

**Vol. 4 No. 2**  
**July 2018**

# *Barind Medical College Journal*



Systemic Lupus Erythematosus (SLE) is a chronic disorder which affects the younger age group, mostly females. In clinical practice we should follow the ACR recommendation for testing ANA titer. And anti ds DNA antibodies have limited value in clinical correlation and in predicting disease flares and subset in SLE.

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**OFFICIAL JOURNAL OF  
BARIND MEDICAL COLLEGE**  
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Volume 4 Number 2 July 2018

Official Journal of Barind Medical College

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**Alexander of Tralles**

**Alexander** of Tralles in Lydia (c. 525 c. 605) was one of the most eminent of the ancient physicians in the reign of Justinian I (AD 527-65). He had very extensive experience with treatment of several forms of illnesses and healing of physical traumas. He was also a pioneer in mental illnesses recognition. Alexander also discovered that depression can lead to homicidal and suicidal tendencies. Alexander's chief work, titled *Twelve Books on Medicine*, which was translated in different languages, like Latin, Arabic and Hebrew.

BMCJ, a peer reviewed biannual medical journal, is the official journal of Barind Medical College, Rajshahi, Bangladesh.

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Published By  
Barind Medical College  
Rajshahi, Bangladesh

Annual Subscription  
Tk. 200/- for local subscribers  
US\$ 20 for overseas subscribers



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## Official Journal of Barind Medical College

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July 2018

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## Changing face in medicine: a new trend

Md. Anayet Ullah

Despite all odds in society and lagging of women behind men in many sectors in Bangladesh, the country's girls are going ahead of the male counterparts in the medical education and health services.

The first Bangladeshi woman physician, **Zohra Begum Kazi** (15 October 1912 - 7 November 2007), graduated (MBBS) in 1935 from Lady Hardinge Medical College for Women in Delhi. She ranked First Class First and was awarded the Viceroy of India's Medal. She came from Kazi family of Gopalpur in the Madaripur District what was in the Bengal. She has been called the Florence Nightingale of Dhaka.<sup>1</sup> About 73 years later, Bangladeshi women started to outnumber men in admissions to medical colleges. According to official statistics female students make up around 60% of the enrolled medical students and the trend continues to grow stronger every year. During the last five years, Bangladesh produced female doctors in the same proportion.<sup>2</sup>

Not only in Bangladesh, this increase is keeping with the worldwide trend. Over the past 30 years the proportion of women attending medical schools has steadily risen in many countries including the UK, US, Canada, and Australia. In 2002-3, all UK medical schools had more female students than male, with the percentage of women exceeding 65% in some.<sup>3</sup> In the neighborhood, India and Pakistan, there is much higher proportions of woman than man in medical colleges, 55% and 70%, respectively.<sup>4</sup> For many years the relative lack of female doctors was bemoaned, but the picture has been turning and soon male doctors will be in a minority.

As the female students are more attentive and serious about their studies they get admission in medical colleges on merit. The male students spend more time on unnecessary pursuits and less on their studies. By

concentrating on their studies the female students easily outscore the male students in the admission tests.

Too many female graduates are bad for medicine, just as too many male ones have been in the past. The numbers of men and women entering medical school should roughly reflect the numbers in society. The case for this is simply on grounds of equal opportunity.<sup>3</sup> Medicine needs and wants to attract the best and brightest people, whatever their sex. Some patients prefer to see the same sex doctor as themselves, so we should ideally have equal numbers of men and women.

Though literature suggested that female physicians endure bias, and a larger burden with home duties. They are more likely to cut back professionally to accommodate household responsibilities. Female physicians are also more likely to face work-family conflicts, even divorce than male physicians. They also face a greater risk of burnout / depression than male counterpart.<sup>5</sup> However it is a good sign of women empowering and for the health services as well in Bangladesh. It would be better for the country's health service to have more female doctors known for their inherent quality to care for others.

Since women now constitute a majority in the ranks of younger doctors, a transition that is likely to put pressure on healthcare institutions to change their practices around scheduling, supporting and promoting female physicians. As women become a major force within the medical community, healthcare executives and administrators, many of whom are men, are tasked with creating an environment that prioritizes retaining and supporting female physicians in order to maintain a robust workforce, like provision of flexibility in scheduling, part time job, maternity and paternity leave, adequate day

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Cite this as:  
BMCJ 2018;4(2): 1-2

Received : 15 May 2018  
Accepted : 11 June 2018



care service at working place, secure accommodation facilities specially in rural community. Hopefully, all these changes contribute to accommodate the new trend in medicine.

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## Clinical evaluation of Systemic Lupus Erythematosus patients admitted in a tertiary care hospital of Bangladesh.

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### Abstract

**Background:** Systemic Lupus Erythematosus is a rare connective tissue disorder. It causes considerable morbidity and mortality among affected patients. **Objective:** To present the demographic profiles and clinical features of Systemic Lupus Erythematosus (SLE) patients admitted in Rajshahi Medical College Hospital. **Methods:** This was a cross sectional descriptive study conducted on 31 Systemic Lupus Erythematosus (SLE) patients admitted in Rajshahi Medical College Hospital from July 2017 to December 2017 for a period of 6 months. Patients were diagnosed as having SLE on the basis of Revised American Rheumatism Association criteria. **Results:** A total 31 patients having SLE, 26 (83.9%) patients were female and 5 (16.1%) patients were male. Majority (77.4%) of the patients were young adults =30 years. All the patients had intermittent polyarthritis (100%). Other common presentations of them were skin lesions (83.9%), fever & constitutional symptoms (83.9%), hematological involvement (58.1%), ankle edema (32.3%), bed side proteinuria (32.3%), generalized swelling (29%). Antinuclear antibody (ANA) was positive among 29 patients (93.5%) and anti-double stranded DNA antibodies (anti ds DNA) was positive in 24 (77.4%) patients. **Conclusion:** Systemic Lupus Erythematosus is a chronic disorder which affects the younger age group, mostly females. It not only causes increased morbidity but also reduce the quality of life. In clinical practice we should follow the ACR recommendation for testing ANA titer. And anti ds DNA antibodies have limited value in clinical correlation and in predicting disease flares and subset in SLE.

**Key words:** Systemic Lupus Erythematosus(SLE), ANA titer, anti-dsDNA.

### Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, recurrent, potentially fatal multisystem inflammatory disorder that can be difficult to diagnose.<sup>1,2</sup> It is a connective tissue disease characterized by dysregulation of immune responses, autoantibody production often directed at components of the cell, nucleus, and widespread tissue damage. It is a rare disease with a prevalence that ranges from about 0.03% in Caucasians to 0.2% in Afro-Caribbeans. Some 90% of affected patients are female and the peak age at onset is between 20 and 30 years. Lupus is associated with considerable morbidity and a five-fold increase in mortality compared to age- and gender-matched controls, mainly because of an increased risk of premature cardiovascular disease.<sup>3</sup>

The diagnosis of Systemic Lupus Erythematosus based on clinical and laboratory criteria. The criteria set developed by the American College of Rheumatology

(ACR) is most widely used.<sup>4,5</sup> Elevation of the antinuclear antibody(ANA) titer to 1:40 or higher is the most sensitive of the ACR diagnostic criteria. More than 99 percent of patients with systemic lupus erythematosus have an elevated ANA titer at some point,<sup>4,6</sup> although a significant proportion of patients may have a negative ANA titer early in the disease.<sup>2</sup> The present study evaluated the clinical and laboratory features of a SLE cohort admitted in a tertiary hospital.

### Methods

It was a cross sectional descriptive study conducted on 31 Systemic Lupus Erythematosus (SLE) patients admitted in Rajshahi Medical College Hospital from July 2017 to December 2017 for a period of 6 months. Patients were diagnosed as having SLE on the basis of Revised American Rheumatism Association criteria.<sup>3</sup> Patients meeting 4 or more criteria including ANA or anti-double stranded DNA antibodies (Anti

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Cite this as:  
BMJ 2018;4(2): 3-7  
Received : 5 April 2018  
Accepted : 21 May 2018



Ds DNA) positive are included in this study. All patients were examined thoroughly and information were collected in a preformed data collection sheet. Data collection sheet was designed to record the information on demographic characteristics, clinical presentations and antibody titers. Data were entered in the computer and processed using SPSS 16. Descriptive statistics such as frequency distribution, computation of percentage etc. were applied.

## Results

A total 31 patients having SLE, diagnosed on the basis of Revised American Rheumatism Association (ARA) criteria, 26 (83.9%) patients were female and 5 (16.1%) patients were male. Thus most of the affected patients were female. Majority (77.4%) of the patients were young adults =30 years and the rest 22.6% were older than 30 years. None of the patients were above 40 years.

**Table 1: Clinical presentations of the SLE patients**

Presentation	Present N (%)
Multiple joint pain & swelling	31 (100)
Skin manifestations	26 (83.9)
Fever and constitutional symptoms	26(83.9)
Haematological involvement	18 (58.1)
Ankle oedema	10 (32.3)
Bed side proteinuria	10(32.3)
Edema and generalised swelling	9 (29.0)
Abdominal pain and vomiting	8 (25.8)
Cardiopulmonary	7 (22.6)
Neurological manifestations	4 (12.9)
Eye involvement	4 (12.9)
Jaundice	1 (3.2)
Deep venous thrombosis	1 (3.2)
Lymphadenopathy	1 (3.2)
Flapping tremor	1(3.2)

All the patients presented with multiple joint pain (100%), followed by skin lesions (83.9%), fever & constitutional symptoms (83.9%), hematological involvement (58.1%), ankle edema(32.3%), bed side proteinuria (32.3%), generalized swelling (29%), abdominal pain & vomiting (25.8%), cardiopulmonary (22.6%), neurological involvement (12.9%) and others ( Table 1).

**Table 2: Antibody titer among SLE patients**

Autobnantibody	Present	Absent
ANA	29 (93.5%)	2 (6.5%)
Anti ds DNA	24 (77.4%)	7 (22.6%)

ANA was positive among 29 patients (93.5%) and anti ds DNA was positive in 24 (77.4%) patients (Table 2).

## Discussion

We have assessed 31 patients with Systemic Lupus Erythematosus during 6 months period in medicine department of Rajshahi medical college. Among them 83.9% patients were female and only 16.1% were male with male to female ratio of 1:5. All the female SLE patients were in reproductive age. This finding is inconsistency with other studies in Bangladesh and abroad.<sup>7-9</sup>

There are different hypotheses that might explain the development of SLE. 1st, patients with SLE have abnormally low total T cell DNA methylation (more activated genes). Because women have 2 X chromosomes, one of which has genes that are mostly inactivated, failure to inactivate affects women more than men. Demethylation of sites on an inactive X could contribute to female susceptibility to lupus. A child is conditioned by the inactivated X chromosomes in utero or early childhood event to be susceptible to SLE. 2nd, unmasking of susceptibility may require exposure to one or many environmental insults, such as a virus. Third. At female puberty (but not male puberty), high levels of estradiol may be permissive (or testosterone may be suppressive), allowing clinical disease to occur.<sup>10</sup> The present study findings i.e. female predominance of SLE and its occurrence in young adulthood goes in favour of third hypothesis.

All of the patients in the present study presented with intermittent polyarthritis, varying from mild to disabling, characterized by soft tissue swelling and tenderness in



joints, most commonly in hands, wrists, and knees. No joint deformities were present. This findings is consistent with other studies.<sup>11</sup> Skin involvement along with constitutional features also affecting majority of our patients. Schur PH and Gilboe IM<sup>11</sup>, Husby G<sup>12</sup> also stated that Systemic lupus erythematosus most often manifests as a mixture of constitutional symptoms along with skin involvement. In our series skin involvement consist of butterfly rash, discoid lupus erythematosus (DLE), systemic rash, subacute cutaneous lupus erythematosus (SCLE), or "other." Most common haematological abnormalities in our series was anaemia, leukopenia, thrombocytopenia. Only one patient present with generalised lymphadenopathy. Renal involvement, in the form of bed side proteinuria found in 10 patients. Abdominal pain and vomiting was found in 8 of our patients, which can be manifestations of an SLE flare, as can diffuse abdominal pain caused by autoimmune peritonitis and/or intestinal vasculitis. Cardiopulmonary involvement in the form of pericarditis, pleural effusion were found in 7 patients. Cardiopulmonary involvement in SLE is usually due to accelerated atherosclerosis, which probably results from chronic inflammation and/or chronic oxidative damage to lipids and to organs. The most common pulmonary manifestation of SLE is pleural effusion. Most common neurological manifestations involving our patients were headache and one patient presented with acute confusional state. Nonspecific conjunctivitis occurs 4 of our patients. Jaundice, DVT and flapping tremor were found in one patient each.<sup>13</sup> However, it not only causes increased morbidity among the affected but also reduce the quality of life.

Elevation of the antinuclear antibody (ANA) titer to 1:40 or higher is the most sensitive of the ACR diagnostic criteria. Less than 1% of patients with SLE have not an elevated ANA titer at some point.<sup>12,14</sup> But more than 6% of the present study subjects had a negative ANA titer. It may be due to early stage of the

disease process in some present study subjects. Because a significant proportion of the patients may have a negative ANA titer early in the disease.<sup>2</sup> However, in clinical practice we should follow the ACR recommendation for testing ANA titer i.e. ANA testing in patients with two or more unexplained signs or symptoms of systemic lupus erythematosus.

Anti-dsDNA antibodies have been a hallmark of lupus erythematosus for decades.<sup>15</sup> There are contradictory observations regarding the role of anti-dsDNA antibodies in SLE including predicting the disease flares and its subgroups. Most of the previous literatures identified anti-dsDNA as a pathogenetic role in the kidney injury and initiate the lupus nephritis.<sup>16,17,18</sup> But recent studies<sup>19,20</sup> revealed that these antibodies have limited value in clinical correlation and in predicting disease flares and subset in SLE. In addition, they are not likely to be the initiating auto-antibodies in lupus nephritis. The present study findings goes in favor of the recent observations. Because in this present study, though more than two third of the study subjects had anti-dsDNA positive but only less than one third of the study subjects had clinical features those correlate with lupus nephritis.

Systemic Lupus Erythematosus is a chronic disorder which affects the younger age group, mostly females. It not only causes increased morbidity among the affected but also reduce the quality of life. In clinical practice we should follow the ACR recommendation for testing ANA titer. And anti-dsDNA antibodies have limited value in clinical correlation and in predicting disease flares and subset in SLE.

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## Role of magnetic resonance imaging in the evaluation of intraspinal tumor

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### Abstract

**Background:** Magnetic resonance imaging (MRI) is a noninvasive diagnostic tool in patient with spinal tumors. MRI has made a significant impact on the differential diagnosis of intraspinal tumor. **Objective:** To evaluate the validity of MRI as a diagnostic tool in patient with spinal tumors. **Methods:** This cross sectional study was conducted in Radiology & Imaging Department (RID) of Dhaka Medical College Hospital, Dhaka. Total 50 clinically suspected patients of Intraspinal tumor referred to RID for MRI were included in this study. MRI of cervical, dorsal and lumbar spine were done according to requirement. After operation histopathology report of the mass was collected in each case. This histopathological report was taken as gold standard test for identifying the type of the intraspinal mass. The validity indices namely sensitivity, specificity, positive predictive value and negative predictive values of MRI report to detect the intraspinal mass were calculated. **Results:** A total of 50 patients, 30 (60.0%) were male and the rest 20(40.0%) were female with mean age of 38.89 years. Weakness of the limbs was the most common (46, 92%) symptoms of the patients. Another common symptom was back pain (45, 92%) patients. On MRI the commonest location of spinal tumors was intradural extramedullary (29, 58%). The highest number { 13 cases (26%) } were identified as Schwannoma, followed by Meningioma { 11 cases (22%) }, then Ependymoma { 7 cases (14%) }. Most of the tumors show hypointense signal on T1WI (52%) and hyperintense signal on T2WI (62%) and post contrast heterogeneous enhancement (44%). Sensitivity and specificity of MRI to detect intraspinal tumor were 92.68% and 88.0% respectively. **Conclusion:** MRI can be accepted as the most effective imaging modality in the diagnosis of intraspinal tumor.

**Key words:** MRI, validity, intraspinal tumor

### Introduction

Intraspinal tumor are not uncommon lesion, that may result in serious morbidity. Their clinical symptoms are often non specific and include back pain, radicular symptom and slowly progressive neurological deficits such as limb weakness, paresthesia, gait problem, impotence, bowel and bladder dysfunctions are the most common. Less common are acute headache, skeletal deformity such as kyphoscoliosis. Intraspinal tumor are classified as either extradural or intradural. Intradural tumors are further divided into intramedullary or extramedullary.<sup>1</sup> Spinal tumors account for approximately 5-15% of the nervous system neoplasm.<sup>2</sup> Intradural extramedullary spinal cord tumor constitute approximately two third (about 53-65%). Extradural tumors are about 28-30% and intramedullary tumor estimated to be 7-22%. Spinal intramedullary neoplasm account for

about 4% - 10% of all central nervous system (CNS) tumors and 2% - 4% of CNS glial tumors. Although spinal cord tumors constitute only 20% of all intraspinal tumors in the adult population, they constitute 35% of such tumors in children. Most spinal cord tumors are malignant and 90% - 95% are classified as gliomas. Most of the glial tumors are either ependymomas or astrocytomas. Ependymomas are the most common glial tumors in adults, whereas astrocytomas are the most common intramedullary tumor in children.<sup>3</sup>

In conventional myelography, CT myelography all have radiation hazards and also need experienced technician. CT has prefixed protocol which may missed the lesion. MRI has made a significant impact on the differential diagnosis of intraspinal tumor. MRI has made multiplanar imaging,

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Cite this as:  
BMCJ 2018;4(2): 8-13

Received : 3 April 2018  
Accepted : 15 May 2018

cross sectional anatomical details, sagittal, coronal, axial reformate.<sup>4</sup> The enhancement of intradural extramedullary lesion with gadolinium is often dramatic. Even small nodules generally enhance brightly and are easily seen.<sup>5,6</sup>

MRI has proven to be an excellent technique for visualizing the spinal cord and its tumor. MRI has several general well-recognized advantage over the imaging methods, including superior soft tissue discrimination ability to directly image in the sagittal and coronal planes, more specifically to imaging the spinal cord.<sup>4</sup>

In the detection and identification of intraspinal tumors by MRI accuracies are found 92% correlation between MRI and histopathology have been reported.<sup>7</sup> In multi institutional prospective study, the sensitivity of contrast MRI for detection of intraspinal tumor was 95%.<sup>4</sup> Gd-DTPA enhanced MR imaging improves the reliability and spinal tumor diagnosis and increases MRI sensitivity and specificity.<sup>8,9</sup> This study was done to identify the efficacy of MRI to detect intraspinal tumor.

### Methods

This cross sectional study was conducted in Radiology & Imaging Department (RID) of Dhaka Medical College Hospital, Dhaka. The patients clinically suspicion of Intraspinal tumor referred to RID for MRI were constituted the study population. Total 50 patients were included in this study, who were referred from July 2008 to March 2010. MRI of cervical, dorsal and lumbar spine were done according to requirement. After operation histopathology report of the mass was collected in each case. This histopathological report was taken as reference (gold standard) test for identifying the type of the intraspinal mass. Data were collected in a predesigned data collection sheet from MRI and histopathological reports. Data were compiled, analyzed and results were prepared. The validity indices namely sensitivity, specificity, positive predictive value and negative predictive values of MRI report to detect the intraspinal mass were calculated.

### Protocol of the MR scan of the spine

MRI of the spine was performed in the axial and sagittal planes using a combination of pulses sequences. The study was performed while patients lying supine with their median sagittal plane coinciding with the midline of the scanner table. We performed all MR scan was done on 0.3-Tesla open MR machine (AIRIS-II-HITACHI) was used. Images were taken of T1WI, T2WI and T1 contrast sequences in sagittal, axial and coronal plane. A circular surface (synergy body) coil was used to obtain a high signal-to-noise ratio and high spatial resolution. The sequences performed are shown in Table 1.

Paramagnetic contrast gadopentetate dimeglumine diethylenetriaminepenta-acetic acid (Gd-DTPA).

Table 1: Shows protocol of MRI in spinal tumors imaging

Parameters	Sagittal T1	Sagittal T2	Axial T1	Axial T2
TR	6000	3500	431	4000
TE	10	100	10	100
FOV	45x30	45x30	20	20
MTX	256x384	256x384	192x384	224x320
FA	90/180	90/180	90/180	90/180
NAQ	2	2	2	2

### Results

A total of 50 patients, 30 (60.0%) were male and the rest 20(40.0%) were female. The mean age of them was 38.89 years with the range of 11- 70 years.

Weakness of the limbs was the most common (46, 92%) symptoms of the patients. Another common symptom was back pain (45, 92%) patients. Twenty patients (40%) had loss of bowel and bladder control and 15 (30%) patients had paraplegia. Only 10 (20%) patients had loss of sensation.



**Table 2: Comparison between histopathological and MRI findings.**

Diseases	Histopathological findings		MRI Findings	
	No. of cases(N)	Percentage (%)	No. of cases	Percentage (%)
Schwannoma	13	26.0	13	26.0
Neurofibroma	1	2.0	1	2.0
Meningioma	11	22.0	11	22.0
Ependymoma	07	14.0	07	14.0
Astrocytoma	05	10.0	04	8.0
Metastasis	02	4.0	02	4.0
Hemangioma	01	2.0	01	2.0
Chordoma	01	2.0	00	0.0
Others/Negative for Intraspinal tumor	09	18.0	11	22.0
	<b>50</b>	<b>100</b>	<b>50</b>	<b>100</b>

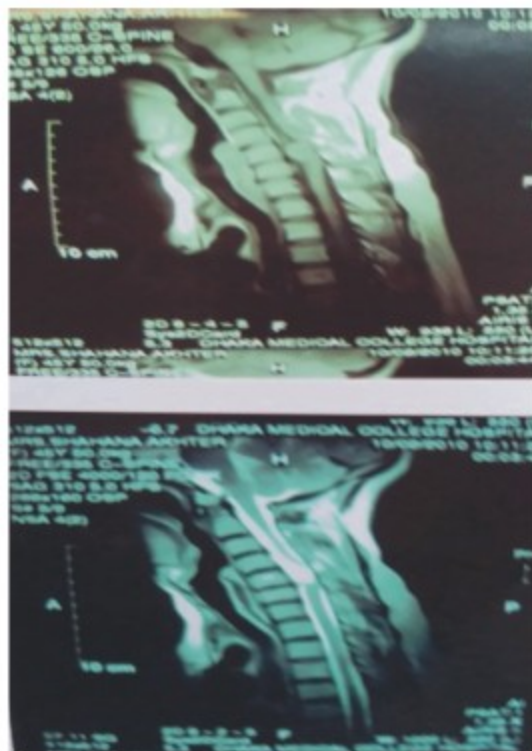
**Table 3: Validity of MRI evaluation to detect intraspinal tumors.**

MRI report	Histopathology report		Total
	Positive result	Negative result	
Positive result	38 (True positive)	1 (False Positive)	39
Negative result	3 (False Negative)	8 (True Negative)	11
Total	41	9	50

Out of 50 cases, on MRI the commonest location of spinal tumors was intradural extramedullary (29, 58%) followed by intradural intramedullary (13, 26%) and extradural (8, 16%). The highest number 13 cases (26%) were identified as Schwannoma, followed by Meningioma 11 cases (22%), then Ependymoma 7 cases (14%). Among 11(22%) cases identified as other than intraspinal tumors, 5(10%) were sequestered disk, 3 (6%) were chronic inflammatory lesion, and the rest 3 cases were identified as epidural abscess, intramedullary abscess and intramedullary hematoma respectively. The MRI findings of the tumors were more or less same as the histopathological reports (Table 2) On T1WI 22(44%) tumors were hypointense and 28(56%) tumors are isointense. On T2WI 4(8%) tumors were hypointense, 15(30%) were isointense and 31(62%) were hyperintense. After I/V contrast 17 (34%) cases were enhanced homogeneously and 22 (44%) were enhanced heterogeneously. Ring enhancement were 8(16%) and non enhancing was 1 (2%).

Among the 50 cases MRI diagnosed 39 cases as intraspinal tumor and 11 cases as other than intraspinal tumor (5 cases as sequestered disc, 3 cases as chronic inflammatory lesion, 1 case as intramedullary abscess, 1 case as intramedullary haematoma and 1 case as epidural abscess). Of the 39 cases of intraspinal tumors reported by MRI, 38 were correctly diagnosed as intraspinal tumors except one. A patient with intramedullary abscess was falsely diagnosed (false positive) as intramedullary astrocytoma on MRI. On the other hand MRI failed to detect three intraspinal tumors (false negative). The 3 patients, who were falsely reported negative for intraspinal tumor on MRI, two were Astrocytoma and another was Chordoma intraspinal tumour confirmed by histopathologically. In eight patients MRI correctly diagnosed the lesion to be other than intraspinal tumors (Table 3 ). The sensitivity, specificity, positive predictive value and negative predictive values of MRI report were 92.68%, 88.88%, 97.00% and 72.74% respectively.





**Fig 1:** Intraspinal Neurofibroma : Sagittal T1WI (A) Pre contrast shows isointense signal (B) Post contrast shows hyperintense signal.



**Fig 2:** Intraspinal schwannoma (A) Sagittal Pre-contrast shows isointense signal (B) Sagittal post contrast shows intense enhancement.



**Fig 3:** Intramedullary Ependymoma involving conus medullaries. (A) Sagittal T1WI shows isointense signal (b) Axial T1WI after contrast shows heterogeneous enhancement.

### Discussion

In this study with intraspinal peak incidence ranging from 41-50 years. Mean age was 38.89 years. The mean age of the patients with intraspinal tumour were ranging from 37 to 39.5 years. The age range of the present study which is almost similar to the studies.<sup>8,10</sup>

As regards to sex incidence of intraspinal tumors, 30(60%) were male and 20(40%) were female. Male to female ratio was 3:2 in this study. Similar result was found in the study of Holtas et al.<sup>10</sup> and Jinkins et al.<sup>11</sup> Parizel et al.<sup>8</sup> have mentioned intraspinal tumors are slightly more common in male which is consistent with this study. In another study, Dillon et al.<sup>9</sup> found that 36% were female which is almost close to the findings of present study.

Analysis of clinical features revealed that most common presenting symptom were Back pain, loss of sensation, loss of bowel and bladder control, neck pain and weakness.<sup>1</sup> Most of the symptoms were related to mass effect by the tumor. Maximum (30%) patients present with back pain. Xu et

al.<sup>12</sup> and Smoker et al.<sup>4</sup> observed loss of sensation, weakness and pain presented with intramedullary spinal cord tumor which is almost same in the present study.

This study suggests, the most common location of intraspinal tumor is intradural extramedullary compartment. Haaga JR et al.<sup>13</sup> mentioned that intradural intramedullary tumors are the most common intra spinal tumors followed by intramedullary tumor. In present study most common intradural extramedullary location (58%), intramedullary (26%) and extradural (16%) which correlate with the study.<sup>3</sup>

In this study majority (53%) of schwannoma tumors were iso intense and 46% were hypo intense on T1WI. On T2WI 85% schwannoma were hyper intense. Heterogeneous contrast enhancement was noted in 62% cases. This findings are almost similar to the result.<sup>3,5,14</sup> Eleven cases detected meningioma 81% were isointense and 19% hypointense on T1WI. On T2WI 55% were isointense and 18% were hyperintense and 27% were hypo intense. After I/V contrast immediately and homogeneous enhancement occurs in all. In this study which strongly correlate with the study.<sup>3,8,9</sup>

In this study more than 50% of astrocytoma was hypointense and rest are isointense on T1WI. On T2WI image 100% of astrocytoma was hyperintense. After contrast all astrocytoma tend to enhance in more patchy irregular way, consistent with a more diffusely infiltrating tumor. In case of ependymoma 100% were isointense with cord.

On T2WI 100% of ependymoma were hyperintense. After contrast 100% of ependymoma showed intense, homogenous and sharply margined focal enhancement. These findings are almost similar to the result.<sup>8,9,15</sup> On T1WI and T2WI all vertebral hemangioma shows intermediate signal intensity and enhancement occurs after I/V contrast which strongly correlate with the study.<sup>16</sup>

From the result of the present study the overall sensitivity of MRI as a diagnostic modality is 92.68%, Specificity with 88%. Accuracy 92%. Predictive value of positive test 97% and predictive value of negative test 72.7%. as well as the findings obtained by others.<sup>8,9,11</sup>

It is conceivable that MR scanning is a highly accurate and sensitive modality in the evaluation of intraspinal tumors.

MRI is crucial in patients with spinal tumors for assessment of the spinal cord and osseous and soft tissue structures. This is especially important when an accurate clinical examination and history are limited because of soft tissue swelling or disturbed consciousness level. The various MR findings in spinal cord tumors are correlated well with histopathological findings. It can be concluded that MRI can be accepted as the most effective imaging modality in the diagnosis of intraspinal tumor.

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## Career preference of undergraduate medical students and its underlying factors

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### Abstract

**Objective:** To explore the nature of career preferences (either general practice or specialty practice) in Malaysian undergraduate medical students and its underlying factors. **Methods:** Total 210 1st year MBBS undergraduate medical students of the Universiti Sains Malaysia were invited to participate in this study. Data were collected by self administered questionnaire and Focus Group Discussion (FGD). Chi-square, Mann-Whitney test and Multiple logistic regression were applied to find out the influencing factors of career choice.

**Results:** A total of 210 students, 146 (70%) students responded in this study. Among the 146 respondents, 105 (71.9%) students preferred specialty practice (SP) and 20 (13.7%) preferred general practice (GP) as their future career. Medical life style and societal orientation were statistically significant predictors of career preferences. Student preferences general practice as their future career increased by about 8% and 7% for each additional medical life style and societal orientation score respectively. Students preferred general practice mainly due to its diversity, role model and life style option. **Conclusion:** Assessment of the societal orientation and medical life style factors of the candidates should be encompassed with the medical school admission policies for enhancing the number of GP. Medical schools should be encouraged to increase the number of GP teachers/academics involved in teaching their medical students. Health policy makers should be more concentrated on the life style factors to attract the medical students towards general practice by offering a superior work-life balance of GPs.

**Key words:** Career preference, undergraduate students, Malaysia

### Introduction

During the undergraduate course from first year to fifth year, medical students construct their future career identity through a process of medical socialization.<sup>1</sup> The choice of the future career is a complex personal decision resulted as the multi-factorial interaction during preclinical and clinical Phases. Several factors, like demography, culture and societal values, perception about the future career, attitudes towards specific specialties have been identified as the interacting factors.<sup>2-4</sup>

Recently, the medical career choice issue has become an important determinant of the health status of individuals, communities and nations. There is a negative impact of geographic and professional specialty maldistribution on healthcare quality and equity.<sup>5-7</sup> The relationship between specialty distribution and the performance of a health care system is now largely accepted. Most of

the countries in the World, primary care career enhancement is a national goal and a means to address the noxious effects of specialty maldistribution.<sup>5-10</sup>

Over the last couples of decades, the number of medical students choosing general practice/family medicine as a career has steadily decline in different countries of the world.<sup>2,11,12</sup> Considering the importance of the supply side of this equation, especially in light of recent trends towards a relative lack of primary care /generalists doctors, the topic of medical students' career interests is worthy of research.

The purpose of the study is to explore the nature of career preferences (either general practice or specialty practice) and its underlying factors of undergraduate medical students during preclinical year (phase I) in the Universiti Sains Malaysia.

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Cite this as:  
BMJ 2018;4(2): 14-21

Received : 25 March 2018  
Accepted : 27 May 2018

## Methods

This was a cross-sectional study among the 1<sup>st</sup> year undergraduate medical students, Universiti Sains Malaysia. All 210 1st year students were invited to participate in this study.

### Data collection

#### *Techniques and Instrument*

After receiving approval from the Medical school ethics Committee at the Universiti Sains Malaysia, data were collected by survey through self administered questionnaires and focus group discussion (FGD). The questionnaires were distributed to the first year students at the end of a lecture class and were collected with the responses. Written informed consent forms were signed by the students before responding to the questionnaires. The self administered questionnaire was divided into three sections. The first section was designed to record a student's career preference. The 2<sup>nd</sup> section was Career Preference Factors Scale (CPFS)<sup>13</sup> designed to measure the student's perceived influencing factors of this preference. CPFS included 19 items comprised medical lifestyle, economy and prestige, societal orientation, hospital orientation and ease to built up career factors respectively. The items were rated with a 5-point Likert. The 3<sup>rd</sup> section was for demographic characteristics of the students including gender, ethnicity, entry qualification and place of family residence.

#### *Focus Group Discussion*

After identification of the students who preferred general practice from the data collected by self administered question, FGDs were conducted. Total 20 students preferred general practice. Two sessions of FGD were conducted with 10 students in each group. At the beginning of FGD, the facilitator welcomed participants and anonymity was discussed. He also outlined the ground rules to the participants. The participants were also informed that they might be interrupted to redirect the conversation. After introduction of the

participants, they were asked to express what the 'general practice' / 'family medicine' meant to them, gradually drawing them to the specific topic of inquiry (reasons to prefer general practice). They were interrupted when they no longer focused on issues relevant to the study. In these cases, they were brought back to the topic of inquiry using key questions or prompts such as "why you are interested to do general practice?" Finally, participants were asked to summarize the important reasons to prefer general practice. After that, the moderator closed the discussion with expressing thanks to the participants. The whole FGD sessions were recorded in a tape recorder and same time transcribed by the recorders.

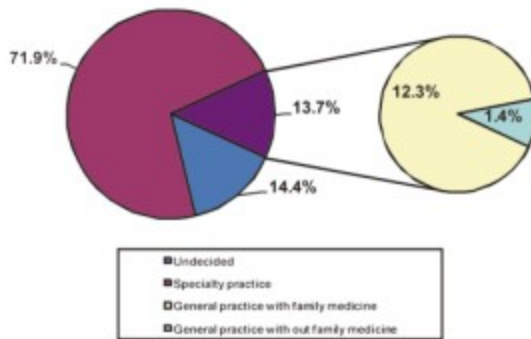
### Data analysis

Quantitative Data (collected by survey) were analyzed in computer using SPSS for windows (version 18.0). Descriptive statistics involving frequency distribution, computation of percentage, proportions etc were used. Since the 5 domains (factors) of the CPFS were not in equal range of scores, the total scores of the 5 factors were standardized by converting percent score before analysis. Exploratory data analysis was conducted to establish the distribution of all the factor scores. Chi-square test was applied to find out the association between career choice and demographic factors (categorical variables). Kolmogorov-smirnov test and the values of the skewness and kurtosis of the factor scores suggested that these scores were non-normally distributed. Non-parametric statistics, Mann-Whitney test was applied to find out the association of the students career preference (either general practice or specialty practice) and the factor scores (medical life style, societal orientation, economy and prestige, hospital orientation and ease to build up career). Multiple logistic regression was applied using career preferences (general practice vs specialty practice) as criterion variable, and the student perceived influencing factors of their preferences and demographic characteristics as predictor variables.



## Results

Out of 210 1<sup>st</sup> year undergraduate medical students in Universiti Sains Malaysia, 146 (70%) students responded in this study. Of the 146 respondents, 105 (71.9%) students preferred specialty practice and 20 (13.7%) preferred general practice as their future career. The rest 21 (14.4%) students remained undecided about their preferences (Figure 1).



**Figure 1** Career preferences of 1<sup>st</sup> year undergraduate medical students in Universiti Sains Malaysia

General surgery was the top (n=28, 26.6%) of the specialty list preferred by the students as future career. Pediatrics and Obstetrics & gynecology were the second (n=21, 20.0%) and third (n=16, 15.2%) position respectively (Table 1).

**Table 1: Specialty preferences of first year undergraduate medical students in Universiti Sains Malaysia.**

Specialty	Frequency N (%)
General Surgery	28 (26.6)
Pediatrics	21 (20.0)
Obstetrics & Gynecology	16 (15.2)
Emergency medicine	11 (10.5)
Internal Medicine	7 (6.7)
Orthopedics	4 (3.8)
Pathology	4 (3.8)
Cardiology	3 (2.9)
Psychiatry	2 (1.9)
Otorhinolaryngology	2 (1.9)
Neurosciences	2 (1.9)
Oncology	2 (1.9)
Others	3 (2.9)

**Table 2: Distribution of the factor scores of the students in Career Preference Factors Scale**

Factor	Mean (SD)	Median (Interquartile range)	Skewness (Std.error)	Kurtosis (Std.error)	Kolmogorov-Smirnov* (p-value)
Medical life style	66.3 (16.6)	68.0 (18.0)	-.662 (.217)	.582 (.430)	.000
Economic and prestige	60.6 (17.9)	60.0 (25.0)	-.167 (.217)	-.468 (.430)	.022
Social orientation	77.8 (12.4)	80.0 (15.0)	-.324 (.217)	-.515 (.430)	.000
Hospital orientation	67.1 (15.3)	66.7 (26.7)	-.140 (.217)	-.505 (.430)	.000
Ease to build up	47.6 (19.5)	46.7 (26.7)	.278 (.217)	-.476 (.430)	.002

\*Lilliefors Significance Correction

The median scores of Social orientation factor was the highest (80.0) among the factors those influenced the students' career preferences measured in CPFS and the median of ease to build up factor was the lowest (46.7). The skewness and kurtosis values with their Std.errors of the factor scores suggested non-normality distribution of them. The results of Kolmogorov-Smirnov test of the factors' scores confirmed that the distribution of the individual factors' scores differed from normal (Table 2).

**Table 3: Students' demographic characteristics and their career preference n = 125**

Demographic characteristics	Career preference		Chi-square	
	General practice N (%)	Specialty practice N (%)	Statics	P value
Gender				
Male (n = 39)	6 (15.4)	33 (84.6)	.016	.563
Female (n = 86)	14 (16.3)	72 (83.7)		
Ethnicity				
Malay (n = 64)	12 (18.8)	52 (81.3)	.738	.270
Others (n = 61)	8 (13.1)	53 (86.9)		
Place of family residence				
Urban (n = 89)	13 (14.6)	76 (85.4)		
Rural (n = 36)	7 (19.4)	29 (80.6)	.446	.337
Entry qualification				
Matriculation (n = 95)	17 (17.9)	78 (82.1)	1.057	.234
STPM/others (n = 30)	3 (10.0)	27 (90.0)		

**Table 4: Relationship of students' CPFS scores and their career preferences**

Factors	Median CPFS scores (inter-quartile range)		Test statistics	
	General practice	Specialty practice	Z value	P value
Medical life style	78.0 (18.0)	64.0 (20.0)	-3.726	.000
Economic and prestige	60.0 (26.2)	60.0 (25.0)	-.490	.624
Societal orientation	85.0 (10.0)	80.0 (20.0)	-2.795	.005
Hospital orientation	60.0 (25.0)	66.7 (23.3)	-1.702	.089
Ease to build up	53.3 (30.0)	46.7 (26.7)	-1.633	.103

Mann-Whitney test was applied

Gender, ethnicity, place of family residence and entry qualification of the medical students were not associated with the preference of general practice as their future career (Table 3). The median medical life style and societal orientation factor scores of the students, who preferred GP as their future career, were significantly higher than those, who preferred SP (78.0 & 85.0 V. 64.0 & 80.0 respectively). The preference either or SP as future career was significantly associated with the medical life style ( $p = 0.000$ ) and societal orientation ( $p = .005$ ) factor scores (Table 4).

societal orientation scores were 1.083 and 1.075 respectively. Student preference general practice as their future career increased by about 8% and 7% for each additional medical life style and societal orientation score respectively (Table 5).

Three reasons emerged from focus group discussion of the students for preferring general practice as their future career. Several Students preferred general practice due to its diversity. Interaction and establish a relationship with different varieties of patients attracted them towards general practice:

*Because it is exciting to meet different people every day. Treating them, talking with them and give their smile back brings satisfaction and happiness to me. (Za'aimuddin, aged 19)*

Role model also be identified as a reasons for preferring general practice by the students:

*Yusri: I am a bit influenced by my father who is a general practitioner.*

Some students preferred general practice due to their life style option:

*Because for me as general practitioner, I will have more time for my self and family and I think it is not as being a specialist. (Malek, aged 20)*

## Discussion

Over the last two decades, the number of medical students choosing general practice as a career has been steadily declined across the world specially in developed countries. The proportion of medical students selecting general practice as a first choice for a residency has decreased in Canada substantially, from 44% in 1992 to 28% in 2005.<sup>13</sup> In the United States, the proportion of students matching to careers in general practice has fallen from a high of 72.6% in 1996 to 40.7% in 2005, the lowest percentage ever.<sup>14</sup> The results of this study comparing with the previous studies<sup>15-18</sup> revealed that students' choice of general practice has not

**Table 5: Multiple logistic regression analysis : predictors of career preferences**

Factors	Odds ratio	95% CI	p-value
Female	1.190	0.336 4.211	0.788
Rural	1.634	0.390 6.846	0.502
Malay	1.456	0.380 5.575	0.584
Medical life style	1.083	1.026 1.144	0.004
Economic and prestige	0.972	0.934 1.011	0.160
Societal orientation	1.075	1.011 1.143	0.022
Hospital orientation	0.960	0.921 1.001	0.053
Ease to build up	1.027	0.995 - 1.059	0.096

The multiple logistic regression showed that medical life style and societal orientation were statistically significant predictors of career preferences. The odds ratios of students' preferences general practice as their future career for medical life style and



been declined in Malaysia as like the developed countries, it is remained as it was before. But considering the importance of the supply side of the equation, students' preferences for general practice/family medicine in Malaysia should be increased. This would help to overcome the shortage of general physicians in Malaysia. Because Malaysia needs more general practitioners to develop an advanced health system with a vision to a developed country status by the year 2020.<sup>9,10,19</sup>

Many Studies<sup>20-23</sup> in the 1990s revealed that female students often prefer more general practice/family medicine than male due to its flexibility regarding working place, time and schedule. But this study findings did not agree with them. Multiple factor may be responsible for this disagreement, like changing expectations of gender roles in society, personality changes of female medical students and feminization of medicine. Men are also seeking opportunities for flexible and part-time work to fit with domestic responsibilities for greater participation in family life and a more balanced lifestyle.<sup>24</sup> There is also evidence that personality changes have occurred among the female medical students where they have become more action oriented and aggressive. That is why formerly male-dominated specialties are now a days over represented by women.<sup>17</sup> Additionally due to feminization formerly male-dominated specialties are now a days over represented by women also.<sup>25</sup> Recently in 2008, Maiorova et al.<sup>26</sup> also suggested that men and women do not differ substantially in their interest in general practice. Life style factor, which are mainly the preference of women, are not important at the undergraduate stage. This finding also consistent with the present study, the mean score of the medical lifestyle factor score of male and female students was very close (66.6 vs 66.1).

Ethnicity is weakly related to the students' choice of general practice as their career.<sup>27</sup> The present study findings also suggest that

ethnicity is not a significant predictor of students choice the general practice as their career.

The present study findings suggest that student of rural background has no effect on student preference the general practice as their future career. In early literatures,<sup>21,23,27</sup> students with small towns or rural backgrounds were more likely to choose general practice career. One of the explanations of it in literatures was that rural students may had greater exposure to the general practitioner role model than clinical specialist role model.<sup>12,28</sup> In Malaysia general practice specially in private sector is urban based. More than 8000 private general practitioners and 7454 private primary care clinics have been running through out the country, especially urban areas.<sup>29</sup> These clinics are largely run by either single-handed or a group of 2-3 general practitioners.<sup>9</sup> This facilitates the urban students general practitioners role model exposure also same as the rural students. However, it need to explore.

In this study, societal orientation is the highest scored student perceived factors for the preference of their future career. It may be due to the motives of the students before entering medical school. Because majority of the students, choose the medicine due to socially oriented motives, like to help the people, establish relationship with the people, a practice in a underserved areas etc.<sup>16</sup> The present study also suggests that societal orientation positively influence the first year medical students to select general practice as their future career. It is consistent with the other studies.<sup>2,30</sup>

The present study suggests that hospital orientation plays an important role to determine the career preference of the first year students. Surgery, Obstetrics & Gynecology and others surgery based specialties has been reported previously to be the most popular among medical students at matriculation.<sup>31,32</sup> This preadmission

perception may be one of the explanation of high influence of hospital orientation on career preference among the first year students. But the study suggests that hospital orientation had no influence to select general practice as their first preference by the first year students. It indicates that hospital orientation factor is equally important to both the groups of students preferred either general practice or specialty practice. It may be due to exposure of the students to the clinic based general practice, which is very common in Malaysia.<sup>9,29</sup>

Literatures revealed that medical lifestyle factors like fixed hours of practice, time allocation for the family, acceptance on call schedule are the important determinant of general practice preference by the medical students and newly graduated physicians.<sup>2,12,18</sup> But recently in 2008, Maiorova et al. (2008)<sup>26</sup> suggested that at the undergraduate stage, medical life style factors seem less important to the medical students. The question of a balance between work and private life is a question of later concern. The present study findings don't agree with Maiorova et al. (2008)<sup>26</sup>, it suggests that it not a matter of later concern, fresh medical students are also aware about a balance between work and private life from the first year.

The present study suggests that societal orientation and medical life style factors are the important predictors of general practice preference rather than the other perceived factors like, hospital orientation, economy and prestige, and easy to build up career and their demographic characteristics among the first year medical students.

The study have a number of limitations. Firstly, it was a cross-sectional study, we do not know the ultimate career choices of the this cohort, shifting in career preferences might be occurred during later year in medical school that must be taken into consideration during interpretation of the

results. Secondly, only students' demographic and perceived influencing factors were examined in relation to their career preferences. Possible other factors such as personality types of the students, institutional characteristics, curricular features were not considered in this study. Thirdly only first year USM medical students participated in this study, it might not be generalized.

Despite of these limitations of this study, a number of findings have implications for student selection of medical schools, career choice and further research. Assessment of the societal orientation and medical life style factors of the candidates should be encompassed with the medical school admission policies for enhancing the number of GP. Medical schools should provide counselling of the medical students for maintaining and increasing the socially oriented motives, like to help the people, establish relationship with the people, a practice in a underserved areas etc. Medical schools should be encouraged to increase the number of GP teachers/academics involved in teaching their medical students. Such people act as positive role models to the students. Health policy makers should be more concentrated on the life style factors to attract the medical students towards general practice by offering a superior work-life balance of GPs. Further study is needed on the practice of the student's perceived factors as admission criteria of the medical schools to get the desire number of future general practitioners. It is also needed to reexamine the role of rural back ground as a selection criteria for increasing the general practitioners.

#### Acknowledgements

We would like to express our gratitude to Universiti Sains Malaysia for this short term grant to carry out the study.



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## Effectiveness of linezolid over traditional antibiotics in osteomyelitis in adults : a review

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### Abstract

Osteomyelitis is rare but complicated and challenging disease, mainly caused by staphylococcus aureus. Although bone is normally resistant to bacterial colonization, some events such as trauma, surgery may disrupt bony integrity and lead to bone infection. Appropriately designed antibiotic regimens are critical to manage the all stages of osteomyelitis. Methicillin, Vancomycin, Fluoroquinolone, clindamycin and so many antibiotics are used. Recently, several newer agents with good activity against causative organisms have been introduced include linezolid, daptomycin, tigecycline, telavancin and ceftaroline. Their roles in the treatment of acute and chronic osteomyelitis are still being evaluated. The best studied of these is linezolid, a bacteriostatic antibiotic. The comparative role of linezolid and other antibiotics in osteomyelitis are thoroughly evaluated in this review article.

### Introduction

Osteomyelitis is one of the oldest disease. When microorganisms are introduced into bones hematogenously, contiguously or from direct inoculation related to foreign body, trauma, osteomyelitis can occur. When bone infection persists for months then referred as chronic osteomyelitis and may be polymicrobial.<sup>1</sup> Osteomyelitis is estimated to affect 2 out of every 10,000 people in United States and around 80% of cases develop it because of open wound.<sup>2</sup> Another study showed that the incidence of osteomyelitis is approximately 13 per 100,000 in children and approximately 90 per 100,000 in adults.<sup>3,4</sup> Early and specific treatment is important in osteomyelitis and identification of causative organisms is essential for antibiotic therapy.<sup>5</sup> The most important consideration for antibiotic selection is spectrum of action. Route of administration by intravenous or oral route is less important than drug levels that are achievable at the site of infection. Intravenous beta-lactam and vanomycin are the treatment of choice for methicillin resistant staphylococcus aureus (MRSA) osteomyelitis. Rifampicin combined with other anti-staphylococcus agents may increase cure rates, especially for device associated infections. Oral fluoroquinolones with beta lactam agents can be used for treatment of gram negative osteomyelitis, but increasing resistance has complicated

management of this infection.<sup>6</sup> Successful management requires a combination of targeted antimicrobial therapy and surgical removal of necrotic and devitalized tissue. Consensus recommendation for prolonged (? 6 weeks) antibiotic therapy for most osteomyelitic patients.<sup>7</sup> Antibiotic susceptibility is determined by MIC and susceptibility interpretations are based on achievable serum level. An ideal agent would achieve adequate bone concentration to meet pharmacokinetic and pharmacodynamic targets for bacterial cell death and eradication of infection.<sup>8</sup> Linezolid, approved by FDA in 2000 for MRSA infection like skin and soft tissue infection, diabetic foot ulcer, osteomyelitis.<sup>9</sup> Linezolid has been shown to be clinically useful in the treatment of osteomyelitis, where traditional bactericidal agents have been required.<sup>10</sup> Successful outcomes or cure were reported in several articles.<sup>11-14</sup> The aim of this present work is to provide an effective role of linezolid over traditional antibiotics to treat osteomyelitis.

### Osteomyelitis

When a bacteria adhere to bone by expressing receptors for component of bone matrix (Fibronectin, laminin, collagen and bone siloglycoprotein); the expression of the collagen-binding adhesion permits the attachment of the pathogen to cartilage.<sup>15</sup> During acute infection phagocyte attempt to

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Cite this as:  
BMJ 2018; 4(2): 22-29

Received : 5 March 2018  
Accepted : 25 April 2018

combat invading microorganism and in the process generate toxic oxygen radicals and release proteolytic enzymes that may lyse the surrounding tissues.<sup>7</sup> If the infection is not treated, dead neutrophils were accumulate inside the bone, forming an abscess or pocket of pus. Pus spread into vascular channel, raising the intraosseous pressure and impair blood flow. In chronic osteomyelitis, the bone may actually die. So, antibiotic should be started after taking necessary steps.

### Steps in the progression of chronic osteomyelitis



### METHICILLIN AND VANCOMYCIN

Methicillin, an antistaphylococcal penicillin mostly used in osteomyelitis. After isolation of methicillin-resistant strains, glycopeptides particularly vancomycin is preferred extensively. Unfortunately in 1996 resistance to this antibiotic has been recognized. It also achieves low bone penetration.<sup>16</sup> The recurrence rate of vancomycin is two times higher than beta-lactam antibiotics.<sup>17</sup> Data suggest that vancomycin is losing its clinical and microbiological potency.<sup>18</sup>

### Linezolid

The prevalence of MRSA is increasing and their susceptibility to vancomycin is decreasing.<sup>19</sup> Therefore, linezolid is choiced after considering: potential causative micro-organisms and their corresponding range of MICs (minimum inhibitory concentrations), pharmacokinetic and pharmacodynamic properties, mechanism of action, tolerability, and host toxicity.<sup>20</sup> Some clinical studies are given in Table 2.

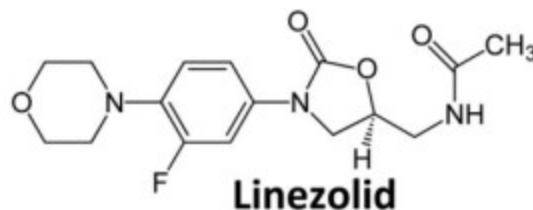


Figure: Chemical structure of Linezolid

### Pharmacodynamics

Linezolid belongs to the group of oxazolidinones. It is a synthetic, broad spectrum antibacterial agent available in both oral and parenteral dosage form.<sup>21</sup> It binds to 23s rRNA of the 50s ribosomal subunit and prevent formation of 70s complex, which initiates bacterial protein synthesis.<sup>22</sup>

### Pharmacokinetic profile

Linezolid achieve maximum plasma concentration within 1-2 hours and oral bioavailability reaches approximately 100% and demonstrates good bone penetration.<sup>23</sup> It exhibits low protein binding and eliminated via renal and non-renal route.<sup>24</sup> Organisms for which the MIC of linezolid is  $< 4 \mu\text{g/ml}$  are considered susceptible, whereas those for which the MIC is  $= 8 \mu\text{g/ml}$  are considered resistant.<sup>25</sup> The peak plasma concentration of linezolid significantly surpasses the MIC of enterococci and staphylococci.<sup>26</sup> The pharmacokinetics of different antibiotics including Linezolid are presented in Table 1.<sup>16,27</sup>

### Microbiologic activity

*Staphylococcus aureus* is the most common pathogenic organism recovered from bone followed by *Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Viridans streptococci*, *Staphylococcus epidermidis*, *Serratia*.<sup>28</sup> Mycobacterial and fungal infections have been reported in patients with osteomyelitis, but these are uncommon and generally found in patient with impaired immune function.<sup>29</sup> Linezolid is active against a wide range of gram-positive aerobic bacteria, some gram positive anaerobes and some gram-negative anaerobes. It has good activity against resistant strains of several



gram-positive aerobes such as MRSA, PRP (penicillin resistant pneumococci).<sup>30</sup>

### Cost effectiveness of linezolid

Linezolid is a costly medication especially compared to other antibiotic like doxycycline, co-trimoxazole, vancomycin, rifampicin, ciprofloxacin.<sup>31</sup>

**Table 1: Pharmacokinetics of antibiotic**

Antibiotic	Dose	Peak plasma concentration (µg/ml)	Oral bioavailability	Bone concentration
Ciprofloxacin	750mg	2.6	60-80%	27-48%
TMP/SMX	7-10mg/kg/day	7.4/14.3	90-100%	50%/1.5%
Linezolid	600mg	18	100%	40-50%
Rifampicin	450-600mg	5-7	70-90%	-----
Clindamycin	450-600mg	5-15	90%	40-67%

### Fluoroquinolone

The fluoroquinolones have gained popularity in osteomyelitis in recent years. They achieve bactericidal levels in blood and tissue. The second generation fluoroquinolones like ciprofloxacin, levofloxacin, ofloxacin, lomefloxacin are mostly advisable against gram-negative and some gram-positive organism. The fourth generation fluoroquinolone like moxifloxacin, gatifloxacin has improved streptococcal activity.<sup>33</sup> To prevent emergence of resistance fluoroquinolone is recommended in combined with other agents in osteomyelitis.<sup>34</sup> Some clinical studies are reported in Table-3.

**Table 2: Clinical studies of linezolid (600mg) monotherapy in osteomyelitis**

No. of patients	Type of infection	Organism	Clinical cure rate	
40	Osteomyelitis	MSSA3, MRSA19	90%	Broder et al <sup>35</sup>
53	Osteomyelitis	VRE18		
		MRSA21, MSSA6	98%	Rod and Hamilton <sup>36</sup>
		MRCONS17,		
22	Implant associated Osteomyelitis	MSCoNS2 Enterococci7	100%	Vercillo et al <sup>37</sup>
		Monomicrobial9		
		polymicrobial13 MRSA10,VRE5		
55	Chr. Osteomyelitis	MRSA25, VRE17	81.8%	Rayner et al <sup>13</sup>
		MSSA3, & others		

VRE- Vancomycin resistant enterococci

MRCONS-Methicillin resistant coagulase negative staphylococci

MSCONS-Methicillin sensitive coagulase negative staphylococci

Post treatment follow up period was >1 year

But soon after it was approved, the cost savings was appreciated because of its early switching from intravenous to oral therapy.

### Adverse events of linezolid

Duration related adverse effects including gastrointestinal disturbances, increases in hepatic enzymes levels, reduction of platelet and hemoglobin are expected. Hematological indices decrease slowly over time and can be detected with the appropriate monitoring of complete blood cell counts during treatment with linezolid.<sup>32</sup>

### TMP - SM (Trimethoprim Sulfamethoxazole)

The combination of Trimethoprim-Sulfamethoxazole are bactericidal and having the activity against staphylococcus aureus, pseudomonas aeruginosa, enterobacteriaceae, E.coli and streptococci. A study showed 45% cure rate in osteomyelitis out of 66 patients in double strength of combination.<sup>41</sup> Another study showed 89% cure rate in combination of rifampicin and TMP-SMX.<sup>42</sup> Now- a- days TMP-SMX resistance among staphylococcus aureus isolates are increasing.<sup>43</sup>

**Table 3: Clinical studies of Ciprofloxacin (750mg) monotherapy in osteomyelitis**

No. of patients	Type of infection	Organism	Clinical cure rate	References
39	Chronic Osteomyelitis	S.aureus19, S.epidermidis2, Gram negative pathogen18	66.7% Staphylococci	Dellomonie et al <sup>38</sup>
31	Chronic Osteomyelitis	Various (S. aureus8)	77% (100% in S. aureus)	Gentry and Rodriguez <sup>39</sup>
14	Chronic Osteomyelitis	Enterobacteriaceae18 Pseudomonas aeruginosa16, S.aureus4	50%	Greenberg et al <sup>40</sup>

**Rifampicin**

Rifampicin is a broad spectrum, bactericidal antimicrobial agent achieves high intracellular concentration. It has potent antistaphylococcus activity. It is not used alone due to rapid emergence of resistance.<sup>6</sup> Some clinical studies are reported in table-4.

**Clindamycin**

It is a lincosamide antibiotic, active against most gram positive bacteria. It has been successfully used in osteomyelitis especially in children but rarely in adults.<sup>44</sup> A study showed 42% cure rate out of 12 adult patients.<sup>45</sup> Currently, it is given orally after initial intravenous treatment for 1-2 weeks.<sup>33</sup>

**Beta lactam antibiotics**

Beta lactam antibiotics like nafcillin, cefazolin, ceftriaxone are less effective in osteomyelitis when used alone. In a study 79% cure rates was found when ceftazidime or nafcillin combinedly used with amikacin.<sup>39</sup>

**Discussion**

Acute osteomyelitis results from bacteremic seeding of bone (19%) and chronic osteomyelitis is generally secondary to open fractures, open wound, bacteremia, and contiguous soft tissue infection. Post traumatic osteomyelitis accounts for as many as 47% of cases.<sup>49</sup> Diabetic patient are at a greater risk of getting this infection. In middle aged, spinal osteomyelitis may be associated with urinary bladder infection. It may occur as a complication of many diseases such as typhoid, syphilis, tuberculosis or sickle cell anemia. Diagnosis is confirmed by radionuclear bone scan. Others are- estimation of erythrocyte sedimentation rate, C - reactive protein level, leucocyte scan, positron emission tomography (PET), musculoskeletal ultrasonography, and technetium-99 bone scintigraphy. The precise cause of infection is determined by culture of blood and bone biopsy.<sup>50</sup> Linezolid has proven to be a valuable addition to the antibiotic

**Table 4: Clinical studies of Rifampicin combination therapy in osteomyelitis**

Antibiotic regimen	No. of patients	Organism	Clinical cure rate	References
Rifampicin(600mg)+Ofloxacin (200mg)	20	Monomicrobial (15)+Polymicrobial(5)	76.5%	Senneville et al <sup>46</sup>
Rifampicin (600mg)+Levofloxacin (500mg)	7	MSSA(5), Streptococci 1, MScNS1	86%	Frippiat et al <sup>47</sup>
Rifampicin(900mg)+ Linezolid(600mg)versus Rifampicin(10mg/kg)+ TMP-SXT(8/40mg/kg)	56	MRSA21,MSSA2 MRCNS18,MScNS 3, Others	89.3% versus 78.6%	Nguyen et al <sup>48</sup>
Post treatment follow up period was >2 years				



armamentarium against staphylococcus aureus. To date it is the first and only oxazolidinone, which is used to treat staphylococcus aureus osteomyelitis.<sup>51</sup> Rifampicin, vancomycin, clindamycin, fluoroquinolone takes more time for patient discharging. Hepatitis, interstitial nephritis, enterocolitis and QTc prolongation are more common following administration of rifampicin, vancomycin, clindamycin and fluoroquinolone. So dose adjustment must be required. But linezolid can be used safely in patient with liver disease and renal insufficiency. These antibiotics have different dose, different mechanism of action, but all of them have effective role in osteomyelitis. The varying cure rates may be related to variable diagnostic criteria, surgical debridement or duration of follow up. Linezolid has higher cure rates than others. It has post antibiotic effect. It is hopeful that linezolid resistant strains are not established still now. In the past, chronic osteomyelitis was treated parenterally. Now-a-days it is proved that oral therapy is therapeutically equivalent to parenteral therapy.<sup>52</sup> Because of excellent oral bioavailability, linezolid is easier to switch from intravenous to oral formulation with consequent earlier patient discharge and lower in patient costs. Current treatment consists of surgery with prolonged (>6weeks) antibiotic therapy. The goal of success should limit the spread of infection to adjacent healthy bone and tissues and linezolid covers it. Treatment limiting toxicities occurred in one-third of patients. Lactic acidosis, optic neuritis, peripheral neuropathy are rare.<sup>53</sup> Most of the adverse effects are reversible upon cessation of therapy and no cross resistance occur to other antibiotics.<sup>54</sup> As osteomyelitis is common in developing countries and recurrence rate is 30%, which might be related to incomplete resection of infected bone or to resistant micro-organism, an accurate antibiotic is necessary.<sup>55</sup> On this ground, this review supports linezolid as a good choice for patient with osteomyelitis.

## Conclusion

Acute osteomyelitis could be brought under control with antibiotic, but chronic osteomyelitis is potentially curable. Adequate blood supply is essential for delivery of antibiotic to the chronically infected bone. Surgery is needed to improve the blood supply to the affected bone. Standard of living, hygiene and nutrition are important for declining the incidence of osteomyelitis. Attention should always be paid to the adverse reactions that are possibly related to linezolid application. Cost containment issues impact antibiotic stewardship policies and healthcare settings with limited resources. Although not officially accredited for, linezolid seems to be a good alternative in the management of osteomyelitis caused by multiresistant bacteria. So, additional clinical studies are needed to explore better role of linezolid and further research on the cost effectiveness and outcome measurements.

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## Appendicular calculi and carcinoid tumor of the vermiform appendix: a case report

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### Abstract

Two uncommon distinct pathology occurring in the same patient without any symptom related to the organ is fascinating and interesting. In this case transabdominal hysterectomy was done in a woman aged 38 years for dysfunctional uterine bleeding. In addition appendisectomy was done as the appendix was found inflamed. Gross examination revealed two calculi at the tip and histopathology confirmed carcinoid tumor of the appendix.

**Key words:** vermiform appendix; calculi; carcinoid tumor.

### Introduction

Weisfiog was the first to make a correct preoperative diagnosis of appendicular calculus radiologically.<sup>1</sup> In 1947 Felson and Bernhard<sup>2</sup> estimated that just over 100 cases had been reported; this number had increased to 120 by 1951<sup>3</sup>, and to between 130 and 155 by 1957.<sup>4,5</sup> Regarding neoplastic diseases, carcinoid tumors (CT) are the most common neoplasm of the vermiform appendix.<sup>6</sup> The overall incidence of carcinoid tumors has been estimated to 1 to 2 cases per 1000 appendisectomies in surgical specimens.<sup>7</sup> CTs are discovered usually during the course of another procedure.<sup>8</sup> In this case there are two stones situated at the tip and CT is situated in the mid portion in the same vermiform appendix.

### Case report

A 38 year old woman, was admitted into a private hospital with the history of dysfunctional uterine bleeding (DUB) and lower abdominal pain for 6 months. On examination she was anemic with low grade fever. The estimated Hb level was 6.2 gm/dL. Abdominal and transvaginal sonography (TVS) was performed which revealed mild bulky uterus with an uterine fibroid. Considering the patient's clinical condition surgery was performed. Total abdominal hysterectomy (TAH) with appendisectomy was done. The appendix was found inflamed with distension of the tip, which was solid and firm on palpation. Gross examination has shown vermiform appendix measuring 9.0x1.0x1.0 cm, cut section

revealed 2 stones (the larger one measures 1.0x0.8x0.8 cm) at the tip (Figure 1) and a mass measures 1.0x1.0x1.0 cm at the mid point of its length. The histological examination revealed a typical CT of the appendix (Figure 2) and tumor-free margin in all specimens. The tumor was consisted of small island of uniform cell with scant, pink granular cytoplasm and a round to oval stippled nucleus. The muscular layer is infiltrated by the tumor cell nests. The mitotic activity was insignificant. The patient's postoperative course was uncomplicated and she was discharged on the 4<sup>th</sup> postoperative day. Diagnosis of appendicular calculus is not particularly difficult when the condition is borne in mind. A straight X-ray film of the abdomen in every patient with undiagnosed abdominal symptoms reveals a characteristically lamellated calculus, usually in the right iliac fossa. It is readily distinguished from the mottled appearance of calcified mesenteric nodes; ureteric calculi lie in the axis of the ureter, and gallstones are not usually so low. In case of gallstones and ureteric calculi, cholecystography and intravenous pyelography may be very useful adjuncts respectively.

### Discussion

The simultaneous presence of appendicular calculi and CT in the same appendix is a rare pathological entity. The great majority of patients with appendicular calculi may present as acute abdominal emergencies. Since the calculus will in most cases have lain in the appendix for months or years, gradually

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Cite this as:  
BMCJ 2 018;4(2): 30-32

Received : 6 February 2018  
Accepted : 4 March 2018

increasing in size in a confined space, it is surprising that a history of previous attacks of colicky abdominal pain or of symptoms suggestive of 'grumbling appendix' is seldom present. Eventually the typical picture of acute obstructive appendicitis develops and prompt surgical intervention becomes necessary. Early surgical treatment is therefore indicated when an appendicular calculus is revealed, by intention, by chance, or by radiological examination of the abdomen.<sup>9</sup>

In a study carried out by Forbes GB in 1966,<sup>9</sup> two thousand appendices were examined for evidence of calculous disease. One thousand eight hundred were specimens removed surgically and 29 of them harbored stony-hard calculi. The incidence of calculous disease in 1,000 consecutive appendisectomy specimens was 08%. An additional calculus was observed radiologically in a case of appendicular actinomycosis. All but five of the 30 calculus-containing appendices were acutely inflamed and 50% of these were gangrenous or perforated. Others have reported fistula formation as a complication of calculous disease.

From the reports in the literature it can be clearly seen that stone in the appendix is very prone to cause serious illness, often with perforation and generalized peritonitis. Some patients harboring a calculus in the appendix will be seen in a non-acute phase, sometimes with vague symptoms. Felson and Bernhard<sup>2</sup> record the case history of a 39-year-old male who complained of low back pain. In the preceding year he had three attacks of epigastric pain, and one attack in the right lower quadrant. In this case the patient had history of low back pain.

In case of CT, the clinical presentation is similar to acute appendicitis, but the CT can be an incidental finding during surgical procedures. In this case CT was diagnosed incidentally during TAH. It was confirmed on histological examination of the removed appendix.

In 60 cases reviewed by Felson and Bernhard<sup>2</sup> most patients were between the ages of 10 and 30, and there was a male preponderance of nearly 4:1. In our case, the patient is a female and much older than the patients in Felson's study.

In the 75% of cases the tumor is localized at the tip of the appendix, in 20% and 5% cases, it affects the mid portion and the base respectively.<sup>10</sup> The tumor's median diameter is 6 mm.<sup>8,10</sup> In our case, the diameter of the tumor was 1 cm and it was situated at the mid portion. Generally, carcinoid tumors located at the tip of the appendix and measuring less than 10 mm and usually mimics the clinical presentation of acute appendicitis, while tumors measuring more than 20 mm and located at the base of the appendix may present with clinical signs of peritonitis.<sup>11,12</sup> The site and the size rather than the depth, are used for the assessment of the tumor.<sup>8</sup> The prognosis is directly related to the tumor size. Localized disease has an excellent prognosis. The prognosis of patients with metastatic CT is very poor. If the tumor is smaller than 2 cm and has perforated the serosa, the treatment of choice is appendisectomy, whatever the location. Tumors measuring 2 cm or more in diameter may have widespread metastases upon detection. Symptoms of the carcinoid syndrome as flushing, diarrhea, cardiac disease have been rarely reported and usually associated with liver or retroperitoneal metastases.<sup>13,14</sup> In our case, CT was localized and the patient had no symptoms related to carcinoid syndrome.

Most interesting and surprising is that the patient in our case harboring appendicular calculi and carcinoid tumor simultaneously.

### Conclusion

Our case highlights the rarity of the location of these two uncommon pathology with an emphasis on the diagnosis of these entities to generate clinical awareness, early diagnosis and proper management, thus decreasing significantly morbidity and mortality.





Figure 1: Gross appearance of the appendix with calculi.

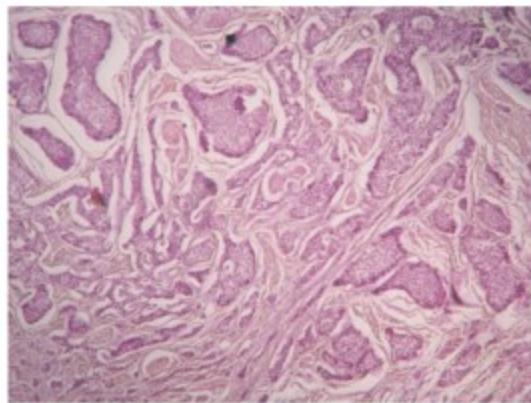


Figure 2: Histological section of carcinoid tumor of the appendix showing island of uniform cell (H&E stain x 400).

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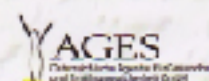
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