as per institutional protocol. HER2/neu overexpression was assessed using immunohistochemical equivocal cases using a HER2 DNA Probe Kit (Abbott Laboratories, Abbott Park, IL, USA). A HER2:CEP17 ratio of 2:1 or higher was considered HER2/neu positive.

Breast cancer diagnosis was made by examining either fine needle aspiration or TruCut biopsies, and correlated with clinical and radiological findings. Staging was done in accordance with the American Joint Committee on Cancer's TNM classification, 5<sup>th</sup> edition. The tumor grade was assessed by the modified Scarff-Bloom-Richardson grading system. Tumor size was estimated using the TNM clinical T stage, where T1:  $< 2$  cm, T2:  $> 2$  cm but  $\leq 5$  cm and T3:  $> 5$  cm, all in the largest dimension. T4 was defined as any size with direct extension to the chest wall and/or to the skin.

### Statistical Analysis

Patient characteristics were summarized using frequency, percentage, mean and standard deviation (SD). Fisher's exact test was used to study the associations among the estrogen, progesterone and HER2/neu receptor expression and comorbidities, adjusted for confounding factors with logistic regression. Associations between clinical T-stage and comorbidities were estimated using the Kendall's Tau test. A P-value  $< 0.05$  with a confidence interval of 95% was considered statistically significant. Statistical analyses were executed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Macintosh, Version 21.0. Armonk, NY: IBM Corp.)

## RESULTS

### Patient Characteristics

A hundred and ten Saudi females were included in the analysis. Mean age was 47 years (SD  $\pm 10$ ). Premenopausal women comprised the majority of subjects, totaling 91 patients (82.7%). Mean BMI was 32 kg/m<sup>2</sup> (SD  $\pm 7.16$ ) and obesity was prevalent in 62 patients (56.4%). The most common histological subtype in this cohort was intraductal carcinoma (IDC), present in 93 patients (87.7%). A total of 51 patients (46.4%) were estrogen positive, 42 (38.2%) were progesterone positive and 64 (58.2%) were HER2/neu positive. Comorbidities were recorded in 75 patients (68.2%) (Table 1).

**Table 1:** Patient characteristics

Characteristics	n (%)	Mean ( $\pm$ SD)
Age groups		
< 25	2 (1.8)	23 ( $\pm$ 0)
25 - 35	13 (11.8)	32 ( $\pm$ 3)
36 - 45	29 (26.4)	40 ( $\pm$ 3)
> 45	66 (60)	53 ( $\pm$ 7)
Total	110 (100)	47 ( $\pm$ 10)
BMI groups		
Below 18.5	1 (0.9)	15.7 ( $\pm$ 0)
18.5 - 24.99	17 (15.5)	22.4 ( $\pm$ 1.87)
25 - 29.99	30 (27.3)	27.8 ( $\pm$ 1.35)
30 and above	62 (56.4)	36.92 ( $\pm$ 5.16)
Total	110 (100)	32.00 ( $\pm$ 7.16)
Menopausal status		
Premenopausal	91 (82.7)	
Postmenopausal	19 (17.3)	
Total	110 (100)	
Hormone receptors		
Estrogen		
Negative	59 (53.6)	
Positive	51 (46.4)	
Total	110 (100)	
Progesterone		
Negative	68 (61.8)	
Positive	42 (38.2)	
Total	110 (100)	
HER2		
Negative	46 (41.8)	
Positive	64 (58.2)	
Total	110 (100)	
Comorbidities		
DM		
No DM	86 (78.2)	
DM	24 (21.8)	
Total	110 (100)	
HTN		
No HTN	80 (72.7)	
HTN	30 (27.3)	
Total	110 (100)	
Dyslipidemia		
No dyslipidemia	99 (90)	
Dyslipidemia	11 (10)	
Total	110 (100)	
Obesity		
Not obese	48 (43.6)	
Obese	62 (56.4)	
Total	110 (100)	
Clinical T stage		
T1	35 (31.8)	
T2	44 (40)	
T3	20 (18.2)	
T4	9 (8.2)	
Missing	2 (1.8)	
Total	110 (100)	
Clinical N stage		
N0	49 (44.5)	
N1	35 (31.8)	
N2	14 (12.7)	
N3	12 (10.9)	
Total	110 (100)	
Clinical M stage		
0	81 (73.6)	
1	29 (26.4)	
Total	110 (100)	

## Analysis

No significant findings were noted among the expression of estrogen or progesterone receptors and presence of diabetes mellitus, dyslipidemia, hypertension or obesity. No significance was found after adjusting for confounders.

Hypertension was associated with HER2/neu positivity ( $p = 0.020$ ). The relationship was still significant after adjusting for confounding factors ( $p = 0.045$ , OR = 2.817 (1.023 - 7.754)). No other significant associations were found among HER2/neu expression and diabetes mellitus, dyslipidemia or obesity (Table 2).

Hypertensive patients were also found to present with earlier clinical T-stages when compared to non-hypertensives ( $p = 0.045$ ). Diabetes mellitus, dyslipidemia and obesity did not show any correlation with the clinical T-stage (Table 3).

## DISCUSSION

We did not find any statistically significant associations linking the expression of estrogen and progesterone receptors, with the presence of diabetes mellitus, hypertension, dyslipidemia or obesity. Relationships among HER2/neu expression and the presence of comorbidities were also investigated. It was observed that hypertensive patients were more likely to have HER2/neu positive tumors, an effect that was not observed with the other comorbidities. A decreasing trend in clinical T stage among patients with hypertension was noted. Hypertensives tended to present with earlier clinical T stages (T1, T2) than non-hypertensives.

Our findings on estrogen and progesterone receptors are similar to what was found in a study conducted in southwest China, which showed that diabetes mellitus did not affect estrogen and progesterone receptor expression<sup>[18]</sup>. Another study also demonstrated that hyperglycemia, hypertension, obesity and dyslipidemia had no effect on estrogen receptor expression<sup>[19]</sup>. A 2013 study found that postmenopausal patients with a BMI > 25 showed a higher incidence of estrogen positive and progesterone positive tumors<sup>[20]</sup>. Interestingly enough, the same study found breast cancer receptor expression was not influenced by BMI in premenopausal women, a finding that corroborates ours, given that 82% of our sample is premenopausal.

There remains some contradictory evidence in the literature. Breast cancer data from a 2003 Nurses' Health Study showed that patients with type 2 diabetes mellitus were found to have an increased risk of developing estrogen positive tumors<sup>[21]</sup>. BMI has been associated with receptor expression. Increased BMI was linked to increased expression of estrogen

**Table 2:** Relationship between receptor status and associated comorbidity

Comorbidity	Unadjusted P-value			Adjusted* P-value, OR (95%CI)					
	ER+	PR+	Her2-Neu+	ER+	PR+	Her2-Neu+	ER+	PR+	Her2-Neu+
Hypertension	0.371	0.497	0.020†	0.246	1.79 (0.66 - 4.82)	0.348	1.60 (0.98 - 4.28)	0.045†	2.81 (1.02 - 7.75)
Diabetes Mellitus	0.602	0.581	0.068	0.592	0.72 (0.22 - 2.32)	0.503	0.66 (0.20 - 2.18)	0.131	0.40 (0.12 - 1.13)
Obesity	0.150	0.790	0.453	0.168	0.58 (0.26 - 1.25)	0.853	0.92 (0.42 - 2.04)	0.264	1.59 (0.70 - 3.59)
Dyslipidemia	0.949	0.896	0.372	0.841	0.84 (0.16 - 4.40)	0.905	0.90 (0.16 - 4.83)	0.351	0.44 (0.08 - 2.44)

OR = Odds ratio; CI = Confidence interval; ER = Estrogen receptor; PR = Progesterone receptor; Her2-Neu = human epidermal growth factor receptor

\* Adjusted for obesity, diabetes, hypertension and dyslipidemia

† Designates significant values. P < 0.05

and progesterone receptors in postmenopausal breast cancer patients<sup>[22-24]</sup>, while a meta-analysis demonstrated that obese women are more likely to develop triple-negative breast cancer<sup>[25]</sup>.

**Table 3:** Relationship between comorbidities and clinical T stage

Comorbidity	Clinical T stage					P-value
	T1 n (%)	T2 n (%)	T3 n (%)	T4 n (%)	Total N (%)†	
Diabetes mellitus	8 (34)	6 (26)	5 (21)	4 (17)	23 (21)	0.481
Hypertension	15 (50)	9 (30)	4 (13)	2 (7)	30 (27)	0.045†
Dyslipidemia	6 (54)	3 (27)	2 (18)	0 (0)	11 (10)	0.141
Obesity	17 (28)	28 (46)	11 (18)	4 (7)	60 (55)	0.764

\* Total sample size is 108; † Designates significant values; P < 0.05

The effect of hypertension on the expression of HER2/neu has not been described in the literature, to the best of our knowledge. A prospective study associated high levels of low density lipoprotein cholesterol (LDL-C) with HER2/neu positivity<sup>[26]</sup>. Our findings regarding diabetes mellitus and obesity with HER2/neu expression are consistent with findings in aforementioned studies<sup>[18,19]</sup>.

We aimed to identify possible factors implicated in hormone receptor expression. The significance of this association lies in the ability to create prediction models of receptor expression patterns in breast cancer, which could be of use in policymaking and resource management. Although these results are observational, we cannot exclude the possibility that there are underlying mechanisms that remain unknown. Prospective studies would help to establish causality and temporality of the relationships, as opposed to our retrospective design. Other limitations of our study are the small sample size, lack of data regarding the severity and management of the diseases studied and the inability to account for important confounders. Although we accounted for the occurrence of multiple comorbidities (diabetes mellitus, hypertension, dyslipidemia and obesity), we were not able to account for other confounding factors

such as occurrence of multiple receptors, menopausal status and estrogen exposure.

Future work should be guided towards identifying biological factors influencing receptor expression. Special attention should be devoted to the factors affecting occurrence of multiple receptor and triple negative breast cancers, as these have not been investigated thoroughly.

## CONCLUSION

We did not find a relationship among diabetes mellitus, obesity and dyslipidemia with clinical T stage. In contrast, the southwest China study found that diabetics had larger tumor sizes in comparison to non-diabetics<sup>[18]</sup>. A different study found the same to be true of patients with high BMI<sup>[19]</sup>. Furthermore, high LDL-C was associated with larger tumors sizes<sup>[26]</sup>. Our result linking hypertension with lower clinical T-stage has not been described previously in the literature.

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## Original Article

# Anti-Diabetic Medication Reduces Risk of Pulmonary Tuberculosis in Diabetic Patients: A Population-based Cohort Study in Taiwan

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## ABSTRACT

**Objective:** The increased risk of pulmonary tuberculosis (PTB) in patients with diabetes mellitus (DM) remains to be clarified with cohort study. The present study further examined whether the anti-diabetic drug treatment associates with developing PTB.

**Design:** Nation wide cohort study

**Setting:** China Medical University Hospital

**Subjects:** From the Taiwan National Health Insurance database, we identified 22,256 adult patients newly diagnosed with DM in 2000-2006 as DM cohort and 89,024 persons without DM frequency matched with sex, age and DM diagnosed year as non-DM comparison cohort.

**Intervention:** None

**Main outcome measures:** Both cohorts were followed till the end of 2009 to document PTB incidence. Medications were analyzed for the DM cohort to examine the hazard of developing PTB.

**Results:** The incidence of PTB was 1.64-fold higher in DM cohort than in comparison cohort (52.1 Vs 31.8 per 10,000

person-years) with an adjusted hazard ratio of 1.53 (95% CI = 1.40 - 1.67), measured using multivariable Cox proportional hazards regression analysis. Men were at higher risk than women to have PTB. The age-specific incidence rates showed that DM cohort to comparison cohort incidence rate ratio was higher in younger group. However, the Cox model measured HR increased with age. Alcoholism, chronic obstructive pulmonary disease, alcoholic liver damage and chronic kidney diseases were comorbidities independently associated with PTB. In the DM cohort, anti-DM medications significantly reduced the risk of PTB with a HR of 0.52 for those who had taken metformin, followed by alpha-glucosidase inhibitors, thiazolidinediones, insulins and sulfonylureas (HR = 0.76). The effects of all anti-diabetic drugs were statistically significant.

**Conclusions:** These findings show patients with DM are associated with an elevated risk of developing PTB, but treatment with anti-diabetic drugs may mediate the risk significantly.

KEYWORDS: diabetes, pulmonary tuberculosis, Taiwan National Health Insurance Program

## INTRODUCTION

Tuberculosis (TB) and diabetes mellitus (DM) are major global health problems of great concern. The prevalence of DM is increasing worldwide, especially in developing areas, where TB is a highly endemic disease<sup>[1]</sup>. TB has been the second major cause of

deaths worldwide, with an estimated 9.2 million new cases and 1.6 million deaths in 2006<sup>[2]</sup>. There were 246 million patients with DM being estimated worldwide in 2007<sup>[3]</sup>. The link between TB and DM has recently attracted great attention again because of their global impact<sup>[4-6]</sup>. The concern is that the rapid escalation

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of DM may conceivably have a great impact on TB control<sup>[4]</sup>. In fact, this link had been proposed much earlier primarily in the United States and Europe<sup>[7-9]</sup>. A systematic review of 13 observational studies found a consistent positive relationship between DM and the risk of TB<sup>[10]</sup>. The case-control studies showed patients with TB have a history of DM with odds ratios ranging from 1.16 to 7.83. The meta-analysis of three cohort studies showed patients with DM are at an overall relative risk (RR) of 3.11 (95% CI = 2.27 to 4.26) for developing TB. However, among these three cohort studies, one is an Asian cohort and the other two studies are among patients with renal transplant. The Asian study, based on medical records of civil servants in Korea, found the RR of developing confirmed TB is 5.15-fold higher for DM cohort than non-DM cohort<sup>[11]</sup>. Another population based cohort study in Southern Mexico<sup>[5]</sup> and two recent case-control studies in Northern Denmark and Tanzania confirmed this relationship<sup>[4,6]</sup>.

The convergent attack of both DM and TB epidemics may lead to increased comorbidity of other types and impair treatment and preventive efforts in the TB control for disadvantaged populations<sup>[12]</sup>. Diabetes has been associated with poor outcome from TB care for patients afflicted with both DM and TB. A recent systemic review and meta-analysis has measured the DM impact on TB treatment outcomes<sup>[13]</sup>. According to this systemic review, diabetes is associated with not only the increased risk of death from TB (adjusted RR = 4.95) but also the relapse of TB (RR = 3.89). However, no impact of DM treatment has been estimated in these studies. Investigation of the DM treatment protocol may clarify whether the medications benefit patients by reducing the TB risk. The present study used insurance claims data to compare cohorts with and without DM to investigate the subsequent risk of developing PTB. We further investigated whether DM treatment alters the risk of PTB development.

## MATERIAL AND METHODS

### Data sources

The National Health Insurance (NHI) of Taiwan is a universal insurance system for all people established in 1995 by reforming 13 existing insurance programs. This system has a coverage rate of 99% of 23 million residents and contracted with 97% of hospitals and clinics in Taiwan<sup>[14,15]</sup>. We obtained from the National Health Research Institute (NHRI) a claims data set of 1 million randomly selected insured people for the years 1996 to 2009. The NHI program provides all citizens with comprehensive medical services, including outpatient and inpatient cares, emergency services and home cares. We used scrambled patient identifications to link all claims files and patient registry such as the

information on patient gender, birth date, and other demographic data. The surrogate identifications of insured subjects secure their privacy. The study was approved by the Institutional Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

### Study Design

The diagnoses of diseases were defined according to the International Classification of Diseases 9<sup>th</sup> Revision, Clinical Modification (ICD-9). We identified the patients aged 20 and older newly diagnosed with diabetes (ICD-9 250.XX and A-code A181) from the claims data of 2000 - 2006 as the DM cohort. For each diabetic case, we randomly selected four persons without medical claims for diabetes care in the non-DM cohort, frequency matching with age (every five-year span) and sex in the same time period. Patients with known history of PTB (ICD-9 010.X, 011.X, 012.X, 018.X and A-code A020 and A021) at the baseline were excluded from this study. To measure the incidence of PTB, both diabetic and non-diabetic groups were followed up until the subject received the diagnosis of PTB, or until the end of 2009, or until the subject was censored because of death or withdrawal from the insurance program. The entry index date for a study subject was defined by the date at which the individual was identified from the claims data.

### Statistical analysis

Proportional distributions of demographic status and comorbidity were compared between DM and comparison cohorts, and examined using Chi-square test. We estimated the incidence rate by dividing the number of newly diagnosed PTB cases with the total follow-up person-years by demographic variables, selected types of comorbidity, and follow-up year. The DM cohort to non-DM cohort incidence rate ratios (IRR) and 95% confidence interval (CI) by these variables were measured as well. Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) of PTB and 95% CI for DM cohort, compared with non-DM cohort. The co-morbidity that might increase the risk of subsequent PTB were investigated, including: alcoholism (ICD-9 303, 305.00, 305.01, 305.02, 305.03, V11.3 and A-code A215), chronic obstructive pulmonary disease (ICD-9 491.X, 492.X, 493.X and 496.X), pneumoconiosis (ICD-9 500, 502, 503, 504 and 505), asbestosis (ICD-9 501), cirrhosis (ICD-9 571.2, 571.5 and 571.6), alcoholic liver damage (ICD-9 571.0, 571.1, and 571.3), nonalcoholic fatty liver disease (ICD-9 571.8), hepatitis B infection (ICD-9 V02.61, 070.20, 070.22, 070.30 and 070.32), hepatitis C infection (ICD-9 V02.62, 070.41, 070.44, 070.51 and 070.54), chronic kidney diseases (ICD-9 585, 586, 588.8

**Table 1:** Baseline characteristics between diabetic cohort and comparison cohort identified in 2000–2006

Characteristics	Diabetes mellitus				P-value*
	No N = 89024		Yes N = 22256		
	n	%	n	%	
Sex					1.00
Female	40180	45.1	10045	45.1	
Male	48844	54.9	12211	54.9	
Age group (years)					1.00
20–39	9012	10.1	2253	10.1	
40–64	54432	61.1	13608	61.1	
≥65	25580	28.7	6395	28.7	
Mean (SD) (years)	56.8	13.7	56.8	13.4	0.72
Baseline co-morbidities					
Alcoholism	606	0.68	297	1.33	< 0.0001
Chronic obstructive pulmonary disease	12653	14.2	4534	20.4	< 0.0001
Pneumoconiosis	637	0.72	183	0.82	0.10
Asbestosis	69	0.08	15	0.07	0.62
Cirrhosis	1149	1.29	697	3.13	< 0.0001
Alcoholic liver damage	678	0.76	525	2.36	< 0.0001
Nonalcoholic fatty liver disease	1348	1.51	1128	5.07	< 0.0001
Hepatitis B	1637	1.84	635	2.85	< 0.0001
Hepatitis C	835	0.94	396	1.78	< 0.0001
Chronic kidney diseases	1137	1.28	657	2.95	< 0.0001
Malignancies	2118	2.38	625	2.84	0.0002
HIV/AIDS	27	0.03	5	0.02	0.54

\*Chi-square test comparing patients with and without diabetes

and 588.9), malignancies (ICD-9 140–208), and HIV/AIDS (ICD-9 042). The data analysis further estimated the risk of developing TB associated with anti-diabetic drugs taken in the DM cohort using the Cox model. The anti-diabetic drugs prescribed for patients included metformin, sulfonylureas, thiazolidinediones, alpha-

glucosidase inhibitors, D-phenylalanine derivatives, dipeptidyl peptidase 4 inhibitors, incretin mimetic agents, and insulins. The statistical significance level was set at two-sided probability value of <0.05. All analyses used the SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

**Table 2:** Incidence density of pulmonary tuberculosis estimated by sex, age, and follow-up years for Diabetic cohort and comparison cohort by the end of follow-up in 2009

	Non-Diabetic cohort				Diabetic cohort					
	N	Case	Person years	Incidence <sup>†</sup>	N	Case	Person years	Incidence <sup>†</sup>	IRR	(95% CI)
All	89024	1736	545670	31.8	22256	682	130900	52.1	1.64	(1.50 - 1.79)
Sex										
Female	40180	602	248388	24.2	10045	202	60030	33.6	1.39	(1.18 - 1.63)
Male	48844	1134	297281	38.2	12211	480	70870	67.7	1.78	(1.60 - 1.98)
Age, years										
20 – 39	9012	50	56498	8.85	2253	46	13977	32.9	3.72	(2.49 - 5.55)
40 – 64	54432	680	344614	19.7	13608	321	83614	38.4	1.95	(1.70 - 2.22)
≥ 65	25580	1006	144558	69.6	6395	315	33309	94.6	1.36	(1.20 - 1.54)
Follow-up										
< 6 months	89024	161	44269	36.37	22256	108	10938	98.74	2.72	(2.13 - 3.46)
6 - 12 months	88071	158	43806	36.07	21648	66	10736	61.47	1.70	(1.28 - 2.27)
1 - 2 years	87164	286	86347	33.12	21311	104	21033	49.45	1.49	(1.19 - 1.87)
≥ 2 years	85524	1131	371247	30.5	20777	404	88194	45.8	1.50	(1.34 - 1.68)

<sup>†</sup> Incidence rate: per 10,000 person-years

IRR (incidence rate ratio): diabetic Vs non-diabetic (95% CI)

N: population size; Cases: new patients of pulmonary tuberculosis; CI : Confidence Interval



## RESULTS

### Incidence of pulmonary tuberculosis

This study consisted of 22,256 patients in the DM cohort and 89,024 persons in comparison cohort, with similar sex and age distributions and mean age of 56.8 years (Table 1). The DM cohort was much more prevalent with most of comorbidity, excepting pneumoconiosis, asbestosis and HIV/AIDS at the baseline.

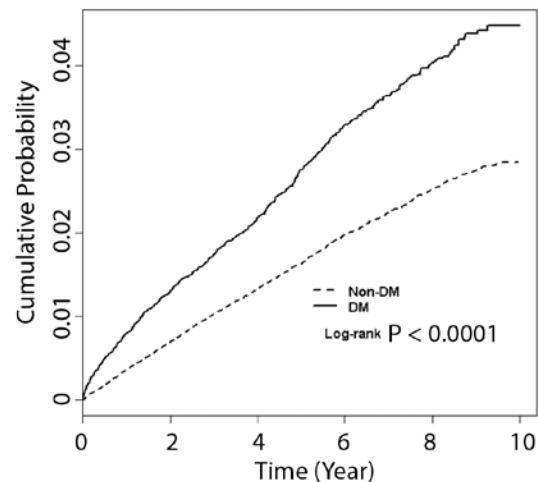
During the follow-up period, the incidence of pulmonary TB was 1.64-fold greater in the DM cohort

than in comparison cohort (52.1 person-years Vs. 31.8 per 10,000 person-years). The sex-specific IRR shows that men were at higher risk than women. The age-specific IRR was the highest in diabetic subjects aged 20 - 39 years (3.72, 95% CI = 2.49 - 5.55), followed by those aged 40 - 64 (1.95, 95% CI = 1.70 - 2.22), and aged 65 years and older (1.36, 95% CI = 1.20 - 1.54). The risk for the disease was the highest in the first six months of follow-up, followed by those following up for 6 - 12 months,  $\geq 2$  years and 1 - 2 years (Table 2). Fig 1 shows the cumulative incidence of pulmonary TB was 1.8 percent higher in the DM cohort than in the comparison cohort after the 10-year follow up.

**Table 3:** Multivariable Cox proportional hazards regression measured hazard ratios (HR) and 95% confidence intervals (CI) of pulmonary tuberculosis associated with diabetes mellitus and covariates identified in 2000 - 2006

Variable	Crude		Adjusted†	
	HR	(95% CI)	HR	(95% CI)
Sex				
Female	1.00	(reference)	1.00	(reference)
Male	1.68	(1.54 - 1.83)	1.80	(1.66 - 1.96)
Age, years				
20-39	1.00	(reference)	1.00	(reference)
40-64	1.72	(1.39 - 2.12)	1.69	(1.37 - 2.09)
$\geq 65$	5.41	(4.40 - 6.66)	4.75	(3.85 - 5.86)
Diabetes mellitus				
No	1.00	(reference)	1.00	(reference)
Yes	1.63	(1.49 - 1.78)	1.53	(1.40 - 1.67)
Alcoholism				
No	1.00	(reference)	1.00	(reference)
Yes	2.48	(1.82 - 3.38)	2.13	(1.54 - 2.93)
Chronic obstructive pulmonary disease				
No	1.00	(reference)	1.00	(reference)
Yes	3.17	(2.91 - 3.45)	2.18	(1.99 - 2.38)
Cirrhosis				
No	1.00	(reference)	1.00	(reference)
Yes	1.76	(1.35 - 2.30)	1.06	(0.80 - 1.40)
Alcoholic liver damage				
No	1.00	(reference)	1.00	(reference)
Yes	2.06	(1.54 - 2.75)	1.54	(1.14 - 2.09)
Nonalcoholic fatty liver disease				
No	1.00	(reference)	1.00	(reference)
Yes	1.12	(0.85 - 1.46)	--	--
Hepatitis B				
No	1.00	(reference)	1.00	(reference)
Yes	1.06	(0.79 - 1.42)	--	--
Hepatitis C				
No	1.00	(reference)	1.00	(reference)
Yes	1.53	(1.10 - 2.14)	1.19	(0.85 - 1.66)
Chronic kidney diseases				
No	1.00	(reference)	1.00	(reference)
Yes	2.43	(1.93 - 3.06)	1.35	(1.07 - 1.70)
Malignancies				
No	1.00	(reference)	1.00	(reference)
Yes	1.62	(1.29 - 2.04)	1.20	(0.96 - 1.51)

† Adjusted for sex, age, diabetes mellitus, alcoholism, chronic obstructive pulmonary disease, cirrhosis, alcoholic liver damage, hepatitis C, chronic kidney diseases, and malignancies



**Fig 1:** Kaplan-Meier model measured cumulative incidence of pulmonary tuberculosis for patients with diabetes mellitus and compared subjects

### Hazard associated with comorbidity

The multivariable analysis of Cox model revealed an over all adjusted HR of 1.53 (95% CI = 1.40 - 1.67) in developing PTB for diabetic patients (Table 3). Men had a higher HR than women and the HR increased with age. The comorbidity independently associated with the elevated risk of PTB for the DM cohort, included alcoholism (HR = 2.13, 95% CI = 1.54 - 2.93), chronic obstructive pulmonary disease (HR = 2.18, 95% CI = 1.99 - 2.38), alcoholic liver damage (HR = 1.54, 95% CI = 1.14 - 2.09), and chronic kidney diseases (HR = 1.35, 95% CI = 1.07 - 1.70).

### Impact of medications

Table 4 shows the multivariable Cox model estimated effectiveness of anti-diabetic medications on reducing the risk of PTB, performed using only the diabetic cases controlling for sex, age, and comorbidity. Compared to patients not taking any anti-diabetic drugs, the HRs of developing PTB reduced to 0.76 (95%



**Table 4:** Incidence of pulmonary tuberculosis identified in follow-up by anti-diabetic drug prescribed and Cox model measured hazard ratios (HR) and 95% confidence intervals (CI) of pulmonary tuberculosis associated with anti-diabetic drug

Anti-diabetic drug	N	Case	Person years	Incidence†	Crude HR	(95% CI)	Adjusted HR	(95% CI)
Insulins								
Non-use	6622	225	35849	62.8	1.00	(reference)	1.00	(reference)
Use	15634	457	95051	48.1	0.78	(0.67 - 0.92)	0.76	(0.64 - 0.89)
Metformin								
Non-use	3320	167	15227	109.7	1.00	(reference)	1.00	(reference)
Use	18936	515	115673	44.5	0.42	(0.35 - 0.50)	0.52	(0.43 - 0.62)
Sulfonylureas								
Non-use	3943	136	18523	73.4	1.00	(reference)	1.00	(reference)
Use	18313	546	112377	48.6	0.68	(0.56 - 0.82)	0.76	(0.63 - 0.92)
Thiazolidinediones								
Non-use	17745	572	100272	57.0	1.00	(reference)	1.00	(reference)
Use	4511	110	30628	35.9	0.64	(0.52 - 0.79)	0.75	(0.61 - 0.93)
Alpha-glucosidase inhibitors								
Non-use	16753	574	94666	60.6	1.00	(reference)	1.00	(reference)
Use	5503	108	36234	29.8	0.50	(0.41 - 0.61)	0.55	(0.44 - 0.67)

Adjusted HR: adjusted for sex, age, alcoholism, chronic obstructive pulmonary disease, cirrhosis, alcoholic liver damage, hepatitis C, chronic kidney diseases, and malignancies

† Incidence: per 10,000 person-years; CI : Confidence Interval

CI = 0.64 - 0.89) for those taking insulins, 0.52 (95% CI = 0.43 - 0.62) for those taking metformin, 0.76 (95% CI = 0.63 - 0.92) for those taking sulfonylureas, 0.75 (95% CI = 0.61 - 0.93) for those taking thiazolidinediones, and 0.55 (95% CI = 0.44 - 0.67) for those taking alpha-glucosidase inhibitors.

## DISCUSSION

It is essential to deliberate the complexity of all risk dimensions of TB in order to control and prevent the disease. Many studies have explored the association between DM and TB. In developed countries, studies dating to the first half of the past century have already demonstrated considerable increased risk of the tuberculosis infection among patients with DM<sup>[8,9]</sup> with the comorbidity of TB prevalence ranging widely from 1.0% to 9.3%<sup>[16,17]</sup>. Other studies have shown a higher prevalence of DM among individuals with TB<sup>[10]</sup>. Similar results in few studies have later addressed this association for populations in developing countries<sup>[18,19]</sup>. However, these studies have been clinic or hospital based, and therefore, it is difficult to extrapolate their findings to the general population<sup>[11]</sup>. Cohort studies performed in Europe and the United States in the 1930s found that DM showed a 3 - 4 fold increased risk of subsequent TB<sup>[8]</sup>. The present population based retrospective cohort study does prove DM patients are at a higher risk of subsequent PTB than comparison population. The finding is consistent with the Korean cohort study and the Hong Kong study<sup>[11,20]</sup>. The relative risk in our study was not as high as that in the Korean study (1.53 Vs. 3.47). The HR for active PTB in Hong Kong study is 1.77, somewhat similar to our finding.

Our data have also demonstrated other types of comorbidity as significant predictors associated with the PTB development, including alcoholism, chronic obstructive pulmonary disease, liver illnesses and chronic kidney disease<sup>[20]</sup>. Whether this association was confounded by other socio-economic or demographic factors is not mentioned. The risk is higher for those with alcohol related damages, and chronic obstructive pulmonary disease. Two case-control studies from Spain<sup>[21,22]</sup>, one from South Africa and another case-control study from Texas have also reported alcohol as a significant risk for TB, with significant ORs ranging from 1.6 to 2.2<sup>[23,24]</sup>. To the best of our knowledge, no previous study has reported how chronic obstructive pulmonary disease may have association with the subsequent TB risk. The present study demonstrates a more than 2-fold risk for patients with chronic obstructive pulmonary disease to develop PTB.

Studies examining the effect of DM treatment in TB outcomes are limited. The Hong Kong study found an elevated risk of PTB in DM patients with baseline hemoglobin A1c > 7%, but not in those with hemoglobin A1c < 7%, but no effect of medication was reported. Our study further showed that the beneficial effect of DM medication in reducing PTB risk is the best for those taking metformin. Other medicines that may reduce the PTB risk include insulins, sulfonylureas, thiazolidinediones and alpha-glucosidase inhibitors. These data demonstrate that all anti-diabetic drugs have beneficial effect of reducing the PTB risk. However, the reason for the impact of using anti-diabetic drugs on the risk of pulmonary tuberculosis is not known. Singhal *et al* found metformin controls the growth of drug-resistant *Mycobacterium tuberculosis*

strains, increases production of mitochondrial reactive oxygen species, and facilitates phagosome-lysosome fusion<sup>[25]</sup>. These data indicate that metformin is a promising candidate host-adjunctive therapy for improving the effective treatment of PTB. Garnett *et al* found hyperglycaemia promotes respiratory *Staphylococcus aureus* infection, and metformin modifies glucose flux across the airway epithelium to limit hyperglycaemia-induced bacterial growth<sup>[26]</sup>. Metformin might, therefore, be of additional benefit in the prevention and treatment of respiratory infection. Tuberculosis is associated with DM and diabetic control was shown to be the predominant determinant of increased tuberculosis risk in the other study<sup>[20]</sup>. So the correlation of anti-diabetic drugs and pulmonary tuberculosis may be related with the severity of DM. Anti-diabetic drugs can improve blood sugar control, further reducing the risk of pulmonary tuberculosis. Future studies are needed to confirm this hypothesis.

We confirm that DM is a risk factor associated with developing tuberculosis. Our findings are important given the growing number of patients with DM in Taiwan and other parts of the world and the complications associated with this patient population<sup>[27,28]</sup>. From a policy standpoint, the results from this study indicate the need for a better understanding of the underlying factors leading to the association between tuberculosis and DM, especially in regions where both diseases are highly prevalent. The profile of patients with DM at high risk of developing tuberculosis must be established with more precision in prospective studies. These criteria should be adopted by the local health departments. Patients are promptly identified and offered chemoprophylaxis before the development of symptoms. Patients can be diagnosed at the early stages of disease before developing advanced, cavitary and contagious forms of the infection. Establishing the level of diabetes control may also be particularly important, because patients with high glucose levels are likely to be more prone to the most complicated forms of tuberculosis, including multi-drug resistant tuberculosis<sup>[29]</sup>.

There are possible limitations in our methodology and study design. The study did not collect information on hemoglobin A1c data due to the natural limitation of the dataset used, so it is difficult to assess the relevance between glycemic control and pulmonary tuberculosis. Choice of DM treatment is influenced by a host of factors, including age of patient, duration of DM, presence of complications and comorbidities, as well as by socioeconomic factors, compliance with therapy and health-seeking behavior. Most, if not all, of these factors can also influence risk of TB. We were not able to adjust for these factors that may modify or confound the association between diabetes and

TB. The possibility of undiagnosed diabetics in the control group, the absence of an evaluation of how well the diabetes is controlled amongst the diabetics (for example, diabetics not using medications may be because they had milder disease that is adequately controlled with lifestyle modification), and the fact that prescription with a drug is not the same as treatment, since participants may have for whatever reasons not been compliant on the medication.

## CONCLUSION

Diabetes mellitus is associated with tuberculosis in Taiwan and the difference in the cumulative incidence of PTB between diabetic cohort and non-diabetic cohort markedly increases with follow-up time. This may have implications for tuberculosis control and patient care in this region. Males, chronic obstructive pulmonary disease, alcoholic liver damage, and chronic kidney diseases are also associated with PTB. Anti-diabetic drugs may reduce the risk of PTB, but further studies are needed to confirm it.

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**Conflict of interest statement:** The authors disclose no conflicts of interest.

**Authorship:** The first three authors contributed equally to this study

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## Original Article

# Differential Expression and Localization of Nanog, Oct 3/4 and C-Kit in Mouse Ovarian Tissue According to Age

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## ABSTRACT

**Objective:** To investigate the expression of embryonic/pluripotent stem cell markers including Nanog, Octamer – Binding Protein <sup>3</sup>/<sub>4</sub> (Oct 3/4) and c-Kit from the newborn to aging period in the ovary tissues of mouse.

**Design:** Experimental study using mouse ovary tissues. The expression and localization of Nanog, Oct 3/4 and c-Kit expression were studied in newborn, pubertal, adult and aging ovary.

**Setting:** Department of Histology and Embryology, Pamukkale University, School of Medicine, Turkey

**Subjects:** Newborn (n = 6), pubertal (38-day-old) (n = 6), adult (12-week-old) (n = 6) and aged (24-week-old) female Balb/c mice were used in this study.

**Intervention :** No intervention

**Main Outcome Measure:** The expression of Nanog, Oct 3/4 and c-kit was evaluated by immunohistochemistry and

reverse transcriptase chain reaction (PCR).

**Results:** Nanog, Oct 3/4 and c-Kit expression were positive in oocytes of newborn, pubertal and adult ovary. But they were negative in granulosa cells in newborn groups. The expression of these markers in adult period was increased. In addition, positive reaction for Nanog, Oct 3/4 and c-Kit was observed in granulosa cells in secondary and tertiary follicles in pubertal and adult ovary. Ovarian surface epithelium were positive for all stem cells markers in adult and aged. In addition to that, only c-kit positive expression was found in theca cells.

**Conclusion:** According to our findings, each of the three stem cell markers may play an important role in folliculogenesis and ovarian pathology. However, c-kit may be more effective than others because stromal cells were positive in adult and pubertal ovaries as well as in aged ovary.

KEY WORDS: immunohistochemistry, ovary, stem cells,

## INTRODUCTION

The most fundamental dogma of reproductive medicine in the ovary is a certain number of oocytes and their possibility to increase. The basis of this doctrine was, first time taken in the 1870s<sup>[1]</sup>. This doctrine was further strengthened in the 1950s<sup>[2]</sup>. But in the recent years in a serial study the accuracy of this dogma began to be questioned. The first concept of postnatal oogenesis in mice was emerged in 1923<sup>[3]</sup> and then in humans in 1932<sup>[4]</sup>. Tilly and his team reviewed the idea of postnatal oogenesis showing oocytes regeneration using peripheral blood and bone marrow<sup>[5,6]</sup>. They counted healthy and atretic follicles in mouse ovary sterilized with chemotherapeutic agents and they showed a rapid

increase in the number of follicles. By the end of two months, they showed that no difference in follicle number was found between control and administered chemotherapeutic agents ovary. Moreover, they observed that the construction of oocytes re-formed in ablated ovary was not found after bone marrow transplant. In later years, oocytes were produced by using the stem cells derived from skin epithelium and amniotic epithelial cells<sup>[7,8]</sup>. Until now, oogonial stem cells (OSCs) have been isolated from the ovaries of adult mice<sup>[9,10]</sup> and rats<sup>[11]</sup> bovine<sup>[12]</sup> and humans<sup>[10]</sup>. These results showed that in vitro culture conditions these stem cells found in mammals can produce oocytes which have the ability to fertilize and result in a live birth.

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Based on previous experience it seems that ovarian surface epithelium stem cells retain the characteristic of embryonic stem cells<sup>[13-16]</sup>. The ovarian surface epithelium (OSE) obtained from adult and even menopausal mouse and human ovaries showed a difference in oocyte-like cells under defined in vitro culture conditions by several groups<sup>[13,15,17]</sup>.

Biological importance of ovarian stem cells and their relation with ovarian function are not clear. However, ovarian stem cells can be considered as a remedy for prevention of reproductive aging, preovarian failure, polycystic ovary syndrome (PCOS) and ovary cancer<sup>[16,18,19]</sup>.

In this study we have studied expressions, locations and distribution of Nanog, Oct 3/4 and c-Kit markers of pluripotent /embryonic stem cells in newborn, pubertal, adult and aged ovarian tissues using the immunohistochemical technique and reverse transcriptase polymerase chain reaction analysis. So, it has been identified that the embryonic/ pluripotent stem cell markers expression is consistent during ovary development throughout the life. This determination is important to find causes of diseases of the reproductive system, especially in the ovary the pathophysiology and treatment of ovarian cancer are quite significant and greatly contribute in a better understanding of the ovarian functions, fertility and causes of diseases such as PCOS, preovarian failure and ovary cancer, and of course in developing new treatment approaches.

## SUBJECTS AND METHODS

### Animals

Newborn (n = 6), pubertal (38-day-old) (n = 6), adult (12-week-old) (n = 6) and aged (24-week-old) female Balb/c mouse were used in this study. They were kept at a constant temperature ( $21 \pm 1$  °C) and controlled light conditions (light 07.00 – 19.00). Food (standard pellet diet) and tap water were supplied ad libitum. All the animals in whole groups were anaesthetized via intramuscular injection of xylazine (5 mg/kg) and ketamine (90 mg/kg) and were killed by cervical dislocation for collection of ovary. Right ovaries were prepared for immunohistochemistry, left ovaries were prepared for RT-PCR. All studies with animals used in this study were reviewed and approved by the University of Pamukkale Animal Ethics committee.

### Fixation and Tissue Preparation

Right ovaries were removed and were put in 10% neutral buffered formalin for 72 hours and then embedded in paraffin. Paraffin sections (5 mm) were deparaffinized in xylene and rehydrated through a graded series of ethanol solutions. Three sections from each animal were processed for Nanog, Oct 3/4 and

c-Kit immunocytochemistry. Negative controls were performed by omitting the primary antibody.

### Antibodies and Staining Procedure

Endogenous peroxidase activity was blocked in 3% hydrogen peroxidase for 10 minutes and sections were incubated with sponin to help easy binding of primer antibody to antigenic areas. Epitopes were stabilized by application of serum blocking solution (Goat serum, Lot# 20570999, Zymed Laboratories INC) for 20 minutes. Sections were incubated with primer antibody Oct 3/4 (C0411, Lot # C01411, Santa Cruz), Nanog (Lot # 823892, Abcam) and c-Kit (C-19, Lot # B2410 Santa Cruz), (diluted 1:100 in PBS) at +4 °C overnight. After applying with anti rabbit Ig, avidin-biotin complex peroxidase (ABC, Lot# 20570999, Zymed Laboratories INC) was applied to slides. Diaminobenzidine (DAB, Lot# 10163354, Zymed Laboratories INC) was used as chromogen. Afterwards, slides were counterstained with hematoxyline for 1 minute, dehydrated in graded ethanol and mounted in conventional medium. Slides were examined by three experienced histologists.

The intensity of immunoperoxidase reaction was classified as follows: negative (-) when the cells were devoid of any detectable Oct 3/4, Nanog and c-Kit expressions, slightly positive (+), moderately positive (++) and strongly positive (+++). Estimation of intensity of immunoperoxidase was blind with respect to the status of the animal (ovariectomized, or not, or phase of cycle). Negative controls were performed by omitting the primary antibodies resulting in no staining.

### RNA Isolation and Semiquantitative RT-PCR Analysis

Nanog, Oct 3/4 and c-Kit mRNA expression profiles in the mouse ovary tissue were examined by RT-PCR. In semiquantitative RT-PCR reaction, Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is used as a housekeeping gene. Isolation of RNA from fresh frozen tissue using Trizol (Sigma), was processed according to the manufacturer's protocol. All the animals in whole groups were anaesthetized via intramuscular injection of xylazine (5 mg/kg) and ketamine (90 mg/kg). Ovarian tissues were taken and they were put on an ice-cold glass stage. Total RNA was extracted from the tissues using an RNA isolation reagent, Tri-Reagent (Sigma, St. Louis, MO, USA). The single-tube one-step RT-PCR was standardized using the one-step RT-PCR kit (Qiagen, USA). Briefly, one-step RT-PCR was carried out in a 50 µL reaction mixture containing 1 µg total RNA, 10 pmol each primer, 10 µL 5X buffer (12.5 mM MgCl<sub>2</sub>), 2 µL dNTPs mix (containing 10 mM of each dNTP), and 2 µL of a mixture

**Table 1:** Expression and distribution of Nanog in developing mouse ovary

Nanog expression	Newborn groups	Pubertal groups	Adult groups	Aged groups
Surface Epithelium	+++	+++	+++	+++
Oocytes of primordial follicles	-	+	+	-
Granulosa cells of primordial follicles	-	-	-	-
Oocytes of primary follicles	+++	+	++	-
Granulosa cells of primary follicles	-	+	-	-
Oocytes of secondary follicles	Not available	++	+++	-
Granulosa cells of secondary follicles	Not available	++	++	Not available
Oocytes of tertiary follicles	Not available	++	+++	Not available
Granulosa cells of tertiary follicles	Not available	++	+++	Not available
Corpus Luteum	Not available	-	+++	-
Theca cells	Not available	-	-	-
Blood vessels	++++	++	+++	+++
Ovarian stroma	-	++	+++	+++
OSE	+++	+++	+++	+++

of Ominiscript and Sensiscripts reverse transcriptases and Hot Star Taq DNA polymerase. Gene expression was presented as the yield of PCR products from target sequences relative to the yield of PCR products from the GAPDH gene. In each instance, the amount of reverse transcription (RT)-PCR product for the gene of interest was normalized to the amount of GAPDH in the same sample. The primer sequences used in this study and cycling conditions are summarized in Table 1. The experiments were repeated two times using duplicates in each group. The RT-PCR products were analyzed by electrophoresis using 2% Molecular Screening Agarose gel (Roche Diagnostics, GmbH, Mannheim, Germany) and visualized by UV light.

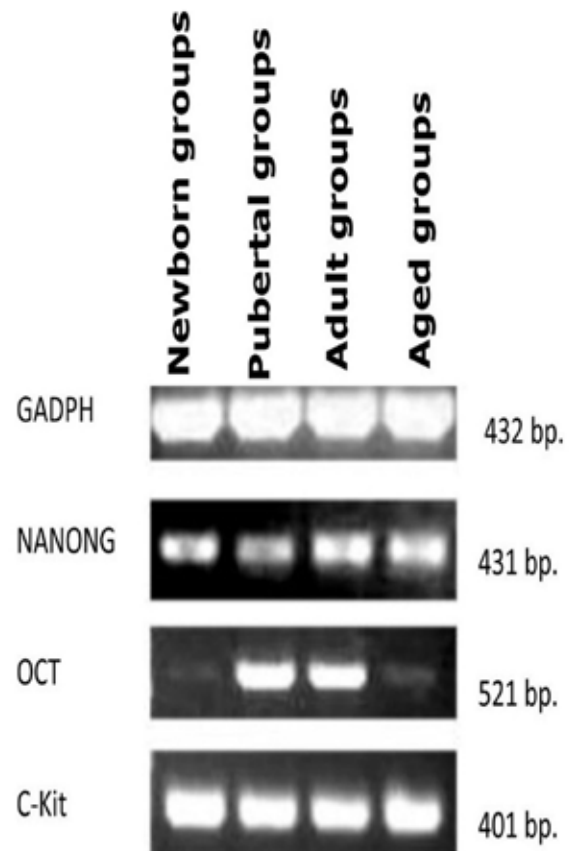
## RESULTS

### RT-PCR Results

Nanog, Oct 3/4, c-Kit mRNAs expression profiles of mouse ovarian tissue was examined by RT-PCR. Semi quantitative RT-PCR reaction and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene expression were used as the control of gene expression (housekeeping gene expression).

The results of RNA of Nanog gene expression levels in newborn were similar to pubertal groups. However, Nanog gene expression was increased in adult ovarian tissues when compared with newborn and puberty. Oct 3/4 RNA expression results showed that gene expression in aged and newborn ovarian tissues is much less than adult and pubertal ovarian tissues. RNA expression of c-kit results was found to be similar among the groups. However, it was observed that expression levels of Nanog gene has increased in aged and 2-month-old mouse ovarian tissues as in the tissues of newborn and puberty mice. According to this finding, Nanog expression in mouse ovarian tissue is considered to increase gradually in the developmental period. In newborn and aged groups, Oct 3/4 gene expressions were much less as

compared with adult and pubertal group. The results of the c-Kit mRNA expression were evaluated, and a similar expression has been observed among the groups. According to this finding, the expression of c-Kit gene is considered to be protected from newborn up to the aged group. In this group, the ovarian stroma was found to be strongly positive as compared to the neonatal group (Fig 1).



**Fig 1:** The RT-PCR gen expression profiles of mouse embryonic stem cells

### Immunohistochemical results

Expression of Nanog in Ovarian Tissues: The distribution and localization of nanog expression in newborn, pubertal, adult and aged ovarian tissues are summerized in Table 1.

**Newborn groups:** In this group, negative reaction for Nanog was observed in follicular epithelial cells. However, oocytes of some primary follicles had positive reactions, and some of them were negative. While blood vessels in ovarian stroma showed a strong positive staining for Nanog, the stromal cells were negative. A strong expression of Nanog was also found in ovarian surface epithelium (Fig 2 A, B).

**Pubertal groups:** No immunoreactivity was observed in primary and secondary follicles' granulosa cells. Some of the tertiary follicles' granulosa cells had positive reaction, whereas the others had a negative one (Fig 2C). A moderate staining was observed in blood vessels and ovarian stroma. OSE in pubertal group like in the newborn group showed positive staining, however, these cells were negative for Nanog (Fig 2 D).

**Adult groups:** Primordial follicles cells and oocytes showed negative reactions. Combination of negative and positive reactions was observed in primary follicles cells. Although a weak staining was detected in primary follicles oocytes, an increased expression of Nanog was noted in oocytes of secondary and tertiary follicles. In this group, expression of Nanog was increased in secondary and tertiary follicular cells compared to pubertal groups. Luteal cells cytoplasm showed positive reaction for Nanog but their nucleus had no immunoreactions in corpus luteum. In adult groups, OSE, blood vessels and stroma demonstrated strong staining. (Fig 2 E, F)

**Aged groups:** It was observed that the number of follicles decreased, but the number of corpus luteum increased. It was interesting to observe that stromal cells and atretic follicles had a positive reaction, whereas luteal cells had a negative reaction. Both positive and negative reactions for Nanog were found on ovarian surface epithelial cells in aged mice (Fig 2 G, H).

**Expression of Oct 3/4:** The distribution and localization of Oct3/4 expression in newborn, pubertal, adult and aged ovarian tissues are summerized in Table 2.

**Newborn groups:** It was interesting to observe that oocytes in some primordial and primary follicles had strong immunoreactions, whereas some of them were negative or weak positive. In addition, granulosa cells and OSE displayed negative staining (Fig 3 A, B).

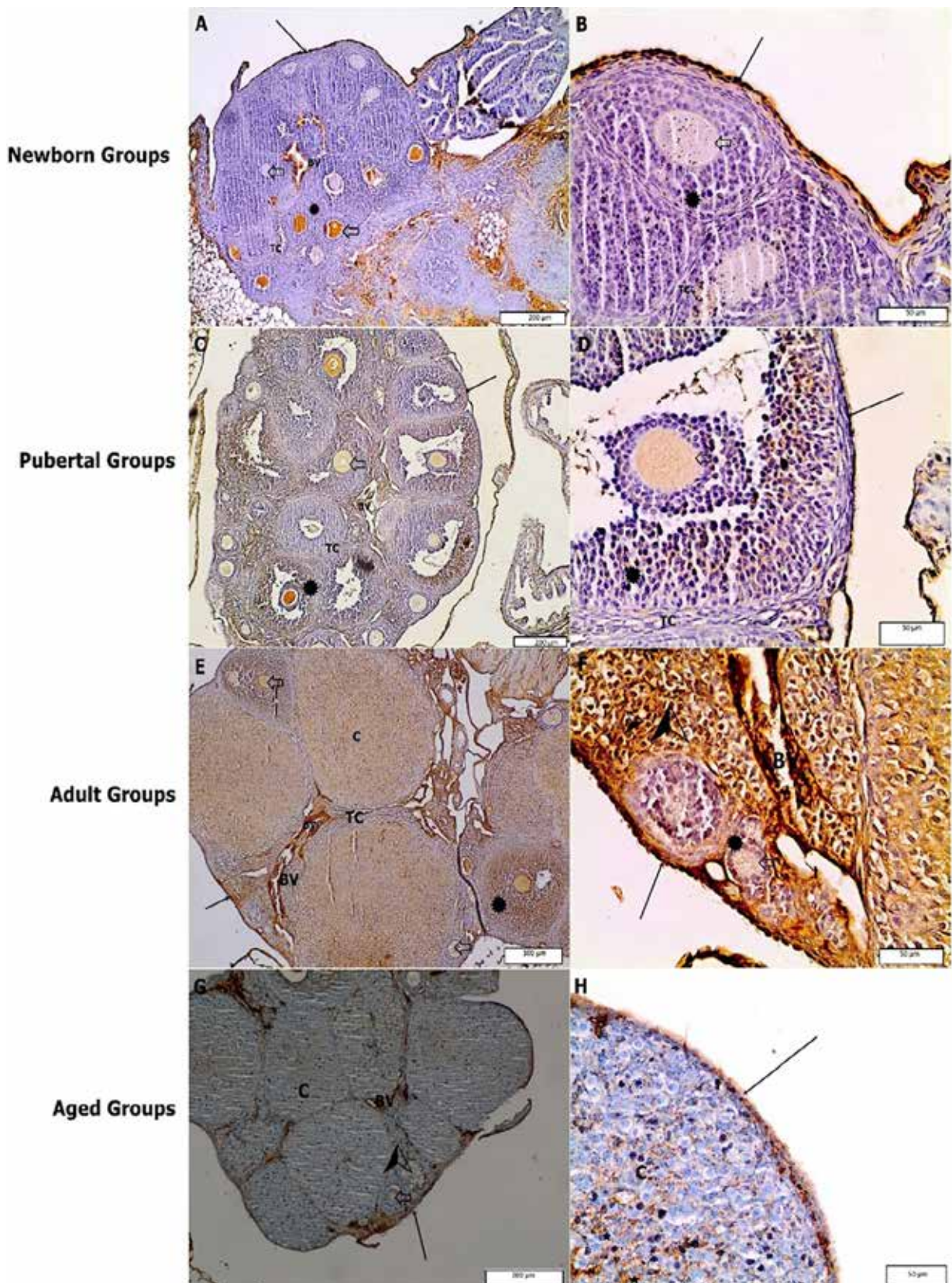
**Pubertal groups:** Negative and poor reactions were observed in oocytes in primary follicles; however, oocytes in secondary and tertiary follicles demonstrated strong positive reactions. Besides, we noticed that granulosa cells of primary and secondary follicles showed negative reaction but tertiary follicles consisted of cells showing both positive and negative reactions. In pubertal groups, OSE, theca cells and stroma exhibited negative reaction for Oct 3/4 (Fig 3 C, D).

**Adult groups:** In this group, not only negative but also positive staining oocytes were noted. While negative immunostaining was found in primordial granulosa cells, positive immunostaining was detected in primary, secondary and tertiary follicles' granulosa cells. Cytoplasmic positive staining for Oct 3/4 was observed in corpus luteal cells. Positive staining for Oct 3/4 which gradually changes from weak to strong

**Table 2:** Expression and distribution of Oct3/4 in developing mouse ovary

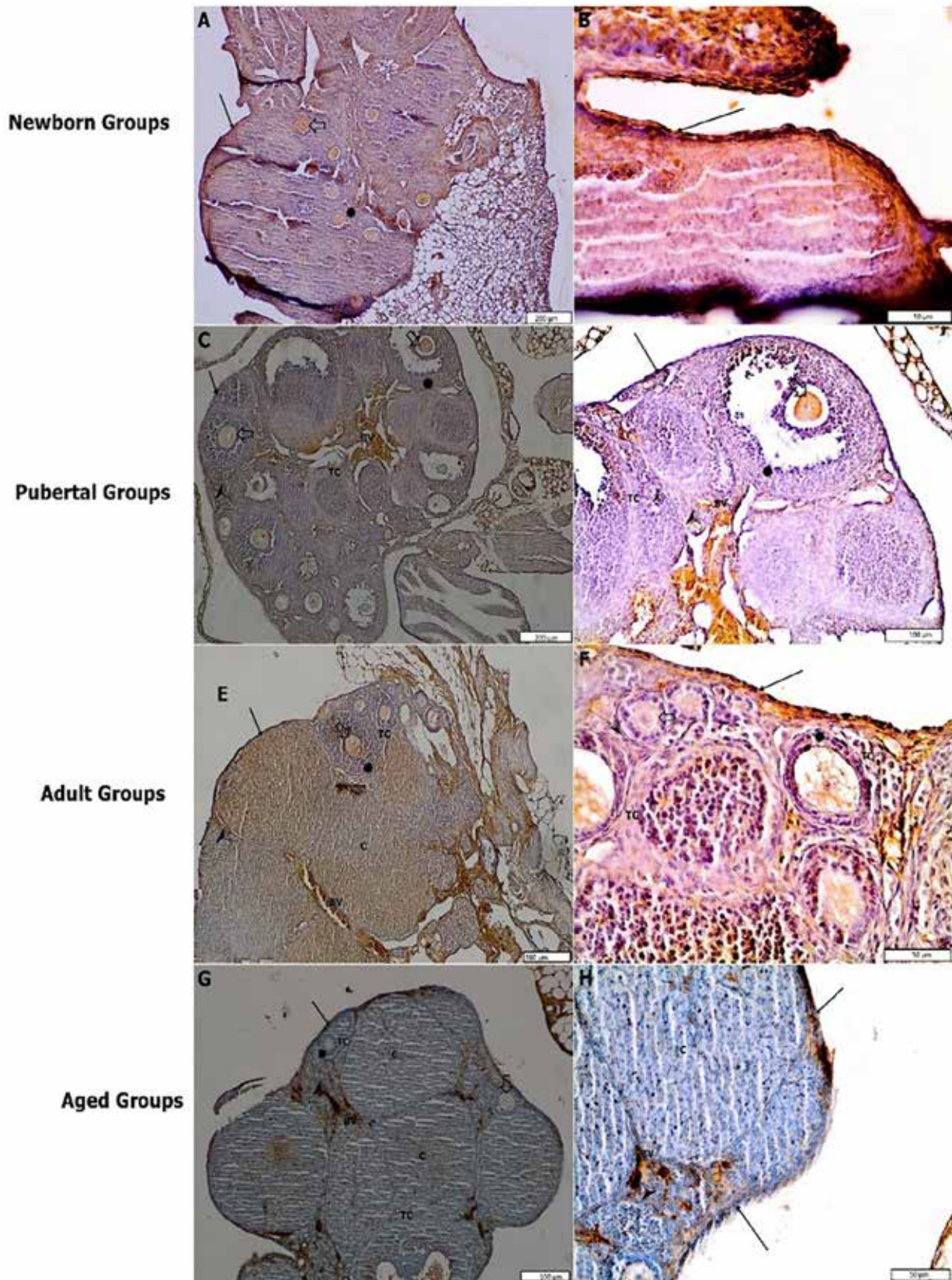
Oct 3/4 expression	Newborn groups	Pubertal groups	Adult groups	Aged groups
Surface epithelium	-	-	+++	+++
Oocytes of primordial follicles	-	+	+	
Granulosa cells of primordial follicles	-	-	-	
Oocytes of primary follicles	++	++	++	-
Granulosa cells of primary follicles	-	-	-	-
Oocytes of secondary follicles	Not available	++	++	Not available
Granulosa cells of secondary follicles	Not available	+	++	Not available
Oocytes of tertiary follicles	Not available	+	++	Not available
Granulosa cells of tertiary follicles	Not available	+	-	-
Corpus Luteum	Not available	-	+++	-
Theca cells	Not available	-	-	-
Blood vessels	-	+++	+++	+++
Ovarian stroma	+	-	+	+++
OSE	-	-	+++	+++





**Fig 2:** The localization and distribution of Nanog expression in developing mouse ovary. (A-B): Newborn groups, (C-D): Pubertal groups, (E-F): Adult groups, (G-H): Aged groups; Ovarian surface epithelium: (arrow), oocyte: (thick arrow), granulosa cells: (asterisk), theca cells: (TC), corpus luteum: (C), stromal cells: (arrow head), blood vessels: (BV).





**Fig 3:** The localization and distribution of Oct3/4 expression in developing mouse ovary. (A-B): Newborn groups, (C-D): Pubertal groups, (E-F): Adult groups, (G-H): Aged groups, ovarian surface epithelium; (arrow), oocyte; (thick arrow), granulosa cells; (asterisk), theca cells; (TC), corpus luteum; (C), stromal cells; (arrow head), blood vessels; (BV).

**Table 3:** Expression and distribution of c-Kit in developing mouse ovary

c-Kit expression	Newborn groups	Pubertal groups	Adult groups	Aged groups
Surface epithelium	+	+++	+++	+++
Oocytes of primordial follicles	-	++	+	-
Granulosa of primordial follicles	-	+	-	-
Oocytes of primary follicles	++	++	+++	-
Granulosa cells of primary follicles	-	+	+	-
Oocytes of secondary follicles	Not available	+++	+++	Not available
Granulosa cells of secondary follicles	Not available	+++	++	Not available
Oocytes of tertiary follicles	Not available	+++	+++	Not available
Granulosa cells of tertiary follicles	Not available	+++	++	Not available
Corpus Luteum	Not available	++	+++	-
Theca cells	Not available	++	+++	-
Blood vessels	-	+++	+++	+++
Ovarian stroma	+	+++	+++	+++
OSE	+++	+++	+++	+++

was observed on the surface epithelium in adult mice. (Fig 3 E, F). In this group, theca cells were observed negative while blood vessels observed strong positive staining.

#### Aged groups

In aged groups, the OSE layer consists of cells showing positive and negative immunoreactions. Negative immunoreaction was demonstrated in oocytes and granulosa cells. While luteal cells had negative reactions, stromal cells and atretic follicles showed positive reactions (Fig 3 G, H).

**Expression of c-Kit:** The distribution and localization of c-Kit expression in newborn, pubertal, adult and aged ovarian tissues are summarized in Table 3.

**Newborn groups:** In this group, negative reaction was observed in follicular cells; however, some oocytes showed strong positive reactions and some of them had no reaction. In addition, ovarian stromal cells demonstrated a weak positive staining for c-Kit. Poor positive c-Kit immunoreaction was observed on the surface epithelium in newborn groups (Fig 4 A, B).

#### Pubertal groups

Poor positive reaction was detected in granulosa cells of primordial and primary follicles. Moderate positive reaction was observed in the granulosa cells of secondary follicles which are close to the lumen, and in tertiary follicles positive staining intensity gradually increased. While oocytes in primordial and primary follicles showed a moderate positive staining, secondary and tertiary follicles' oocytes showed a strong positive staining for c-Kit. In addition, corpus luteal cells, theca cells and stromal cells demonstrated strong immunoreactivity for c-Kit. In the pubertal ovary, c-Kit expression was higher compared to OCT3/4 and NANOG expression.

The OSE showed strong positive staining in pubertal groups (Fig 4 C, D).

#### Adult groups

Moderate and strong staining was determined in granulosa cells of primordial follicles, whereas oocytes of primordial follicles were negative for c-Kit. We noticed that oocytes and basal granulosa cells in secondary and tertiary follicles exhibited strong positive reactions for c-Kit. Strong positive c-Kit staining was found on OSE and corpus luteum in 12-week adult groups (Fig. 4: E, F). Theca cells, stroma and blood vessels were also strong positive in these groups.

#### Aged groups

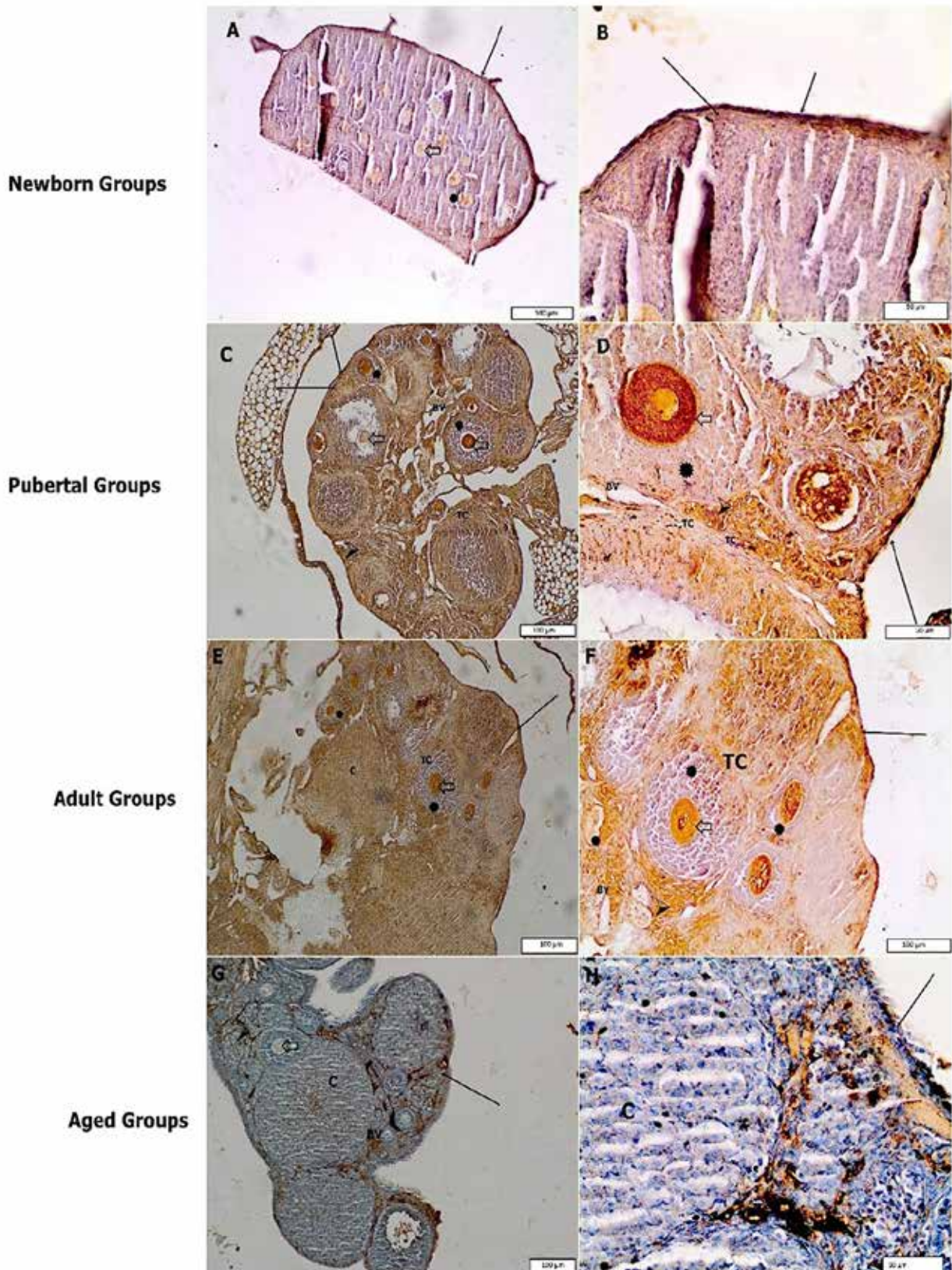
In the aged group, staining pattern is similar to other groups. Negative and positive cells for c-Kit were determined on surface epithelium. Atretic follicles and stromal cells stained strongly but negative reaction was observed in luteal cells (Fig 4 G, H).

## DISCUSSION

The present study provides a comprehensive evaluation of pluripotent stem cell expression in developmental ovary using immunohistochemistry and PCR technique. Importantly, the study demonstrates the expression of multiple stem cell markers shown collectively in ovary tissues from newborn to aged period. Information from this study describes the expression of multiple embryonic/pluripotent stem cell markers in granulosa cells, oocytes and OSE cells during ovary development to help evaluate the pluripotent nature of these cells.

Oct 4 (Oct 3/4, Oct 3) is the most important transcription factor and it is expressed in embryonic stem cells, primordial germ cells, germ cells and also in germ cell tumors<sup>[20,21]</sup>. Oct 4 inhibits differentiation of embryonic cells<sup>[22,23]</sup>. Decreasing expression of Oct





**Fig 4:** The localization and distribution of c-Kit expression in developing mouse ovary. (A-B): Newborn groups, (C-D): Pubertal groups, (E-F): Adult groups, (G-H): Aged groups, ovarian surface epithelium; (arrow), oocyte; (thick arrow), granulosa cells; (asterix), theca cells; (TC), corpus luteum; (C), stromal cells; (arrow head), blood vessels; (BV).

3/4 initiates differentiation in embryonic cells and with the beginning of differentiation the synthesis of Oct 4 decreases. In a study by Gota *et al*, it was established that Oct 3/4 was expressed in germ cells at intrauterine 17<sup>th</sup> and 24<sup>th</sup> weeks and its expression decreased in later periods<sup>[24]</sup>. After birth, Oct 3/4 is not expressed by germ cells. Contrary to Gota's findings, our study showed a strong positive Oct 3/4 expression in oocytes of newborn, pubertal and adult ovary. Also, granulosa cells in pubertal ovary were positive. In adult mouse ovary, granulosa cells of secondary and tertiary follicles were positive while theca cells were negative. The surface epithelium showed positive staining in newborn, adult and aged ovary. In addition, stromal cells were positive in adult groups. In aged ovary, only the surface epithelium observed positive staining for Oct 3/4.

Another stem cell marker Nanog was discovered in 2003. Pre-implantation embryos, embryonic stem cells, embryonic germ cells and embryonic carcinoma cells were positive for Nanog using immunohistochemical techniques and RT-PCR studies. It was also reported that unfertilized oocytes were negative for Nanog<sup>[25-27]</sup>. In another study in 2005 by Yamaguchia *et al*, negative expression for Nanog in ovarian follicles of eight weeks mice was found<sup>[28]</sup>. In contrast to these studies, we found positive reactions in oocytes of newborn, pubertal and adult ovary. We also found a moderate staining for Nanog in granulosa cells of pubertal and adult groups and a negative staining in stroma of newborn ovary. A moderate staining in stroma cells was seen in pubertal groups while theca cells were negative. In aged groups, a strong staining in stroma cells and corpus lutei were observed. Nanog expression was negative in adult ovary as in the pubertal groups. In aged ovarian tissue, only OSE cells and stromal cells showed positive expression.

C-Kit receptor is a type III receptor tyrosine kinase and it plays a role in oocyte-granulosa interaction<sup>[29]</sup>. Robinson *et al* showed c-Kit mRNA in oogonia which produced mitotic activity<sup>[30]</sup>. Yoshida and colleagues (1997) reported that when the primary follicles were developed, the expression of c-Kit was blocked<sup>[29]</sup>. Driancourt (2000) showed that c-Kit expression was positive on 8 - 14 pc days and also oocytes of primordial follicles and growing follicles had strong positive in postnatal period<sup>[31]</sup>. Human primordial germ cells showed positive c-Kit in between the 7<sup>th</sup> and 13<sup>th</sup> week during 21 weeks of gestation. Stoop (2005) reported that ovarian tissue had positive reaction for c-Kit during intrauterine life<sup>[32]</sup>.

Kang (2003) notified oocytes of primordial and primary follicles were positive in postnatal seven days and also granulosa cells had positive reaction for c-Kit

in 21 days<sup>[33]</sup>. Our results supported these findings, we also found positive c-Kit expression in oocytes of primordial and primary, secondary, tertiary follicles in newborn, pubertal and adult groups. However in adults, pubertal and neonatal period, granulosa cells of primordial and primary follicles did not demonstrate positive staining for c-Kit. Contrary to granulosa cells of primordial, primary, secondary and tertiary follicle' granulosa cells, the theca cells showed moderate staining in pubertal groups and strong staining in adult groups for c-Kit.

OSE has an important role in the physiology of the ovary and ovarian cancers. 85 - 90% of ovarian cancer originated from OSE and these cancers are lethal<sup>[34]</sup>. Very little differentiated OSE, epithelial tissue, unlike many, suffered both at the change of epithelial and mesenchymal markers.

OSE exhibited epithelial and mesenchymal markers apart from many epithelial tissues<sup>[35]</sup>. In recent years, several studies have shown the presence of mature OSE stem cells<sup>[35]</sup>. Parte and his colleagues showed that the cultured stem cells are derived from OSE expressed Oct 3/4 and SSEA-4. Virant-Klun reported that stem cells derived from OSE are similar to embryonic stem cells and they showed Sox-2, Oct 4 and Nanog expression<sup>[17]</sup>. Virant-Klun isolated OSE cells from postmenopausal woman who had naturally no follicles and from premature ovarian failure patients and these epithelial cells were transformed to oocytes by them. In 2008, Zhang *et al* characterized cells expressing germ cell markers Oct 3/4, MVH, the SCF-R (the c-Kit-CD117) and SSEA-1 in nonfollicle structures in ovary<sup>[36]</sup>. In our study, it was interesting to observe that all OSE groups were positive for Nanog and for c-Kit. On the other hand, OSE was negative for Oct in newborn and pubertal period but had positive reaction in aged and adult groups. These results may be effective in strengthening the understanding of postnatal oogenesis and development of ovarian cancer.

## CONCLUSION

In this study, oocytes in newborn groups were positive for all the three stem cells markers but granulosa cells were negative. In pubertal and adult stage, oocytes and granulosa cells of secondary and tertiary follicles were positive while primary follicles' granulosa cells were negative for Oct 3/4, c-Kit and Nanog by using immunohistochemical and RT-PCR techniques (Fig 1-4). Hormones or paracrine effects in puberty can cause the negative expression in granulosa cells of secondary and tertiary follicles to change to positive expression. These findings suggest that Nanog, Oct 3/4 and c-Kit may be very effective on

folliculogenesis. Theca cells were positive only for c-Kit and also in the pubertal ovary, c-Kit expression was higher compared to Oct 3/4 and Nanog expression. As a result of these findings, we assumed that the staining of c-Kit may be related to estrogen hormone.

Adult ovarian tissues showed a stronger Oct 3/4, c-Kit and Nanog staining as compared to newborn, pubertal groups. Particularly granulosa cells and oocytes of secondary and tertiary follicles in adult groups had strong immune reactions for Oct 3/4, c-Kit and Nanog. Moreover, granulosa cells of both secondary and tertiary follicles showed nuclear and cytoplasmic staining. This type of staining pattern was observed in different studies and it was reported that these molecules may be related to both nuclear DNA and mitochondrial DNA in cytoplasm. Particular granulosa cells were positive for Nanog, Oct 3/4 and c-Kit which may play a role in normal folliculogenesis.

In our study, aged groups showed positive reaction in the stromal and surface epithelial cells for all three markers and they may also be transformed into oncogenic stem cells.

Regarding the results, stromal cells, OSE cells and ovarian follicles may be a reference for further research for normal and pathological processes. According to our findings, each of the three stem cell markers may play an important role in these processes. However, c-Kit may be more effective than others, because stromal cells were positive in adult and pubertal ovaries as well as in aged ovary.

#### ACKNOWLEDGMENT

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## Original Article

# Pitted Keratolysis: An International Study in Five Occupational Groups

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**ABSTRACT**

**Objective:** The aim of the study was to evaluate the incidence of Pitted Keratolysis (PK) in two groups from two different countries, to estimate the importance of hyperhidrosis, warm and occlusion in inducing PK.

**Design:** Prospective study

**Setting:** Department of Dermatology, 6<sup>th</sup> Military Support Unit, Ustka, Poland

**Subjects:** One thousand nine hundred and eleven people were examined and the control group consisted of 229 people, randomly selected. Those surveyed were divided into five groups.

**Intervention:** None

**Main outcome measures:** A two-center, clinical survey was done in order to estimate variable parameters in patients diagnosed with PK, including age, gender, work status,

associated skin problems, presence of hyperhidrosis, use of occlusive shoes, recurrences, complaints and impact on work and social life.

**Results:** PK was diagnosed in a total of 152 (7.95%) people, and two (0.87%) in the control group. Out of these, 19 (90.48%) patients had hyperhidrosis, 7 (63.63%) were homeless, 13 (30.23%) were farmers, 10 (7.04%) were athletes, and 103 (6.08%) were soldiers. In 82.89% (126) persons, presence of lesions was related to wearing shoes that were not breezy enough.

**Conclusion:** The presence of PK is connected with the chronic effect of sweat, occlusion, or increased humidity. A large role in the etiology of diseases is played by injuries, micro trauma and inadequate hygiene of feet.

KEY WORDS: corynebacterium, pitted keratolysis, soldier, skin diseases, stratum corneum

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**INTRODUCTION**

Pitted keratolysis (PK) is a bacterial infection of the skin first described in 1910 by Castelani as *Keratoma plantare sulcatum*. In his opinion, the disease was specific to people living in tropical and subtropical areas.

In 1965, Zaias changed the name of the disease to Pitted Keratolysis, as it is well accepted today.

*Corynebacterium triad* is a clinical entity that includes PK, *trichomycosis axillaris* (trichobacteriosis) and *erythrasma*, caused by the same pathogen *Corynebacterium spp*<sup>[1]</sup>. *Kryptococcus sedentarius*, *dermatophilus congolensis* and *streptomices* have also been reported to induce the disease<sup>[2]</sup>.

*Corynebacterium spp* are Gram-positive bacteria that invade and proliferate within plantar stratum

corneum of feet favored by over warming, humidity, occlusion, overstressed feet and poor hygiene<sup>[3,4]</sup>. *Corynebacterium spp* produce keratolytic enzymes which damage stratum corneum, especially in the presence of hyperhidrosis. It is considered that hyperhidrosis is present in 95% of all cases of PK<sup>[5]</sup>.

PK affects people of all ages, being mostly described in adult males, more often in soldiers<sup>[3,5]</sup>, homeless<sup>[6]</sup>, athletes<sup>[4]</sup>, farmers<sup>[7]</sup>, and silk workers<sup>[6]</sup>. The lesions are typically located on the soles of the feet<sup>[8]</sup> and only one foot or both feet may be affected.

Unpleasant smell of rancid apples is frequently described by the patients diagnosed with PK<sup>[8]</sup>. Pain sometimes occurs, burning while walking, and desquamation of the skin are common complaints of patients<sup>[6]</sup>.

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Keratolytic enzymes produced by *Corynebacterium* spp destroy the stratum corneum of the epidermis, explaining the presence of characteristic, more or less visible, shallow or deep crater-shaped sores. Two histological types of PK are admitted: superficial type with discrete depressions and deep variant with larger depression<sup>[9]</sup>. The depressions' depth varies between 0.5 – 1.0 mm and may achieve the depth of 2 mm<sup>[10]</sup>.

Wood lamp examination, although it is of great help in erythrasma and trichomycosis, is not a useful diagnostic tool in PK<sup>[11]</sup>.

Different treatment modalities have been tried in PK: topical antibiotics (erythromycin 2%, clindamycin 1%), antiseptics (chlorhexidine, isopropyl alcohol 40-60%), sometimes accompanied by botulinum toxin injections for hyperhidrosis<sup>[4,5,12]</sup>.

## SUBJECTS AND METHODS

In the study period of five months, 1911 people were examined – males and females aged 18 – 86 (average 52 years old), pursuing a variety of professions and originating from different social groups. The control group consisted of 229 people, randomly selected – males and females aged 19 – 77 (average 48 years old). Those surveyed were divided into five groups:

1. soldiers – 1694 people, males aged 18 – 27 (average 22.5 years old);
2. farmers – 43 people, men aged 44 – 86 (average 65 years old);
3. athletes – 142 people, males and females aged 19 – 34 (average 26.5 years old), among whom were basketball players (24 people), volleyball players (32 people), football players (56 people), light athletics competitors (22 people) and martial arts competitors (8 people);
4. Homeless people – 11 individuals, males aged 41 – 53 (average 47 years old);
5. Patients with hyperhidrosis – 21 people, males aged 19 – 33 (average 26 years old).

Eligibility criteria for participants were people from different social groups and carrying out certain professions.

In addition, those examined were interviewed about their history of foot injuries, chronic diseases and treated skin diseases on the feet (all those with diagnosed hyperhidrosis were included in group 5).

The limitation of this study was the presence of other foot diseases including dermatomycosis. In doubt, mycological examination was performed with KOH on clinical lesions.

The study was conducted in two Departments of Dermatology, the 6th Military Support Unit in Poland and in the Apollonia University Iasi in Romania.

**Exclusion criteria included:** The study excluded people with physical disabilities and children.

**Inclusion criteria required:** All able-bodied people above the age of 18 years were included in the study groups. Soldiers of the Polish Army, farmers and homeless from Poland and Romania, professional athletes from Poland and Romania, and patients with hyperhidrosis for at least one year.

This study was approved by the 6<sup>th</sup> Military Support Unit in Poland and by Apollonia University Iasi in Romania.

## Ethics

This study was performed on human subjects; thus, all patients were aware of the presence of the study.

## RESULTS

Pitted keratolysis was diagnosed in 7.95% of the cases (152 of those examined) and in 0.87% of cases in the control group (2 individuals).

The vast majority of those diagnosed with PK (90.48%, equaling 19 people) were individuals suffering with hyperhidrosis. The order of the remaining cases was as follows: the homeless constituting 63.63% of cases (7 people), farmers with the percentage of 30.23% (13 individuals), athletes – 7.04% (10 people) and soldiers – 6.08% (103 people) (Table 1).

In 82.89% cases, the lesions had to do with wearing shoes that were not breezy enough. Almost 85% of lesions were located on the sole of the foot, in the forefoot area or on a heel, and only 2.63% lesions affected the whole foot. The subjective symptoms those questioned complained about were: unpleasant smell (86.84%), hyperhidrosis of feet (78.29%) and pain while walking (19.74%).

Additional features and factors favoring the formation of PK as well as subjective experience (subjective symptoms) are presented in Table 1.

In addition, among the respondents, there were 161 cases reporting tinea pedis (8.42% of those examined), including as many as 8.50% soldiers (144 individuals), four cases reported type II diabetes (0.21% of respondents) and four cases of varicose veins in lower legs and vasomotor disorders (0.21% of respondents).

After obtaining all data, five groups were identified:

1. Soldiers – 1694 people, men, aged 18 - 27 (average 22.5);
2. Farmers – 43 people, men aged 44 – 86 (average 65);
3. Athletes – 142 people, males and females, aged 19 – 34 (average 26.5), 24 basketball players, 32 volleyball players, 56 football players, 22 light athletics competitors and 8 martial arts competitors;
4. Homeless people – 11 individuals, all men aged 41 – 53 (average 47);



**Table 1:** The features and factors favoring the formation of Pitted Keratolysis as well as subjective experience (subjective symptoms)

Groups	Features					
	Occlusion and / or protective footwear % (n)	Pain when walking % (n)	Unpleasant odor % (n)	Sweating % (n)	Location	
					Forefoot or heel	Whole foot
Soldiers	100 (103)	20.39 (21)	100 (103)	95.15 (98)	100 (103)	-
Homeless	100 (7)	85.71 (6)	100 (7)	100 (7)	71.42 (5)	28.57 (2)
Athletes	40 (4)	10 (1)	90 (9)	50 (5)	100 (10)	-
Farmers	92.31 (12)	15.38 (2)	100 (13)	69.23 (9)	84.62 (11)	15.38 (2)
Summary	82.89 (126)	19.74 (30)	86.84 (132)	78.29 (119)	84.87 (129)	2.63 (4)

5. Persons with hyperhidrosis – 21 people, men, aged 19 – 33 (average 26).

## DISCUSSION

Healthy feet are an important factor in maintaining physical condition mainly in military training (basic training). Foot injuries, acute or chronic diseases could be criteria of elimination of soldiers from training<sup>[5,13]</sup>.

In a study performed by Brzezinski *et al* who followed 3714 soldiers for one year, the results confirmed the presence of foot infections (including PK) in 3.39% persons reported to all skin diseases diagnosed in the same population group<sup>[3]</sup>.

Another survey released on 1694 people by Brzezinski *et al*, soldiers who were checked for skin diseases over a period of two years reported the presence of infections localized on the feet in 2.47% cases<sup>[5]</sup>.

PK is a common disease that occurs in people with chronic venous insufficiency of the inferior limbs, peripheral vasomotor disorders and obesity. The role of circulatory system as a predisposing factor for PK was brought into discussion for the first time by Esterman and Pilotto when examining traumatic lesions in Australian soldiers<sup>[14]</sup>.

Another research conducted by Abdel-Fattah *et al* on soldiers of the Saudi Arabian army concluded that abnormal foot construction (flat feet) was not a major risk factor for excluding a soldier from military exercises<sup>[15]</sup>.

During the last decades, many reports have been published emphasizing the relation between excessive foot sweating and PK. According to Shah *et al*, hyperhidrosis, the presence of tinea unguis, the existence of microtraumas in soldiers and athletics play a major role in the etiology of PK<sup>[16]</sup>.

Fifty-three patients (mean 24.9 years) were observed by Blaise *et al* for a period of two years; over two thirds (68%) of those examined reported hyperhidrosis of the feet, whereas unpleasant smell and foot pain were reported by 66% and 47% of the patients respectively<sup>[17]</sup>; and occlusive footwear was

confirmed by 96.2% of examined persons.

In comparison, a Belgian study in present reports pain only by 19.74% of the Polish patients, 85.71% of them being homeless.

Danpiere also notified the incidence of PK in 30 soldiers partaking in a mission in the rainforests of Guyana<sup>[18]</sup>.

Frequent occurrences of PK were confirmed in Nigerian and German soldiers<sup>[15,19]</sup>.

Scrutiny of skin diseases in farmers from Southern India, done by Sheno *et al* concluded the presence of PK in 43.4% of people who were examined<sup>[20]</sup>

Kanthraj *et al* noted the presence of skin diseases in 68% of silk workers, out of whom 38% suffered from PK<sup>[21]</sup>.

In a study realized by Pasricha and Baru, PK was found in 51.8% cases of skin disorders among silk workers in Assam, in a proportion of 37.5% in Kamata and presented also in cashew nut workers in Karnataka<sup>[22]</sup>.

Stratigos *et al* performed a survey on 142 homeless living in Boston-USA searching for skin diseases over a three month-period; the results confirmed the occurrence of PK in 20.4% of cases and tinea pedis in 38% of persons<sup>[6]</sup>

## Limitations

There are some limitations in this study. Foremost, it is a retrospective study which compares data over a span of one year. This study included in-patients treated from two different clinical centers and two states. The following year the number of soldiers could rise twice. The soldiers were studied in the first month of military training and number of symptoms could increase in the coming months.

## CONCLUSIONS

Healthy skin of feet plays an important role in maintaining proper physical condition. It is important to wear proper footwear and to take good care of the feet, as well as to maintain good level of hygiene.

Plantar Pitted keratolysis is the disease of "wet feet". The occurrence of PK is related to a chronic influence of sweat, occlusion and increased humidity that are in favor of bacterial infection by *Corynebacterium* spp. A prominent role in the etiology of the disease is played by injuries, microtraumas and inadequate hygiene. Symptoms of the disease were accompanied by an unpleasant smell, hyperhidrosis and foot pain.

The real incidence of PK is not known, although many reports exist concerning high-risk groups: persons prone to prolonged use of occlusive footwear.

Present study highlights the high incidence of PK on a large predisposed population and raises the hypothesis that PK might be more common in large populations.

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## Original Article

# Routine or Selective Histopathology of Gallbladder Specimen after Cholecystectomy for Gallstone Diseases

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## ABSTRACT

**Objectives:** To determine the incidence of incidental gallbladder cancer (IGBC) and to assess the need of routine histopathological examination of all gallbladder specimens after cholecystectomy for benign gallstone diseases

**Design:** Retrospective study

**Setting:** Department of Surgery, College of Medicine, King Saud University, KSA

**Subjects:** This study included all the patients who underwent elective or emergency cholecystectomy for gallstone disease at King Saud Medical City, Riyadh, Saudi Arabia between January 2012 and September 2015. Patients with preoperative suspicion of gallbladder cancer on imaging, or underwent cholecystectomy for gallbladder polyps or porcelain gallbladder were excluded from the study. Medical record of all the selected patients was reviewed and the data were collected.

**Interventions:** Histopathological examination of gallbladder

**Main outcome measures:** IGBC, routine histopathological examination of all gallbladder

**Results:** A total of 2396 patients underwent cholecystectomy for gallstones disease. All gallbladder specimens were sent for histopathological examination. IGBC was detected in nine gallbladder specimens (0.4%). Out of 2396 patients, morphologic abnormalities were observed in 518 specimens (22.6%). There was no reported case of IGBC with normal appearance of gallbladder specimen. Five patients underwent simple cholecystectomy for stage T1b, three patients of stage T2 tumor had further liver resection and one patient received only palliative care.

**Conclusions:** The incidence of IGBC was 0.38%. All cases of IGBC were detected in abnormal looking thick wall gall bladder. Therefore, selective histopathology of abnormally looking specimen is recommended to reduce the cost and work load of pathologists.

KEY WORDS: cholecystectomy, histopathology, gall stones, incidental gall bladder cancer, selective histopathological approach

## INTRODUCTION

Cholecystectomy is one of the most commonly performed surgical operations for gallstone disease<sup>[1]</sup>. Routine histopathology of gall bladder specimens after cholecystectomy has been a standard practice across the globe to detect incidental gall bladder carcinoma (IGBC) at an early and potentially curable stage<sup>[2-7]</sup>. IGBC is defined as carcinoma of gall bladder suspected for the first time during cholecystectomy or accidentally found on histopathological examination<sup>[4]</sup>.

The reported incidence of IGBC varies from 0.19% to 2.9% of cholecystectomies, and it constitutes the main bulk (27 - 72%) of newly diagnosed gall bladder cancer (GBC)<sup>[2,3,8-11]</sup>. Early detection GBC on routine histopathological examination promises a better outcome and prolonged survival<sup>[11,12]</sup>.

However, the routine histopathological evaluation of all gall bladders is associated with increased workload of pathologists and overall cost of health care system. Therefore, a more selective

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histopathological evaluation of gall bladders has been advocated by some authors<sup>[8-11,13-15]</sup>. They argued that it is unnecessary to submit every specimen of gallbladder for histopathology because of economical implication on a larger scale and low prevalence of this disease. Moreover, patients with IGBC usually have suspicious features either on preoperative scans or intra-operatively.

In the presence of these controversies, this study aims to determine the incidence of IGBC in our set-up and to assess the need of routine histopathological examination of all gallbladder specimens after cholecystectomy for benign gall stone diseases.

## SUBJECTS AND METHODS

This retrospective study included all the patients who underwent elective or emergency cholecystectomy for gallstone disease at King Saud Medical City, Riyadh, Saudi Arabia between January 2012 and September 2015. Patients with preoperative suspicion of gallbladder cancer on imaging, or underwent cholecystectomy for gallbladder polyps or porcelain gallbladder were excluded from the study. In our institute, all gallbladder specimens are retrieved in endo-bags, these are opened, flushed with saline and inspected by the operating surgeon for any suspicious pathology (focal or diffuse wall thickening, raised mucosal plaques, polypoid lesions, mucosal ulceration, or any infiltrating masses). Stones are collected in a separate container, and all GB specimens are submitted for routine histopathological examination.

Medical records of all the patients who underwent gall bladder surgery for stones were reviewed and the data regarding age, gender, clinical features, preoperative scan findings, intra-operative findings, type of operative procedure, gross morphology of gallbladder, histopathology reports and the management of patients with IGBC were collected. Details of macroscopic abnormalities were collected from the surgeon's operative notes and from the pathology reports. Patients with IGBC were compared to those patients without IGBC to identify the potential risk factors for malignancy.

All patients who proved to have IGBC were subjected for staging, by using Computed Tomography (CT) Scan and Magnetic Resonant Imaging (MRI). The American Joint Committee on Cancer; Tumor, Node and Metastases (TNM) classification was used for the staging of the gallbladder cancer. Furthermore, these cases were enrolled for discussion in multidisciplinary team meeting, comprising of hepatobiliary surgeon, histopathologist, radiologist and oncologist. All patients were followed up to September 2015 or until death. Ethical approval was obtained from the hospital research and ethical committee before

commencement of this study. Data was analyzed by using Statistical Package for the Social Science (SPSS) version 17. Probability value (P value) of less than 0.05 was considered as statistically significant.

## RESULTS

Between January 2012 to September 2015, 2396 patients underwent cholecystectomy for gallstone diseases in our institute. The median age of patients with benign gall stone disease and patients diagnosed to have IGBC was 46 and 73 years respectively (P = 0.0001). Females outnumbered the male patients with IGBC (2:1). However, this ratio in patients with benign gall stone disease was 1:5. All gallbladder specimens were sent for histopathological examination. IGBC was detected in nine gallbladder specimens (0.38%); eight were adenocarcinomas and one adeno-squamous carcinoma. The incidence of IGBC in emergency and elective cholecystectomy was 1.58% and 0.27% respectively (P = 0.0298). Further detail of histopathological reports of all gall bladder specimens is described in Table 1.

**Table 1:** Histopathology of gallbladder specimens (N = 2396)

Histopathology	n (N = 2396)	Percentage
Chronic cholecystitis	1926	80.3
Acute on chronic cholecystitis	52	2.2
Acute cholecystitis with mucocele	108	4.5
Acute cholecystitis with empyema	29	1.2
Chronic cholecystitis with cholesterosis	243	10.14
Xanthogranulomatous cholecystitis	29	1.2
Chronic cholecystitis with gallbladder cancer	9	0.38

The gall bladder wall thickness ranged between 2.3 to 6.4 mm in preoperative ultrasound of patients with IGBC. Operative notes revealed the successful completion of laparoscopic procedure in four patients, who had IGBC with a conversion rate of 56%, which was significantly higher than patients with benign gall stone disease (P = 0.0041). Reason of conversion was difficult dissection in all the patients, due to fibrous adhesion, bleeding and obscured anatomy of Callot's triangle. Out of 2396 patients, morphologic abnormalities were observed in 518 specimens (22.6%). All GB specimens with IGBC showed morphologic changes. Wall thickening of the gallbladder was the most commonly found abnormality. Others were ulceration, masses, mucosal irregularity, modularity, polyps, calcification, and fistulation (Table 2). There was not a single reported case of IGBC with normal appearance of gallbladder specimen.

The detail of tumor staging in these nine patients is enumerated in Table 3. Cholecystectomy was the only treatment offered to five patients with stage T1b. Three patients, who had stage T2, were re-operated

**Table 2:** Morphologic appearance of gallbladder specimens

Morphologic appearance of gallbladder	No of patients	No of IGBC
A) Normal	1878	0
B) Abnormal	518	9
1. Thickening of gallbladder wall	518	
2. Irregularity	265	
3. Calcification	37	
4. Ulceration	27	
5. Polyps	14	
6. Nodularity	12	

and underwent segmental liver resection (segments V and IV b) and a patient of stage T3 disease received palliative chemo-radiotherapy and prophylactic endoscopic biliary stenting. Six (67%) patients with IGBC died during the study period. Five patients died from the recurrent disease, and one patient died due to postoperative massive pulmonary embolism after liver resection. The mean postoperative survival was 14.8 months (range 6.3 – 28.2 months). The average cost of processing and time spent on one gall bladder specimen was 20 USD and 20 minutes respectively. Thus we could have saved about 37,560.00 USD and 626 working hours of pathologists during the period of 3.5 years by adopting selective pathological examination of abnormal looking specimens.

of all gall bladder specimens has been a standard practice across the globe to detect IGBC<sup>[5-7,15,18-20]</sup>.

However, an increasing body of literature has found this practice unnecessary, as it is unlikely to have IGBC in normal looking gall bladder, especially in younger patients. Hence, a selective approach has been proposed by various authors taking into consideration the economical implication on a larger scale and low prevalence of the disease<sup>[5,8-11,13-15]</sup>. The true incidence of IGBC is unknown, but the reported incidence varies globally between 0.19% to 2.9%<sup>[5,21]</sup>. An incidence of 0.38% in our study is consistent with the literature<sup>[5,21]</sup>.

The distribution of GBC varies across the globe. A higher incidence of GBC is noted in North India, Pakistan, East Asia, Eastern Europe and South America, while it is rare in most of Northern Europe and North America<sup>[5,22]</sup>. Pitt SC *et al* demonstrated in their study that African Americans and Asian races were associated with increased risk of IGBC. They further defined pre-operative predictors of IGBC which included, age of 65 years or older, American Society of Anesthesiologists class 3 or more, diabetes mellitus, hypertension, weight loss more than 10%, alkaline phosphate level 120 units/L or more, and albumen levels 3.6 g/dl or less<sup>[21]</sup>.

Gallbladder cancer is very rare below the age of 50 years and the incidence increases rapidly above

**Table 3:** Details of patients with incidental gallbladder cancer

S/No	Age/ Gender	Nationality	Indications of cholecystectomy	Morphologic changes	Operative procedure	Stage
1	67/F	Saudi	Gallstone pancreatitis	Wall thickening	Laparoscopic cholecystectomy	T1b
2	68/F	Saudi	Acute cholecystitis	Wall thickening and nodular mass in neck	Converted to open cholecystectomy	T2
3	71/M	Indian	Biliary colic	Wall thickening	Laparoscopic cholecystectomy	T1b
4	73/F	Saudi	Biliary colic	Wall thickening	Converted to open cholecystectomy	T2
5	76/F	Saudi	Biliary colic	Wall thickening and ulceration	Converted to open cholecystectomy	T2
6	76/M	Egyptian	Biliary colic	Wall thickening & hard calcification	Converted to open cholecystectomy	T1b
7	78/F	Saudi	Acute cholecystitis	Wall thickening	Laparoscopic cholecystectomy	T1b
8	81/M	Saudi	Biliary colic	Wall thickening	Laparoscopic cholecystectomy	T1b
9	83/F	Saudi	Acute cholecystitis	Wall thickening, mass and fistulation	Converted to open cholecystectomy	T3

## DISCUSSION

Gall bladder cancer is the 5<sup>th</sup> most common cancer involving the gastrointestinal track (GIT). It is usually diagnosed at an advanced stage and therefore carries a dismal prognosis, having five years survival rate of less than 5%<sup>[12]</sup>. However, five years survival improves significantly (90% - 100%), if GBC is detected at an early stage<sup>[16]</sup>. Early diagnosis of GBC is extremely difficult, because its presentation mimics gall stone related symptoms. It is usually discovered as an incidental finding on routine histopathology of gallbladder specimen after cholecystectomy for symptomatic cholelithiasis<sup>[7,17]</sup>. Therefore, a routine histopathology

the age of 60 years<sup>[23]</sup>. Recently, Elshaer M *et al* concluded in their study that age could be used as a significant factor for selective approach of histological examination of gallbladder specimens<sup>[10]</sup>. In our study, none of our patients below the age of 60 had IGBC. We think it is unnecessary to send a normal looking specimen for histopathology after a straightforward laparoscopic cholecystectomy in a young patient.

We found that preoperative ultrasound findings in all the cases of IGBC were not helpful in raising the high index of suspicion for gallbladder cancer. These findings are in accordance with the literature<sup>[6,7]</sup>. Most of the studies described that all their cases of IGBC had

macroscopic abnormalities on gross examination<sup>[8-10]</sup>. A total of 518 gallbladder specimens (21.6%) showed macroscopic abnormalities in our study. IGBC was found in nine out of 518 specimens. The most common morphological abnormality in these cases was wall thickening followed by other abnormalities such as mucosal irregularity, nodularity, ulceration, polyps, fistulation, perforation and calcifications. We did not find any case of IGBC in normal looking specimen. Therefore by excluding about two third of the patients with normal looking gallbladders from histopathology, we could save a significant amount of resources and reduce the work load of pathologists.

The main concern raised by the proponents of routine examination is about the presence of dysplasia and early mucosal malignant lesion (Tis and T1A) in macroscopic normal gall bladder, which could be missed by practicing the selective approach and eventually leading to disastrous results, when diagnosed later as recurrent disease<sup>[5]</sup>. This is responded by the argument that this group requires only simple cholecystectomy as a curative treatment. They don't require any further surgery because re-operation and radical resection doesn't improve their quality of life and long term survival<sup>[12,24]</sup>.

Xanthogranulomatous cholecystitis and Mirrizi syndrome have been reported to have an increased association with gallbladder carcinoma<sup>[25-27]</sup>, yet not a single case of IGBC was found among 29 patients with xanthogranulomatous cholecystitis in our study. However, routine histopathological examination is highly recommended in these scenarios. Patients with IGBC were more likely to have cholecystectomy as an emergency surgery, with high proportion of difficult cholecystectomies and high conversion rate from laparoscopic cholecystectomy to open surgery<sup>[6-9,21]</sup>. Similar findings have been noted in our study.

The treatment of gallbladder cancer depends on the stage of disease at diagnosis. Simple cholecystectomy is considered sufficient for patients with Tis and T1a tumors. However, surgical options for T1b is still debatable; some consider simple cholecystectomy is adequate while the others recommend radical cholecystectomy. T2 tumors are universally treated with radical cholecystectomy (cholecystectomy, lymphadenectomy and liver bed resection). Radical resection or only palliative care, both are acceptable management options in more advanced cases<sup>[12,24]</sup>. Adjuvant chemo-radiotherapy was not found to improve the survival<sup>[12]</sup>. In our study, 5 patients were staged T1b, and had simple cholecystectomy, while three patients, underwent hepatic segmentectomies (segment V & IVb) for stage T2 disease. Only one patient with stage T3 received palliative chemo-radiotherapy and prophylactic endoscopic biliary stenting.

Routine histopathology is associated with significant increase in the work load and cost of treatment. In our institution, the average cost of processing and time spent on each specimen was 20 USD and 20 minutes respectively. About 77% of our patients had normal looking specimens. Thus we could have saved about 37,560.00 USD and 626 working hours of pathologists during the period of 3.5 years by adopting the elective approach. Emmett CD *et al* in their recent study predicted a saving of 25,500 British Pounds per annum by adopting the selective approach<sup>[8]</sup>. Similarly Mittal T also reported a significant reduction in the overall cost and work load of histopathologists by practicing selective approach<sup>[9]</sup>. We think that all the specimens should be opened by the operating surgeons for a detailed macroscopic mucosal examination. All specimens with macroscopic abnormalities, or normal looking gall bladders in high risk patients should be sent for histopathology.

We acknowledge certain limitations in our study. First, the most important is the retrospective study design, similar to most of the studies in literature. Secondly, our findings are from a single institution of the central region of Saudi Arabia, and these findings may not be generalized to other regions. Given the low incidence of IGBC; multi-centric prospective trials are required to eliminate the heterogeneity bias and to evaluate the real impact of selective histological approach on the outcome of patients.

## CONCLUSIONS

The incidence of IGBC was 0.38%. All cases of IGBC were detected in abnormal looking thick wall gall bladder. Routine histopathological examination of normal looking specimens, especially in young patients, is certainly unnecessary. Old age, female sex, difficult surgery, conversion to open surgery, emergency surgery and macroscopic morphologic abnormalities are identified as the considerable risk factors for IGBC. Therefore, a selective histopathological approach in macroscopic abnormal looking specimens and in high risk patients is recommended to reduce the cost and work load of pathologists without compromising the safety of patients.

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## Case Report

# Bizarre Parosteal Osteochondromatous Proliferation (Nora's Lesion) of the Forefoot: Case Report and Review of the Literature

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### ABSTRACT

Bizarre parosteal osteochondromatous proliferation, also known as Nora's lesion, is a benign, surface growing tumor of unknown etio-pathogenesis, most commonly involving small tubular bones of the hand and feet. It is a rare entity with less than 200 cases being reported so far in international literature. Clinically as well as radiologically, it closely mimics other surface growing tumors of the bone. This resemblance to other lesions and its rare occurrence often leads to its misdiagnosis. Recurrence rate is high after

excision and varies from 20% to 55% in different series, so accurate diagnosis and proper preoperative planning to remove the lesion en-block is the key. Histopathology is the key to the diagnosis. Presently, research is going on about chromosomal aberrations that have been found to be associated with this entity.

We here present a twenty year old male with Nora's lesion of proximal phalanx of the fourth toe that was preoperatively mistaken for an osteochondroma or surface chondroma.

KEY WORDS: blue bone, BPOP, chondroma, osteochondroma, parosteal

### INTRODUCTION

Bizarre parosteal osteochondromatous proliferation (BPOP) or Nora's lesion was first described in literature by Nora *et al* in 1983 as a very rare benign, parosteal, exophytic neoplasm of unknown etio-pathogenesis usually involving short tubular bones of extremities and less commonly, long bones and skull-facial bones<sup>[1-4]</sup>. So far less than 200 cases of BPOP have been reported in international literature<sup>[2,5,6]</sup>. Clinically and radiologically, Nora's lesion mimics numerous benign and malignant lesions. Because of its rare occurrence and resemblance with other lesions, the diagnosis of this entity is difficult and often missed<sup>[7,8]</sup>. Currently, marginal excision is the treatment of choice but recurrence rate is high<sup>[8,9]</sup>. Histopathology of the specimen is the key to confirm the diagnosis<sup>[10,11]</sup>. Here we present a case of BPOP of forefoot in a 20 year old male that was misdiagnosed as an osteochondroma or a

periosteal chondroma preoperatively. Histopathology of the excised specimen however, had features of BPOP.

### CASE REPORT

Twenty year old male patient presented to us with chief complaint of progressively increasing swelling of left foot and problems in shoe wear for the last three years. There was no history of trauma in the past. There was no history of similar swelling in any other part of the body. None of the family members had history of such swellings. On clinical examination, there was a lobulated swelling 4 cm × 2.5 cm at the base of the second toe and first web space of the left foot (Fig 1). The overlying skin was normal. On palpation, swelling had bone like consistency and was immobile. There was no neurovascular deficit of the toes. Movements of toes were within normal range.

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Fig 1: Clinical photographs of the forefoot swelling

Routine baseline investigations and inflammatory markers were within normal range. Chest radiograph was unremarkable. Radiograph of the left forefoot had opacity with fine trabeculae suggestive of a bone like mass arising from proximal phalanx of second toe with scalloping of the outer surface of the cortex of the phalanx (Fig 2). There was no cortical destruction, erosions or periosteal reaction of the phalanx. From this clinico-radiological picture, a differential diagnosis of an osteochondroma and periosteal chondroma was made. Magnetic resonance imaging (MRI) of left foot was advised but the patient refused because of financial constraints. Marginal excision of the tumor was planned.

The tumor was approached dorsally. The surface of the mass was smooth, lobulated and had greyish tinge (Fig 3). The mass was attached to the shaft of proximal phalanx of second toe, from which it was excised (Fig 3). The surrounding periosteum was excised and the superficial dorsal cortex of phalanx was shaved off by a chisel. Excessive skin was excised and the wound was closed (Fig 4). The excised mass was sent for histopathologic examination (Fig 4). The histopathology showed a disorganised mixture of cartilage, bone and fibrous tissue. Cartilage component



Fig 2: Antero-posterior and lateral view radiographs of foot showing a calcified mass arising from proximal phalanx of the second toe. There is scalloping of the cortex of the phalanx (bottom row)

was composed of large chondrocytes which were occasionally binucleate. There was immature bone trabeculae interspersed in fibrous tissue. Underlying the cartilage was a blue staining zone with islands of chondrocytes. Haematopoietic tissue was absent in between trabeculae; instead there was connective tissue element consisting of elongated spindle cells. However, nuclear atypia and areas of necrosis were absent. This microscopic picture led to final diagnosis of Nora's lesion. The patient was followed up for one year and there were no features of recurrence, after which follow up was lost.

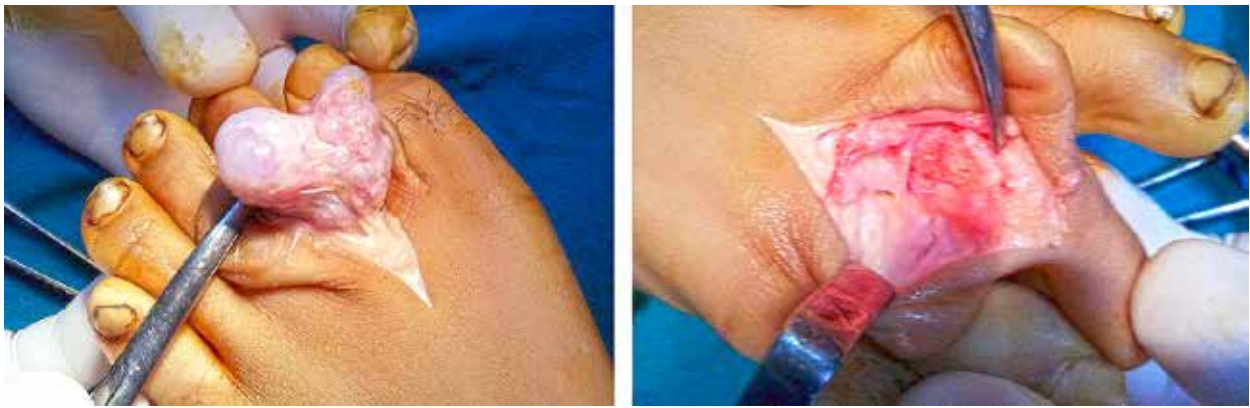


Fig 3: Tumor exposed from dorsal surface of the foot (upper row). Cortical surface after excision (bottom row)



Fig 4: Final appearance after closure of the wound (upper row). Excised mass specimen (bottom row)

## DISCUSSION

Bizarreparostealosteochondromatousproliferation (BPOP) is a rare tumor which was first described in 1983 by Nora FE *et al* and hence the eponym Nora's lesion<sup>[1]</sup>. Series of 35 cases by Nora FE *et al* in 1983, 65 cases by Meneses *et al* in 1993, 24 cases by Dhondt *et al* in 2006, 22 cases by Berber O in 2011, 13 cases by Joseph J *et al* in 2011 and 12 cases by Abramovici L in 2002 are the only large series of BPOP in international

literature and the rest of the literature is limited to isolated case reports and small case series<sup>[1, 3, 4, 9, 11, 12]</sup>.

BPOP is a benign lesion composed of cartilage, bone and fibrous tissue that presents as an exophytic growth from the cortical surface of small tubular bones of hand and feet<sup>[2, 13]</sup>. Hands are four times more commonly involved than feet. Proximal phalanges, middle phalanges, metacarpals, and metatarsals are the sites of predilection. Cases with involvement of long bones, skull bones, clavicle, maxilla, mandible and sesamoid have been reported in literature<sup>[3, 4, 13-23]</sup>. It can occur at any age, with patients between 4 and 78 years being reported, with highest incidence between 20 to 35 years<sup>[8, 24-26]</sup>. Frequency is equal in both sexes<sup>[25, 27]</sup>. Presentation is that of a swelling that grows over months to years with or without pain<sup>[4, 11, 28]</sup>.

The exact aetio-pathogenesis of the lesion is not known<sup>[8, 29]</sup>. Many believe trauma as a trigger, and consider, it represents a reactive lesion in response to trauma like florid reactive periostitis and Turrets exostosis<sup>[30, 31]</sup>. However, history of trauma is an inconsistent feature. In the series by Nora *et al*, no case had history of trauma, while as in that of Meneses *et al* and Joseph J *et al*, 30% and around 20% had history of antecedent trauma respectively<sup>[1, 4, 9]</sup>. Moreover, the discovery of cytogenetic aberrations in these lesions favours a neoplastic aetiology rather than a reactive one. Different chromosomal aberrations have been reported, but t (1:17) (q32; q31) constitutes specific translocation for BPOP<sup>[27, 32-35]</sup>.

Radiology demonstrates a well demarcated mineralized mass arising from the periosteal cortical surface with maintenance of integrity of the underlying cortex. Cortico-medullary continuity, a feature of osteochondroma is characteristically absent<sup>[8, 11, 18, 25]</sup>. However, cases of histologically proven BPOP with cortico-medullary continuity have been reported in literature<sup>[8, 36]</sup>. Cortical scalloping, a feature of periosteal chondroma, cortical flaring and periosteal reaction seen in osteosarcoma are absent. In our case, presence of fine trabeculae in

the mass on radiography favoured the diagnosis of osteochondroma. However, cortical scalloping and absence of cortico-medullary continuity on the other hand suggested periosteal chondroma. BPOP with scalloping of the outer surface of cortex have been reported in literature.<sup>[9]</sup> BPOP with atypical radiological findings have been reported in the past<sup>[5,8,37,38]</sup>. Unfortunately a CT and or MRI could not be obtained in our case for confirming the findings.

Nora's lesion can mimic a number of reactive, benign and malignant lesions of the bone. The reactive lesions which resemble BPOP include florid reactive periostitis, subungual exostosis, Turret exostosis and myositis ossificans. Benign tumors of bone showing resemblance to BPOP are osteochondroma and surface chondroma. Surface chondrosarcoma, periosteal and parosteal osteosarcoma are the malignant bone tumors that can be mistaken for a BPOP<sup>[7,39,40,41]</sup>. Differentiation from malignant lesions is important for treatment purpose in order to avoid unwanted destructive surgery and from benign ones to prevent recurrence<sup>[42]</sup>.

Histopathology is confirmatory and differentiates BPOP from other lesions<sup>[10,11,43]</sup>. It consists of a disorganised proliferation of cartilage, bone and fibrous tissue<sup>[4,40]</sup>. The lesion typically consists of four layers, namely surface layer of thick fibro connective tissue with scattered scanty chondroblasts, underlying irregular cartilaginous cap with atypical, bizarre and occasionally bi-nucleate chondrocytes, zone of 'blue bone' considered hallmark of BPOP having islands of atypical chondrocytes still present but decrease in number until they disappear in the deepest layer and lastly the zone of mature pink bone which contain osteoblast rimmed trabeculae<sup>[2-4,41,44]</sup>. Both blue and pink bone encloses a myxoid connective tissue stroma in the intratrabecular spaces in place of hematopoietic tissue, which is present in osteochondroma and hence a differentiating feature<sup>[44]</sup>. Atypical mitosis or cellular atypia is characteristically absent<sup>[6,11]</sup>.

Surgery is the mainstay of treatment, even in asymptomatic cases<sup>[45]</sup>. There is controversy regarding treatment with advocates of both marginal as well as radical excision<sup>[11]</sup>. Local recurrence rate after surgery is high, ranging from 22 to 55% in different series and hence some surgeons favour the radical approach of treatment<sup>[7,11]</sup>. However, marginal excision still remains the mainstay of treatment<sup>[9]</sup>. Radical surgical approach is recommended for tumors with aggressive behaviour and intramedullary extension<sup>[8]</sup>. Recurrence is seen within months to two years after primary excision<sup>[6]</sup>. Local excision is advocated for recurrence rather than an aggressive approach<sup>[4,26]</sup>. Complete removal of pseudo-capsule, resection of periosteum underneath the tumor and decortications

of underlying bone is the key to prevent recurrence<sup>[5,8]</sup>. Nora's lesion is a benign lesion and metastasis is not a feature. It is not pre-malignant<sup>[22]</sup>. However, one case of malignant transformation to fibrosarcoma has been reported in the literature<sup>[46]</sup>.

## CONCLUSION

Nora's lesion of the bone is a rare lesion that can easily be misdiagnosed as osteochondroma or a surface chondroma. Presence of atypical features like scalloping of cortex, cortico-medullary continuity, flaring of the cortex with the tumor can further make radiological diagnosis difficult. Nora's lesion should always be kept as a differential in case of surface growing tumors of short tubular bones of the extremities. Histopathology of the excised lesion is confirmatory. Presently, detection of cytogenetic aberrations in the lesion is under research and may be of great benefit in the near future.

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## Case Report

# A Rare Cause of Pneumoperitoneum – A Ruptured Infected Endometriotic Cyst

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### ABSTRACT

Pneumoperitoneum is a surgical emergency that results from gastrointestinal tract perforation, most commonly perforation of the duodenum caused by peptic ulcer. It rarely results from nonsurgical causes. We present

a case of rupture infected endometriotic cyst that was presented as acute abdomen with pneumoperitoneum in which exploratory laparotomy was done with salpingo-oophorectomy.

KEY WORDS: acute abdomen, endometriotic cyst, pneumoperitoneum

### INTRODUCTION

Pneumoperitoneum is the result of a gastrointestinal (GI) tract perforation in more than 90% of cases<sup>[1,2,3]</sup>. Perforation of the stomach or duodenum caused by peptic ulcer is considered the most common cause<sup>[1]</sup>. It can also be the result of a ruptured appendicitis or diverticulitis or of an abdominal trauma<sup>[1]</sup>. About 10% of pneumoperitoneum incidents are caused by nonsurgical reasons, in which surgical intervention is usually not required<sup>[1,2,4]</sup>. The reported causes of nonsurgical pneumoperitoneum include: thoracic causes (chronic obstructive pulmonary disease, pneumothorax, cardiopulmonary resuscitation), abdominal causes (connective tissue disease, perforated liver abscess, ruptured necrotic lesion of a liver metastasis, emphysematous cholecystitis, spontaneous bacterial peritonitis, pneumatosis cystoides intestinalis, previous abdominal surgery with retained postoperative air, peritoneal dialysis, endoscopic GI procedure), gynecological causes (pelvic inflammatory disease, recent vaginal examination, perforated pyometra, rough sexual intercourse) and other causes such as jacuzzi usage and scuba diving<sup>[1,2,4]</sup>. The endometriosis is a common gynecological disorder that affects women of reproductive age and characterized by endometriomas (chocolate cysts), peritoneal implant and adhesions. Endometriomas

are complex lesions containing multiple hemorrhagic cysts that contain blood products of different ages within them<sup>[5,6]</sup>. Although the disease is recognized as benign, endometriosis is occasionally accompanied by malignant ovarian tumors, especially endometrioid and clear cell adenocarcinoma<sup>[5,6]</sup>. We present a case of ruptured infected endometriotic cyst that was presented as an acute abdomen with free air under the diaphragm on upright chest X-ray.

### CASE REPORT

A 55-year-old Filipino lady was presented to our emergency department on the 4<sup>th</sup> of July 2014 complaining of abdominal pain, fever, nausea, vomiting, and constipation since four days. The pain was dull aching in nature, generalized, maximum on the lower abdomen, increasing in intensity and associated with distension. She is divorced with no children and had a regular menstrual cycle which stopped two months back. On examination, the abdomen was markedly distended, and tense with guarding and rigidity, maximum in the lower abdomen with absent bowel sounds and empty rectum on digital rectal examination. Vitally she was feverish with a temperature of 39.1 °C and tachycardic (124 beats/min). Erect chest X-ray showed free air under the diaphragm (Fig 1). Laboratory investigations revealed

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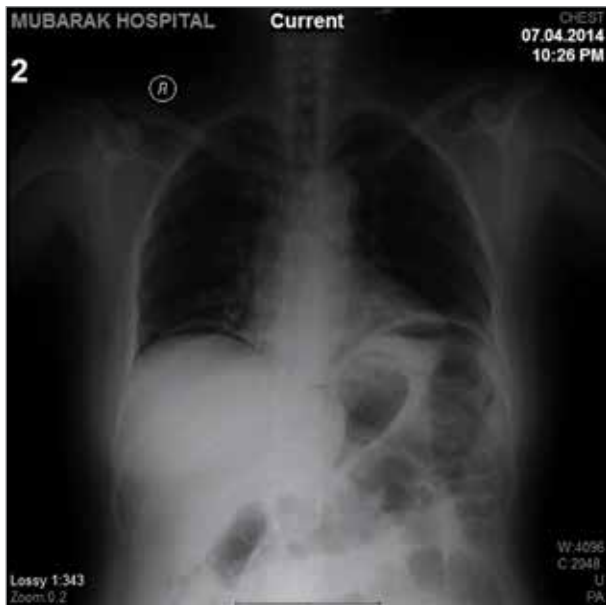


Fig 1: Erect chest X-ray showing free air under the diaphragm

leucocytosis of  $15.5 \times 10^9/L$ , hemoglobin level of 114 g/L and creatinine level of 131  $\mu\text{mol/L}$ . The patient underwent exploratory laparotomy with the diagnosis of a perforated viscus. On exploration, a ruptured left ovarian cyst was found with chocolate paste material and gas spillage from it. No bowel pathology was identified. The gynecologist was contacted who joined the surgery, and left salpingo-oophorectomy was

done with abdominal washing and drain fixation (Fig 2 A&B). The patient tolerated the procedure well. The histopathological examination showed a ruptured endometriotic cyst with suppurative inflammation while the peritoneal swab culture and sensitivity showed *Bacteroides fragilis* species. The CA-125 level was normal.

## DISCUSSION

Endometriosis is defined as the presence of endometrial glands and stroma outside the normal location, which are most commonly found in the pelvic peritoneum, but many can also be found in the ovarian, the rectovaginal septum and the uterus but rarely in the bladder, the pericardium and the pleura. The endometriomas are defined as cystic endometrial lesions which are contained within the ovaries<sup>[7]</sup>. The spontaneous rupture of an endometriotic cyst is very rare. Very few cases have been reported, which usually presents with acute abdominal pain and inflammatory reaction<sup>[7,8]</sup>. It should be dissociated from other causes of acute abdomen such as perforated appendicitis or diverticulitis<sup>[8,9]</sup>. In our case, the endometriotic cyst was infected with *Bacteroides fragilis* species. The *Bacteroides fragilis* is an anaerobic, gram negative bacilli and represents a common cause of endogenous infection in humans<sup>[10]</sup>. It is a component of the normal flora in the human terminal ileum, the colon and the vagina and frequently associated with polymicrobial

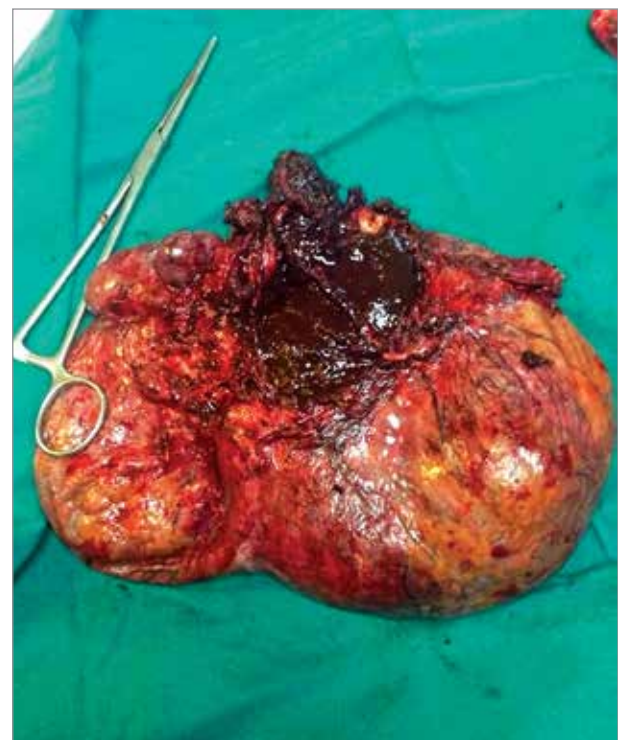


Fig 2: Intra-operative photograph during the dissection of the cyst (A) and the excised cyst (B)



infection such as intra-abdominal, diabetic foot and obstetric-gynecologic tract infection<sup>[10]</sup>. It is considered one of the organisms that are known for gas-producing property in tissue<sup>[11]</sup>. In our case, the rupture of the infected endometrial cyst with gas forming organism lead to an acute abdomen with free gas under the diaphragm. In general, the pneumoperitoneum is commonly present with signs and symptoms of peritonitis, and subphrenic free gas in an upright chest radiograph is the most common radiographic finding<sup>[1,12]</sup>, but abdominal CT is a more sensitive method of diagnosing pneumoperitoneum and identifying the cause of acute abdomen<sup>[13,14]</sup>. The cause of pneumoperitoneum and the clinical presentation determine the mode of treatment, whether surgical or not. When signs and symptoms of acute abdomen are present, surgical management is mandatory, but in case of nonsurgical pneumoperitoneum with mild symptoms and without any signs of peritonitis, conservative treatment is indicated<sup>[15]</sup>. Van Gelder *et al* reported six patients with pneumoperitoneum and clinical signs of acute abdomen who underwent exploratory laparotomy which did not reveal any intra-abdominal pathology<sup>[16]</sup>. Chandler *et al* reported a laparotomy rate of 28% on nonsurgical pneumoperitoneum<sup>[17]</sup>. Mularski *et al* found 196 reported cases of nonsurgical pneumoperitoneum of which 45 underwent surgical exploration without evidence of perforated viscus<sup>[3]</sup>. Furthermore, Mularski *et al* reported that 11 of 36 (31%) miscellaneous or idiopathic causes of nonsurgical pneumoperitoneum underwent surgical exploration<sup>[1]</sup>. In our case, we preferred not to do a CT scan and to go for exploratory laparotomy as the patient was presented with acute abdomen with free air under diaphragm and general picture of sepsis and needed exploration regarding the findings on the CT. A diagnostic laparoscopy is an option for exploration but due to the marked abdominal distension, we preferred the open exploration to avoid any iatrogenic injury.

## CONCLUSION

We present a rare case of free air under the diaphragm, a ruptured infected endometriotic cyst, that can be added to the differential diagnosis of such condition. Exploration is the best way for the diagnosis and treatment.

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## Case Report

# An Unusual *Bacteroides Distasonis* Related Corneal Ulcer: Questions to be Answered

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## ABSTRACT

We herein present an unusual case of *Bacteroides distasonis* related corneal ulcer. A 70-year-old male farmer presented with decreased vision, pain and redness in the left eye that had persisted for 1 week. Ophthalmic examination was highly suggestive of keratitis with corneal ulcer. Empirical fortified antibiotic therapy with fungal coverage was started after corneal swab and microbiological sampling. Since two attempts at pathogen detection were unrevealing and there was no good sign of healing, third attempt was performed with the presence of attending microbiologist. This time, sampling for anaerobic culturing was also performed, which

detected *B. distasonis* as the causative agent. The patient disagreed to be followed as inpatient at this point. Despite pathogen-targeted metranidazole treatment, severe corneal scarring with prominent vascularization was observed forty days after initial presentation. To the authors' knowledge, this is the first reported case of *B. distasonis* related corneal ulcer with a detailed clinical course. In conclusion, it is very crucial to be in close collaboration with the microbiologists to isolate unusual corneal pathogens. Corneal ulcers related with unusual bacterias should be followed up closely with hospitalization.

KEYWORDS: *bacteroides distasonis*, corneal ulcer, keratitis, management, outcomes

## INTRODUCTION

Microbial keratitis can lead to severe visual loss unless diagnosed and treated in a timely manner. In most of the cases, gram positive (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and gram negative aerob bacteria (*Pseudomonas aureuginosa*) are the causative agents<sup>[1]</sup>. Though considered as infrequent, anaerob bacteria can be found as the sole causative agent or a component of polymicrobial infection in a substantial proportion of the cases<sup>[2,3]</sup>. However, there are few reports primarily focused on the course of a keratitis associated with anaerobic etiology<sup>[4]</sup>. We herein present and discuss an unusual *Bacteroides distasonis* related corneal ulcer.

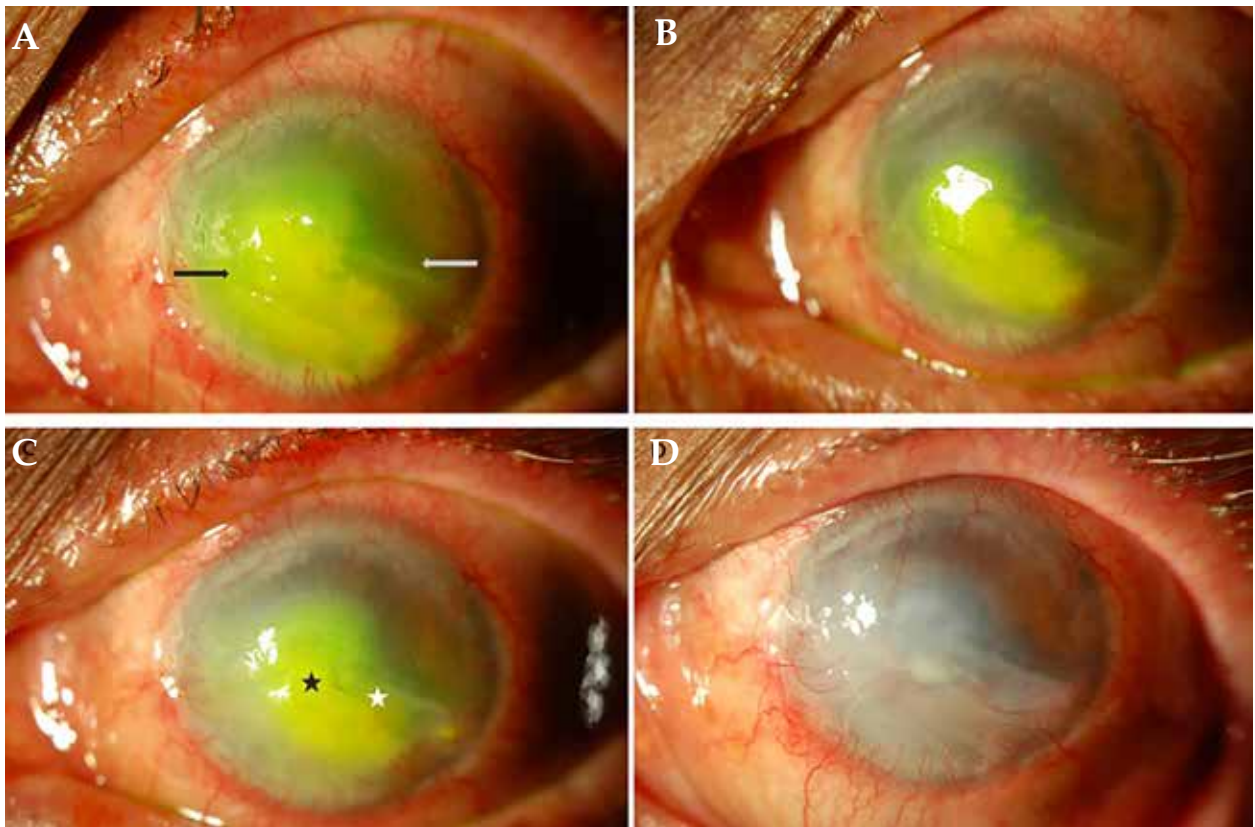
## CASE REPORT

A 70-year-old male farmer presented with decreased vision, pain and redness in the left eye that had persisted for one week. Except for the history

of bilateral cataract surgery one year ago, he did not report any previous ocular trauma or ocular surface disease on both eyes. His medical history was only significant for high blood pressure under control with oral treatment. The corrected distance visual acuity was 20/25 in the right eye, and counting fingers at 50 centimeters in the left eye. There were no pathological findings for the contralateral eye. On examination, an eyelid edema, mixed conjunctival injection, chemosis, infiltration of the corneal stroma with a central annular ulcer reaching to inferotemporal limbus, neighbouring wedge-shaped ulcer pointing out to the pupilla, edema of the epithelium, and beginning 360 degree vascularization of the limbal area were recorded in the left eye (Fig 1A). The sensibility of the cornea was intact and equal sensibilities on both eyes. After consultation with the cornea specialist, fortified antibiotic treatment (vancomycin 5 mg/ml and tobramycin 9 mg/ml) was started on hourly regimen promptly after superficial

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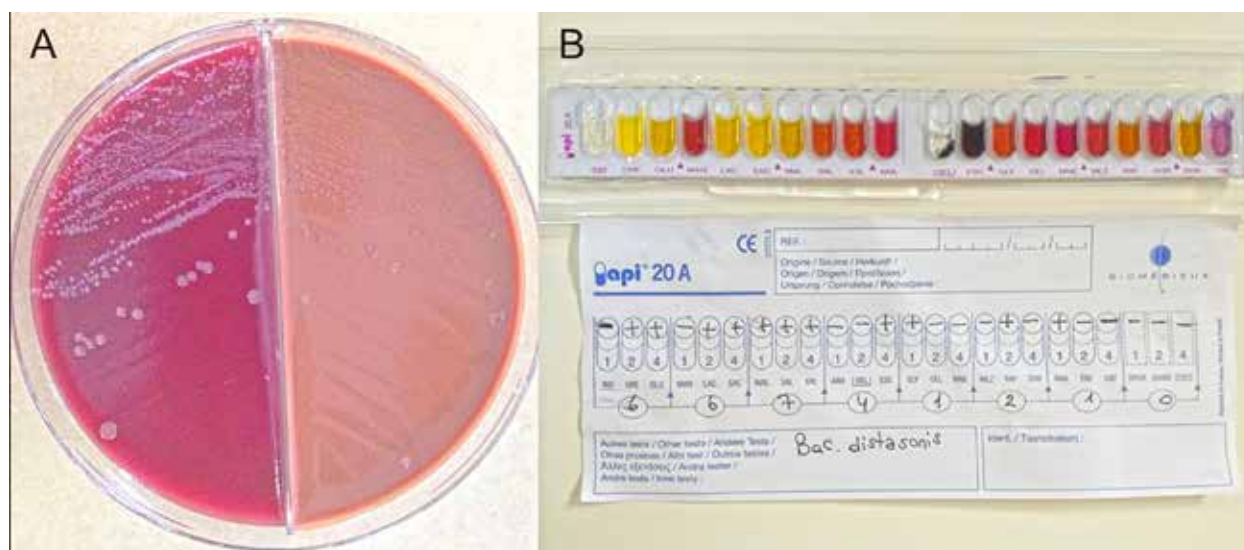
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**Fig 1:** (Slit lamp pictures): (A) taken at initial presentation showing corneal ulcers (black arrow: annular ulcer and white arrow: wedge-shaped ulcer), (B) taken two days after empirical fortified antibiotic therapy showing no satisfactory improvement in ulcer morphology, (C) taken five days after pathogen-targeted metranidazole treatment showing decrease in size of annular ulcer, but enlargement of wedge-shaped ulcer (black asterisk: annular ulcer and white asterisk: wedge-shaped ulcer), (D) taken forty days after presentation showing severe corneal scarring with vascularization

corneal swab. Topical flucanazole 0.2% was added because of suspicion of a fungal etiology. The swabs were inoculated onto blood agar, chocolate agar, and Sabouraud's Dextrose Agar (SDA) making multiple "C" shaped marks. Some of the specimens were separated for Gram's staining and 10% KOH wet mounting procedure. Blood agar and chocolate agar plates were incubated at 37 °C temperature, while SDA was incubated at 25 °C. The cultures were examined after 24 hours on incubation. If organism had not grown, plates were further incubated and finally proclaimed as culture negative after 48 hours. The cultures (SDA) were examined daily for the growth of fungus for up to 10 days and declared as fungal culture negative after 10 days. As the first attempt for culturing was negative, corneal scraping with a surgical blade was performed and scrapings were reexamined with the same culture and staining. Though we insisted, the patient did not accept any hospitalization, and was followed as outpatient. As both the culture results were negative, and there was no improvement at forty-eight hour control, corneal scraping was repeated with the presence of attending microbiologist (Fig 1B).

This time, in addition to the previous inoculations, Columbia Agar and Thioglycolate Broth inoculations were also performed for anaerobic bacteria. Columbia Agar and Thioglycolate broth were placed in anaerobic jar with a gas pack (AnaeroGen gas pack, Hampshire, United Kingdom) to deplete the oxygen. Anaerobic jar, blood agar and chocolate agar plates were incubated at 37 °C temperature in a standard incubator. SDA was incubated at 25 °C. Growth of small to medium, convex, semiopaque, entire edge colonies was detected after the second day of incubation on Columbia agar. Single colonies were collected and tested with the API 20A identification card (bioMerieux, France). These colonies were identified as *B. distasonis* by using the API 20A anaerobic bacteria identification test (Fig 2). No bacteria were observed in microscopic examination. Susceptibility tests performed by the agar dilution method revealed susceptibility to clindamycin, tetracycline, amoxicillin/clavulanic acid and metronidazole. Soon after obtaining the results, treatment was changed to topical metranidazole 1% and moxifloxacin 0.5% on an hourly regimen. Five days after this treatment, there was decrease in the size of



**Fig 2: (A)** Colonies on blood agar and chocolate agar (Salubrius, Istanbul,Turkey) are small to medium. They lack pigmentation and are semiopaque. Colonies are circular in form with an entire margin. They have a convex elevation; **(B)** These colonies from blood agar were subjected to biochemical analysis by API 20A identification card (bioMerieux, France). The colonies was identified as *B. distasonis* by API 20A with a high probability (99%).

the annular ulcer, but increase in the size of the wedge-shaped ulcer (Fig 1C). In the mean time, questioning for non-compliance with the treatment was inconclusive. Therefore, we proceeded with diagnostic corneal biopsy after two day holiday from eye drops, results of which were unrevealing. Treatment was started again with the addition of topical flucanazole 0.2%. The frequency of both eye drops was reduced in order to avoid toxicity. Forty days after the presentation, visual acuity was hand motion at 10 centimeters, and all the cornea but a small area in the upper part was scarred with prominent vascularization and some intrastromal hemorrhage (Fig 1D). The patient did not accept any corneal trasplantation surgery at this stage.

## DISCUSSION

After three attempts at culturing, we were able to isolate *B. distasonis* from corneal ulcer. Despite starting metranidazole therapy after a reasonable period from presentation, the medication did not lead to any improvement. Questions are: 1) Did we use the appropriate antibiotic with appropriate concentration?; 2) Did we miss the other pathogens involved in this case?; 3) Were we supposed to add topical steroid to antimicrobials to avoid scarring? 4) What could be the other diagnostic or therapeutic options? These questions are discussed below.

Though the evidence-based data is lacking, it is shown that 1% concentration of metranidazole has good corneal penetration<sup>[5]</sup>. Moreover, in one study, all *B. distasonis* isolates were susceptible to metranidazole<sup>[6]</sup>. Therefore, our isolate was susceptible to metranidazole and the authors are of the opinion

that metranidazole was one of the best options for the targeted therapy. However, we can't be sure that the patient followed the treatment recommendations since he did not accept hospitalization.

In the case of such a complicated corneal ulcer, one should bear in mind that there may be some other aerobic or anaerobic pathogens involved. However, identification of all is often difficult as some have special growth requirements and sample size from ocular tissues is relatively small. Some molecular methods like PCR may be very helpful, but its high sensitivity can be misdirecting in such a way that it can detect small nuclear fragments from secondary colonization of the ulcer<sup>[7]</sup>. It is also possible for this case to have *B. distasonis* as a secondary colonization of an aerobic corneal infection. However, he presented with a 1-week history of corneal infection without any treatment, and three attempts at culturing were negative for any other aerobic bacterias. Even so, he was under antibiotic coverage for such a possibility during the course of the treatment.

The use of steroid in conjunction with topical antimicrobials was found to be safe in corneal infections, if there is good evidence of healing after 48-72 hours from initiation of the antimicrobial therapy<sup>[8]</sup>. We did not consider adding steroid as the ulcer was not healing sufficiently well.

Diagnostic corneal biopsy is also highly recommended in recalcitrant cases<sup>[9]</sup>. We opted to submit the specimen for only histopathologic examination as we had already cultured three times. However, the results of the histopathology were not contributory. Some authors support use of collagen

cross-linking in nonhealing corneal ulcers, however, some evidence-based data is yet to be established, and it is not yet available at our institution<sup>[10]</sup>. As the final option for diagnostics, keratoplasty specimen would be submitted for pathology and microbiology, but the patient did not accept any surgery.

## CONCLUSION

To the best of our knowledge, this is the first *B. distasonis* related corneal ulcer case presented and discussed in details. It is very crucial to be in close collaboration with the microbiologists to isolate unusual corneal pathogens. Corneal ulcers related with unusual bacterias should be followed up closely with hospitalization.

## ACKNOWLEDGMENT

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**Conflict of interest:** No conflicting relationship exists for any author

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## Case Report

# FloTrac/EV1000 Guided Management of Amlodipine Induced Refractory Hypotension During Renal Transplantation

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### ABSTRACT

Patients scheduled to undergo renal transplantation are often the most complex ones that an anaesthesiologist may encounter, as intraoperative hemodynamic instability can adversely affect the outcome of renal transplantation. Amlodipine is the commonly prescribed drug to patients with end stage renal disease (ESRD) for control of hypertension. Preoperative use of amlodipine may rarely present as intraoperative hypotension. Amlodipine induced hypotension is usually refractory to commonly

used vasopressors. Combination of calcium, different sympathomimetic agents and fluids with minimal invasive monitoring with FloTrac/EV 1000 can be helpful in this situation. It is important to titrate antihypertensive medications in perioperative period to prevent intraoperative hemodynamic instability during renal transplantation as it can affect the graft function. We report a case of successful management of intraoperative refractory hypotension after therapeutic dose of amlodipine during renal transplantation.

KEYWORDS: amlodipine, floTrac/EV 1000, intraoperative refractory hypotension, renal transplantation

### INTRODUCTION

Refractory hypotension after calcium channel blockers overdose is well known<sup>[1]</sup>, but reports of intra-operative hypotension after therapeutic dose of amlodipine are scarcely reported<sup>[2,3]</sup>. Hypotension due to amlodipine is difficult to treat, as it has a long half-life, high protein binding and large volume of distribution. We successfully managed amlodipine induced refractory hypotension with calcium, different sympathomimetic agents, fluids and FloTrac guided cardiac monitoring during renal transplantation. Patient was discharged with well-functioning graft and good urine output.

### CASE PRESENTATION

A 52-year-old male weighing 60 kg was scheduled for renal transplantation. Medical history included end-stage renal disease secondary to hypertension

and was on maintenance hemodialysis thrice a week. He had no other significant comorbidity. There was no history of allergic reaction to any drug. Preoperative laboratory values were normal except for serum creatinine of 6.22 mg/dl. Preoperative chest X-ray and electrocardiogram (ECG) were normal and echocardiography showed 55% left ventricular ejection fraction with no regional wall motion abnormality. His blood pressure was controlled with amlodipine 5 mg twice a day. It had been 12 hours since his last haemodialysis. On the day of surgery, patient received scheduled morning dose of amlodipine 5 mg at 6:00 am as his blood pressure was 144/84 mmHg. Patient was shifted to operation theatre (OT) at 11:30 am. In OT, patient's heart rate was 90/min and blood pressure was 130/82 mmHg, he was premedicated with glycopyrrolate 0.2 mg and fentanyl 150 µg, general anaesthesia was induced with

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thiopentone sodium 350 mg, and atracurium 30 mg was given to facilitate endotracheal intubation. Oxygen, nitrous oxide, isoflurane and atracurium were used for maintenance of anaesthesia. Monitoring included ECG with automated ST segment analysis,  $\text{SPO}_2$ ,  $\text{ETCO}_2$ , non-invasive blood pressure, airway pressures and temperature. Standard central venous catheter was inserted via right internal jugular vein to measure central venous pressure, which was 12 cm of  $\text{H}_2\text{O}$ .

After induction of anaesthesia, patient's blood pressure gradually decreased to 80/44 mmHg and was not recovered in 10 minutes even though all administered anaesthetic agents were stopped immediately. Ephedrine 5 mg IV bolus twice and fluid challenge with 500 ml of normal saline was given with no effect, then dopamine infusion (10 - 20  $\mu\text{g}/\text{kg}/\text{min}$ ) was started; later on, noradrenaline infusion (0.1 - 1.0  $\mu\text{g}/\text{kg}/\text{min}$ ) and vasopressin infusion (0.01 - 0.05 IU/min) were added one after another, without much improvement in blood pressure. At this time patient's heart rate was 94/min, blood pressure 94/60 mmHg, CVP 16 cm of  $\text{H}_2\text{O}$  and there were no sign of myocardial ischemia on ECG. As hypotension was not responding to usual measures, it was decided to start continuous cardiac monitoring using FloTrac/EV1000 as it is less invasive than conventional cardiac monitoring using pulmonary artery catheter besides it provides stroke volume variation (SVV) which predicts fluid responsiveness. Twenty gauge arterial cannula was inserted in right radial artery and arterial blood pressure was measured using FloTrac transducer coupled to EV1000 clinical platform (Edwards Life sciences, USA). Parameters provided by FloTrac/EV1000 were stroke volume (SV) 41 ml/b, systemic vascular resistance (SVR) 900 dyne-s/cm<sup>2</sup>, cardiac output (CO) 3.8 L/min, cardiac index (CI) 2.5 L/min/m<sup>2</sup>, stroke volume variation (SVV) 5% and CVP 17 cm of  $\text{H}_2\text{O}$ . Dobutamine (10-20  $\mu\text{g}/\text{kg}/\text{min}$ ) infusion was started as SV was low, but without much improvement in blood pressure. Arterial blood gas (ABG) was done which showed normal pH and electrolytes. After excluding all the possible causes of hypotension, it was thought that it may be due to exaggerated effect of amlodipine. Calcium gluconate 10%, 20 ml over 5 - 10 minutes was given and repeated every 10 - 15 minutes for total of three doses, followed by an infusion of calcium gluconate 5 ml/h with serum calcium ranging from 1.21 - 1.35 mmol/L. Patient responded to this treatment and blood pressure gradually increased to 133/74 mm Hg with heart rate 105/min, SV 71 ml/b, CO 7.6 L/min, CI 4.7 L/min/m<sup>2</sup>, SVR 795 dyne-s/cm<sup>2</sup>, SVV 6% and CVP 20 cm of  $\text{H}_2\text{O}$ . As patient was hemodynamically stable, surgery was continued, mannitol 30 gm and furosemide 60 mg IV was given before vascular clamp release and

urine output was established after two minutes. Rest of the surgical course was uneventful and gradually vasopressors were tapered. Surgery lasted for eight hours, at the completion of surgery trachea was extubated with standard doses of neostigmine and glycopyrrolate and patient was shifted to ICU with noradrenaline infusion, in stable haemodynamic condition.

In ICU, ECG and echocardiography was done which did not reveal any abnormality. Simultaneously complete blood count (CBC), and cardiac enzymes levels were also done, which were normal. Noradrenaline infusion was tapered gradually and then stopped after 16 hours as patient was maintaining blood pressure 130/80 mmHg and urine output of 400-500 ml/h and after eight days, patient was discharged with good urine output and serum creatinine 1.9 mg/dl.

## DISCUSSION

Intraoperative hypotension is a known risk factor for delayed or slow graft function and increased vascular thrombosis<sup>[4,5]</sup>. Causative factors should be found and treated immediately. The causes of intraoperative hypotension are multifactorial including anaesthetic overdose, hypovolemia, septicaemia, anaphylaxis, myocardial depression, thromboembolism, pneumothorax, hypothermia and prolonged action of antihypertensive drugs taken preoperatively. In our patient, initial CVP and later on SVV were normal so hypovolemia was ruled out. Pre and post-operative total blood counts were normal so septicaemia seemed unlikely. Anaphylaxis can also cause severe hypotension but there were no clinical signs of anaphylactic reaction so anaphylaxis was excluded. As intraoperative ECG, pre and postoperative echocardiography, post-operative cardiac enzymes were normal, ruling out any cardiac event. Thromboembolism and pneumothorax were also ruled out with normal capnogram, airway pressures, postoperative chest X-ray and echocardiography. Hypothermia may also cause severe hypotension<sup>[6]</sup> but our patient was normothermic through-out the procedure. Next probable cause of hypotension was considered to be exaggerated response to preoperative antihypertensive medication. Patient was on amlodipine 5 mg twice a day for control of blood pressure and had received morning dose preoperatively.

Amlodipine is a dihydropyridine group of calcium channel blocker (CCB) which has higher vascular selectivity and smaller negative inotropic effect compared to other CCB, half-life of amlodipine is 30-50 hours and peak plasma levels are reached after 6 - 12 hours<sup>[1]</sup>. There are many case reports of refractory hypotension after amlodipine overdose<sup>[7]</sup>, but very

few case reports of intra-operative hypotension after therapeutic doses of amlodipine are available in literature<sup>[2,3]</sup>. As there are no clear guidelines, whether amlodipine needs to be withheld on the day of surgery, it is believed that most of the calcium channel blocker can be continued in the perioperative period<sup>[8]</sup>.

In our patient, hypotension occurred 6 - 7 hours after last dose of amlodipine, which coincides with peak plasma level of amlodipine. Amlodipine induced hypotension is usually refractory to different vasopressors, although calcium has a role in improving conduction, contractility and hypotension but optimum dose of calcium is still unclear<sup>[9]</sup>. Kenny *et al* has suggested 10 mL of 10% calcium chloride or 20 - 30 mL of calcium gluconate IV and depending on clinical response to be repeated 15 - 20 minutes up to four doses with monitoring of serum calcium<sup>[10]</sup>. As it remains unclear which sympathomimetic agent is better than other for CCB induced hypotension<sup>[11]</sup>, we had to use combination of different vasopressors and calcium to control severe hypotension.

Routine haemodynamic monitoring parameters (HR, MAP and CVP) are often insensitive and sometimes misleading in the assessment of circulating blood volume. However, the appropriateness of their interventions is often crucial to avoid the deleterious effects of under or over resuscitation. Stroke volume variation (SVV) is not an indicator of actual preload but has been shown to be efficacious in predicting fluid responsiveness<sup>[12]</sup>, and in this regard may serve as an intraoperative tool to guide fluid resuscitation. SVV has been shown to have a very high sensitivity and specificity when compared to traditional indicators of volume status (HR, MAP and CVP) and their ability to determine fluid responsiveness.

To measure SVV and continuous cardiac monitoring, we used newer and advanced FloTrac system consisting of EV1000 platform. FloTrac/EV1000 provides continuous haemodynamic monitoring based on arterial pulse pressure measurement and display key flow parameters like CO, CI, SV, SVI, SVR, SVRI, SVV and Frank-Starling curve.

In our case, when the hypotension was not responding to vasopressors, we started minimal invasive cardiac monitoring using FloTrac/EV1000, it showed SVV 6% which ruled out fluid responsiveness, SV was 41 ml/beat which was below normal, then we started dobutamine followed by calcium gluconate bolus and then infusion 5 ml/hour, after this treatment SV and CO were increased and patient started improving hemodynamically.

## CONCLUSION

We conclude that careful titration of antihypertensive therapy in perioperative period is very important especially in patients who are taking long acting dihydropyridines. Calcium has a significant role in management of amlodipine induced refractory hypotension. During operative situations, where objective determination of cardiac parameters is critical to clinical decision making, cardiac monitoring using FloTrac/EV1000 may improve the outcome in high risk patients undergoing major surgeries.

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## Case Report

# Extraluminal Migrating Esophageal Foreign Body

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### ABSTRACT

Foreign body ingestion is a commonly encountered emergency in otolaryngology practice. The extraluminal migration of esophageal foreign bodies is extremely rare. Although case reports of different foreign bodies migrating out of esophagus are well documented in the literature, potentially life threatening complications are possible due to this migration, especially suppurative and vascular complications such as aorta oesophageal fistula, subclavian-

esophageal fistula and retropharyngeal abscess and that's why removal is essential. This paper reports a very rare presentation of migrating esophageal foreign body that migrates posteriorly to the prevertebral muscles reaching vertebral bodies level, and we report the use of Intra-operative fluoroscopy guidance using metallic probe to locate the exact position of the foreign body during neck exploration.

KEY WORDS: esophagus, metal wire, soft tissue neck

### INTRODUCTION

Foreign bodies that are accidentally ingested and lodged in the esophagus is one of the most common otolaryngological emergency. However, esophageal foreign bodies that perforate and migrate into soft tissues of the neck are rare<sup>[1]</sup>. Literature review showed that most of the migrating foreign bodies are fish bones which are eventually found in the soft tissue of the neck<sup>[2]</sup>. Different presentations of sharp penetrating foreign body in the esophagus are documented. They may become embedded into the deeper layers of the esophagus or sometimes the foreign bodies may penetrate the esophageal wall and migrate to soft tissues of the neck<sup>[3-4]</sup> and into the thyroid gland<sup>[3]</sup>, the common carotid artery<sup>[5]</sup> or exit spontaneously through the skin<sup>[1]</sup>. Rarely, as in our case, the penetrating foreign body migrates posteriorly to be embedded in the prevertebral muscles reaching vertebral bodies level. Migrating foreign bodies into the soft tissue of the neck may remain asymptomatic or may cause life threatening complications<sup>[6]</sup>, hence, removal of the migrated foreign body is mandatory.

### CASE REPORT

A 14-year-old boy, medically free, presented to our emergency department complaining of throat pain and foreign body sensation for 10 days following eating a sandwich from a local restaurant. His condition is associated with odynophagia and mild dysphagia to solids. The patient denied any history of shortness of breath, stridor, change in voice, hemoptysis or fever.

On physical examination, the patient appeared well, not in distress. Examination of his nose, throat, ears and neck did not reveal any abnormalities. A neurologic examination was grossly intact.

His laboratory workup was within normal limits.

X-ray of soft tissue of the neck and chest showed shadow of radiopaque foreign body at the level of 7<sup>th</sup> cervical spine (Fig 1).

The patient was admitted under otolaryngology team, and he underwent rigid esophagoscopy, flexible upper GI endoscopy and direct laryngobronchoscopy examination under general anesthesia but findings showed no evidence of foreign body in the esophagus

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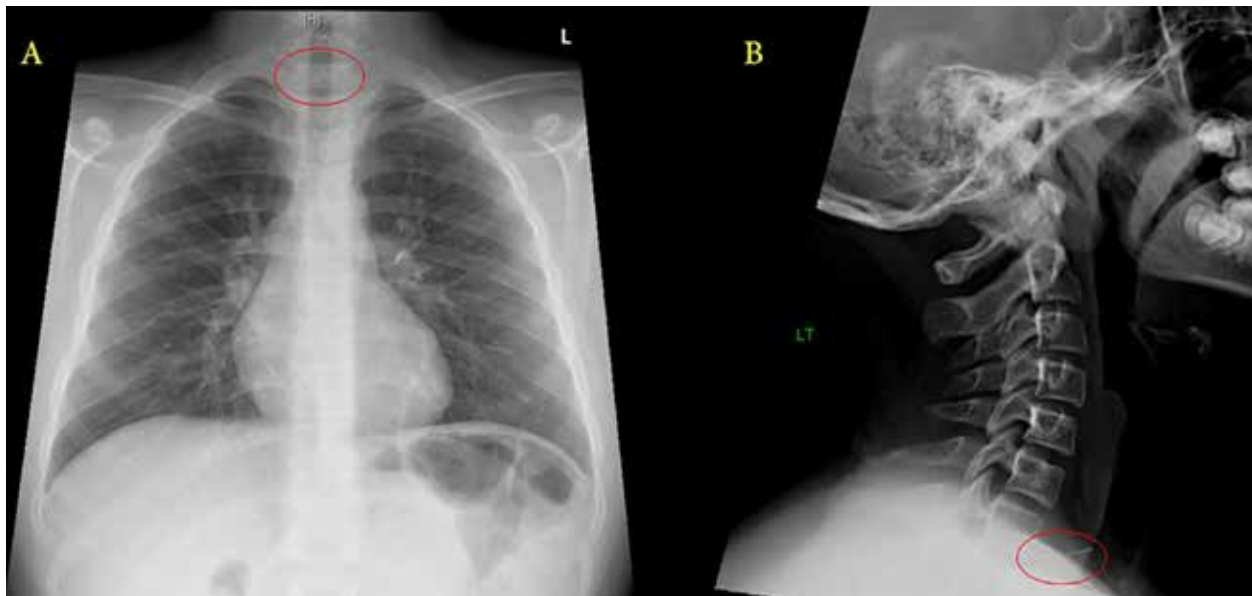


Fig 1: A: chest X-ray, B: lateral neck soft tissue X-ray, both showing radiopaque foreign body at the level of C7.

or the airway, with no signs of trauma. Portable x-ray done in the theater while patient was anesthetized showed that the foreign body was still in its location (Fig 2).

The procedure was aborted and CT neck was requested. Computed Tomography (CT) of the neck showed foreign body where its upper limit is reaching anterior to the disc between C7-T1 vertebral bodies (Fig 3).

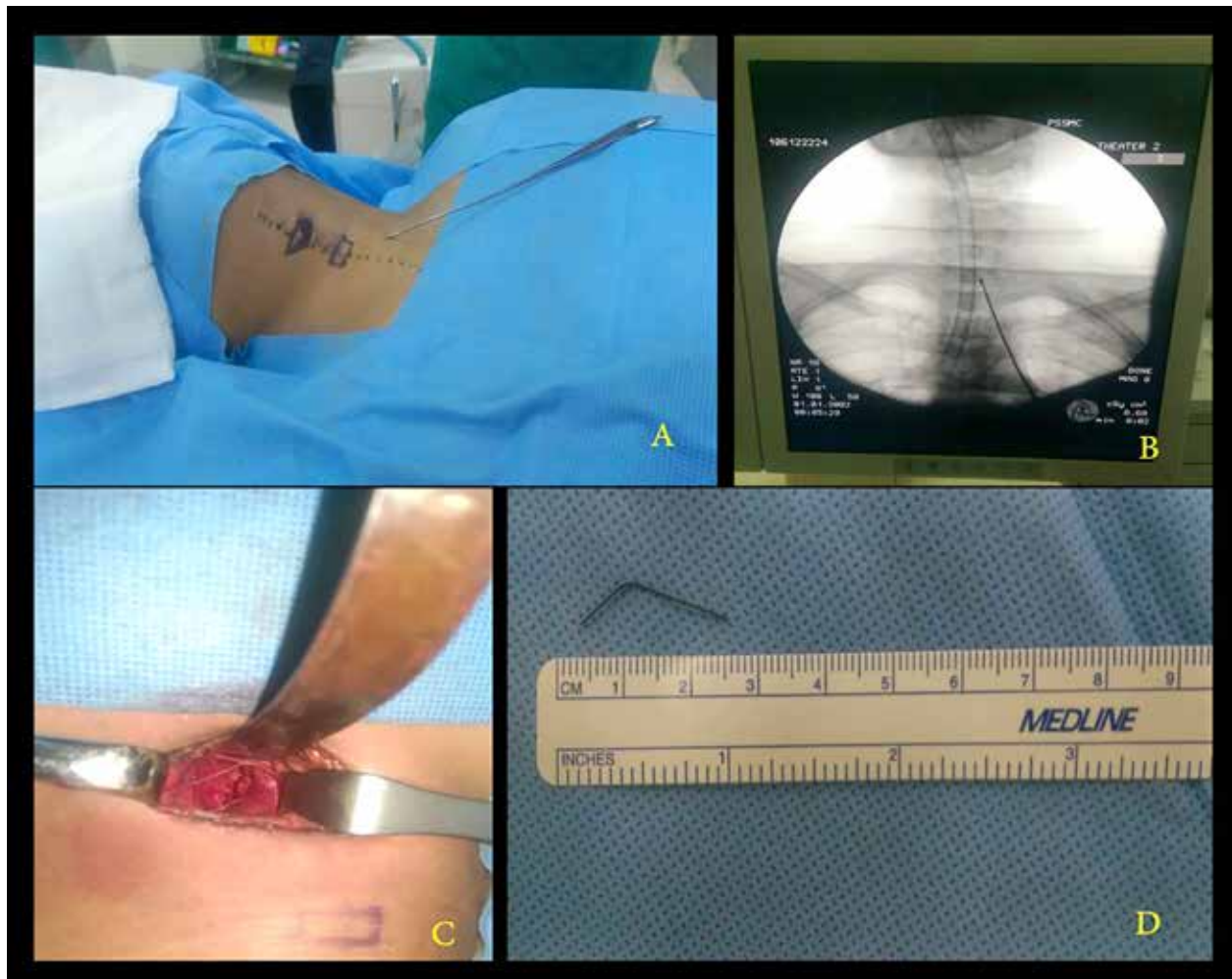
The patient then underwent neck exploration and foreign body was removed under fluoroscopy guidance (Fig 4). Day 1 post operatively, the patient underwent chest X-ray that revealed normal results, and also he underwent upper GI gastrografin study that showed no leakage (Fig 5).



Fig 2: Portable chest X-ray image done in the theater showing the radiopaque foreign body at its same location.



Fig 3: CT-Scan of the neck showing FB anterior to T1 where its upper limit reaching anterior to the disc between C7-T1 vertebral bodies, the scan also showing the anterior aspect of FB is embedded within the posterior wall of esophagus and its right extent reaching the prevertebral soft tissue.



**Fig 4 A:** Intra-operative identification of neck landmarks with using of probe to identify the FB location under fluoroscopy guidance. **B:** intra-operative X-ray showing the probe pointing to the location of FB. **C:** neck exploration to the level of prevertebral muscles. **D:** metallic wire FB post removal.

## DISCUSSION

Esophageal foreign bodies are one of the most common emergencies in otolaryngological practice. Foreign bodies can get lodged in different anatomical locations such as tonsils, base of the tongue, pyriform fossa or cervical esophagus. Foreign bodies rarely penetrate the esophageal wall and even more rarely migrate to soft tissues of the neck<sup>[4]</sup> as we report in this paper. It is a very rare presentation of migrating esophageal foreign body that's lodged into the prevertebral muscles. There have been many isolated case reports of migratory foreign bodies, however, the largest series to date by Remson *et al* reported 321 penetrating esophageal foreign bodies from 1918 to 1983, of which 43 were extraluminal, representing almost only 13% of the total cases<sup>[7]</sup>. In a more recent series of 24 cases of penetrating esophageal foreign bodies, only eight had extraluminal migration<sup>[8]</sup>. A migrated foreign body may remain asymptomatic but also may



**Fig 5:** Upper GI gastrografin study showing no contrast leakage is noted to suggest residual perforation, also no stricture or tracheo-esophageal fistula is seen.

lead to life threatening complications, examples of reported complications include retropharyngeal and parapharyngeal abscess<sup>[9]</sup>, epidural abscess<sup>[10]</sup>, thyroid abscess, mediastinitis<sup>[6]</sup>, carotid rupture, penetration of facial artery, aorto-esophageal fistula, and innominate-esophageal fistula<sup>[11]</sup>. Patient's usual presentation with perforated foreign body is foreign body sensation, odynophagia or hemoptysis and sometimes patient presented with fever and neck swelling. Our patient complained of dysphagia, odynophagia and foreign body sensation. A migrated foreign body should be suspected when identification of foreign body using esophagoscopy fails and postoperative X-ray imaging confirms its presence and in this situation, CT scan of the neck is the gold standard investigation to identify exact foreign body location and its relation to the surrounding structures<sup>[12]</sup>. As the soft tissue of the neck are mobile in relation to the surrounding structures, foreign body may not be situated exactly at the time of surgery as where it is seen in the CT scan. Therefore, the use of the C-arm fluoroscopy guidance with probe marker is recommended to localize the foreign body in the neck intraoperatively<sup>[11]</sup>, as we did in this case. The foreign body can be removed via external neck exploration with minimal morbidity.

## CONCLUSION

Migrating esophageal foreign bodies need a high suspicion index to diagnose. Esophagoscopy examination and CT scan of the neck are the mainstay for diagnosis.

Early neck exploration with intraoperative fluoroscopy guidance is highly recommended for accurate foreign body detection and to prevent possible life-threatening complications.

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## Case Report

# Secondary Seminal Vesicles Tumor: A Case Report

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### ABSTRACT

Secondary seminal vesicle tumors are rarely malignant. Tumor metastasis from colonic cancer arising in this location is even rarer and has only been described in case reports.

Due to the rarity of such tumors, the appropriate optimal treatment remains unclear. We report this case of secondary tumor in the seminal vesicle.

KEYWORDS: neoplasms, seminal vesicle

### INTRODUCTION

Tumors of the seminal vesicle are extremely rare. Among them, there is a spectrum of primary tumors derived from both epithelium and stroma or secondary tumors arising from other organs<sup>[1]</sup>. Herein, we present a patient with a secondary malignant tumor in this unusual location.

### CASE REPORT

An Asian single male patient, 34 years old, presented to surgical casualty complaining of recurrent abdominal pain, constipation and vomiting since two weeks. He had no chronic diseases. On clinical examination, the patient was febrile and the abdomen was mildly distended with palpable hard rectal mass, about 7 cm from anal verge on digital rectal examination. His laboratory investigations revealed mild leucocytosis, Hemoglobin 13.9 gm and normal renal and liver function tests. Multiple fluid levels were observed on erect abdomen X-ray. The patient was admitted to surgical ward as sub-acute intestinal obstruction, the patient passed motion and pain subsided. Abdomino-pelvic CT with oral, rectal and IV contrast showed dilated appendix with small phlebolith inside, circumferential mural wall thickening of terminal ileum and ileo-cecal junction associated with proximal dilatation of proximal ileal and distal jejunal bowel loops, mild free intra-

peritoneal fluid collection and multiple scattered enlarged mesenteric lymph nodes, and soft tissue lesion was seen insinuating between and inseparable from right seminal vesicle and lateral rectal wall with suspected focal infiltration of right aspect of posterior urinary bladder wall (mostly neoplastic lesion, exophytic from right lateral rectal wall or originating from seminal vesicle) and normal filling of urinary bladder. PSA is 1.061 ng/ml. Colonoscopy was done and visualised caecal polypoidal mass and biopsy were taken but histopathological examination reported nonspecific inflammation. Then the patient underwent diagnostic laparoscopy (showed inflamed appendix, dilated small bowel, enlarged mesenteric lymph nodes and hard extraperitoneal mass between urinary bladder and rectum but failed to see any mass in the colon), and appendectomy. Lymph node biopsy and peritoneal fluid sampling were done. The histopathological examination reported lymph node metastatic adenocarcinoma of unknown origin and inflamed appendix. At the same time, diagnostic cystoscopy was done which showed right trigone pushed up from outside by irregular mass distorting both ureteric orifices with no visible invading mass. Right retrograde study revealed compression of right lower ureter by pelvic mass. Right DJS fixation and multiple Transrectal ultrasound (TRUS) guided biopsies from the pelvic mass performed

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and detected a hypoechoic  $2 \times 1.7$  cm tumor in the right seminal vesicle. The histopathological examination of these biopsies revealed portion of normal seminal vesicle tissue with an occasional highly atypical gland infiltrating the smooth muscle. The gland showed focal mucin secretion favoring metastatic colorectal adenocarcinoma. The patient had refused any surgical removal of semen vesicle and therefore, he was explored through a midline abdominal incision and a complex mass posterior to urinary bladder was identified. A palpable hard mass lesion was discovered on ascending colon and therefore, right hemi colectomy and ileo-mid transverse colon anastomosis were performed. Then he was sent to our Oncology Center for further management with chemotherapy and radiation. The final histopathological examination reported poorly differentiated adenocarcinoma of the colon (pT3pN2pMx) Stage IIIC, Duckes C. The patient's postoperative recovery was uneventful. One year after surgery, a CT scan showed no signs of recurrence with stabilization in the size of the seminal vesicle tumor. He is currently alive and well.

## DISCUSSION

We have reported here a rare case of a secondary tumor of the seminal vesicle. Usually, these malignant tumors have only minor complaints, such as nonspecific lower abdominal pain or urinary frequency<sup>[2]</sup>. Diagnosis should be considered in the presence of a mass located superior to prostate and posterior to bladder, protruding the rectal wall. In cases of suspicious masses of the seminal vesicles, abdominal ultrasound first showed the existence of a pelvic mass with possible origin from the seminal vesicle, as confirmed by subsequent transrectal ultrasound (TRUS) due to excellent visualization of the seminal vesicles and adjacent structures. At the same time, it offers the opportunity of performing a TRUS-guided biopsy of the seminal vesicles for histological confirmation<sup>[3]</sup>. Additional radiological evaluation with magnetic resonance imaging (MRI) and computed tomography (CT) are required to visualize the exact extent of metastases and concomitant pelvic pathology<sup>[4]</sup> (Fig 1).

Differential diagnosis is made with expansive injuries of retrovesical space such as carcinomas and cystic tumors<sup>[4]</sup>. Immunohistochemical analysis using prostate specific antigen and prostatic acid phosphatase may be done to exclude prostatic origin<sup>[5]</sup>.

The aim of treatment of primary seminal vesicles is curative radical surgery prior to any infiltration of neighboring organs or even a metastatic disease. However, chemotherapy and radiotherapy seem to

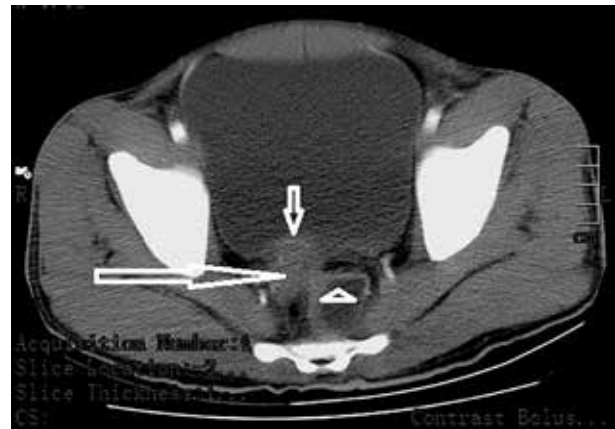


Fig 1: CT scan of the pelvis (soft tissue window) showing: 36 x 32 mm oval shaped mass lesion at the right semino-vesicle angle (long arrow), extending between the base of the urinary bladder (arrow head) and the rectum wall (short arrow)

be effective as adjuvant treatment modalities<sup>[6]</sup>. For secondary seminal vesicle tumor, there isn't large experience on management of such neoplasm (Fig 2, 3).

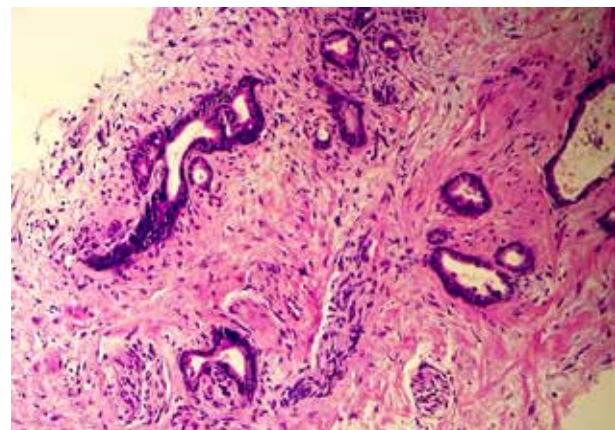


Fig 2: Photomicrograph exhibiting highly atypical glands of adenocarcinoma in the stroma of seminal vesicle (H&E 200X)

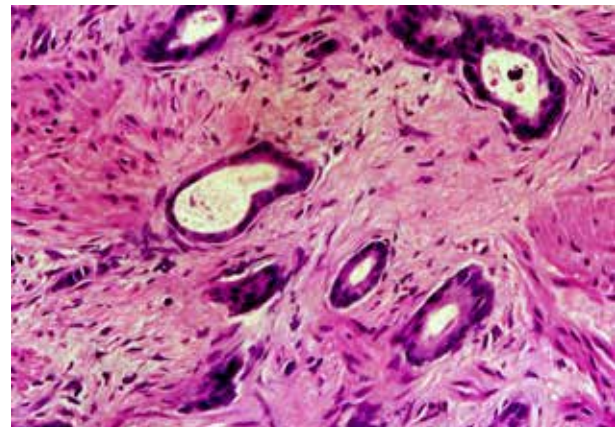


Fig 3: Photomicrograph showing infiltrating tumor tissue (adenocarcinoma) in the wall of the large bowel. The tumors have similar morphology as seen in the stroma of seminal vesicle (H&E 400X)

The diagnostic laparoscopy was inconclusive in establishing the diagnosis. Transrectal ultrasound guided biopsies of the seminal vesicle led us to do an exploratory laparotomy, in this case, it is logic to remove the whole tumor and involved seminal vesicle, but as our patient was still unmarried, had refused such management because of the possibility of erectile dysfunction and infertility. Due to the fact that histological findings of a poorly differentiated adenocarcinoma of the colon is an advanced disease with evidence of lymph node metastasis, we decided to perform systemic chemotherapy with local pelvic radiation<sup>[7,8]</sup>. This management led to the stabilization of the disease.

### CONCLUSION

Secondary seminal vesicle tumors are rare. To the best of our knowledge, we have presented a very rare case of a patient with poorly differentiated metastatic adenocarcinoma of the seminal vesicle diagnosed due to his presentation with Ileus. The prognosis of such cases with lymph node metastases is poor. In our case, chemotherapy with radiation led to stabilize the disease, which was followed up by active surveillance.

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## Case Report

# A Giant Angiomyolipoma of the Kidney: A Case Report

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### ABSTRACT

Angiomyolipoma (AML) is a rare benign renal tumor. Most frequently, it takes the form of small single tumor occurring sporadically. In some cases, the tumor may reach a very large size and cause serious complications. Herein, we present

the case of a 25-year-old female patient, suffering from left loin pain, in whom a ruptured giant AML was diagnosed involving the left kidney and treated successfully with selective arterial embolization.

KEYWORDS: angiomyolipoma, embolization, renal tumor

### INTRODUCTION

Renal Angiomyolipoma (AML) is a benign tumor, arising from mesenchymal elements of the kidney. It is four-fold more frequent in women and the peak of incidence falls between the 30<sup>th</sup> and 50<sup>th</sup> years of life<sup>[1]</sup>. It can occur sporadically, which is often solitary, and accounts for 80% of the tumors, or may be associated with tuberous sclerosis complex in 20% of cases. It has an incidence of 0.3 - 3% and is increased due to advancement in imaging modalities<sup>[2]</sup>. Histologically, it is composed of varying proportion of mature adipose tissue, smooth muscle and abnormal thick walled blood vessels<sup>[2]</sup>.

### CASE REPORT

A 25-year-old single Asian female patient presented to surgical casualty with recurrent left loin pain since five days and one day fever with no associated lower urinary tract symptoms or hematuria. She has no history of chronic disease. Clinically temperature was 38 °C with tenderness and fullness of left renal angle. Her Hb was 9.3 gm/dl, normal renal function tests. Abdominal ultrasound revealed well defined hyperechoic lesion with central hypoechogenicity in the lower pole of left kidney with a large eccentric component measuring about 12.5 x 8.5 cm with no increased vascularity on Doppler study (Fig 1a). Triphasic computed tomography (CT) of abdomen and pelvis reported large soft tissue mass lesion arising

from lower pole of left kidney 12.5 x 10.5 x 8.5 cm in dimensions, with heterogeneous texture but mainly of fat density, moderately enhanced after contrast administration with moderate to marked stranding of perinephric fat planes coupled with mild perinephric hematoma (Fig 1b). The findings were suggestive of ruptured large AML. Additionally noted multiple small left renal cortical lesions (almost only fat CT density) largest is midzonal eccentric and measures 10 mm features of other smaller left AML. DMSA-Renogram study reported that left kidney contributes to 48% of total renal function with no cortical defect. Patient was initially managed conservatively with bed rest, intravenous injection of a broad spectrum cephalosporin antibiotics (cefotaxime sodium, 1 gm every eight hours for five days), IV fluids and blood transfusion. Since there was a suspicion of severe bleeding from a huge renal angiomyolipoma, we prepared the patient for open left nephrectomy, but she became clinically stable and she refused this planned surgical intervention. We consulted our interventional radiologist for selective arterial embolization of this renal mass, initial renal arteriography showed tortuous, hypervascular, and aneurysm-forming angiogenic components without extravasation of the contrast agent (Fig 2). Immediate complete obliteration with metallic coil was technically successful and her hemodynamic status was stabilized a week later without any complication in the post-operative period (Fig 2). She

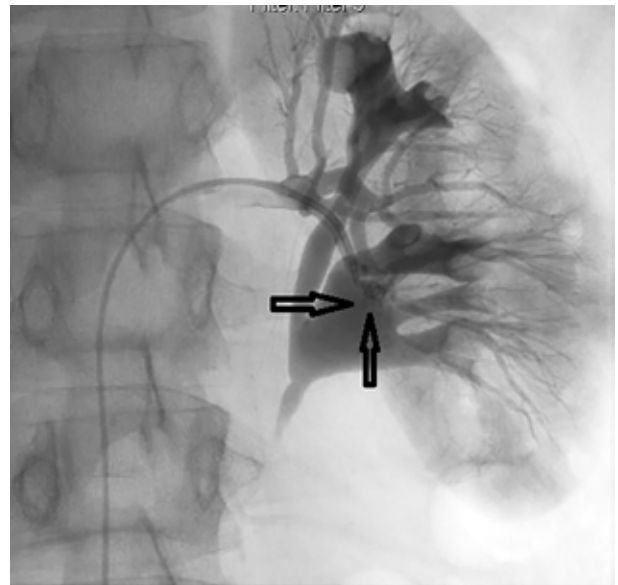
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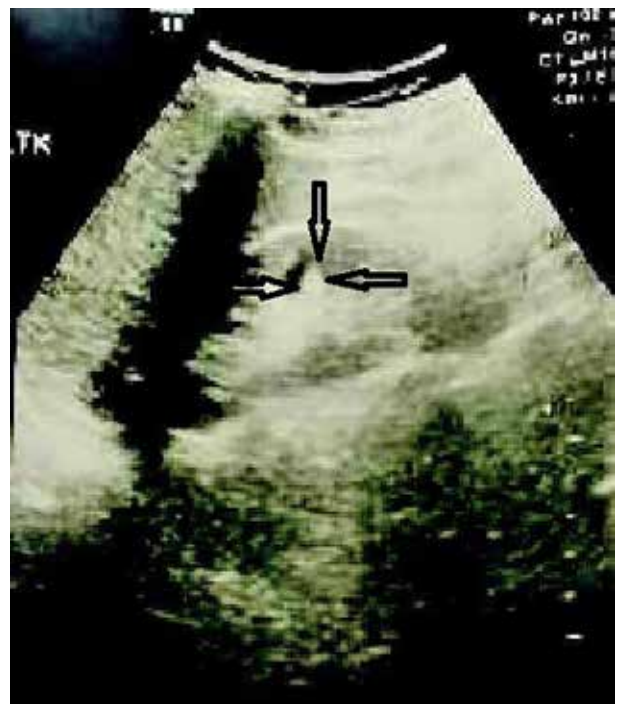
**Fig 1: A:** Ultrasound imaging, showing a 12.5 x 8 cm large AML, arrows, involving the left kidney



**Fig 2:** Angiography film, post embolization, showing complete occlusion of the main artery of the left renal angiomyolipoma with metallic coil, arrows



**Fig 1B:** CT scan imaging, sagittal view, showing a large renal mass lesion with fat content, AML, arrows



**Fig 3:** Ultrasound imaging, 18 months post selective arterial embolization, showing only a small 5 mm in size residual AML (arrow), with complete disappearance of the previously detected large AML tumor.

was discharged asymptotically for follow up in our outpatient clinic. Serial follow up with nuclear study of the renal function, Ultrasound and CT (Abdomen, Pelvis) after 3 and 6 months showed stable renal function and significant reduction of the size of the renal AML. One and half years later, the ultrasound study showed only single 5 mm left renal AML and

disappearance of the above mentioned renal mass (Fig 3). The patient is still under our care in out-patient clinic with a very good general condition.

**DISCUSSION**

Angiomyolipoma (AML) is a rare benign hematoma renal tumor that contains various proportions of

smooth muscle, adipose tissue and blood vessels. Most frequently these tumors are unilateral, small and singular<sup>[3]</sup>. In the remaining case, they coexist with tuberous sclerosis and they may achieve significant size and could be multiple and bilateral<sup>[3]</sup>. The diagnosis of angiomyolipoma, which is most often found incidentally, depends on CT scan imaging which helps in identifying fat in the renal lesion<sup>[4]</sup>. Also these lesions need to be differentiated from malignant renal tumors which often contain areas of calcification, whereas calcifications are rare in the benign angiomyolipoma<sup>[5]</sup>. Annual follow up with CT scan or ultrasound can be performed to assess disease stability versus progression<sup>[6]</sup>.

Renal AML usually grows slowly; therefore, depending also on the location of these lesions, the patients with smaller renal AML have no apparent clinical symptoms<sup>[7]</sup>. Asymptomatic and small lesions less than 4 cm often do not require any interventions<sup>[7]</sup>. When a renal AML enlarges, it usually becomes more vascular, with tortuous vessels; some of them have insufficient elastic layer and muscle wall, leading to the formation of aneurysms that are prone to spontaneous rupture, resulting in hemorrhage<sup>[8]</sup>.

Patients may have sudden lower back pain, resulting in dramatically increased tumor volume. When the tumor growth reaches the renal capsule, the patients may have an acute abdomen or hemorrhagic shock caused by retroperitoneal hemorrhage, which may cause life-threatening hypovolemic shock that requires nephrectomy or nephron-sparing surgery<sup>[8]</sup>. It is generally agreed that AML which is bigger than 10 cm and affects a whole organ is considered a 'giant' AML and asymptomatic lesions more than 8 cm should be treated similarly to those with symptomatic lesions more than 4 cm<sup>[9]</sup>.

The therapeutic options include surgery (partial or total nephrectomy) and selective embolization of these lesions which are clinically important due to their propensity to bleed<sup>[10]</sup>. The improvements and increasing skills of techniques of selective transcatheter arterial embolization led it to being widely used to treat acute hemorrhage caused by ruptured renal AML either alone or in conjunction with surgical intervention<sup>[11]</sup>. The advantages of this method include the preservation of functional renal parenchyma, and avoiding the need of anesthesia. Various materials have been used, including pure alcohol, absorbable gelatin sponged, polyvinyl alcohol particles and metal coils<sup>[12]</sup>. Complications of post embolization syndrome, which is widely thought to be an inflammatory response to necrotic tissue after embolization, can include fever and flank pain<sup>[13,14]</sup>.

In our case, the patient was a young lady, presented with acute retroperitoneal bleeding, due to a ruptured

huge renal angiomyolipoma. As the patient became dramatically hemodynamically stable only with blood transfusion and parenteral antibiotics, and she had refused any surgical intervention including nephrectomy, we advised her to do selective arterial embolization of the AML to prevent the possible spontaneous rupture in future and its consequences, especially hemorrhage. When she agreed, the above mentioned technique was performed successfully using a metal clip. The patient was almost asymptomatic in the post embolization period, and subsequent follow up with imaging showed stabilization of the disease and gradual decrease in the size of the lesion with only a small non-significant residual AML with preservation of the function of the involved kidney. Regarding the management of such cases of huge renal angiomyolipoma, and in the light of the previous published studies in literature, we found the technique of selective arterial embolization of a giant AML as a safe, attractive, minimally invasive and cost-effective method, which may help stabilization and treatment of these tumors. As we have a significant number of relatively small sized renal AML cases, which was managed conservatively, we will try in the future, when it's possible to collect more cases of huge AML, which may need this technique that help us to establish such management in our department.

## CONCLUSION

Renal angiomyolipoma is a tumor with a generally benign nature, which can be managed conservatively. Sometimes the giant sized type of this tumor may take a complicated course with spontaneous rupture and subsequent bleeding, that can be managed with selective transarterial embolization, which we found to be a well-tolerated procedure and is associated with minimal adverse reaction to preserve the function of the involved kidney. However further studies with more cases are needed to establish such a management.

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## Letter to the Editor

# Evidence of the Safety of Axillary Vein Catheterization in Newborns

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Kuwait Medical Journal 2017; 49 (1): 76 - 77

### Short summary

Li *et al* insisted that an axillary vein catheterization in newborns was superior to other veins with regard to puncture success rate, retention time, and complication rate. However, evidence of the safety of axillary vein catheterization, especially in newborns, seems insufficient.

### To the Editor:

I read, with great interest, the article by Li *et al*<sup>[1]</sup>. Our previous article cited as follows: "As a rescue infusion pathway for critically ill newborns, compared with catheterization in other body parts, axillary vein catheterization has been reported to be superior in the puncture success rate, retention time, and complication rate<sup>[2]</sup>." However, this sentence might be misleading regarding the safety of axillary vein catheterization in newborns.

In our article<sup>[2]</sup>, we concluded that it seemed difficult to utilize the axillary vein for pediatric central venous catheterization (CVC) only from the standpoint of vein diameter and depth. In our previous study of 50 children, diameter of the axillary vein was approximately 0.6 times and depth was approximately 1.5 times that of the internal jugular vein<sup>[2]</sup>. In fact, in that study, we did not puncture any axillary vein. As a result, we did not indicate the puncture success rate, retention time, or complication rate through the pediatric axillary vein. In another study, in 35 children less than 80 cm in height, depth (average, 9.9 mm) to width (average, 3.0 mm) ratio of the axillary vein averaged 3.6, and CVC through the axillary vein was difficult<sup>[3]</sup>. However, in seven children more than 100 cm in height, depth (average, 10.4 mm) to width (average, 6.4 mm) ratio averaged 1.7, and CVC seemed

relatively easy<sup>[3]</sup>. Only in a 3-year-old boy, did we successfully puncture the axillary vein and place a vascular access port under ultrasound guidance after failure of landmark-guided puncture<sup>[3]</sup>.

In 52 children with an axillary vein catheterization success rate of 79% (41/52), median success age of 0.9 years, and mean unsuccessful age of 0.7 years, success and complication rates were comparable to jugular catheterization<sup>[4]</sup>. In 48 consecutive pediatric patients (mean age, 12.3 ± 4.6 years) who underwent pacemaker/implantable cardioverter-defibrillator lead implantation through the axillary vein (average diameter, 7.9 mm) under guidance with contrast venography, the axillary vein approach was effective in 93.7% of patients. However, younger patients with smaller vein diameter are at high risk for unsuccessful procedure<sup>[5]</sup>.

Ultrasound-guided supraclavicular subclavian vein cannulation may demonstrate its safety and gain popularity in infants<sup>[6,7]</sup>. In addition, axillary vein catheterization without ultrasound guidance may be safe in newborns, as shown in the article by Li *et al*<sup>[1]</sup>. However, evidence of the safety of percutaneous axillary vein catheterization in newborns, especially with ultrasound guidance, seems insufficient. Therefore, evidence should be carefully collected.

### ACKNOWLEDGMENT

**Financial disclosures:** None

**Conflicts of interest:** None

**Contributions:** Kenji Kayashima conducted the procedure, wrote the manuscript, and approved the final manuscript.

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## Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2016; 48 (1) :

### Investigating Factors Involved in Post Laparoscopic Sleeve Gastrectomy (LSG) Neuropathy

Alsabah A<sup>1</sup>, Al Sabah S<sup>2</sup>, Al-Sabah S<sup>1</sup>, Al-Serri A<sup>1</sup>, Al Haddad E<sup>3</sup>, Renno WM<sup>1</sup>

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**Obes Surg 2016 Nov 26 [Epub ahead of print]**

**Background:** Laparoscopic sleeve gastrectomy (LSG) has gained popularity as the leading bariatric procedure for the treatment of morbid obesity. Due to the rising numbers of bariatric surgeries, neurologic complications have become increasingly recognized. Our aim was to examine biochemical and hormonal factors that are associated with neuropathy post-LSG.

**Methods:** Thirty-two patients were included: 16 patients with neuropathy in the neuropathic group (NG) and 16 patients without neuropathy in the control group (CG). Diagnosis was made by a consultant neurologist, and blood samples were taken to examine vitamin deficiencies and hormones involved in neuropathy.

**Results:** There was no significant difference between the BMI ( $p = 0.1$ ) in both groups as well as excess weight loss percentages post-LSG at 12 months ( $p = 0.6$ ). B12 levels were within normal range, but higher in NG ( $p = 0.005$ ). Vitamin B1 and B2 levels were significantly lower in NG;  $p$  values are 0.000 and 0.031, respectively. Vitamin B6 levels were significantly higher in NG ( $p = 0.02$ ) and copper levels were lower in NG ( $p = 0.009$ ). There was no significant difference in GLP-1 response in both groups.

**Conclusion:** Our data showed post-LSG neuropathy is associated with lower levels of vitamin B1, B2, and copper, plus patients who are older in age. Vitamin B6 was significantly higher in the NG, which is, at toxic levels, associated with neuropathy. No difference in preoperative BMI, excess weight loss percent at 1 year, and GLP-1 levels was found. Larger data is required to validate our results.

### The Relationship between Patients' Knowledge of Diabetes Therapeutic Goals and Self-Management Behaviour, Including Adherence

Waheedi M<sup>1</sup>, Awad A<sup>2</sup>, Hatoum HT<sup>3</sup>, Enlund H<sup>4</sup>

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<sup>4</sup>Finnish Medicines Agency, Kuopio, Finland

**Int J Clin Pharm 2016 Nov 23 [Epub ahead of print]**

**Background:** The Middle East region has one the highest prevalence rates of diabetes in the world. Little is known about the determinants of adherence and the role of knowledge in diabetes self-management within these populations.

**Objective:** To investigate the relationship between patients knowledge of diabetes therapeutic targets with adherence to self-care measures in a sample of patients with type 2 diabetes in Kuwait.

**Setting:** Primary care chronic care clinics within the Ministry of Health of Kuwait.

**Methods:** A cross sectional survey was carried out with 238 patients from six clinics. A multistage stratified clustered sampling method was used to first randomly select the clinics and the patients.

**Main Outcome Measure:** Self-reported adherence to three behaviours: medication taking, diet and physical activity.

**Results:** Respondents were able to correctly report a mean (SD) of 1.6 (1.3) out of 5 of the pre-specified treatment targets. Optimal adherence to physical activity, diet and medications was reported in 25, 33 and 47 % of the study cohort, respectively. A structural equation model analysis showed better knowledge of therapeutic goals and own current levels translated into better adherence to medications, diet and physical activity.

**Conclusion:** Knowledge of therapeutic goals and own recent levels is associated with adherence to medications, diet, or physical activity in this Kuwaiti cohort of patients with diabetes. Low adherence to self-care management and poor overall knowledge of diabetes is a big challenge to successful diabetes care in Kuwait.

## Role of the Pharmacist in Parenteral Nutrition Therapy: Challenges and Opportunities to Implement Pharmaceutical Care in Kuwait

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**Pharm Pract (Granada) 2016; 14:680. doi: 10.18549/PharmPract.2016.02.680. Epub 2016 Jun 15**

**Background:** Pharmacists can provide beneficial pharmaceutical care services to patients receiving Parenteral Nutrition (PN) therapy by working within Nutrition Support Teams (NSTs).

**Objective:** This study was designed to explore pharmacists' role in PN therapy in hospitals of Kuwait, sources of PN-related information, opinions on NSTs, perceptions about the barriers to pharmaceutical care implementation and views on how to enhance their practices.

**Methods:** Data were collected via face-to-face semi-structured interviews with the senior Total Parenteral Nutrition (TPN) pharmacists at all the hospitals which provide TPN preparation services (six governmental hospitals and one private hospital) in Kuwait. Descriptive statistics were used to describe pharmacists' demographic details and practice site characteristics. The interviews were audio-recorded, transcribed verbatim and analysed using thematic analysis.

**Results:** The pharmacists mainly performed technical tasks such as TPN compounding with minimal role in providing direct patient care. They used multiple different sources of TPN-related information to guide their practice. They reported positive and negative experiences with physicians depending on their practice environment. None of the hospitals had a functional NST. However, pharmacists expressed preference to work within NSTs due to the potential benefits of enhanced communication and knowledge exchange among practitioners and to improve service. Pharmacists perceived several barriers to providing pharmaceutical care including lack of reliable sources of TPN-related information, lack of a standard operating procedure for TPN across hospitals, insufficient staff, time constraints and poor communication between TPN pharmacists. To overcome these barriers, they recommended fostering pharmacists' education on TPN, establishing national standards for TPN practices, provision of pharmacy staff, development of NSTs, enhancing TPN pharmacists' communication and conducting TPN-research research.

**Conclusion:** TPN pharmacists in Kuwait are confined to performing TPN manufacturing processes. There are promising avenues for future development of their role in patient care. This can be achieved by overcoming the barriers to pharmaceutical care practice and providing pharmacists with educational opportunities to equip them with the clinical competencies needed to practise as nutrition support pharmacists with patient-centred roles.

## Prognostic Indicators of Secondary Progression in A Paediatric-Onset Multiple Sclerosis Cohort in Kuwait

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**Mult Scler** 2016; 22:1086-1093. doi: 10.1177/1352458515608960. Epub 2015 Oct 9

**Background:** The frequency of paediatric-onset multiple sclerosis (POMS) and the precise risk of secondary progression of disease are largely unknown in the Middle East. This cross-sectional cohort study assessed the risk and examined prognostic factors for time to onset of secondary progressive multiple sclerosis (SPMS) in a cohort of POMS patients.

**Methods:** The Kuwait National MS Registry database was used to identify a cohort of POMS cases (diagnosed at age <18 years) from 1994 to 2013. Data were abstracted from patients' records. A Cox proportional hazards model was used to evaluate the prognostic significance of the variables considered.

**Results:** Of 808 multiple sclerosis (MS) patients, 127 (15.7%) were POMS cases. The median age (years) at disease onset was 16.0 (range 6.5-17.9). Of 127 POMS cases, 20 (15.8%) developed SPMS. A multivariable Cox proportional hazards model showed that at MS onset, brainstem involvement (adjusted hazard ratio 5.71; 95% confidence interval 1.53 - 21.30; P = 0.010), and POMS patient age at MS onset (adjusted hazard ratio 1.38; 95% confidence interval 1.01 - 1.88; P = 0.042) were significantly associated with the increased risk of a secondary progressive disease course.

**Conclusions:** This study showed that POMS patients with brainstem/cerebellar presentation and a relatively higher age at MS onset had disposition for SPMS and warrant an aggressive therapeutic approach.

## Awareness of Food Allergies: A Survey of Pediatricians in Kuwait

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**BMC Pediatr** 2017; 17:11. doi: 10.1186/s12887-016-0773-9

**Background:** Early diagnosis of food allergies (FA) is important for a favorable prognosis. This study aimed to determine the level of awareness of FA among pediatricians in Kuwait.

**Method:** A 43-item self-administered questionnaire was designed and distributed to pediatricians working at 4 government hospitals in Kuwait.

**Results:** A total of 140 pediatricians completed the questionnaire, with a participation rate of 51.1% (81 males and 59 females). The mean age of participants was 40.81 years, and the mean number of years working in pediatrics was 13.94 years. The mean overall knowledge score was 22.2. The pediatricians' overall knowledge scores were found to be significantly associated with their age (older pediatricians had higher overall scores) and years of experience as a pediatrician but were independent from hospital site, gender, or rank. A multiple linear regression revealed pediatrician age and gender were the only variables



that were significantly associated with the overall knowledge score. Only 16.4% of the participants answered at least 2/3 of the survey questions correctly. The questions that were correctly answered by  $\leq 2/3$  of the participants constituted 80% of clinical presentation questions, 66.6% of diagnostics questions, 77.7% of treatment questions, and 42.8% of prevention questions. Interestingly, among 68 pediatricians (48.5%) who determined that they felt comfortable evaluating and treating patients with FA, only 12 (17.6%) passed the questionnaire.

**Conclusions:** This survey demonstrates that there is a noteworthy deficiency of pediatricians' awareness about FA. The implementation of strategies to improve pediatricians' awareness is critical to diagnose food allergy patients early and improve their health and outcomes.

## Exome Sequencing Discerns Syndromes in Patients from Consanguineous Families with Congenital Anomalies of the Kidneys and Urinary Tract

Vivante A<sup>1,2</sup>, Hwang DY<sup>1,3</sup>, Kohl S<sup>1,4</sup>, Chen J<sup>1</sup>, Shril S<sup>1</sup>, Schulz J<sup>1</sup>, van der Ven A<sup>1</sup>, Daouk G<sup>1</sup>, Soliman NA<sup>5,6</sup>, Kumar AS<sup>7</sup>, Senguttuvan P<sup>7</sup>, Kehinde EO<sup>8</sup>, Tasic V<sup>9</sup>, Hildebrandt F<sup>10,11</sup>

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**J Am Soc Nephrol 2017 Jan;28(1):69-75. doi: 10.1681/ASN.2015080962. Epub 2016 May 5.**

Congenital anomalies of the kidneys and urinary tract (CAKUT) are the leading cause of CKD in children, featuring a broad variety of malformations. A monogenic cause can be detected in around 12% of patients. However, the morphologic clinical phenotype of CAKUT frequently does not indicate specific genes to be examined. To determine the likelihood of detecting causative recessive mutations by whole-exome sequencing (WES), we analyzed individuals with CAKUT from 33 different consanguineous families. Using homozygosity mapping and WES, we identified the causative mutations in nine of the 33 families studied (27%). We detected recessive mutations in nine known disease-causing genes: ZBTB24, WFS1, HPSE2, ATRX, ASPH, AGXT, AQP2, CTNS, and PKHD1. Notably, when mutated, these genes cause multiorgan syndromes that may include CAKUT as a feature (syndromic CAKUT) or cause renal diseases that may manifest as phenocopies of CAKUT. None of the above monogenic disease-causing genes were suspected on clinical grounds before this study. Follow-up clinical characterization of those patients allowed us to revise and detect relevant new clinical features in a more appropriate pathogenetic context. Thus, applying WES to the diagnostic approach in CAKUT provides opportunities for an accurate and early etiology-based diagnosis and improved clinical management.

## Forthcoming Conferences and Meetings

Compiled and edited by  
Babichan K Chandy

Kuwait Medical Journal 2017; 49 (1) : 82 - 92

28<sup>th</sup> International Symposium on **Cerebral Blood Flow, Metabolism & Function** / 13<sup>th</sup> International Conference on Quantification of Brain Function with Pet

Apr 1 - 4, 2017

Germany / Berlin

Contact: MCI Deutschland GmbH

Phone: 011-49-30-204-590; Fax: 011-49-30-204-5950

Email: brain2017@mci-group.com

2<sup>nd</sup> International **Ayurveda** Congress

Apr 1 - 2, 2017

United Kingdom / London

Contact: M. Rickinger, International Maharishi Ayurveda Foundation

Phone: 011-31-4-7553-9546

Email: info@imavf.org

New Treatments in **Chronic Liver Disease**

Apr 1 - 2, 2017

United States / California / San Diego

Contact: Scripps Conference Services & CME

Phone: 858-652-5400

Email: med.edu@scrippshealth.org

2017 British Society for **Parasitology** (BSP) Spring Meeting

Apr 2 - 5, 2017

United Kingdom / Dundee

Contact: BSP

Phone: 011-44-12-3421-1015; Fax: 011-44-12-3448-1015

Email: info@bsp.uk.net

8<sup>th</sup> Adaptive Designs in **Clinical Trials**

Apr 3 - 4, 2017

United Kingdom / London

Contact: SMi Group, SMi Group

Phone: 011-44-20-7827-6000

Email: hdegracia@smi-online.co.uk

15<sup>th</sup> World Congress on **Public Health**

Apr 3 - 7, 2017

Australia / Melbourne

Contact: MCI Australia

Phone: 011-61-3-9320-8600

Email: info@populationhealthcongress.org.au

2017 Association for **Molecular Pathology** Global Congress on Molecular Pathology

Apr 3 - 5, 2017

Germany / Berlin

Contact: MCI Deutschland GmbH

Phone: 011-49-30-20-4590; Fax: 011-49-30-204-5950

Email: amp-berlin@mci-group.com

2017 British Society for **Investigative Dermatology** Annual Meeting

Apr 3 - 5, 2017

United Kingdom / Manchester

Contact: British Association of Dermatologists

Email: conference@bad.org.uk

34<sup>th</sup> British Society for **Dermatological Surgery** (BSDS) Annual Surgery workshop

Apr 3 - 5, 2017

United Kingdom / Newcastle

Contact: BSDS

Email: info@bsds.org.uk

Bone Research Society (BRS) training course:

**Osteoporosis** & other Metabolic Bone Diseases

Apr 3 - 5, 2017

United Kingdom / Oxford

Contact: Janet Crompton, Course Organizer, BRS

Phone: 011-44-14-5354-9929

Email: events@boneresearchsociety.org

2017 Mayo Clinic **Extracorporeal Membrane Oxygenation** workshop

Apr 4 - 5, 2017

United States / Arizona / Scottsdale

Contact: Mayo School Of CPD, Mayo Clinic

Phone: 480-301-4580

Email: mca.cme@mayo.edu

2017 World Congress for **Cervical Pathology & Colposcopy**

Apr 4 - 7, 2017

United States / Florida / Orlando

Contact: American Society for Colposcopy & Cervical Pathology

Phone: 800-787-7227

Email: education@asccp.org

**Advanced Skills in Breast disease management**

Apr 4 - 7, 2017

*United Kingdom / London*

Contact: Education, Royal College of Surgeons of England

Phone: 011-44-20-7869-6300

Email: education@rcseng.ac.uk

**Operative Skills in Urology: Modules 3 & 4**

Apr 4 - 5, 2017

*United Kingdom / London*

Contact: Education, Royal College of Surgeons of England

Phone: 011-44-20-7869-6300

Email: education@rcseng.ac.uk

**57<sup>th</sup> Annual Update in General Surgery**

Apr 5 - 8, 2017

*Canada / Ontario / Toronto*

Contact: Continuing Professional Development, University of Toronto

Phone: 888-512-8173 or 416-978-2719

Email: info-sur1704@cpdtoronto.ca

**Practical Advances in Musculoskeletal & Sports Care Live Course**

Apr 5 - 8, 2017

*United States / Nevada / Las Vegas*

Contact: American Academy of Family Physicians

Phone: 800-274-2237 or 913-906-6000; Fax: 913-906-6075

**11<sup>th</sup> Annual Risk & Recovery Forensic Conference**

Apr 6 - 7, 2017

*Canada / Ontario / Hamilton*

Contact: Josie Cosco, Forensic Psychiatry Program, St. Joseph's Healthcare Hamilton

Phone: 905-522-1155 Ext. 35415

Email: jcosco@stjoes.ca

**1<sup>st</sup> Cologne Conference on Lung Cancer**

Apr 6 - 7, 2017

*Germany / Köln*

Contact: Kongress- und Kulturmanagement GmbH, Kongress- und Kulturmanagement GmbH

Phone: 011-49-3643-2468-0

Email: info@kukm.de

**13<sup>th</sup> Emirates Critical Care Conference**

Apr 6 - 8, 2017

*United Arab Emirates / Dubai*

Contact: Anala Jamir, Project Manager, Infoplus Events Llc

Phone: 011-971-4-421-8996; Fax: 011-971-4-421-8838

Email: eccc@infoplusevents.com

**2017 Multidisciplinary Update in Pulmonary & Critical Care Medicine**

Apr 6 - 9, 2017

*United States / Arizona / Phoenix*

Contact: Mayo School of CPD, Mayo Clinic

Phone: 480-301-4580

Fax: 480-301-4580

Email: mca.cme@mayo.edu

**Operative Skills in Ear, Nose & Throat Surgery**

Apr 6 - 7, 2017

*United Kingdom / London*

Contact: Education, Royal College of Surgeons of England

Phone: 011-44-20-7869-6300

Email: education@rcseng.ac.uk

**2<sup>nd</sup> PCR Tokyo Valves**

Apr 7 - 9, 2017

*Japan / Tokyo*

Contact: Secretariat, PCR online

Email: sec-tokyovalves@congre.co.jp

**2017 Immune Profiling World Congress USA**

Apr 10 - 12, 2017

*United States / District of Columbia / Washington*

Contact: Ina Luft, Terrapinn

Phone: 011-44-20-7092-1191

Email: ina.luft@terrapinn.com

**Influenza & Respiratory Vaccine Conference**

Apr 10 - 12, 2017

*United States / Washington DC*

Contact: Ina Luft, Terrapinn

Phone: 011-44-20-7092-1191

Email: ina.luft@terrapinn.com

**6<sup>th</sup> Global Experts Meeting on Cardiovascular Pharmacology & Cardiac Medications**

Apr 13 - 14, 2017

*United Arab Emirates / Dubai*

Contact: Alisa Craig, Program Manager, Conference Series Llc

Phone: 702-508-5200

Email: cardiacpharmacology@conferenceseries.net

**6<sup>th</sup> International Conference & Expo on Cosmetology, Trichology & Aesthetic Practices**

Apr 13 - 14, 2017

*United Arab Emirates / Dubai*

Contact: Alisha, Cosmetology 2017, Omics

Phone: 650-268-9744

Fax: 650-618-1414

Email: cosmetology@surgeryconferences.org

7<sup>th</sup> Annual Case Base Approached to Controversies in  
**Cardiovascular Disease**

Apr 13 - 14, 2017

*United Arab Emirates / Dubai*

Contact: Umair Khan, Project Manager, InfoPlus  
Events LLC

Phone: 011-971-4-421-8996; Fax: 011-971-4-421-8838

Email: Cardiovascular@InfoPlusEvents.com

2017 American Society of **Nephrology** Highlights / 2<sup>nd</sup>  
Seha Nephrology & Primary Care Conference

Apr 14 - 15, 2017

*United Arab Emirates / Abu Dhabi*

Contact: Basil Kadara, General Manager, Diaedu  
Management Consultancy

Phone: 011-971-4-453-2975

Email: contact@diaedu.com

3<sup>rd</sup> International Conference on **Neurological  
Disorders and Brain Injury**

Apr 18 - 19, 2017

*United Kingdom / London*

Contact: Conference Series.com

Email: braininjury@neuroconferences.com

12<sup>th</sup> International Society of **Dermatology (ISD)**  
International Congress of Dermatology

Apr 18 - 22, 2017

*Argentina / Buenos Aires*

Contact: Cindy Froehlich, Executive Director, ISD

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Email: info@intsocderm.org

18<sup>th</sup> World Congress of the World Association for  
**Dynamic Psychiatry**

Apr 19 - 22, 2017

*Italy / Florence*

Contact: Secretariat, Net Congress & Education

Phone: 011-39-2-9143-4000; Fax: 011-39-2-9143-4059

Email: segreteria@netcongresseducation.com

2017 **Influenza Vaccines** for the World

Apr 19 - 21, 2017

*Switzerland / Lausanne*

Contact: John Herriot, Planning Director, Meetings  
management

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Email: jherriot@meetingsmgmt.u-net.com

2017 International **Liver Congress**

Apr 19 - 23, 2017

*Netherlands / Amsterdam*

Contact: Congress Organizer, European Association  
for the Study of the Liver

Phone: 011-41-2-2807-0360

Email: com@easloffice.eu

2017 **Congenital** & Structural Interventions Dubai

Apr 20 - 22, 2017

*United Arab Emirates / Dubai*

Contact: Denise Thom, Congress Organization, cme4u  
GmbH

Phone: 011-49-69-2561-2857

; Fax: 011-49-69-2562-8658

Email: info@cme4u.org

2017 European Knee Society **Arthroplasty** Conference  
4<sup>th</sup> Quality Of Life & **Cancer** Clinical Trials

Conference

Apr 20 - 21, 2017

*Belgium / Brussels*

Contact: Conference Secretariat, QOL

Email: qolconference@eortc.be

18<sup>th</sup> Annual National Conference on **Fetal Monitoring**

Apr 20 - 22, 2017

*United States / Nevada / Las Vegas*

Contact: Symposia Medicus

Phone: 800-327-3161

Fax: 925-969-1795

42<sup>nd</sup> Annual Meeting of the Society for **Sex Therapy &  
Research (SSTAR)**

Apr 20 - 23, 2017

*Canada / Quebec / Montreal*

Contact: SSTAR

Phone: 847-647-8832

Email: info@sstarnet.org

4<sup>th</sup> Singapore-Australian & New Zealand **Intensive  
Care** Society Intensive Care Forum

Apr 20 - 24, 2017

*Singapore / Singapore*

Contact: Francisca Ang Wei Hoon, Kenes Asia

Phone: 011-65-6389-6616

Email: fang@kenes.com

5<sup>th</sup> Emirates International **Orthopaedic Congress**

Apr 20 - 22, 2017

*United Arab Emirates / Dubai*

Contact: Epin Kurra, Project Manager, Infoplus  
Events

Phone: 011-971-4-421-8996

Fax: 011-971-4-421-8838

Email: ortho@infoplusevents.com

6<sup>th</sup> World Congress on **ADHD**

Apr 20 - 23, 2017

*Canada / British Columbia / Vancouver*

Contact: Congress Organizer, CPO Hanser Service

Email: adhd2017@cpo-hanser.de

Advanced Principles of **Fracture** Management  
 Apr 20 - 23, 2017  
*United States / California / San Diego*  
 Contact: AO North America  
 Phone: 800-769-1391 or 610-695-2459  
 Fax: 610-695-2420  
 Email: customerservice@aona.org

**Urological Anatomy** for Surgery  
 Apr 21, 2017  
*United Kingdom / London*  
 Contact: Education, Royal College of Surgeons of England  
 Phone: 011-44-20-7869-6300  
 Email: education@rcseng.ac.uk

25<sup>th</sup> Annual International Society for **Magnetic Resonance in Medicine** (ISMRM) Meeting & Exhibition  
 Apr 22 - 27, 2017  
*United States / Hawaii / Honolulu*  
 Contact: Melisa Martinez, Meetings Coordinator, ISMRM  
 Phone: 510-841-1899; Fax: 510-841-2340  
 Email: melisa@ismrm.org

27<sup>th</sup> European Congress of **Clinical Microbiology & Infectious Diseases**  
 Apr 22 - 25, 2017  
*Austria / Vienna*  
 Contact: Conference Secretariat, European Society of Clinical Microbiology & Infectious Diseases  
 Phone: 011-41-61-508-0172  
 Email: eccmidinfo@escmid.org

**Non-Small Cell Lung Cancer** Hands-On Summit  
 Apr 22, 2017  
*United States / Missouri / St. Louis*  
 Contact: American College Of Chest Physicians  
 Phone: 800-343-2227 (Us Only) Or 224-521-9800  
 Fax: 224-521-9801

102<sup>nd</sup> American **Occupational Health** Conference  
 Apr 23 - 26, 2017  
*United States / Colorado / Denver*  
 Contact: American College of Occupational & Environmental Medicine  
 Phone: 847-818-1800; Fax: 847-818-9266

1<sup>st</sup> World Congress on **Maternal Fetal Neonatal Medicine**  
 Apr 23 - 26, 2017  
*United Kingdom / London*  
 Contact: Congress Organizer, MCA Scientific Events  
 Phone: 011-39-2-3493-4404  
 Email: info@worldmfnm.eu

85<sup>th</sup> European **Atherosclerosis** Society Congress  
 Apr 23 - 26, 2017  
*Czech Republic / Prague*  
 Contact: Congress Secretariat, Aim Group International - Milan Office  
 Phone: 011-39-2-56-6011; Fax: 011-39-2-5660-9045  
 Email: eas2017@aimgroup.eu

**Radiology** in Venice  
 Apr 23 - 29, 2017  
*Italy / Venice*  
 Contact: Denise Mora, Radiology International, Inc.  
 Phone: 800-481-1873 (Us) Or 860-225-1700  
 Email: denise@radiologyintl.com

10<sup>th</sup> Annual **Antibodies & Proteins** Congress  
 Apr 24 - 25, 2017  
*United Kingdom / London*  
 Contact: Danielle Dalby, Senior Marketing Manager, Oxford Global  
 Phone: 011-44-18-6524-8455; Fax: 011-44-18-6525-0985  
 Email: d.dalby@oxfordglobal.co.uk

4<sup>th</sup> Annual **Peptides** Congress  
 Apr 24 - 25<sup>2017</sup>  
*United Kingdom / London*  
 Contact: Guillaume Alonso, Marketing Executive, Oxford Global  
 Phone: 011-44-18-6524-8455  
 Email: g.alonso@oxfordglobal.co.uk

Advanced Educational Courses in **Plastic Surgery: Head & Neck, Facial Palsy**  
 Apr 24 - 25, 2017  
*United Kingdom / Manchester*  
 Contact: Secretariat, British Association of Plastic Reconstructive & Aesthetic Surgeons  
 Phone: 011-44-20-7831-5161  
 Email: secretariat@bapras.org.uk

**Cardiothoracic & Body Imaging**  
 Apr 24 - 27, 2017  
*United States / California / Rancho Mirage*  
 Contact: Lori Ehrich, Manager, Radiology CME, Penn Medicine/Department of Radiology  
 Phone: 215-662-6904; Fax: 215-349-5925  
 Email: cme@rad.upenn.edu

Operative Skills in **Neurosurgery**  
 Apr 24 - 26, 2017  
*United Kingdom / London*  
 Contact: Education, Royal College of Surgeons of England  
 Phone: 011-44-20-7869-6300  
 Email: Education@Rcseng.Ac.UK

2017 World Association for **Disaster & Emergency Medicine** (WADEM) Congress on Disaster & Emergency Medicine  
Apr 25 - 28, 2017  
*Canada / Ontario / Toronto*  
Contact: Wadem  
Phone: 608-819-6604; Fax: 608-819-6055  
Email: info@wadem.org

Intermediate Skills in **Laparoscopic Surgery**  
Apr 25 - 26, 2017  
*United Kingdom / London*  
Contact: Education, Royal College of Surgeons of England  
Phone: 011-44-20-7869-6300  
Email: education@rcseng.ac.uk

2017 British **Renal Society** (BRS) Conference  
Apr 26 - 28, 2017  
*United Kingdom / Nottingham*  
Contact: British Renal Society  
Phone: 011-44-15-4344-2153  
Fax: 011-44-12-1355-2420  
Email: brs@britishrenal.org

2017 Combined **Otolaryngology** Spring Meetings  
Apr 26 - 30, 2017  
*United States / California / San Diego*  
Contact: Marisa Villalba, Meeting or Hotel Inquiries  
Phone: 312-202-5322  
Email: mvillalba@facs.org

76<sup>th</sup> Annual Society for **Investigative Dermatology** (SID) Meeting  
Apr 26 - 29, 2017  
*United States / Oregon / Portland*  
Contact: Sid  
Phone: 216-579-9300  
Fax: 216-579-9333  
Email: sid@sidnet.org

Challenges in **Male & Female Sexual Healthcare**  
Apr 26 - 29, 2017  
*United States / Florida / St. Petersburg*  
Contact: Symposia Medicus  
Phone: 800-327-3161  
Fax: 925-969-1795

15<sup>th</sup> International **Integrative Oncology** Conference  
Apr 27 - 29, 2017  
*United States / California / San Diego*  
Contact: Debbie Curtis, Administrator, Best answer for Cancer Foundation  
Phone: 512-342-8181  
Email: admin@bestanswerforcancer.org

2017 American Association of **Genitourinary Surgeons** (AAGUS) Annual Meeting  
Apr 27 - 30, 2017  
*United States / Florida / Key Biscayne*  
Contact: Jeannette Sofia  
Phone: 708-216-5100; Fax: 708-216-8991  
Email: aagusorg@yahoo.com

Speciality Skills in **Emergency Surgery & Trauma**  
Apr 27 - 28, 2017  
*United Kingdom / London*  
Contact: Education, Royal College of Surgeons of England  
Phone: 011-44-20-7869-6300  
Email: education@rcseng.ac.uk

2017 American Congress of **Rehabilitation Medicine** (ACRM) Mid-Year Meeting  
Apr 28 - 29, 2017  
*United States / Georgia / Atlanta*  
Contact: Acrm  
Phone: 703-435-5335; Fax: 866-692-1619  
Email: info@acrm.org

4<sup>th</sup> Annual Clinical Advances in **Arrhythmias & Cardiovascular Disease**  
Apr 28 - 30, 2017  
*United States / California / San Diego*  
Contact: Scripps Conference Services & Cme  
Phone: 858-652-5400  
Email: med.edu@scrippshealth.org

CME on the Run! 2016-2017 - **Palliative Care & Geriatrics**  
Apr 28, 2017  
*Canada / British Columbia / Vancouver*  
Contact: Conference Registration, Ubc Cpd  
Phone: 604-875-5101; Fax: 604-875-5078  
Email: cpd.info@ubc.ca

What every hand surgeon should know about the wrist: **Distal Radius, Carpus & Ulnar-Sided Wrist Pain**  
Apr 28 - 29, 2017  
*United States / Colorado / Denver*  
Contact: American Society for Surgery of the Hand  
Phone: 312-880-1900  
Email: info@assh.org

Evidence Based **Assistive Reproductive Technology**: 1<sup>st</sup> International Symposium  
Apr 29 - 30, 2017  
*Turkey / Antalya*  
Contact: Merih Altun, Mrs., Gelecek the Center for Human Reproduction  
Phone: 011-90-24-2324-2526  
Email: tbmd2016@gmail.com



11<sup>th</sup> International Society of **Physical & Rehabilitation Medicine** Congress

Apr 30 - May 4, 2017

*Argentina / Buenos Aires*

Contact: Secretariat, Kenes International

Phone: 011-41-22-908-0488

Email: isprm@kenes.com

6<sup>th</sup> World **Intracranial Hemorrhage & Heads** Conference

May 1 - 3, 2017

*United States / Maryland / Baltimore*

Contact: Kenes Group, Congress Secretariat, Kenes Group

Phone: 011-90-53-4517-2181

Email: atoraman@kenes.com

Intermediate Skills in **Plastic Surgery**: Facial Soft Tissue Reconstruction

May 2 - 3, 2017

*United Kingdom / London*

Contact: Education, Royal College of Surgeons of England

Phone: 011-44-20-7869-6300

Email: education@rcseng.ac.uk

2017 **Myelodysplastic Syndromes** Symposium

May 3 - 6, 2017

*Spain / Valencia*

Contact: Ron Marcovici, Kenes Group

Phone: 011-41-22-908-0488

Email: rmarcovici@kenes.com

19<sup>th</sup> Annual International Society for **Bipolar Disorders** Conference

May 4 - 7, 2017

*United States / Washington*

Contact: Ron Marcovici, Kenes Group

Phone: 011-41-22-908-0488

Email: rmarcovici@kenes.com

2017 Advances in **Rhinoplasty** Course

May 4 - 7, 2017

*United States / Illinois / Chicago*

Contact: American Academy of Facial Plastic & Reconstructive Surgery

Phone: 703-299-9291

Email: info@aafprs.org

2017 **Arteriosclerosis, Thrombosis & Vascular Biology** | Peripheral Vascular Disease Scientific Sessions

May 4 - 6, 2017

*United States / Minnesota / Minneapolis*

Contact: American Heart Association

Phone: 888-242-2453 or 214-570-5935

Email: scientificconferences@heart.org

2017 Division of **Child & Adolescent Psychiatry** Annual Conference

May 5, 2017

*United Kingdom / London*

Contact: Faye Slote, London Health Sciences Centre

Phone: 519-685-8500 Ext. 75783

Email: faye.slote@lhsc.on.ca

2017 Society for **Endocrinology, Metabolism & Diabetes** of South Africa Congress

May 5 - 7, 2017

*South Africa / Johannesburg*

Contact: Carolyn Melnick, Congress Secretariat, Scatterlings Conference & Events

Phone: 011-27-21-422-2402; Fax: 011-27-86-620-4555

Email: caro@soafrica.com

8<sup>th</sup> European Meeting on **Adult Congenital Heart Disease** (Euroguch 2017)

May 5 - 6, 2017

*Switzerland / Lausanne*

Contact: Sarah Krein, Paragon Group

Phone: 011-41-22-533-0948

Email: skrein@paragong.com

Primary Care: Topics in **Allergy, Immunology & Dermatology** Baltic Adventure Cruise

May 5 - 17, 2017

*Denmark / Copenhagen*

Contact: Continuing Education Inc

Phone: 800-422-0711

Email: registrar@continuingeducation.com

2017 American Society of **Pediatric Nephrology** (ASPn) Annual meeting

May 6 - Jun 9, 2017

*United States / California / San Francisco*

Contact: Aspnn

Phone: 346-980-9752; Fax: 346-980-9752

Email: info@aspneph.com

2017 **Preventive Medicine & Preventive Cardiology**

Update Western Mediterranean Cruise

May 8 - 18, 2017

*Spain / Barcelona*

Contact: Continuing Education Inc

Phone: 800-422-0711

Email: registrar@continuingeducation.com

2017 Lab-On-A-Chip & **Microfluidics**

May 10 - 11, 2017

*Germany / Munich*

Contact: Delegate Sales, Selectbio

Phone: 011-44-17-8731-5110

Email: delegatesales@selectbio.com

20<sup>th</sup> Annual American Society of **Gene & Cell Therapy** (ASGCT) Meeting  
 May 10 - 13, 2017  
 United States / District of Columbia / Washington  
 Contact: Asgct Executive Office  
 Phone: 414-278-1341  
 Email: info@asgct.org

9<sup>th</sup> International Conference on Advances in **Diabetes & Insulin Therapy**  
 May 11 - 13, 2017  
 Serbia / Belgrade  
 Contact: Rok Bolcina, Registration Manager, Agada, Diabetes Education & Research Institute  
 Email: info@adit-conf.org

17<sup>th</sup> International Workshop on **Chronic Lymphocytic Leukemia**  
 May 12 - 15, 2017  
 United States / New York / New York  
 Contact: Kraig Steubing, Bio Ascend  
 Phone: 888-476-9129  
 Email: iwcll2017@bioascend.com

65<sup>th</sup> Annual Society for **Pediatric Urology** (SPU) Meeting  
 May 12 - 14, 2017  
 United States / Massachusetts / Boston  
 Contact: Lorraine O'grady, Executive Director, Spu  
 Phone: 978-927-8330  
 Fax: 978-524-0498

Vision for **Multiple Sclerosis** (MS)  
 May 12, 2017  
 United Kingdom / Edinburgh  
 Contact: Caroline Mackenzie, Conference Organiser, Zibrant  
 Phone: 011-44-77-8654-6824  
 Email: info@visionmsconference.com

Controversies in **Perioperative Medicine**  
 May 14 - 20, 2017  
 Portugal / Evora  
 Contact: Dale Grzegorzcy, Benefactor Travel  
 Phone: 800-801-6147  
 Fax: 905-842-2196  
 Email: dale@benefactortravel.com

2017 World Live **Neurovascular Conference** (WLNC)  
 May 15 - 17, 2017  
 United States / California / Los Angeles  
 Contact: Registration Office, Wlnc  
 Fax: 011-90-212-347-6363  
 Email: registration@wlnc.org

13<sup>th</sup> World Congress on **Endometriosis**  
 May 17 - 20, 2017  
 Canada / British Columbia / Vancouver  
 Contact: Andreas Hinnerth, Conference Manager, World Endometriosis Society / ICS Ltd.  
 Email: wce2017@icsevents.com

2017 Osseo: 6th International Congress on **Bone Conduction Hearing** & related technologies  
 May 17 - 20, 2017  
 Netherlands / Nijmegen  
 Contact: Congress Secretariat, Congress Care  
 Phone: 011-31-7-3690-1415  
 Email: osseo2017@congresscare.com

25<sup>th</sup> Annual Symposium: New Developments in **Prenatal Diagnosis & Medical Genetics**  
 May 17, 2017  
 Canada / Ontario / Toronto  
 Contact: Elizabeth Gan, CME Administrative Course Director, University of Toronto / Mount Sinai Hospital  
 Phone: 416-586-4800 Ext. 2489; Fax: 416-586-5958  
 Email: cmeobgyn@mtsinai.on.ca

1<sup>st</sup> International Congress of **Micro-Immunotherapy**  
 May 18 - 20, 2017  
 Spain / Mallorca  
 Contact: Polly Gartrell, Congress Coordinator, Dimi S.L  
 Phone: 011-34-9-7162-2478  
 Email: polly.gartrell@icomi2017.org

2017 World Congress of the European Association for **Palliative Care**  
 May 18 - 20, 2017  
 Spain / Madrid  
 Contact: Lena Schneider, Interplan Ag  
 Phone: 011-49-89-5482-3437  
 Email: eapc2017@interplan.de

**Menopause** Special Skills Module  
 May 18 - 19, 2017  
 United Kingdom / Leeds  
 Contact: Kate Ellis, British Menopause Society  
 Phone: 011-44-16-2889-0199  
 Email: kate.ellis@bms-whc.org.uk

Whole Body MRI in **Myeloma & Bone Disease** – How to do it  
 May 18, 2017  
 United Kingdom / London  
 Contact: British Institute of Radiology  
 Phone: 011-44-20-3668-2220; Fax: 011-44-20-3411-6354  
 Email: conference@bir.org.uk

**15<sup>th</sup> World Medical Nanotechnology Congress &**

Expo

May 22 - 23, 2017

*Japan / Osaka*

Contact: Jonathan Casio, Conference Series Llc

Phone: 702-508-5200; Fax: 702-508-5200

Email: medicalnanotechnology@conferenceseries.com

**2017 Family Medicine Congressional Conference**

May 22 - 23, 2017

*United States / District of Columbia / Washington*

Contact: American Academy of Family Physicians

Phone: 800-274-2237 or 913-906-6000

Fax: 913-906-6075

**2017 Skin Vaccination Summit**

May 22 - 24, 2017

*Netherlands / Leiden*

Contact: Caroline Sumner, Meetings Management

Phone: 011-44-14-8342-7770; Fax: 011-44-14-8342-8516

Email: csumner@meetingsmgmt.u-net.com

**World Heart Congress**

May 22 - 24, 2017

*Japan / Osaka*

Contact: Akira Jacob, Program Manager, Conference Series LLC

Phone: 702-508-5200

Email: heart@conferenceseries.com

**5<sup>th</sup> Bit International Congress of Gynaecology & Obstetrics**

May 25 - 27, 2017

*Czech Republic / Prague*

Contact: Cathy Han, Ms, Bit Group Global Ltd.

Phone: 011-86-411-8479-9609 Ext. 816

Fax: 011-86-411-8479-6897

Email: cathy@congress-icgo.com

**2017 International Neuromodulation Society (INS) Congress**

May 27 - Jun 1, 2017

*United Kingdom / Edinburgh*

Contact: Tia Sofatzis, Executive Director, Ins

Executive Offices

Phone: 415-683-3237

Fax: 415-683-3218

Email: ins@neuromodulation.com

**13<sup>th</sup> International Stereotactic Radiosurgery Society (ISRS) Congress**

May 28 - Jun 1, 2017

*Switzerland / Montreux*

Contact: Secretariat, ISRS

Phone: 011-33-4-9509-3800; Fax: 011-33-4-9509-3801

Email: isrs@myeventonline.net

**44<sup>th</sup> International Society for the Study of the Lumbar****Spine (ISSLS) annual meeting**

May 29 - Jun 2, 2017

*Greece / Athens*

Contact: Katarina Olinder, Issls

Phone: 011-46-31-786-4436

Email: katarina.olinder@gu.se

**2<sup>nd</sup> International Conference on Cytokine Signaling In Cancer**

May 30 - Jun 4, 2017

*Greece / Heraklion*

Contact: Aegean Conferences

Phone: 610-527-7630; Fax: 610-527-7631

Email: info@aegeanconferences.org

**Definitive Surgical Trauma Skills**

May 30 - 31, 2017

*United Kingdom / London*

Contact: Education, Royal College of Surgeons of England

Phone: 011-44-20-7869-6300

Email: education@rcseng.ac.uk

**Surgical Anastomosis Techniques**

May 31, 2017

*United Kingdom / Glasgow*

Contact: Ruth Gurd, Event Coordinator, Royal College of Physicians &amp; Surgeons of Glasgow

Phone: 011-44-14-1241-6228

Email: ruth.gurd@rcpsg.ac.uk

**11<sup>th</sup> Asian Society of Cardiovascular Imaging Congress**

Jun 1 - 3, 2017

*Japan / Kyoto*

Contact: Congress Secretariat, Convention Linkage, Inc.

Phone: 011-81-6-6377-2188; Fax: 011-81-6-6377-2075

Email: asci2017@c-linkage.co.jp

**1<sup>st</sup> International Conference on Fatty Liver**

Jun 1 - 3, 2017

*Spain / Seville*

Contact: Kenes Group, Kenes Group

Phone: 011-41-2-2908-0488

Email: icfl@kenes.com

**14<sup>th</sup> Asian Society of Paediatric Anaesthesiologists (ASPA) Conference**

Jun 3 - 4, 2017

*India / Mumbai*

Contact: Jessie Tan, Aspa Secretariat, Department of Paediatric Anaesthesia, KK Women's &amp; Children's Hospital

Email: jessie.tan.hl@kkh.com.sg

Optimizing Patient Care: **Chronic Pain & Urology**  
Iceland Tour  
Jun 3 - 9, 2017  
*Iceland / Reykjavik*  
Contact: Kirsten Dawick, Communications  
Coordinator, Sea Courses Cruises  
Phone: 604-684-7327; Fax: 604-684-7337  
Email: cruises@seacourses.com

11<sup>th</sup> Biennial International Society of **Arthroscopy, Knee Surgery** & Orthopaedic Sports Medicine (ISAKOS) Congress  
Jun 4 - 8, 2017  
*China / Shanghai*  
Contact: Isakos Office  
Phone: 925-807-1197; Fax: 925-807-1199

18<sup>th</sup> International Congress of **Comparative Endocrinology**  
Jun 4 - 9, 2017  
*United States / Alberta / Lake Louise*  
Contact: Hamid R. Habibi, Conference Organizer,  
Department of Biological Sciences, University Of  
Calgary  
Email: icce18@ucalgary.ca

2017 **Plant-Based Vaccines Antibodies** & Biologics Meeting  
Jun 5 - 7, 2017  
*Portugal / Albufeira*  
Contact: John Herriot, Meetings Management  
Phone: 011-44-14-8342-7770  
Email: jherriot@meetingsmgmt.u-net.com

Intermediate Skills in **Laparoscopic Surgery**  
Jun 5 - 6, 2017  
*United Kingdom / London*  
Contact: Education, Royal College of Surgeons of  
England  
Phone: 011-44-20-7869-6300  
Email: education@rcseng.ac.uk

Specialty Skills in **Vascular Surgery**  
Jun 5 - 6, 2017  
*United Kingdom / London*  
Contact: Education, Royal College of Surgeons of  
England  
Phone: 011-44-20-7869-6300  
Email: education@rcseng.ac.uk

2017 European Society of **Paediatric and Neonatal Intensive Care** meeting  
Jun 6 - 9, 2017  
*Portugal / Lisbon*  
Contact: Yoni Grysman, Kenes International  
Phone: 011-41-22-908-0488  
Email: Ygrysman@Kenes.Com

2017 Joint **Chest-SGP Congress**  
Jun 7 - 9, 2017  
*Switzerland / Basel*  
Contact: Congress Secretariat Joint Chest-Sgp  
Congress 2017, Congrex Switzerland Ltd.  
Phone: 011-41-61-686-7777  
Email: registration.chestswitzerland2017@congrex.com

Advanced Skills in **Vascular Surgery**  
Jun 7 - 9, 2017  
*United Kingdom / London*  
Contact: Education, Royal College of Surgeons of  
England  
Phone: 011-44-20-7869-6300  
Email: education@rcseng.ac.uk

2017 **Abdominal Wall Reconstruction** Conference  
Jun 8 - 10<sup>2017</sup>  
*United States / Washington DC*  
Contact: Alison Marinelli, Cine-Med Inc  
Phone: 203-263-0006

2017 ICED: International Conference for **Eating Disorders**  
Jun 8 - 10, 2017  
*Czech Republic / Prague*  
Contact: Academy for Eating Disorders  
Phone: 703-234-4079  
Fax: 703-435-4390  
Email: info@aedweb.org

Stoller: **Musculoskeletal Imaging** tutorial  
Jun 8 - 9, 2017  
*United States / Nevada / Las Vegas*  
Contact: Administrator, Cme Science  
Phone: 650-440-4424  
Email: info@cmescience.com

**Transanal Total Mesorectal Excision** Course  
Jun 8, 2017  
*Canada / Ontario / Toronto*  
Contact: Continuing Professional Development,  
University of Toronto  
Phone: 888-512-8173 or 416-978-2719  
Email: info-sur1621@cpdutoronto.ca

2<sup>nd</sup> International Conference on the long & the short of **Non-Coding RNA S**  
Jun 9 - 14, 2017  
*Greece / Heraklion*  
Contact: Aegean Conferences  
Phone: 610-527-7630  
Fax: 610-527-7631  
Email: info@aegeanconferences.org

2017 Society of **Nuclear Medicine & Molecular Imaging** (SNMMI) annual meeting  
 Jun 10 - 14, 2017  
*United States / Colorado / Denver*  
 Contact: Snmmi  
 Phone: 703-708-9000

8<sup>th</sup> International Conference on **Children's Bone Health**  
 Jun 10 - 13, 2017  
*Germany / Würzburg*  
 Contact: Janet Crompton, Conference Organizer  
 Phone: 011-44-14-5354-9929  
 Fax: 011-44-14-5354-8919  
 Email: iccbh@ectsoc.org

**Pain Medicine & MSK Ultrasound** Cadaver Course  
 Jun 10 - 11, 2017  
*United States / Illinois / Chicago*  
 Contact: American Society of Regional Anesthesia & Pain Medicine  
 Phone: 855-795-2772 (USA) Or 412-471-2718  
 Email: asraassistant@asra.com

11<sup>th</sup> Global Gastroenterologists Meeting: **Gastro 2017**  
 Jun 12 - 13, 2017  
*Italy / Rome*  
 Contact: Adam Johnson, Director, Conference Series Llc  
 Phone: 650-268-9744 | M 702-508-5202 Ext. 8063  
 Email: ukgastro2016@gmail.com

6<sup>th</sup> International Conference on **Tissue Engineering**  
 Jun 14 - 19, 2017  
*Greece / Heraklion*  
 Contact: Aegean Conferences  
 Phone: 610-527-7630; Fax: 610-527-7631  
 Email: info@aegeanconferences.org

2017 **Neurorehabilitation**  
 Jun 15 - 17, 2017  
*United States / Massachusetts / Waltham*  
 Contact: Harvard Medical School Department of Continuing Education  
 Phone: 617-384-8600  
 Email: ceprograms@hms.harvard.edu

2017 Updates in **Gastroenterology/Rheumatology** for the Primary Care Provider Adriatic & Italy Cruise  
 Jun 15 - 24, 2017  
*Italy / Venice*  
 Contact: Continuing Education, Continuing Education, Continuing Education, Inc  
 Phone: 800-422-0711  
 Email: registrar@continuingeducation.com

6<sup>th</sup> International Congress on **Neuropathic Pain**  
 Jun 15 - 18, 2017  
*Sweden / Gothenburg*  
 Contact: Ron Marcovici, Kenes Group  
 Phone: 011-41-22-908-0488  
 Email: rmarcovici@kenes.com

9<sup>th</sup> International Conference on **Genomics & Pharmacogenomics**  
 Jun 15 - 16, 2017  
*United Kingdom / London*  
 Contact: Sharon Williams, 9<sup>th</sup> International Conference on Genomics & Pharmacogenomics, Conferenceseries.Llc  
 Phone: 650-268-9744  
 Email: genomics@conferenceseries.net

14<sup>th</sup> International Conference on **Innate Immunity**  
 Jun 19 - 24, 2017  
*Greece / Heraklion*  
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 Email: info@aegeanconferences.org

1<sup>st</sup> Copenhagen **Surgical Pathology** Update – Sharing our best  
 Jun 19 - 21, 2017  
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 Phone: 011-45-70-222-130  
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*United Kingdom / London*  
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 Phone: 702-508-9028  
 Email: pharmamicrobiology17@gmail.com

2017 Belfast **Pathology**  
 Jun 20 - 23, 2017  
*United Kingdom / Belfast*  
 Contact: The Pathological Society of Great Britain & Ireland  
 Phone: 011-44-20-7347-5751 / 5752  
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2017 **Computer Assisted Radiology & Surgery** (CARS) 31<sup>st</sup> International Congress & Exhibition - Joint Congress of IFCARS / ISCAS / CAD / CMI / IPCAI  
 Jun 20 - 24, 2017  
*Spain / Barcelona*  
 Contact: Mrs. Franziska Schweikert, Cars conference office  
 Phone: 011-49-7742-922-434; Fax: 011-49-7742-922-438  
 Email: office@cars-int.org

**2017 World Summit on Pediatrics**

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*Italy / Rome*

Contact: Dr. Angelo Raganato, Osservatorio Paidoss

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**10<sup>th</sup> International Conference on Complement Therapeutics**

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*Greece / Heraklion*

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**13<sup>th</sup> European Congress of Clinical Pharmacology & Therapeutics**

Jun 24 - 27, 2017

*Czech Republic / Prague*

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**3<sup>rd</sup> Congress of the European Academy of Neurology**

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*Netherlands / Amsterdam*

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**17<sup>th</sup> Quadrennial Meeting of the World Society for Stereotactic & Functional Neurosurgery**

Jun 26 - 29, 2017

*Germany / Berlin*

Contact: Organizing Secretariat, Mco Congrès

Phone: 011-33-4-9509-3800; Fax: 011-33-4-9509-3801

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**2017 Tissue Engineering & Regenerative Medicine**

International Society (TERMIS) European Conference

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*Switzerland / Davos*

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Email: swilburn@termis.org

**7<sup>th</sup> World Glaucoma Congress**

Jun 28 - July 1, 2017

*Finland / Helsinki*

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Phone: 011-31-20-679-3411; Fax: 011-31-20-673-7306

Email: info@worldglaucoma.org

**2017 Macular Meeting: Imaging & Managing Macular Diseases**

July 2 - 4, 2017

*France / Paris*

Contact: Julie Bauwens, Kenes Group

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**2017 Arthroscopy & Arthroplasty**

July 3 - 7, 2017

*Netherlands / Utrecht*

Contact: Arthroscopy &amp; Arthroplasty

Phone: 011-31-30-276 9174; Fax: 011-31-30-276 9251

Email: info@shoulder-elbow-knee.nl

**11<sup>th</sup> International Symposium on Pediatric Pain**

Jul 6 - 9, 2017

*Malaysia / Kuala Lumpur*

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**12<sup>th</sup> Annual Nephrology & Urology Conference**

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*Malaysia / Kuala Lumpur*

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**STI and HIV World Congress**

Jul 9 - 12, 2017

*Brazil / Rio de Janeiro*

Contact: Conference Secretariat, Activia Turismo

Email: STIHIVRIO2017@activiaturismo.com.br

**2017 International Conference on Nanobiotechnology**

Jul 10 - 11, 2017

*United States / Illinois / Chicago*

Contact: Dolly Ackinson, Nanobiotechnology 2017, Conference Series LLC

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**World Congress on Epilepsy and Treatment**

Jul 10 - 12, 2017

*Thailand / Bangkok*

Contact: Pulsus Meetings

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# WHO-Facts Sheet

1. HIV/AIDS
2. Preterm Birth
3. Schistosomiasis
4. Avian and Other Zoonotic Influenza

Compiled and edited by  
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## 1. HIV/AIDS

### Overview

The Human Immunodeficiency Virus (HIV) targets the immune system and weakens people's defence systems against infections and some types of cancer. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient. Immune function is typically measured by CD4 cell count. Immunodeficiency results in increased susceptibility to a wide range of infections, cancers and other diseases that people with healthy immune systems can fight off.

The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS), which can take from 2 - 15 years to develop depending on the individual. AIDS is defined by the development of certain cancers, infections, or other severe clinical manifestations.

### KEY FACTS

- HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2015, 1.1 (940,000 - 1.3 million) million people died from HIV-related causes globally.
- There were approximately 36.7 (34.0 - 39.8) million people living with HIV at the end of 2015 with 2.1 (1.8 - 2.4) million people becoming newly infected with HIV in 2015 globally.
- Sub-Saharan Africa is the most affected region, with 25.6 (23.1 - 28.5) million people living with HIV in 2015. Also sub-Saharan Africa accounts for two-thirds of the global total of new HIV infections.
- HIV infection is often diagnosed through rapid diagnostic tests (RDTs), which detect the presence

or absence of HIV antibodies. Most often these tests provide same-day test results; essential for same day diagnosis and early treatment and care.

- There is no cure for HIV infection. However, effective antiretroviral (ARV) drugs can control the virus and help prevent transmission so that people with HIV, and those at substantial risk, can enjoy healthy, long and productive lives.
- It is estimated that currently only 60% of people with HIV know their status. The remaining 40% or over 14 million people need to access HIV testing services. By mid-2016, 18.2 (16.1 - 19.0) million people living with HIV were receiving antiretroviral therapy (ART) globally.
- Between 2000 and 2015, new HIV infections fell by 35%, AIDS-related deaths fell by 28% with some eight million lives saved. This achievement was the result of great efforts by national HIV programmes supported by civil society and a range of development partners.
- Expanding ART to all people living with HIV and expanding prevention choices can help avert 21 million AIDS-related deaths and 28 million new infections by 2030.

### Signs and symptoms

The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months, many are unaware of their status until later stages. The first few weeks after initial infection, individuals may experience no symptoms or an influenza-like illness including fever, headache, rash or sore throat.

As the infection progressively weakens the immune system, an individual can develop other signs and symptoms, such as swollen lymph nodes, weight

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loss, fever, diarrhea and cough. Without treatment, they could also develop severe illnesses such as tuberculosis, cryptococcal meningitis, and cancers such as lymphomas and Kaposi's sarcoma, among others.

### Transmission

HIV can be transmitted via the exchange of a variety of body fluids from infected individuals, such as blood, breast milk, semen and vaginal secretions. Individuals cannot become infected through ordinary day-to-day contact such as kissing, hugging, shaking hands, or sharing personal objects, food or water.

### Risk factors

Behaviours and conditions that put individuals at greater risk of contracting HIV include:

- having unprotected anal or vaginal sex;
- having another sexually transmitted infection such as syphilis, herpes, chlamydia, gonorrhoea, and bacterial vaginosis;
- sharing contaminated needles, syringes and other injecting equipment and drug solutions when injecting drugs;
- receiving unsafe injections, blood transfusions, tissue transplantation, medical procedures that involve unsterile cutting or piercing; and
- experiencing accidental needle stick injuries, including among health workers.

### Diagnosis

Serological tests, such as RDTs or enzyme immunoassays (EIAs), detect the presence or absence of antibodies to HIV-1/2 and/or HIV p24 antigen. When such tests are used within a testing strategy according to a validated testing algorithm, HIV infection can be detected with great accuracy. It is important to note that serological tests detect antibodies produced by an individual as part of their immune system to fight off foreign pathogens, rather than direct detection of HIV itself.

Most individuals develop antibodies to HIV-1/2 within 28 days and therefore, antibodies may not be detectable early after infection, the so-called window period. This early period of infection represents the time of greatest infectivity; however HIV transmission can occur during all stages of the infection.

It is best practice to also retest all people initially diagnosed as HIV-positive before they enrol in care and/or treatment to rule out any potential testing or reporting error.

### HIV testing services

HIV testing should be voluntary and the right to decline testing should be recognized. Mandatory or

coerced testing by a health-care provider, authority or by a partner or family member is not acceptable as it undermines good public health practice and infringes on human rights.

Some countries have introduced, or are considering, self-testing as an additional option. HIV self-testing is a process whereby a person who wants to know his or her HIV status collects a specimen, performs a test and interprets the test results in private. HIV self-testing does not provide a definitive diagnosis; instead, it is an initial test which requires further testing by a health worker using a nationally validated testing algorithm.

All HIV testing services must include the 5 C's recommended by WHO: informed Consent, Confidentiality, Counselling, Correct test results and Connection (linkage to care, treatment and other services).

### Prevention

Individuals can reduce the risk of HIV infection by limiting exposure to risk factors. Key approaches for HIV prevention, which are often used in combination, include:

#### 1. Male and female condom use

Correct and consistent use of male and female condoms during vaginal or anal penetration can protect against the spread of sexually transmitted infections, including HIV. Evidence shows that male latex condoms have an 85% or greater protective effect against HIV and other sexually transmitted infections (STIs).

#### 2. Testing and counselling for HIV and STIs

Testing for HIV and other STIs is strongly advised for all people exposed to any of the risk factors. This way people learn of their own infection status and access necessary prevention and treatment services without delay. WHO also recommends offering testing for partners or couples. Additionally, WHO is recommending assisted partner notification approaches so that people with HIV receive support to inform their partners either on their own, or with the help of health care providers.

#### 3. Testing and counselling, linkages to tuberculosis care

Tuberculosis (TB) is the most common presenting illness and cause of death among people with HIV. It is fatal, if undetected or untreated, and the leading cause of death among people with HIV- responsible for one of every three HIV-associated deaths. Early detection of TB and prompt linkage to TB treatment and ART can prevent these deaths. TB screening should be offered routinely at HIV care services. Individuals who are

diagnosed with HIV and active TB should be urgently started on TB treatment and ART. TB preventive therapy should be offered to people with HIV who do not have active TB.

#### 4. Voluntary medical male circumcision

Medical male circumcision, when safely provided by well-trained health professionals, reduces the risk of heterosexually acquired HIV infection in men by approximately 60%. This is a key intervention supported in 14 countries in Eastern and Southern Africa with high HIV prevalence and low male circumcision rates.

#### 5. Antiretroviral (ARV) drug use for prevention

5.1: Prevention benefits of ART: A 2011 trial has confirmed if an HIV-positive person adheres to an effective ART regimen, the risk of transmitting the virus to their uninfected sexual partner can be reduced by 96%. The WHO recommendation to initiate ART in all people living with HIV will contribute significantly to reducing HIV transmission.

5.2: Pre-exposure prophylaxis (PrEP) for HIV-negative partner: Oral PrEP of HIV is the daily use of ARV drugs by HIV-uninfected people to block the acquisition of HIV. More than 10 randomized controlled studies have demonstrated the effectiveness of PrEP in reducing HIV transmission among a range of populations including serodiscordant heterosexual couples (where one partner is infected and the other is not), men who have sex with men, transgender women, high-risk heterosexual couples, and people who inject drugs.

WHO recommends PrEP as a prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches.

5.3: Post-exposure prophylaxis for HIV (PEP): Post-exposure prophylaxis (PEP) is the use of ARV drugs within 72 hours of exposure to HIV in order to prevent infection. PEP includes counselling, first aid care, HIV testing, and administering of a 28-day course of ARV drugs with follow-up care. WHO recommends PEP use for both occupational and non-occupational exposures and for adults and children.

#### 6. Harm reduction for injecting drug users

People who inject drugs can take precautions against becoming infected with HIV by using sterile injecting equipment, including needles and syringes, for each injection and not sharing other drug using equipment and drug solutions. A comprehensive package of interventions for HIV prevention and treatment includes:

- needle and syringe programs;
- opioid substitution therapy for people dependent on opioids and other evidence based drug dependence treatment;
- HIV testing and counselling;
- risk-reduction information and education;
- HIV treatment and care;
- access to condoms; and
- management of STIs, tuberculosis and viral hepatitis.

#### 7. Elimination of mother-to-child transmission of HIV (EMTCT)

The transmission of HIV from an HIV-positive mother to her child during pregnancy, labour, delivery or breastfeeding is called vertical or mother-to-child transmission (MTCT). In the absence of any interventions during these stages, rates of HIV transmission from mother-to-child can be between 15-45%. MTCT can be nearly fully prevented if both the mother and the child are provided with ARV drugs throughout the stages when infection could occur.

WHO recommends options for prevention of MTCT (PMTCT), which includes providing ARVs to mothers and infants during pregnancy, labour and the post-natal period, and offering life-long treatment to HIV-positive pregnant women regardless of their CD4 count.

In 2015, 77% (69 - 86%) of the estimated 1.4 (1.3 - 1.6) million pregnant women living with HIV globally received effective ARV drugs to avoid transmission to their children. A growing number of countries are achieving very low rates of MTCT and some (Armenia, Belarus, Cuba and Thailand) have been formally validated for elimination of MTCT of HIV. Several countries with a high burden of HIV infection are closing in on that goal.

#### Treatment

HIV can be suppressed by combination ART consisting of three or more ARV drugs. ART does not cure HIV infection but controls viral replication within a person's body and allows an individual's immune system to strengthen and regain the capacity to fight off infections.

In 2016, WHO released the second edition of the "Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection." These guidelines present several new recommendations, including the recommendation to provide lifelong ART to all children, adolescents and adults, including all pregnant and breastfeeding women living with HIV, regardless of CD4 cell count.

WHO has also expanded earlier recommendations to offer PrEP to selected people at substantial risk

of acquiring HIV. Alternative first-line treatment regimens are recommended, including an integrase inhibitor as an option in resource-limited settings and reduced dosage of a key recommended first-line drug, efavirenz, to improve tolerability and reduce costs. By mid-2016, 18.2.0 million people living with HIV were receiving ART globally which meant a global coverage of 46% (43 - 50%).

Based on WHO's new recommendations, to treat all people living with HIV and offer antiretroviral drugs as an additional prevention choice for people at "substantial" risk, the number of people eligible for antiretroviral treatment increases from 28 million to all 36.7 million people. Expanding access to treatment is at the heart of a new set of targets for 2020 which aim to end the AIDS epidemic by 2030.

### WHO response

The Sixty-ninth World Health Assembly endorsed a new "Global Health Sector Strategy on HIV for 2016 - 2021". The strategy includes five strategic directions that guide priority actions by countries and by WHO over the next six years.

The strategic directions are:

- Information for focused action (know your epidemic and response).
- Interventions for impact (covering the range of services needed)
- Delivering for equity (covering the populations in need of services).
- Financing for sustainability (covering the costs of services).
- Innovation for acceleration (looking towards the future).

## 2. PRETERM BIRTH

### Overview

Preterm is defined as babies born alive before 37 weeks of pregnancy are completed. There are sub-categories of preterm birth, based on gestational age:

- extremely preterm (<28 weeks)
- very preterm (28 to <32 weeks)
- moderate to late preterm (32 to <37 weeks).

Induction or caesarean birth should not be planned before 39 completed weeks unless medically indicated.

### KEY FACTS

- Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising.
- Preterm birth complications are the leading cause of death among children under five years of age, responsible for nearly one million deaths in 2015.

- Three-quarters of them could be saved with current, cost-effective interventions.
- Across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies born.

### The problem

An estimated 15 million babies are born too early every year. That is more than one in 10 babies. Almost one million children die each year due to complications of preterm birth. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems.

Globally, prematurity is the leading cause of death in children under the age of five. And in almost all countries with reliable data, preterm birth rates are increasing.

Inequalities in survival rates around the world are stark. In low-income settings, half of the babies born at or below 32 weeks (2 months early) die due to a lack of feasible, cost-effective care, such as warmth, breastfeeding support, and basic care for infections and breathing difficulties. In high-income countries, almost all of these babies survive.

### The solution

More than three-quarters of premature babies can be saved with feasible, cost-effective care, *e.g.*, essential care during child birth and in the postnatal period for every mother and baby, provision of antenatal steroid injections (given to pregnant women at risk of preterm labour and under set criteria to strengthen the babies' lungs), kangaroo mother care (the baby is carried by the mother with skin-to-skin contact and frequent breastfeeding) and antibiotics to treat newborn infections. For example, continuity of midwifery-led care in settings where there are effective midwifery services has been shown to reduce prematurity by around 24%.

Preventing deaths and complications from preterm birth starts with a healthy pregnancy. Quality care before, between and during pregnancies will ensure all women have a positive pregnancy experience. WHO's antenatal care guidelines include key interventions to help prevent preterm birth, such as counselling on healthy diet and optimal nutrition, and tobacco and substance use; fetal measurements including use of ultrasound to help determine gestational age and detect multiple pregnancies; and a minimum of eight contacts with health professionals throughout pregnancy to identify and manage other risk factors, such as infections. Better access to contraceptives and increased empowerment could also help reduce preterm births.

### Why does preterm birth happen?

Preterm birth occurs for a variety of reasons. Most preterm births happen spontaneously, but some are due to early induction of labour or caesarean birth, whether for medical or non-medical reasons.

Common causes of preterm birth include multiple pregnancies, infections and chronic conditions such as diabetes and high blood pressure; however, often no cause is identified. There could also be a genetic influence. Better understanding of the causes and mechanisms will advance the development of solutions to prevent preterm birth.

### Where and when does preterm birth happen?

More than 60% of preterm births occur in Africa and South Asia, but preterm birth is truly a global problem. In the lower-income countries, on average, 12% of babies are born too early compared with 9% in higher-income countries. Within countries, poorer families are at higher risk.

The 10 countries with the greatest number of preterm births<sup>1</sup>:

- India: 3,519,100
- China: 1,172,300
- Nigeria: 773,600
- Pakistan: 748,100
- Indonesia: 675,700
- The United States of America: 517,400
- Bangladesh: 424,100
- The Philippines: 348,900
- The Democratic Republic of the Congo: 341,400
- Brazil: 279,300

The 10 countries with the highest rates of preterm birth per 100 live births:

- Malawi: 18.1 per 100
- Comoros: 16.7
- Congo: 16.7
- Zimbabwe: 16.6
- Equatorial Guinea: 16.5
- Mozambique: 16.4
- Gabon: 16.3
- Pakistan: 15.8
- Indonesia: 15.5
- Mauritania: 15.4

Of 65 countries with reliable trend data, all but 3 show an increase in preterm birth rates over the past 20 years. Possible reasons for this include better measurement, increases in maternal age and underlying maternal health problems such as diabetes and high blood pressure, greater use of infertility treatments leading to increased rates of multiple pregnancies, and changes in obstetric practices such as more caesarean births before term.

There is a dramatic difference in survival of premature babies depending on where they are born.

For example, more than 90% of extremely preterm babies (< 28 weeks) born in low-income countries die within the first few days of life; yet less than 10% of babies of this gestation die in high-income settings.

### WHO response

In 2012, WHO and partners published a report "Born too soon: the global action report on preterm birth" that included the first-ever estimates of preterm birth by country.

WHO is committed to reducing the health problems and lives lost as a result of preterm birth with the following specific actions:

- working with Member States and partners to implement "Every Newborn: An Action Plan to End Preventable Deaths" adopted in May 2014 in the framework of the UN Secretary-General's "Global Strategy for Women's and Children's Health";
- working with Member States to strengthen the availability and quality of data on preterm births;
- providing updated analyses of global preterm birth levels and trends every 3 - 5 years;
- working with partners around the world to conduct research into the causes of preterm birth, and test effectiveness and delivery approaches for interventions to prevent preterm birth and treat babies that are born preterm;
- regularly updating clinical guidelines for the management of pregnancy and mothers with preterm labour or at risk of preterm birth, and those on the care of preterm babies, including kangaroo mother care, feeding babies with low birth weight, treating infections and respiratory problems, and home-based follow-up care (see WHO 2015 recommendations on interventions to improve preterm outcomes);
- developing tools to improve health workers' skills and assess the quality of care provided to preterm babies; and
- supporting countries to implement WHO's antenatal care guidelines, aimed at reducing the risk of negative pregnancy outcomes, including preterm births, and ensuring a positive pregnancy experience for all women.

### Guidelines to improve preterm birth outcomes

WHO has developed new guidelines with recommendations for improving outcomes of preterm births. This set of key interventions can improve the chances of survival and health outcomes for preterm infants. The guidelines include interventions provided to the mother – for example steroid injections before birth, antibiotics when her water breaks before the onset of labour, and magnesium sulfate to prevent future neurological impairment of the child. As well

as interventions for the newborn baby – for example thermal care (e.g. kangaroo mother care when babies are stable), safe oxygen use, and other treatments to help babies breathe more easily.

### WHO recommendations on interventions to improve preterm birth outcomes

The primary audience for this guideline includes health-care professionals who are responsible for developing national and local health-care protocols and policies, as well as managers of maternal and child health programmes and policy-makers in all settings. The guideline will also be useful to those directly providing care to pregnant women and preterm infants, such as obstetricians, paediatricians, midwives, nurses and general practitioners. The information in this guideline will be useful for developing job aids and tools for pre- and in-service training of health workers to enhance their delivery of maternal and neonatal care relating to preterm birth.

### REFERENCES

1. Blencowe H, Cousens S, Oestergaard M, Chou D, Moller AB, Narwal R, Adler A, Garcia CV, Rohde S, Say L, Lawn JE. National, regional and worldwide estimates of preterm birth. *The Lancet*, June 2012. 9;379(9832):2162-72. Estimates from 2010.

## 3. SCHISTOSOMIASIS

### Overview

Schistosomiasis is an acute and chronic parasitic disease caused by blood flukes (trematode worms) of the genus *Schistosoma*. Estimates show that at least 218 million people required preventive treatment in 2015. Preventive treatment, which should be repeated over a number of years, will reduce and prevent morbidity. Schistosomiasis transmission has been reported from 78 countries. However, preventive chemotherapy for schistosomiasis, where people and communities are targeted for large-scale treatment, is only required in 52 endemic countries with moderate-to-high transmission.

### KEY FACTS

- Schistosomiasis is an acute and chronic disease caused by parasitic worms.
- People are infected during routine agricultural, domestic, occupational, and recreational activities, which expose them to infested water.
- Lack of hygiene and certain play habits of school-aged children such as swimming or fishing in infested water make them especially vulnerable to infection.

- Schistosomiasis control focuses on reducing disease through periodic, large-scale population treatment with praziquantel; a more comprehensive approach including potable water, adequate sanitation, and snail control would also reduce transmission.
- Estimates show that at least 218 million people required preventive treatment for schistosomiasis in 2015.
- More than 66.5 million people were reported to have been treated for schistosomiasis in 2015.

### Infection and transmission

People become infected when larval forms of the parasite – released by freshwater snails – penetrate the skin during contact with infested water.

Transmission occurs when people suffering from schistosomiasis contaminate freshwater sources with their excreta containing parasite eggs, which hatch in water.

In the body, the larvae develop into adult schistosomes. Adult worms live in the blood vessels where the females release eggs. Some of the eggs are passed out of the body in the faeces or urine to continue the parasite's lifecycle. Others become trapped in body tissues, causing immune reactions and progressive damage to organs.

### Epidemiology

Schistosomiasis is prevalent in tropical and subtropical areas, especially in poor communities without access to safe drinking water and adequate sanitation. It is estimated that at least 90% of those requiring treatment for schistosomiasis live in Africa.

There are two major forms of schistosomiasis – intestinal and urogenital – caused by five main species of blood fluke (Table 1).

Schistosomiasis mostly affects poor and rural communities, particularly agricultural and fishing populations. Women doing domestic chores in infested water, such as washing clothes, are also at risk. Inadequate hygiene and contact with infected water make children especially vulnerable to infection.

Migration to urban areas and population movements are introducing the disease to new areas. Increasing population size and the corresponding needs for power and water often result in development schemes, and environmental modifications facilitate transmission.

With the rise in eco-tourism and travel “off the beaten track”, increasing numbers of tourists are contracting schistosomiasis. At times, tourists present severe acute infection and unusual problems including paralysis.

Urogenital schistosomiasis is also considered to be a risk factor for HIV infection, especially in women.



**Table:** Parasite species and geographical distribution of schistosomiasis

Forms of schistosomiasis	Species	Geographical distribution
Intestinal schistosomiasis	<i>Schistosoma mansoni</i>	Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname
	<i>Schistosoma japonicum</i>	China, Indonesia, the Philippines
	<i>Schistosoma mekongi</i>	Several districts of Cambodia and the Lao People's Democratic Republic
	<i>Schistosoma guineensis</i> and related <i>S. intercalatum</i>	Rain forest areas of Central Africa
Urogenital schistosomiasis	<i>Schistosoma haematobium</i>	Africa, the Middle East, Corsica (France)

### Symptoms

Symptoms of schistosomiasis are caused by the body's reaction to the worms' eggs.

Intestinal schistosomiasis can result in abdominal pain, diarrhoea, and blood in the stool. Liver enlargement is common in advanced cases, and is frequently associated with an accumulation of fluid in the peritoneal cavity and hypertension of the abdominal blood vessels. In such cases there may also be enlargement of the spleen.

The classic sign of urogenital schistosomiasis is haematuria (blood in urine). Fibrosis of the bladder and ureter, and kidney damage are sometimes diagnosed in advanced cases. Bladder cancer is another possible complication in the later stages. In women, urogenital schistosomiasis may present with genital lesions, vaginal bleeding, pain during sexual intercourse, and nodules in the vulva. In men, urogenital schistosomiasis can induce pathology of the seminal vesicles, prostate, and other organs. This disease may also have other long-term irreversible consequences, including infertility.

The economic and health effects of schistosomiasis are considerable and the disease disables more than it kills. In children, schistosomiasis can cause anaemia, stunting and a reduced ability to learn, although the effects are usually reversible with treatment. Chronic schistosomiasis may affect people's ability to work and in some cases can result in death. The number of deaths due to schistosomiasis is difficult to estimate because of hidden pathologies such as liver and kidney failure and bladder cancer. WHO estimates that there are about 200,000 deaths globally each year due to schistosomiasis.

### Diagnosis

Schistosomiasis is diagnosed through the detection of parasite eggs in stool or urine specimens. Antibodies and/or antigens detected in blood or urine samples are also indications of infection.

For urogenital schistosomiasis, a filtration technique using nylon, paper or polycarbonate filters is the standard diagnostic technique. Children with *S. haematobium* almost always have microscopic blood in their urine which can be detected by chemical reagent strips.

The eggs of intestinal schistosomiasis can be detected in faecal specimens through a technique using methylene blue-stained cellophane soaked in glycerine or glass slides, known as the Kato-Katz technique.

For people living in non-endemic or low-transmission areas, serological and immunological tests may be useful in showing exposure to infection and the need for thorough examination, treatment and follow-up.

### Prevention and control

The control of schistosomiasis is based on large-scale treatment of at-risk population groups, access to safe water, improved sanitation, hygiene education, and snail control. The WHO strategy for schistosomiasis control focuses on reducing disease through periodic, targeted treatment with praziquantel through the large-scale treatment (preventive chemotherapy) of affected populations. It involves regular treatment of all at-risk groups. In a few countries, where there is low transmission, the elimination of the disease should be aimed for.

Groups targeted for treatment are:

- School-aged children in endemic areas.
- Adults considered to be at risk in endemic areas, and people with occupations involving contact with infested water, such as fishermen, farmers, irrigation workers, and women whose domestic tasks bring them in contact with infested water.
- Entire communities living in highly endemic areas.
- The frequency of treatment is determined by the prevalence of infection in school-age children. In high-transmission areas, treatment may have to be repeated every year for a number of years. Monitoring is essential to determine the impact of control interventions.

The aim is to reduce disease morbidity and transmission: periodic treatment of at-risk populations will cure mild symptoms and prevent infected people from developing severe, late-stage chronic disease. However, a major limitation to schistosomiasis control has been the limited availability of praziquantel. Data for 2015 show that 28.2% of people requiring treatment were reached globally, with a proportion of 42.2% of school aged children requiring preventive chemotherapy for schistosomiasis being treated.

Praziquantel is the recommended treatment against all forms of schistosomiasis. It is effective, safe, and low-cost. Even though re-infection may occur after treatment, the risk of developing severe disease is diminished and even reversed when treatment is initiated and repeated in childhood.

Schistosomiasis control has been successfully implemented over the past 40 years in several countries, including Brazil, Cambodia, China, Egypt, Mauritius, Islamic Republic of Iran and Saudi Arabia. There is evidence that schistosomiasis transmission was interrupted in Morocco. In Burkina Faso, Niger, Sierra Leone and Yemen, it has been possible to scale up schistosomiasis treatment to the national level and have an impact on the disease in a few years. An assessment of the status of transmission is being made in several countries.

Over the past 10 years, there has been scale-up of treatment campaigns in a number of sub-Saharan countries, where most of those at risk live.

#### WHO response

WHO's work on schistosomiasis is part of an integrated approach to the control of neglected tropical diseases. Although medically diverse, neglected tropical diseases share features that allow them to persist in conditions of poverty, where they cluster and frequently overlap.

WHO coordinates the strategy of preventive chemotherapy in consultation with collaborating centres and partners from academic and research institutions, the private sector, nongovernmental organizations, international development agencies, and other United Nations organizations. WHO develops technical guidelines and tools for use by national control programmes.

Working with partners and the private sector, WHO has advocated for increased access to praziquantel and resources for implementation. A significant amount of praziquantel, to treat more than 100 million children of the school age per year, has been pledged by the private sector and development partners.

## 4. AVIAN AND OTHER ZOOONOTIC INFLUENZA

#### KEY FACTS

- Humans can be infected with avian and other zoonotic influenza viruses, such as avian influenza virus subtypes A(H5N1), A(H7N9), and A(H9N2) and swine influenza virus subtypes A(H1N1) and (H3N2).
- Human infections are primarily acquired through direct contact with infected animals or

contaminated environments, but do not result in efficient transmission of these viruses between people. There is no evidence that the avian or zoonotic influenza viruses can infect humans through properly cooked food.

- Avian and other zoonotic influenza infections in humans may cause disease ranging from mild conjunctivitis to severe pneumonia and even death.
- The majority of human cases of A(H5N1) and A(H7N9) infection have been associated with direct or indirect contact with infected live or dead poultry. Controlling the disease in the animal source is critical to decrease risk to humans.
- Influenza viruses, with the vast silent reservoir in aquatic birds, are impossible to eradicate. Zoonotic influenza infection in humans can continue to occur. To minimize public health risk, quality surveillance in both animal and human populations, thorough investigation of every human infection and risk-based pandemic planning are essential.

There are three types of influenza viruses: types A, B, and C. Influenza A viruses infect humans and many different animals. Influenza B viruses only circulate among humans and cause seasonal epidemics. Influenza C viruses can infect both humans and pigs but infections are generally mild and are rarely reported.

Influenza type A viruses are classified into subtypes according to the combinations of different virus surface proteins haemagglutinin (H) and neuraminidase (N). There are 18 different haemagglutinin subtypes and 11 different neuraminidase subtypes. Depending on the origin host, influenza A viruses can be classified as avian influenza, swine influenza, or other types of animal influenza viruses. Examples include avian influenza "bird flu" virus subtypes A(H5N1) and A(H9N2) or swine influenza "swine flu" virus subtypes A(H1N1) and A(H3N2). All of these animal influenza type A viruses are distinct from human influenza viruses and do not easily transmit between humans.

Aquatic birds are the primary natural reservoir for most subtypes of influenza A viruses. Most cause asymptomatic or mild infection in birds, where the range of symptoms depends on the virus properties. Viruses that cause severe disease in birds and result in high death rates are called highly pathogenic avian influenza (HPAI). Viruses that cause outbreaks in poultry but are not generally associated with severe disease are called low pathogenic avian influenza (LPAI).

#### Human infections with avian and zoonotic influenza viruses

Human infections with avian and zoonotic influenza viruses have been reported. Human infections are

primarily acquired through direct contact with infected animals or contaminated environments, but do not result in efficient transmission of these viruses between people.

In 1997, human infections with the HPAI A(H5N1) virus were reported during an outbreak in poultry in Hong Kong SAR, China. Since 2003, this avian virus has spread from Asia to Europe and Africa, and has become entrenched in poultry populations in some countries. Outbreaks have resulted in millions of poultry infections, several hundred human cases, and many human deaths. The outbreaks in poultry have seriously impacted livelihoods, the economy and international trade in affected countries. Other avian influenza A(H5) subtype viruses have also resulted in both outbreaks in poultry and human infections.

In 2013, human infections with the LPAI A(H7N9) virus were reported in China. Since then, the virus has spread in the poultry population across the country and resulted in several hundred human cases and many human deaths.

Other avian influenza viruses have resulted in sporadic human infections including the A(H7N7) and A(H9N2) viruses. Some countries have also reported sporadic human infections with swine influenza viruses, particularly the A(H1) and A(H3) subtypes.

### **Clinical features of avian and other zoonotic influenza infections in humans**

Avian and other zoonotic influenza infections in humans may cause disease ranging from mild conjunctivitis to severe pneumonia and even death. Disease features such as the incubation period, severity of symptoms and clinical outcome depends on the subtype causing infection.

For avian influenza A(H5N1) virus infections in humans, current data indicate an incubation period averaging 2 - 5 days and ranging up to 17 days<sup>[1]</sup>. For human infections with the A(H7N9) virus, incubation period ranges from 1 - 10 days, with an average of five days<sup>[2]</sup>. For both viruses, the average incubation period is longer than that for seasonal influenza (2 days)<sup>[2]</sup>. For human infections with swine influenza viruses, an incubation period of 2 - 7 days has been reported<sup>[2]</sup>.

In many patients infected by A(H5) or A(H7N9) avian influenza viruses, the disease has an aggressive clinical course. Common initial symptoms are high fever (greater than or equal to 38 °C) and cough. Signs and symptoms of lower respiratory tract involvement including dyspnoea or difficulty breathing have been reported. Upper respiratory tract symptoms such as sore throat or coryza are less common. Other symptoms such as diarrhoea, vomiting, abdominal pain, bleeding from the nose or gums, and chest pain have also been reported in the clinical course of some patients.

Complications of infection include hypoxemia, multiple organ dysfunction, and secondary bacterial and fungal infections. The case fatality rate for A(H5) and A(H7N9) subtype virus infections among humans is much higher than that of seasonal influenza infections.

For human infections with avian influenza A(H7N7) and A(H9N2) viruses, disease is typically mild or subclinical. Only one fatal A(H7N7) human infection has been reported in the Netherlands<sup>[3]</sup>. For human infections with swine influenza viruses, most cases have been mild with a few cases hospitalized and very few reports of deaths resulting from infection<sup>[2]</sup>.

### **Antiviral treatment**

Evidence suggests that some antiviral drugs, notably oseltamivir, can reduce the duration of viral replication and improve prospects of survival<sup>[1]</sup>.

In suspected cases, oseltamivir should be prescribed as soon as possible (ideally, within 48 hours following symptom onset) to maximize its therapeutic benefits. However, given the significant mortality currently associated with A(H5) and A(H7N9) subtype infections and evidence of prolonged viral replication in these diseases, administration of the drug should also be considered in patients presenting later in the course of illness. The use of corticosteroids is not recommended. In cases of severe infection with the A(H5) or A(H7N9) virus, clinicians may need to consider increasing the recommended daily dose or the duration of treatment.

In severely ill A(H5) or A(H7N9) patients or in patients with severe gastrointestinal symptoms, drug absorption may be impaired. This possibility should be considered when managing these patients. Most recent A(H5) and A(H7N9) viruses have been resistant to adamantane antiviral drugs, which are therefore not recommended for use.

### **Risk factors for infection**

For avian influenza viruses, the primary risk factor for human infection appears to be direct or indirect exposure to infected live or dead poultry or contaminated environments, such as live bird markets. Slaughtering, defeathering, handling carcasses of infected poultry, and preparing poultry for consumption, especially in household settings, are also likely to be risk factors.

There is no evidence to suggest that the A(H5), A(H7N9) or other avian influenza viruses can be transmitted to humans through properly prepared poultry or eggs. A few influenza A(H5N1) human cases have been linked to consumption of dishes made with raw, contaminated poultry blood. Controlling the circulation of avian influenza viruses in poultry is essential to reducing the risk of human infection.

Given the persistence of the A(H5) and A(H7N9) viruses in some poultry populations, control will require long-term commitments from countries and strong coordination between animal and public health authorities.

For swine influenza viruses, close proximity to infected pigs or visiting locations where pigs are exhibited has been reported for most human cases, but some limited human-to-human transmission has occurred.

### **Pandemic potential**

Influenza pandemics (outbreaks that affect a large proportion of the world due to a novel virus) are unpredictable but recurring events that can have health, economic and social consequences worldwide. An influenza pandemic occurs when key factors converge: an avian or zoonotic influenza virus emerges with the ability to cause sustained human-to-human transmission, and the human population has little to no immunity against the virus. With the growth of global trade and travel, a localized epidemic can transform into a pandemic rapidly, with little time to prepare a public health response.

Ongoing circulation of some avian influenza subtypes in poultry, such as A(H5) or A(H7N9) viruses, are of public health concern as these viruses commonly cause severe disease in humans and the viruses have the potential to mutate to become more transmissible between humans. To date, although human-to-human transmission of these viruses is thought to have occurred in some rare instances when there had been very close and prolonged contact between a very sick patient and caregivers such as family members, there has been no sustained human-to-human transmission. If these viruses adapt or acquire certain genes from human viruses, they could trigger a pandemic.

Whether currently-circulating avian and other zoonotic influenza viruses will result in a future pandemic is unknown. However, the diversity of avian and other zoonotic influenza viruses that have caused human infections necessitates ongoing surveillance in both animal and human populations, detailed investigation of every human infection and risk-based pandemic planning.

### **WHO response**

WHO, in its capacity for providing leadership on global health matters, is monitoring avian and other zoonotic influenza viruses closely through its Global Influenza Surveillance and Response System (GISRS). Specifically, WHO, the World Organisation for Animal Health (OIE), and the Food and Agriculture Organization (FAO) collaborate to track and assess the risk from avian and other zoonotic influenza viruses of public health concern.

Updated findings of risk assessment and recommendations on interventions are communicated timely with Member States to enhance preparedness and response.

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