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Highlights

- Preliminary Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion (ALIF) with stand alone PEEK cage and Anterior Plate Construct at the Bangkok Spine Academy
- LightCycler® MRSA Advanced Test for Rapid MRSA Detection in Referral Patients Admitted to Intensive Care Units
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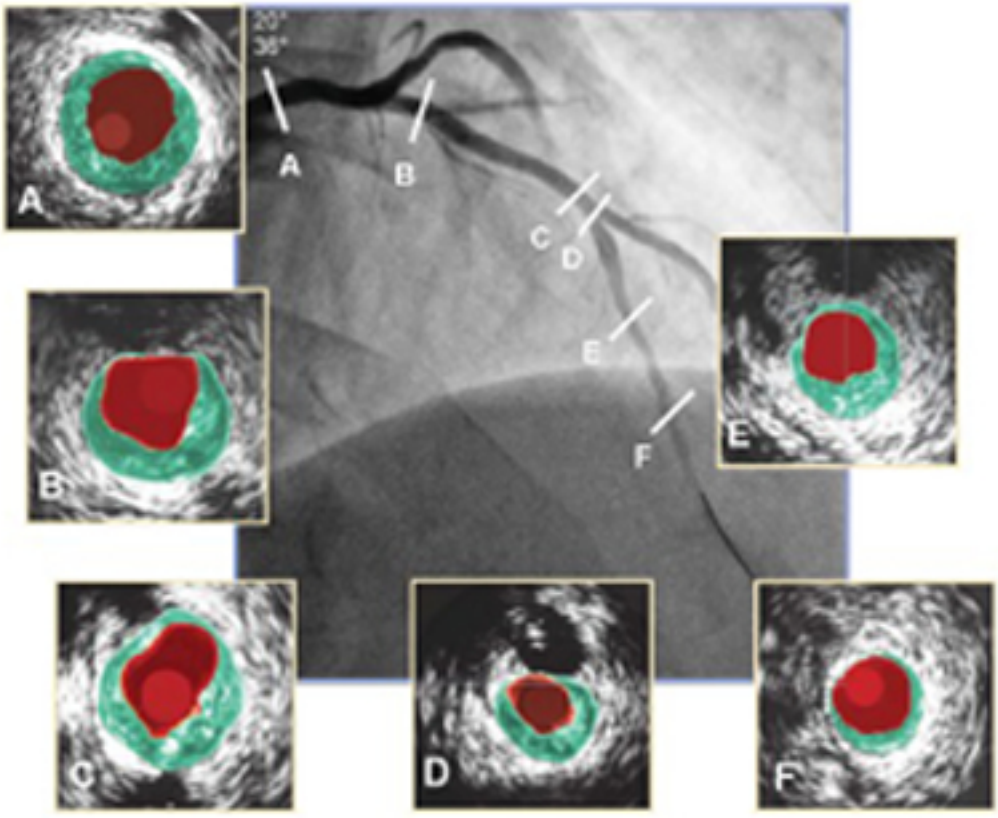
- Transjugular Intrahepatic Portosystemic Shunt (TIPS)
- Mesenchymal Stem Cells

Atheroma and Coronary Artery Spasm



Intravascular ultrasound sonography (IVUS)

Red = Intra-arterial coronary lumen

Green = Thickness of coronary arterial wall

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Editorial

The attentive reader will have noticed in previous editions that a key feature of this Journal is to provide not only a vast array of cases that are interesting in themselves, but also to combine new experience with the body of knowledge built up over time. Thus, in this edition, we have a very specific case involving a rare side effect of a statin, along with a follow-up article on 5 years' experience of the success of stroke fast track at the Bangkok Hospital Medical Centre. This emphasis on range also applies to the use of equipment in hospital treatment, with an article on stress echocardiography, the LightCycler® test for MSRA detection and the ECMO (Extracorporeal Membrane Oxygenator) for life support.

This range also involves the perspective we have on our patients. The Bangkok Medical Journal is not just about doctors and equipment, we believe that people should be at the forefront of our concerns. Hence the human interest in articles on Aeromedical Transport Missions and the survival of an old lady with ALCAPA along with the work on cases of viral pneumonia.

The editorial board has another concern also: to give space both to those authors who are reporting on the practical side of their work, such as the article on clinical and radiographic outcomes of anterior lumbar interbody fusion, and also to authors who have spent time researching a specific area of interest, such as Hirayama's disease, and wish to share their knowledge. In this context, emphasis is also given to the unexpected, such as the article on the successful combination of adult and pediatric fiber optic bronchoscopy.

We would like to highlight the contribution of guest author Ann Weinacker, MD and her update on the management of polytrauma patients. Her overview provides invaluable information to provide the very best care for polytrauma patients, including those injured in motor accidents. These patients account for a significant number of admissions to emergency care.

Perhaps a key expression for an understanding of our approach is "something for everybody". Certainly, anyone looking at this edition and browsing previous ones will find that we have covered an impressive range of issues.

We intend to continue in this vein and hope you, the attentive reader, will continue with us.

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Preliminary Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion (ALIF) with stand alone PEEK cage and Anterior Plate Construct at the Bangkok Spine Academy

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Keywords: anterior lumbar interbody fusion, ALIF

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Disclaimer: The authors received no financial assistance from Synthes Spine for the preparation of this article. Furthermore,the authors do not hold financial interest in Synthes Spine or in the sale of the Synfix® device (Synthes Spine ,West Chester,PA, USA).

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OBJECTIVE: To study the preliminary results of 20 patients who underwent Anterior Lumbar Interbody Fusion (ALIF) and were followed up for more than 6 months at the Bangkok Spine Academy.

MATERIAL AND METHODS: Study of the preliminary results and retrospective chart review of collected clinical and radiographic outcomes in 20 patients who underwent ALIF L1-L5 at Bangkok Hospital from April 2011 to April 2013 as a treatment for degenerative disc disease, spondylolisthesis, recurrent disc herniation and failed back surgery syndrome. Treatment involved using a stand-alone polyetheretherketone (PEEK) cage and an anterior plate construct (Synfix®, Synthes spine, PA, USA).

RESULTS: Of 22 patients who underwent ALIF surgery between April 2011 and April 2013 two were excluded from this series. The remaining 20 cases were followed up regularly until the fusion was complete.

Indications for surgery were degenerative disc disease, spondylolisthesis, pseudarthrosis from previous surgery, and recurrent disc herniation. Most cases experienced both back pain and leg pain from spinal instability and nerve root compression. Five cases underwent surgery because of back pain without any leg pain. The majority of patients (nine cases, 45% of total) were spondylolisthesis, including both degenerative and lytic types. Seven cases (35%) were diagnosed as degenerative disc disease. One case (5%) was treated because of the recurrence of disc herniation. One case (5%) was treated for pseudarthrosis and an implant breakage from previous fusion surgery.

In a total of 20 cases we operated on 23 levels of problematic discs. The mean operative time for each level was 156 (±35.5) minutes (mean ± standard deviation (SD)). The shortest operative time was 115 minutes for each level and the longest was 240 minutes. The intraoperative blood loss averaged at 315.2 (±225) ml.

The initial pain score in self-reported questionnaires (visual analog scale (VAS) back, VAS legs) showed fast and lasting pain relief. The mean VAS preoperative back score was 5.7 (±2.0), which at the two-week visit reduced to 0.6 (±1.1). The mean VAS leg score was 3.55 (±2.8), which reduced to 0.1 (±0.2).

The Oswestry Disability Index (ODI) questionnaire was used to evaluate the improvement of the overall disability status and was found to decrease from 42.0 (±28.2) to 13.9 (±14.3) at the six-week follow up visit. It continued to decrease to 4.3 (±6.4) at the three-month visit and 0.4 (±1.0) at the six-month visit. There was a mean correction of segmental lordosis at an instrumented level from an initial 18.6 (± 8.8) to 21.2 (±8.7) after surgery. There was a significant improvement in the mean coronal angle from 4.1 (±4.5)

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to 1.6 (±2.0) postoperatively. The increase in mean disc height at the middle column was from 8.8 (±3.2)mm to 14.4 (±2.1)mm after surgery. The degree of slip changed from a mean of 16.7 (±5.6)% to 8.4 (±5.9)%, and the average slip improvement was 49.7 (±27.9)% using the stand-alone ALIF technique.

One of the most challenging aspects of this surgery is the difficulty of an anterior retroperitoneal approach. The large venous and arterial channels obstruct exposure of the lumbar intervertebral disc. Of the 22 cases, one had inadvertent intraoperative venous bleeding from an old adhesion from a previous surgery but this was controlled by a vascular surgeon. There were no cases with an abdominal ileus after surgery. One case had retrograde ejaculation that was resolved during the second year follow up visit. There were no cases of neurological problems as this surgery went in from the front of the spine. Because the ALIF implant is large it carries the human body very well, so there were no cases of subsidence, implant breakage or loosening. The fusion was well established because of a big area of fusion on the vertebral end plate. The nature of this surgical technique ensures the patient experiences less back pain after surgery which in turn improves their ability to recover faster and to return to their full activity.

CONCLUSION: This preliminary mid-term report of the stand-alone ALIF procedure at the Bangkok Spine Academy shows satisfactory and consistent results. The benefits of this procedure include: reduction in back and leg pain, minimization of soft tissue injuries especially of uninjured back muscle, and lower likelihood of nerve root injuries. The only disadvantage of this procedure is that the technically demanding anterior approach needs prompt management for any vascular issues. These surgical techniques show fast and long-lasting, satisfactory results with less likelihood of long-term complications.

Spinal fusion is one of the major goals of spinal surgery especially in the case of spinal instability, infection, tumor and traumatic conditions. The history of spinal fusion began in the early 19th century with Russell Hibbs and Fred Albee, who applied an autologous bone graft on the dorsal surface of the spine to treat spinal tuberculosis. The success of this surgical technique is unacceptable because of the high rate of pseudarthrosis.[1,2] After Denis classified the spinal column, minor spinal instability showed that posterior spinal fusion is not sufficient to maintain the whole vertebral column. Some may need anterior vertebral column support and fusion anteriorly. The advantage of anterior spinal fusion is the ability to provide a better biomechanical support, and it can achieve a solid fusion that leads to a more stable fusion than posteriorly.[3] The surgical technique was changed from a transperitoneal approach to a retroperitoneal approach in order to reduce intra-abdominal complications. The implant design was developed from a simple metal cylindrical cage that needs posterior fixation to the well-shaped PEEK cage with an anterior plate constructed in the same shape for stand-alone surgery. The advantage of stand-alone anterior fusion is to avoid complications of posterior fusion disease.[2] The modern anterior inter-body cage device was designed to have a bigger and larger area able to carry the human body weight, and placed around the area of the apophyseal ring of the vertebral end plate which is the strongest bone with the least likelihood of implant subsidence. In conjunction with the mini-plate screws device attached to the front, it improved the anterior-posterior stability of the implanted levels with a lower likelihood of loosening or dislodgement from its position. Due to the big area of graft material in contact with the patient's own bone, there was a high success of bone formation in between the vertebral end plate to produce a solid fusion. This is the key to success in solving spinal instability that can cause chronic back pain.[1] With this well-designed intervertebral cage in full anterior-posterior diameter, there is also the strongest likelihood of opening the intervertebral foramen and neural canal that has collapsed due to spondylolisthesis or degenerative disc disease. As a result this eliminates leg pain from nerve root compression. Due to the nature of a big-round cage to withstand the load when a patient is standing or walking, there is less likelihood of a neural canal collapsing. This makes this technique of surgery appropriate for the patient who wants to have vigorous activity after surgery. The indirect decompression effect from the inserted large cage into the intervertebral space has an advantage over the direct decompression in terms of elimination of the incidence of nerve root injuries and eliminates the chance of post-operative pain from epidural scarring.

One of the major disadvantages of this surgery is the risk of vascular injuries during the anterior retroperitoneal approach: the great venous and the arterial blood vessels lie in front of the vertebral body of L4-5 and L5-S1. The surgeon should be familiar with the possibility of anatomical variation of all blood vessels in order to get an adequate exposure. Some good candidates for ALIF cannot be operated on because of a pathological level of vascular anatomical variation. The technical team must be prepared for any inadvertent condition arising during surgery. These conditions might include vascular leakage or difficulty to mobilize a great vessel due to adhesion. A back-up vascular surgeon should be ready to help the spine surgeon promptly when necessary.

ALIF surgery using this technique (stand-alone PEEK cage with anterior plate construct, Synfix®, Synthes, USA) has been available in Thailand since early 2011 and continues to be performed to the present day. For the purpose of this article, we will discuss the indications and candidates for this operation, the surgical steps, and will include the preliminary results of 20 cases (23 levels) performed between April 2011 and April 2013 with details of blood loss, operative time, radiographic evaluation, and the mid-term clinical outcomes.

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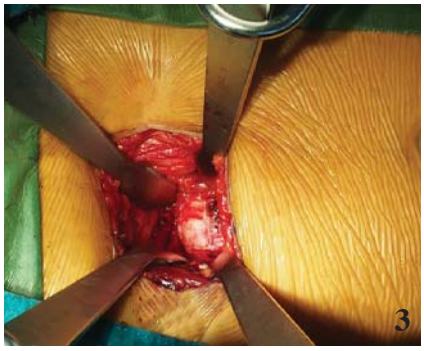

Figure 1: *Stand alone ALIF PEEK cage with anterior plate construct (Synfix®) available in Thailand.*
Figure 2: *Synfix®, stand alone PEEK cage with anterior plate construct was filled with bone graft substitute, Bone Morphogenetic Protein (white).*
Figure 3: *Mini-opened surgery on the front by retroperitoneal approach can expose the entire anterior surface of the pathological disc.*

Material and Methods

Indications and surgical candidates

ALIF is surgically indicated for posterior lumbar decompression or spinal fusion in patients who have axial back pain and or radicular leg pain. Patients with axial back pain from degenerative disc disease, or recurrent disc herniation requiring total removal of the disc material to achieve solid fusion are good candidates for ALIF. The ability to achieve this goal without disturbing soft tissue on the back side makes this procedure ideal for patients who have chronic back pain with a tendency of chronic back pain syndrome in the case of soft tissue scarring from conventional surgery. The advantages of the possibility of achieving solid fusion in ALIF means there is a lower likelihood of back pain remaining from pseudarthrosis, which is generally more prevalent in posterior spinal fusion surgery. The ability to open the disc space height and to reduce the slippage of vertebrae using a big cage is appropriate for spinal stenosis from neural foramina narrowing from collapsing or bulging discs in spondylolisthesis grade 1 and 2 (both degenerative or lytic in origin). The large ALIF cage will result in an automatic reduction in the slipped vertebra into a normal sagittal alignment and also an indirect decompression of the nerve root within the spinal canal. Due to a high success rate in solid fusion with a larger bony contact area around the vertebral end plate, and a greater variety of good graft material, we can choose such an autogenous bone graft, demineralized bone matrix and bone morphogenetic protein compared to posterior surgery. This surgical technique is considered best for patients with failed lumbar fusion surgery.

ALIF is contraindicated for cases of abnormal variation of the great vessel laying in front of the pathological disc level which is an obstacle for adequate exposure. Because of the big intervertebral cage diameter, this procedure requires almost the entire anterior exposure of the desired disc space. At present, the recommended equipment of use includes the abdominal ring retractor, as well as the designed disc Rongeur. These tools make surgery easier and more minimally invasive. That said, this procedure cannot be undertaken if the surgeon cannot mobilize the entire vessel out of the area of the surgical site. Some patients are not eligible for surgery because of adhesion round the affected level from previous abdominal or spinal surgery. There is a risk of massive bleeding from even a small leakage of the great vessel, especially from the venous structure that is easily torn. Also contraindicated are cases of highly collapsed disc space, as there is a chance of auto fusion between both levels. This is because of a tendency of failure in the elevation of the disc space height before the insertion of the cage. Despite this procedure having a low likelihood of cage subsidence in the vertebral body, any patient who suffers from a very severe osteoporotic bone condition is also contraindicated for the ALIF procedure.

Patient selection

The patients included in this study had an indication for spinal fusion and/or spinal decompression. All of them had lesions from L4 to S1, which is the most common pathological level in degenerative spine disease.

Indications

1. Degenerative disc disease (back pain / leg pain).
2. Spondylolisthesis grade 1 and 2 (degenerative / lytic).
3. Recurrent disc herniation.
4. Pseudarthrosis from previous back surgery.

Contraindications

1. Variation in the great vessels that prevent adequate exposure.
2. Adhesion in the retroperitoneal space from either a previous surgery or infection.
3. Severe osteoporosis.
4. Severely collapsed disc where the disc space height cannot be expanded.

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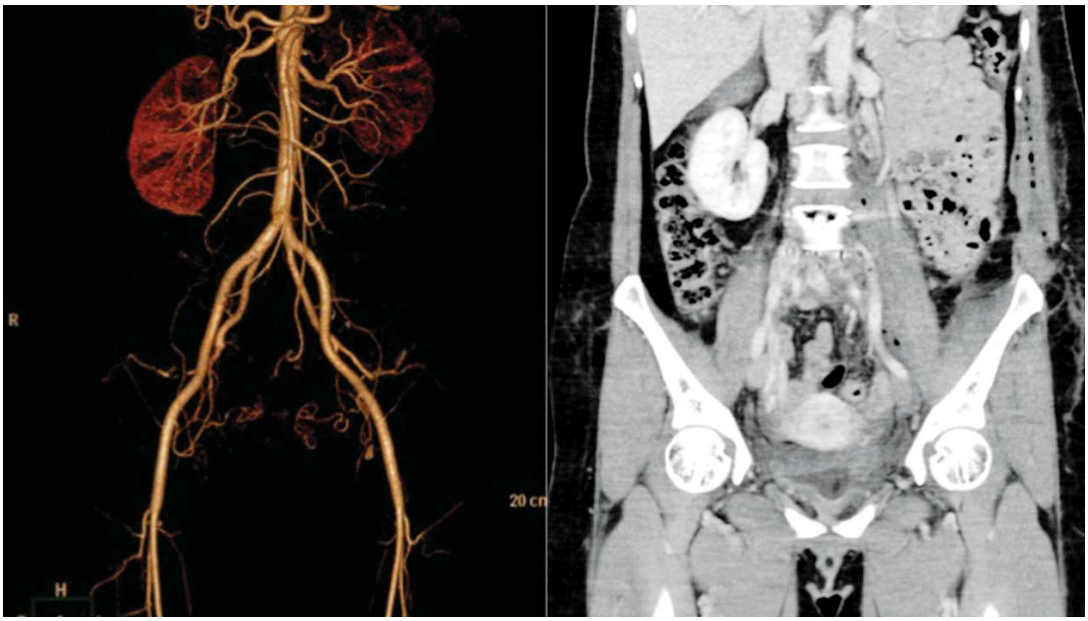

Figure 4: *In a case of suspected variation of the great vessel on the front of the spine, the magnetic resonance angiography is considered.*

Each patient receives comprehensive counseling and advice before the operation is undertaken. The surgeon informs the patients of any inadvertent problems that may arise intraoperatively and postoperatively. Any male patients who wish to undergo this surgery receive counseling about the risk of retrograde ejaculation that can lead to infertility. Men who are planning on having children are advised to do sperm banking. All our cases had back up from a vascular surgeon at our hospital during surgery for prompt management in case of any vascular injuries during the operation.

Study design

Data for this study was obtained through retrospective chart reviews and concurrent follow-up of patients who received ALIF surgery performed by the same spine surgeon (Buranakarl T) at the Bangkok Spine Academy. The outcome data was obtained prospectively preoperatively and at each postoperative visit through self-administered questionnaires. The roentgenographic data was obtained and calculated by another orthopedic doctor (Jaisanuk K) and the medical research department.

The patients' hospital and clinical charts were reviewed to identify any complications and the patient outcomes. The chart review included a compilation of demographics (age, gender), symptoms and diagnosis, surgical details (levels treated, instrumentation use, blood loss, operative time, complications), duration of hospital stay, any additional procedures, results of physical exams, late-occurring complications and patient complaints, prospective collected back and leg pain scores (visual analog scale, VAS), and a disability index. Radiographic measurements were taken before and after surgery to assess any change in the sagittal and coronal plane alignment of the individual operated disc levels, the overall lumbar spine, and the lumbar scoliosis curves. The radiographs were also analyzed for vertebral abnormalities such as fractures or collapses, correction of the sagittal and coronal plane, and vertebral slip correction in the sagittal and coronal plane in each level. At the follow up visits (at six weeks, three months, six months, and twelve months) all patients were re-evaluated using the VAS pain scale and the Oswestry Disability Index (ODI), and for nerve root injury, sexual function, wounds and other complications.

Surgical technique

Under general anesthesia, the patient is prepared in the same manner as normal spine surgery. The intravenous (IV) line and urinary catheter are placed. The patient is transferred to the operating table and placed in a supine Fowler position with a roll of towel underneath the operated lumbar level in order to maintain an extension of the lumbar spine. Both legs are placed on the lithotomy table and attached with an anti-thrombotic calf pump. Both legs are spread out for the first surgeon standing in front of the abdomen and the hip flexor to relax the abdominal muscle. The fluoroscope c-arm is placed underneath the table to ensure it can move freely all the way down without any obstacle to evaluate the disc space and end plate laterally.

After aseptic treatment of the skin, lateral fluoroscopic images are used to identify the correct level of skin incision on an imaginary line from the disc to the abdominal wall. Through this mark, a seven- to nine-centimeter transverse incision is made on the front of the abdominal

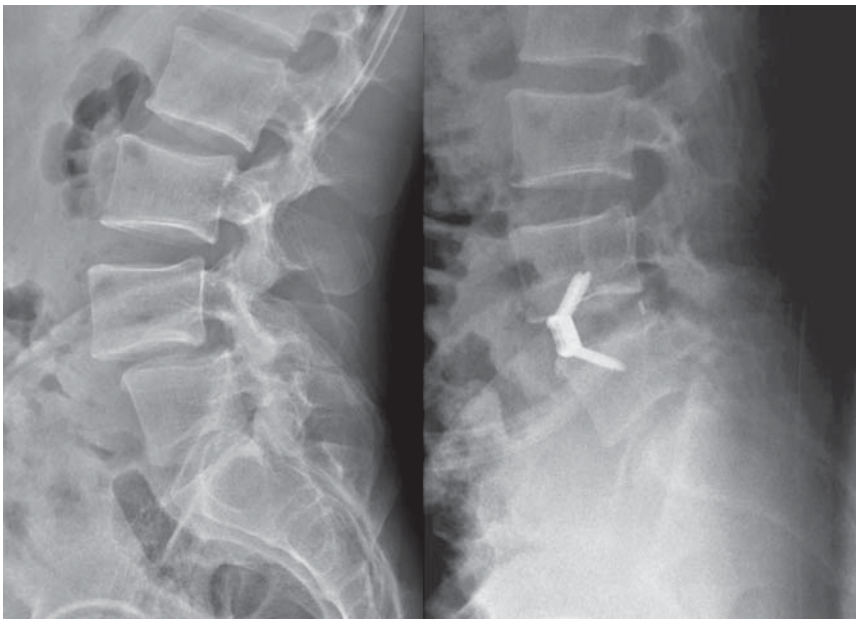

Figure 5: *One of the good candidates for ALIF is lumbar spondylolisthesis grade 1 - 2 with or without radiculopathy. This surgery is able to reduce the slip level to a normal alignment and also enables decompression of the neural foramen.*

wall, starting at the midline and proceeding towards the left. The rectus sheath is identified and split longitudinally. The median border of the rectus muscle is identified and separated. The rectus muscle is retracted laterally and bluntly to keep exposure of the sheath underneath the rectus until it reaches the most lateral aspect of the rectus sheath layer. At this area, the reflected arcuate line (linea arcuata), where the abdominal sheath is attached is identified. The reflected arcuate line is cut longitudinally to enter the retroperitoneal space.

A blunt dissection is carried out within the retroperitoneal space in order to expose the affected disc level. The abdominal content such as bowels and its peritoneum is retracted to the right of patient, and kept just in front of the psoas muscle and vertebra in order to expose the great vascular structure. The synframe® retractor system is applied to keep the peritoneal contents away from the operative field. The interval between the great vessels and the psoas is dissected to identify the vertebral bone. The level is confirmed by using fluoroscope. The dissection is undertaken by gently dissecting and mobilizing the great vessels until the annulus of the disc level is exposed. Four Steinmann pins are inserted into the upper and lower vertebral bodies in order to retract the vessels out of the anulotomy field.

The annulus is cut on the midline with two parallel incisions in order to make an opened door flap. Both left and right flap are sutured at the end and retracted to both sides to expose the inner annulus and its nucleus. The entire disc is removed and the end plate cleaned using a Cobb elevator without damaging the bone. We ensure there is no remaining disc material on the backside of the posterior longitudinal ligament. Posterior osteophytes can be removed using a Kerrison's Rongeur if needed. The disc space is spread to the normal height using an interbody spreader. The cage size is determined by using the standard trial until it fits properly in the space. This is then rechecked by lateral and anteroposterior (AP) fluoroscope, to make sure it is not undersized or oversized when compared to the adjacent disc level.

The correctly sized Synfix® cage is then opened from its container and filled with the bone graft substitute (bone morphogenetic protein (BMP) or demineralized bone matrix graft (DBM)) and inserted into the selected disc space. The position of the ALIF cage is checked within the space by a lateral and anteroposterior (AP) fluoroscope again to make sure the posterior border of the cage is just a millimeter in front of the posterior border of the vertebrae. The roll of towel placed underneath the patient's body is then removed. The cage position is checked once more before the final fixing of the cage to the vertebral body. The synfix® cage, together with the titanium plate placed anteriorly is fixed by four cortical screws and positioned divergently into the upper and lower vertebral body. After the position of the cage is confirmed by fluoroscope, bleeding is stopped, a low pressure drain is put in place, and the abdominal sheath is securely sutured into position layer by layer.

All patients were transferred to the intermediate intensive care unit for close observation ready for treatment should there be any concealed bleeding after the surgery was finished. Most patients were transferred to the normal in-patient ward within 24 hours of surgery and started walking by day two after surgery.

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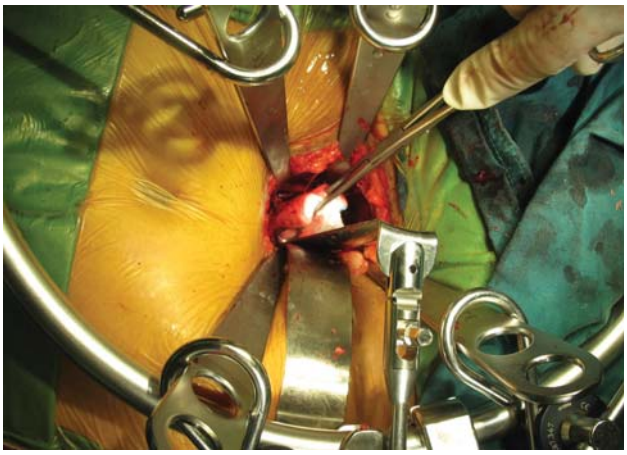

Figure 6: *For the mini-opened anterior approach to the lumbar spine, the Synframe retractor is one of the instruments needed for good exposure.*

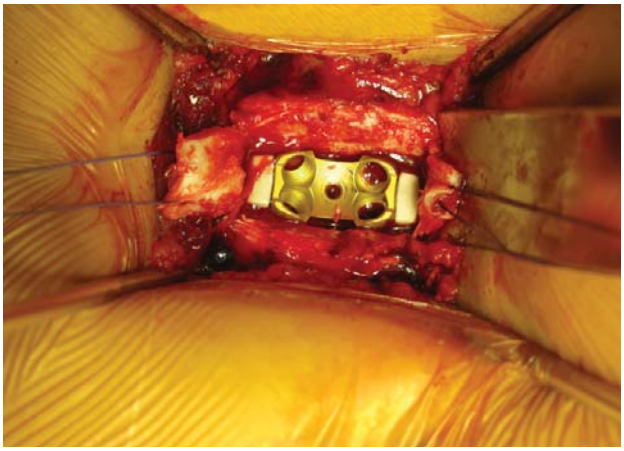

Figure 7: *The proper size of PEEK cage with anterior plate construct (Synfix®) was inserted into the affected disc and fixed with screws.*

Results

Demographic and Clinical Data

Of the 20 patients, 19 were male (95%) and one female (5%). The mean age is 41.2 years with 63 the oldest and 24 the youngest. Twenty-three levels were operated on, with the majority being at the L5-S1 in 15 levels (65.2%), and L4-L5 in eight levels (34.8%). It is not surprising that the distribution of the surgical levels falls mainly between L5-S1. This is because at the L4-5 we ask the patient to consider a more convenient fusion surgery option such as direct lateral interbody fusion (DLIF) or oblique lateral interbody fusion (OLIF). Both are available in our center. All patients chose the ALIF procedure for lumbar degenerative disc disease, spondylolisthesis from degeneration and developmental pars defect, recurrent disc herniation, or failed back surgery from pseudarthrosis. Most cases had indications of back pain with radiation to the leg due to nerve root compression. Five cases (25%) involved back pain only caused by degenerative disc disease also confirmed by provocative discography. There were seven cases (35%) with a diagnosis of degenerative disc disease. Nine cases (45%) were given a diagnosis of spondylolisthesis grade 1 or 2 with some being pars defect in origin. Only one case was given a diagnosis as a recurrent disc herniation and one other (5%) was pseudarthrosis with an implant breakage at L5-S1 from long posterior fusion surgery. Demographic and clinical data is shown in Table 1.

Table 1: Demographic and Clinical data.

Parameter	Mean	Min/Max
Patients (n)	20	
Male	19 (95%)	
Female	1 (5%)	
Age (years)	41.8 (10.7)	24 / 63
Pre-op VAS back	5.7 (±2.0)	3 / 10
Pre-op VAS leg	3.6 (±2.8)	0 / 9
Diagnosis		
Degenerative disc disease	7 (35%)	
Spondylolisthesis	9 (45%)	
Recurrent disc herniation	1 (5%)	
Failed back (Pseudarthrosis)	1 (5%)	
Spine level		
L4-5	8 (34.8%)	
L5-S1	15 (65.2%)	
Improved disc height (mm)	5.68 (±3.0)	
Improvement in coronal angle (degree)	2.6 (±3.8)	-0.8 / 16.9
Improvement in segmental lordosis (degree)	2.5 (±6.3)	-7.4 / 12.9
Improvement slip (percent)	49.7 (±27.9)	20.9 / 100

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Operative and Clinical outcome

The duration of surgery was measured as skin-to-skin time. The mean operative time was 156.5 (±35.5) minutes (mean±SD). The shortest duration of surgery was 105 minutes for each level and the longest surgery took 240 minutes. The operative time seemed to be affected by the time consuming task of establishing exposure, especially the time required for vessel mobilization. Intraoperative blood loss averaged 315.2 (±225.5) milliliters. The lowest blood loss for each level was 50 milliliters and maximum blood loss was 800 milliliters. Blood loss mostly occurred during exposure of the intervertebral levels. One case, an overseas patient that was not therefore completely followed up, had inadvertent blood vessel injuries that caused massive bleeding. The cell server was attached and a vascular surgeon immediately scrubbed in and cleared this situation. This case demonstrates the need for special preparation with a back up vascular surgeon on standby whenever this operation is performed.

Nerve root injuries represent a potential complication, but this is less likely to happen compared to conventional posterior surgery. This is because the direct decompression of the bony canal near the compressed neural structure is not required. The intraoperative complications that come from open surgery, such as the dura tear, do not exist. Injury to the superior hypogastric plexus (which lies beneath the peritoneum, courses to the aorta (anterior view) and crosses anterior to the left common iliac vein) can cause retrograde ejaculation. In the 20 cases reported we had only one case experiencing retrograde ejaculation after surgery and this was resolved within the second year. Other post-operative complications such as post-operative ileus, infection, cage subsidence or implant breakage, and lymphocele did not occur.

The mean back and leg pain measured by VAS before surgery was 5.7 (±2.0) for back pain and 3.6 (±2.8) for leg pain. Some patients had only one symptom, either back or leg pain. After the surgery at the two-week visit, back pain rapidly improved to 0.6±1.1 and leg pain improved to 0.1 (±0.2). We observed that the rapid recovery in back and leg pain from ALIF is faster than posterior opened surgery, which may be because there is minimal soft tissue destruction and the effect of indirect decompression of nerve roots without direct contact that can cause inflammation in open surgery (Figure 8).

This is a preliminary report of ALIF operations at our center, the Oswestry Disability Score is collected before the operation and then compared with post operative status at six weeks, three months and six months and these are not yet all complete for all 20 cases. The 11 patients that completed the questionnaire at six months were examined. These show very satisfactory results with rapid improvement of physical function after surgery. The mean ODI pre-operative visit was 41.9 (±28.2) and this reduced to 13.8 (±14.3) at the six-week visit and continued to reduce to 4.3 (±6.5) at the three-month visit and 0.35 (±1.0) at the six-month visit (Figure 9).

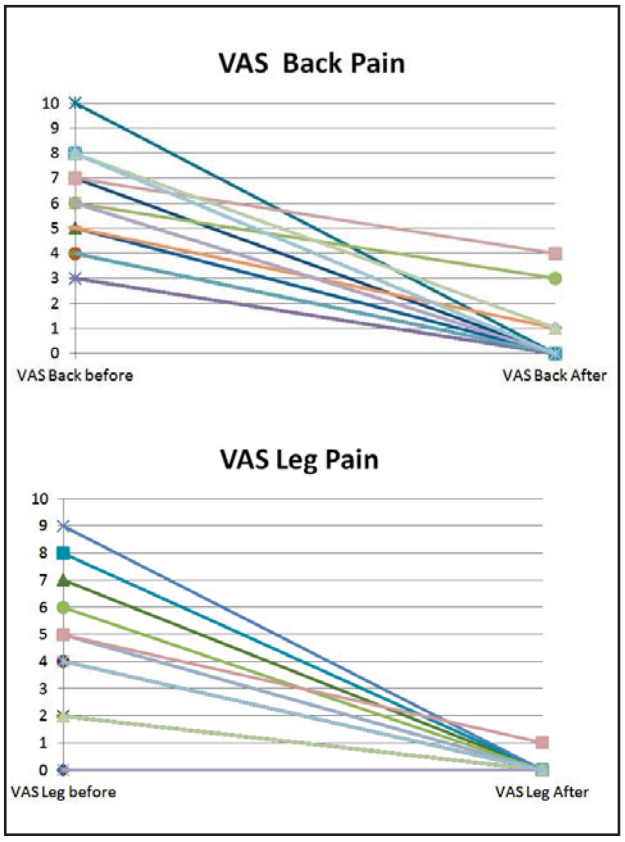

Figure 8

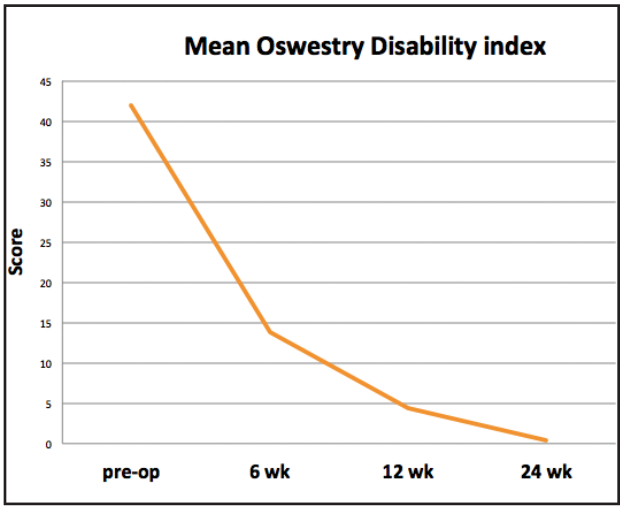

Figure 9

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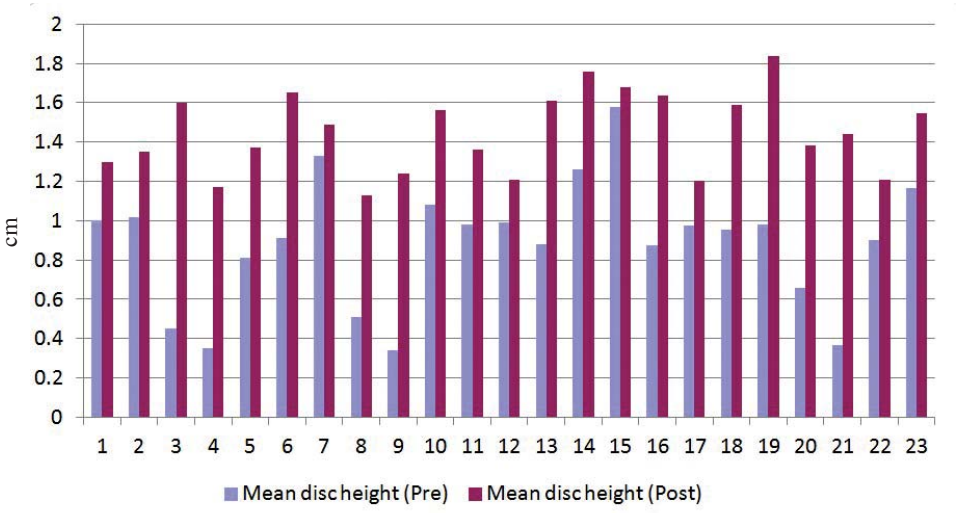

Figure 10

Radiographic outcome

One of the advantages of ALIF surgery is the ability to improve disc space height and the correction of coronal and sagittal alignment. In our study the same positive results as another previous report are shown. (Figure 10) The mean disc height before surgery is 8.8 (±3.2) mm improving to 14.4 (±2.1) after surgery. The mean segmental lumbar lordosis before surgery 18.6 (±8.8) changed to 21.2 (±8.7) after surgery. The coronal angle or scoliosis angle improved from 4.1 (±4.5) to 1.6±2.0 degrees after surgery. Moreover, the degree of slip improved from a mean of 16.7 (±5.6)% to 8.4 (±5.9)%. The mean change of the percentage of slip when compared to before surgery is 49.7 (±27.9)%.

Discussion

Spinal fusion is one of the major goals of spinal surgery especially in the case of spinal instability, infection, tumor and traumatic condition. Russell Hibbs and Fred Albee made the first steps in spinal fusion at the start of the 19th century for the treatment of spinal tuberculosis. They did this by applying the autologous bone graft on the dorsal surface of spine. This surgery became unacceptable because of the high rate of postoperative pseudartrosis. After the spinal column was classified by Denis, it was demonstrated that posterior spinal fusion is not sufficient to maintain the vertebral column. After this, anterior fusion to address the degenerative condition of the spine was studied.[4]

A 1931 surgical publication reported treating patients with spondylolisthesis by inserting a bone spacer from the anterior body by Capener.[5] Shortly after this, there were reports about success in curing spondylolisthesis using this procedure from many orthopedic surgeons such as Mercer,[6] Friberg[7] and Merled'Aubigne.[8] This procedure is used to undertake surgery on the transperitoneal space directly. Reports about using the technique of Anterior Interbody Fusion in patients who have problems from disc disease are reported for the first time by Lane and Moore[4] in 1948. The retroperitoneum technique was proposed by a Japanese surgeon, Iwahara, in 1944.[9] At that time, most indicators for undergoing the operation included detection of spine instability or moving by intervertebral discs of patients.

The posterior decompression is a key factor to mending pinched nerve or nerve compression resulting in sharp leg pain except in the case of foraminal stenosis, such as intervertebral disc collapse or severe listhesis. The surgery to widen the space for nerves from the posterior might not be enough. It is necessary to increase the height of the disc, which results in an indirect decompression and becomes a highly successful fusion, which is based on kinetics as well. The anterior interbody fusion has indications which can solve symptoms of pinched nerves from this cause very well.[10]

The lumbar cage device used in ALIF is a product designed to replace an intervertebral disc. At first, these were made of titanium because titanium can be moulded into many shapes, and can prevent disc space collapse during the healing process and can be fortified by titanium screws.[2,11] The most important thing is to design the cage to provide high stability and load-sharing for the endplate. This is achieved by adapting the biomechanics of the vertebral end plate, by loading the weight, with the ring apophysis area being twice as strong as the central area.[12] Consequently, the shape of the cage plays an important role in the success of the surgery with this material. Obviously, it is not a surprise that at first the cage was not placed on the Apophyseal ring of spine, as this causes problems of subsidence such as we see with as the rectangular cage, Bagby and Kuslich (BAK) cage or LT-Cage®.

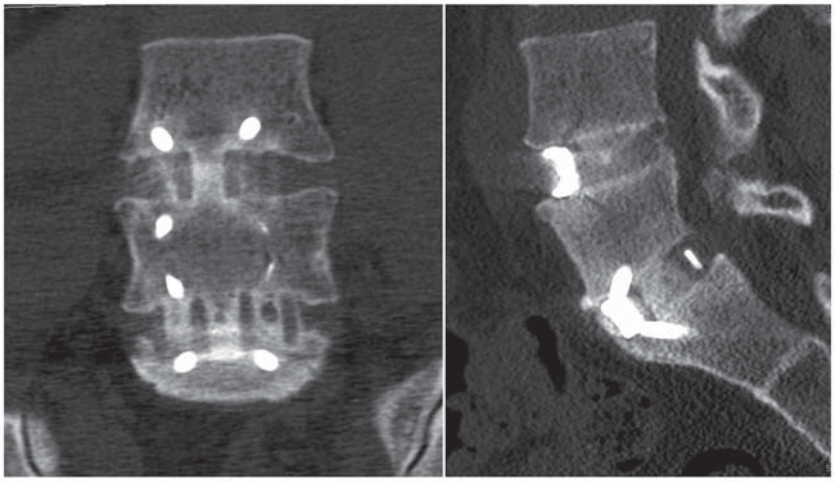

Figure 11: *ALIF has advantages in term of solid fusion. This picture shows solid interbody fusion after 6 month stand alone ALIF with rh-BMP2.*

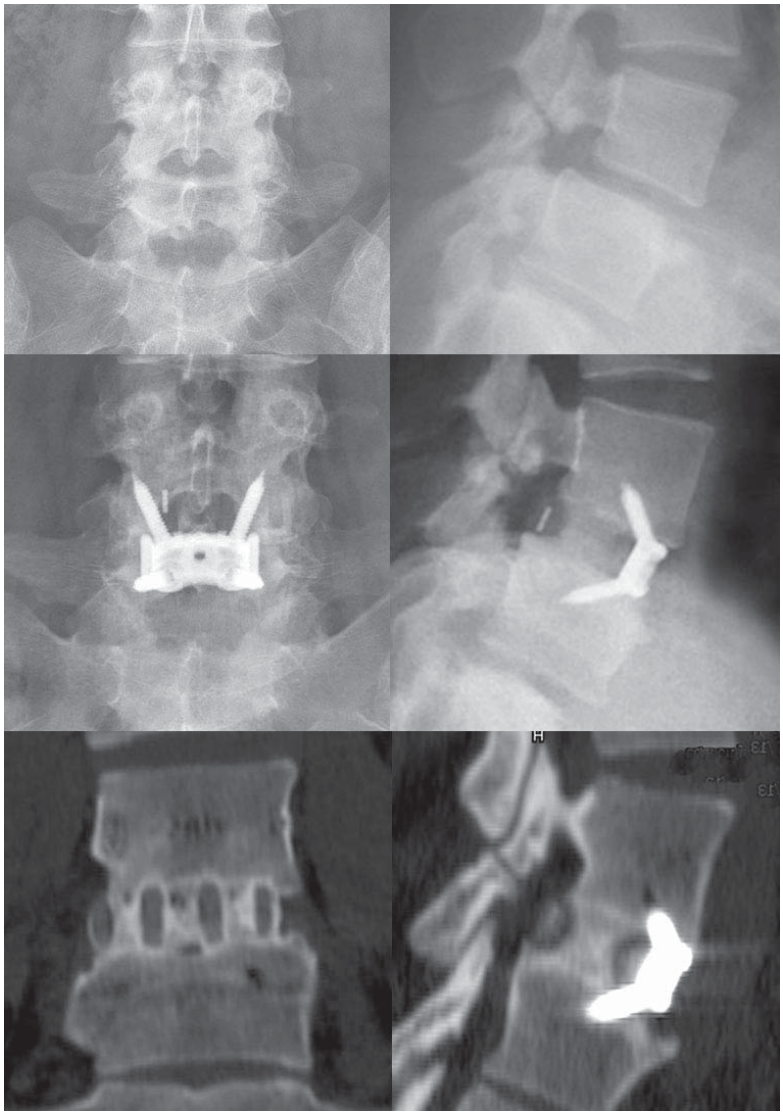

Figure 12: *Stand alone ALIF is also suitable for lytic spondylolisthesis. The pictures show acceptable reduction of slip and solid fusion 6 months later.*

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Later the cage was designed with a very similar shape to an intervertebral disc, and often placed on the cortical ring of the spine. Stability was created by inserting a screw at the front like the Synfix® cage we used in this study.

There are many advantages of anterior interbody fusion compared to posterior interbody fusion. For example, interbody fusion has better back biomechanics because it supports the weight from the front side (anterior column support) and it balances the weight pressure (re-established load transmission.[3,13] Moreover, the rate of spinal fusion is high because of the compression site so the growth of bone is excellent according to Wolff's rules (Juius Wloff 1836-1902). When the bone is completely joined, we achieve solid fusion, which is stronger than posterior interbody fusion.[3] Moreover, the adjustment of Lordosis and disc height has an advantage over posterior fusion (TLIF)[14] as it can avoid muscular damage from posterior surgery (preserved paraspinal musculature and tension band).[15,16] Anterior lumbar spinal fusion also reduces the incidence of adjacent segment degeneration when compared to posterior open surgery.[17]

In our study, there is a range of age groups and indications for surgery. This illustrates the versatility of this operation to address several spinal conditions. ALIF is not only recommended for degenerative conditions of the spine: young patients who suffer from lytic spondylolisthesis in the early adult age group are also suitable candidates for this operation. The disc level considered common for this operation is L5-S1 and L4-L5 because, at these levels, vessels are easy to mobilize, there are fewer organs at risk of being damaged, and the wound is cosmetic.

One of the advantages of ALIF surgery is the factor of disc space correction, the restoration of foraminal height, local disc angle, lumbar lordosis, and sagittal balance when compared to open posterior instrumentation.[18] In our study we showed positive improvements in disc height in all cases after surgery. The olisthesis degree in all listhesis cases has an improvement average of 50% in our study. This corresponds to the outcome of leg pain improvement because it widens the nerve root foramen and the neural canal respectively. The nerve root decompression caused by the anterior widening of spinal foramen and canal without posterior surgical decompression is called the **'indirect decompression'** effect.[10] Moreover, the improvement of segmental lordosis and coronal angle can also improve back pain caused by sagittal and coronal misalignment. In our study, all patients show significant and satisfactory improvement in both back pain and leg pain after surgery.

Anterior interbody fusion is highly suitable for curing chronic back pain originating in disc degeneration. This is because this surgery can take the pain generator (i.e. the disc) out completely and create a solid fusion which results in a rigid and immovable column of bone even in micro motion, which otherwise could be a cause of back pain.[19] This type of surgery incurs minimal damage of back muscles, which lessens the chance of pain from wounded muscles. In our study, patients were diagnosed as having degenerative disc disease through examinations using magnetic resonance imaging (MRI) and Discography.[20] The result of surgery shows marked rapid and sustained reduction of back and leg pain in just a few weeks after surgery. Also, the ODI score shows excellent improvement at the six-week, three-month, and six-month follow ups in all cases, with pain decreasing more than 25 points when compared to pain levels experienced before surgery. Moreover, as in other clinical studies,[2,21] we observed that most of the patients returned to full activity and experienced perhaps even better results than expected from conventional posterior open surgery. This is confirmed with a much lower disability score at the six-month visit.

However, there are some disadvantages with this method. Despite it being an anterior surgery through the retroperitoneum, adjacent organs and blood vessels could be endangered.[22,23] Therefore, professional experience is needed for operating the intervertebral disc area close to arteries and veins. Quraishi and his team studied 304 patients in England finding that there are 4.6% venous injuries that needed to be repaired and 1.6% arterial injuries.[22] Brau and his team found in 1,315 patients 0.5% arterial injuries and 1.4% venous injuries. There are a lot more reports about this risk. That said, the average of arterial injuries is less than 1% and venous injuries account for about 1-3%.[2,23,24] In our study, the mean intraoperative bleeding was around 300 milliliters and this is acceptable and seems close to levels seen in conventional posterior open surgery. The venous vessel was injured in only one case, and there was a blood loss of several thousand milliliters in the reservoir of the cell server. The patient recovered well without any post-operative complications.

A particular risk to be aware of is retrograde ejaculation. This is by sympathetic fibers of the hypogastric plexus, which lie behind the posterior surface of the peritoneum at the L5-S1 level. This event usually occurs in 2-4 % of cases, and 50% of these patients eventually recover fully.[24] Other complications such as abdominal ileus, lymphadenoma, injuries to the ureter, and abdominal hernias have been reported infrequently.

Conclusion

Anterior lumbar interbody fusion (ALIF) is a standard procedure for degenerative disc disease, lumbar spondylolisthesis, recurrent disc herniation and failed lumbar fusion surgery. The main reason is this procedure can provide good exposure for the surgeon to entirely remove the pain generator such as the disc. ALIF can offer a large

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contact surface area for solid fusion and weight bearing procedures, and it has less likelihood of failure. It can increase disc space and create the optimal lumbar lordosis and coronal balance especially in L5-S1. The clinical outcomes show rapid and long-lasting improvement in back pain, leg pain and quality of life.

However, there are some disadvantages of this method. Even though it is an anterior surgery through the retroperitoneum, adjacent organs and blood vessels could be endangered. The incidence of retrograde ejaculation is not high, but it can be a serious problem in younger men who plan to have children. The incidence of blood vessel injuries can be lowered by a well-trained exposure surgeon with back-up support if necessary. The surgical team should be ready for immediate action if any inadvertent problem arises. Although this surgery has some disadvantages it remains one of the leading operations providing the most promising results.

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Original Article

The Characteristics of Aeromedical Transport Missions at Bangkok Hospital, Thailand

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Keywords: aeromedical transport, epidemiology, evacuation, repatriation, air medical transport, aviation medicine, air ambulance, helicopter

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OBJECTIVE: Increasing numbers of foreign tourists, expatriates, and patients seeking medical care in Thailand have resulted in a significant increase in aeromedical transport activity, both evacuation and repatriation over the past decade. However, there is little epidemiological data currently available on the diagnoses, costs and transport characteristics in Thailand and Southeast Asia. We therefore performed a descriptive analysis of evacuation and repatriation cases in order to compare helicopter and fixed-wing transport in various ways such as flight time, distance and economic aspects.

MATERIAL AND METHODS: A retrospective review of medical records of patients in 2011 evacuated or repatriated by the Aviation Medicine Department, Bangkok Hospital. Demographic information, diagnoses, modes of transport, type of aircraft, flight time and financial detail were analyzed.

RESULT: Three hundred and two patients were included in the study, 201 male (66.5 %) and 101 female (33.5%). Patients' ages ranged from 1 day to 105 years, the average age was 50.2 years. (Median 54 years). The top three nationalities of patients were Thai (n = 93, 30.8 %), Myanmar (n = 29, 9.6%) and British (n = 19, 6.3%). The top four diagnoses were Stroke (n = 51, 16.6%), Multiple trauma (n = 41, 13.40%), Acute myocardial infraction (AMI) (n = 30, 9.8%), Cancer (n = 27, 8.9%). Transports were carried out by air ambulance (n = 104, 34%, $202.5/min), helicopter (n = 84, 28%, $87.55/min), scheduled aircraft with regular seating (n = 60, 20%, $9.37/min) and a stretcher in a scheduled aircraft (n = 54, 18% $40.1/min).

CONCLUSION: By comparing the costs per flight time, we showed that a stretcher in a scheduled aircraft is significantly cheaper than an air ambulance. Ideally the most appropriate medical response would be the main criteria when choosing a form of air transportation; however cost-effectiveness is also of considerable importance when selecting from the alternatives available. It is the main role of the physician who is in charge of transport planning to communicate the evaluation of mode of air medical transport.

Thailand is located at the center of the Indochina peninsula in Southeast Asia, bordered to the north by Myanmar and Laos, to the east by Cambodia and to the south by Malaysia. There are many migrants in this region, and the countries have also attracted a number of expatriates from developed countries. In 2007, Thailand had 14.5 million visitors, excluding those from neighboring countries. According to the Tourism Authority of Thailand, 55% of the tourists in 2007 came from the Asia Pacific region. The largest groups of Western tourists come from the United Kingdom, Australia, Germany, the United States and Scandinavia. Medical tourism has become a growing segment of Thailand's tourism and health-care sectors too. When travelers or expatriates become ill or injured, urgent air evacuation to the nearest well equipped medical

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facility is needed, to preserve function and save lives as well as subsequent repatriation to the patient's home country.

Fewer than 0.5% of all travelers actually require medical evacuation.[1] It is estimated that in Thailand thousands of aeromedical evacuation and repatriation are performed annually. The decision-making process surrounding emergency aeromedical transport is based not only on the patient's clinical condition but on many other factors as well.[2] Due to rapid increasing fuel prices over the last decade, the costs of aeromedical transport have increased.[3] Analysis of epidemiological data of aeromedical transportation will support efficacious decision-making of the modes of transport and health care facilities. In a certain subgroup of relatively stable, ventilated patients, transport on commercial airlines offers advantages in terms of cost effectiveness and reduced transport time and acceleration/deceleration trauma as a result of multiple fuel stops.[4] Former literature indicated using helicopters was economically unjustified for transport exceeding 100 miles when an efficient fixed-wing service exists.[5]

Materials and Methods

Data was collected from the Aviation Medicine Center of our tertiary care hospital which operates a helicopter and fixed-wing aeromedical transport service. While handling the data, the regulations of the Ethics Commission of Bangkok Hospital Group were fully respected. Institutional review board approval was obtained, and informed consent was waived. A retrospective electronic medical record review was performed, and the epidemiological data of medical evacuation and repatriation cases were collected from January-December 2011. Data included age, sex, nationality, diagnosis, flight time, mode of transportation, type of aircraft, and cost per flight hour. Data were collected and entered onto a standard spreadsheet format. The median value was calculated.

Results

Patient data

Three hundred and two patients were included in the study, 201 male (66.5 %) and 101 female (33.5%). There were no exclusion criteria. Patient's age ranged from 1 day to 105 years, the average age was 50.2 years (y) (median 54 y). The top five nationality of patients were Thai (n = 93, 30.8 %), Myanmar (n = 29, 9.6%), British (n = 19, 6.3%), German (n = 18, 6%) and Cambodian (n = 16, 5.3%) as shown in Figure 1.

Medical Data

The top five diagnoses were Stroke (n = 51, 16.6%), Multiple trauma (n = 41, 13.40%), Acute MI (n = 30, 9.8%), Cancer (n = 27, 8.9%), and Cerebrocranial trauma (n = 26, 8.6 %) as shown in Table 1 and Figure 2.

The most frequent types of cases were classified according to the following specialties: cardiology (n = 58, 19%), neurology (n = 55, 18%), trauma surgery (n = 41, 14%), orthopedic (n = 32, 11%), cancer (n = 27, 9%) as shown in Figure 3.

Operational Flight Data

The average flight time for air ambulance was 1.1 hours, for helicopter 1.3 hours, for a regular seating 7.36 hours and for a stretcher 4.1 hours respectively, as shown in Figure 4. Most cases of stretcher and regular seat on a commercial flight were repatriation cases and the flight times ranged from 1 hour to 25 hours. All of the helicopter and air ambulance cases were evacuation cases. Most evacuation sites were in Thailand and Indochina countries such as Myanmar and Cambodia.

Mode of transportation

Of the total 302 cases, 209 were evacuation cases (69%) and 93 repatriation cases (31%). Most cases were transported by air ambulance (n = 104, 34 %) but the helicopter (n = 84, 28%), scheduled aircraft with regular seating (n = 60, 20%) and a stretcher in a scheduled aircraft (n = 54, 18%) were also used, as shown in Figure 5.

Type of aircraft

Five different types of aircraft were used in air ambulance cases. The top three were ATR-72 (n = 66, 63.5%), Caravan (n = 12, 11.5%) and Beechjet400 (n = 12, 11.5%) as shown in Figure 6.

Financial Data

The cost per flight minute (min) were calculated for an air ambulance to be $ 202.5/min, for a helicopter $ 87.55/min, for a stretcher in a scheduled aircraft $ 40.1/min, and for a scheduled aircraft with regular seating $ 9.37/min respectively as shown in Table 2 and Figure 7.

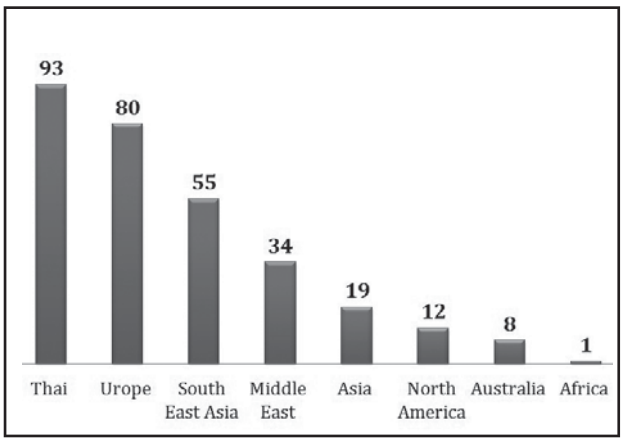

Figure 1: *Nationality of cases.*

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Table 1: Diagnosis of transported cases (n = 302).

Diagnosis	n
1. Stroke	51
2. Multiple trauma	41
3. Acute myocardial infarction (AMI)	30
4. Cancer	27
5. Cerebrocranial trauma	26
6. Fracture of lower extremity	14
7. Heart failure	11
8. Sepsis	10
9. Thoraco-Lumbar spine fracture	9
10.Fracture cervical spine	9
11.Pneumonia	8
12.Chronic obstructive pulmonary disease (COPD)	7
13.Coronary artery disease (CAD)	7
14.Acute respiratory distress syndrome (ARDS)	6
15.Post arrest	6
16.Liver failure	6

Diagnosis	n
17.Renal failure	5
18.Abdominal aortic aneurysm (AAA)	4
19.Epilepsy	4
20.Pulmonary embolism	3
21.Psychosis	3
22.Appendicitis	2
23.Acute pancreatitis	2
24.Gut obstruction	2
25.Burn	2
26.GI Bleed	1
27.Tetanus	1
28.Liver abscess	1
29.Thyroid toxicosis	1
30.Anal abscess	1
31.Acute cholecystitis	1
32.Bleeding per vagina	1

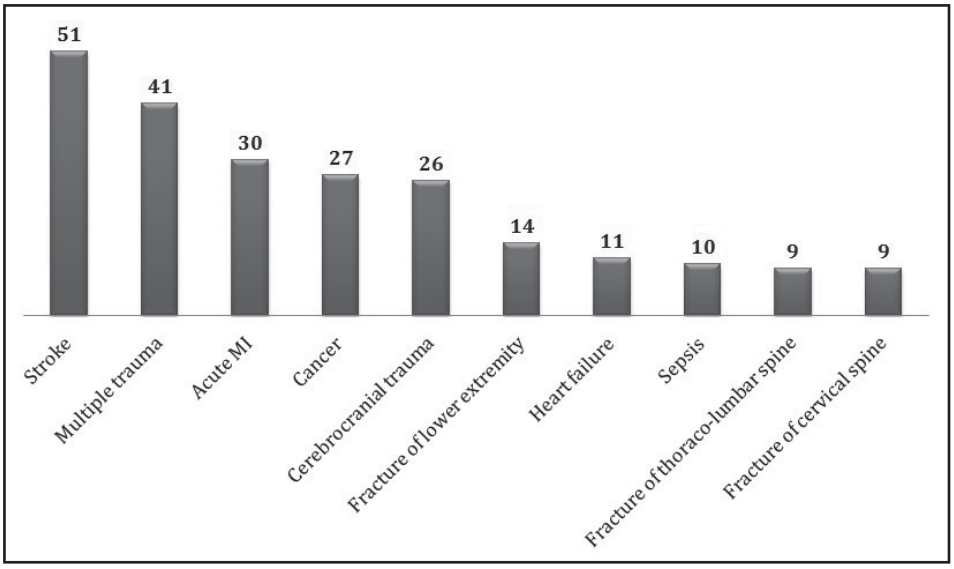

Figure 2: *Diagnosis of transported cases (n = 302).*

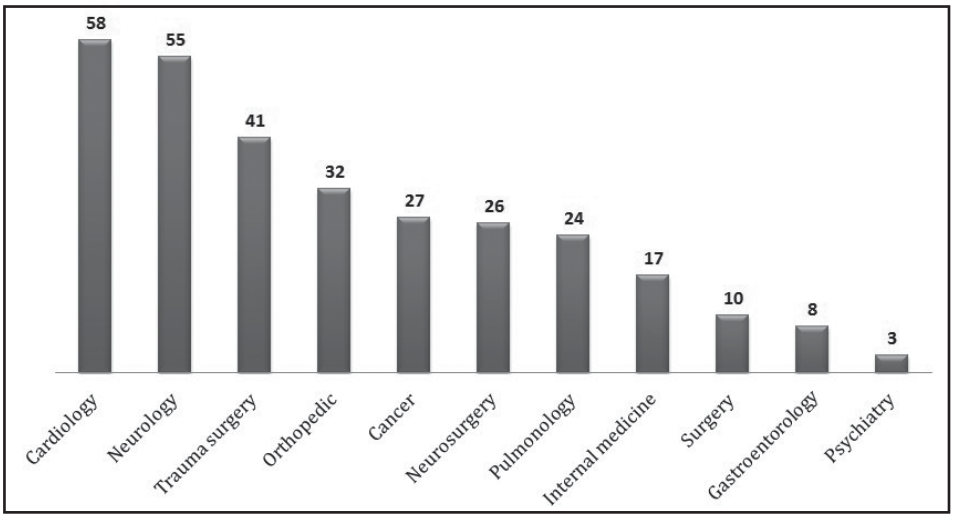

Figure 3: *Diagnosis classified according to the specialty of transported patients (n = 302).*

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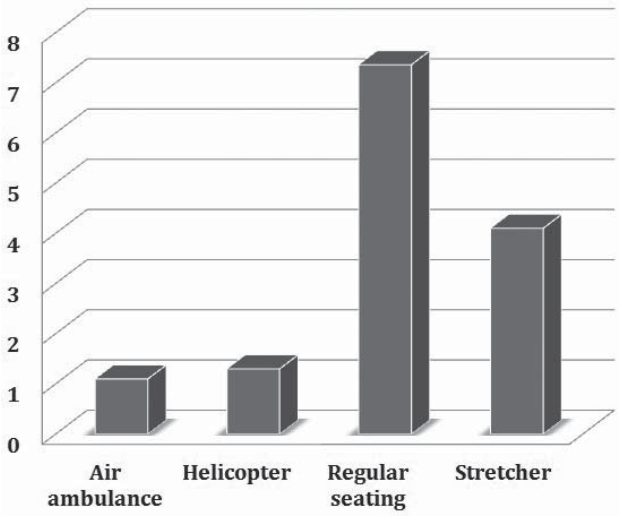


Figure 4: *Average Flight Time (hour) of transported cases.*

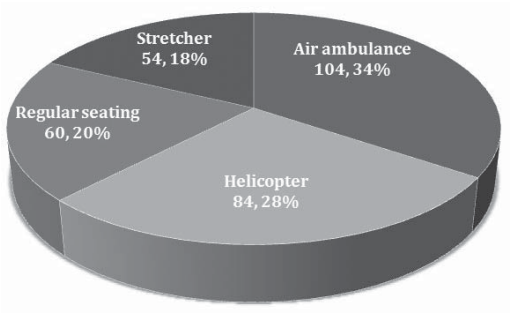


Figure 5: *Mode of transport of transported cases.*

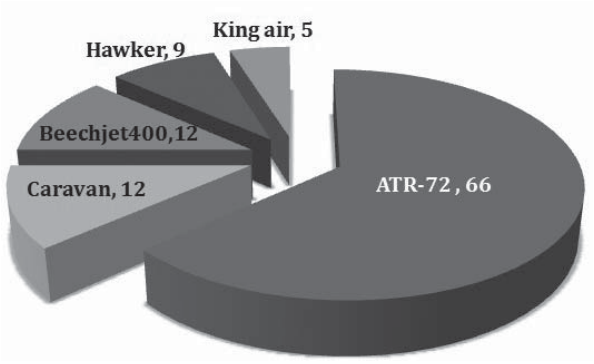
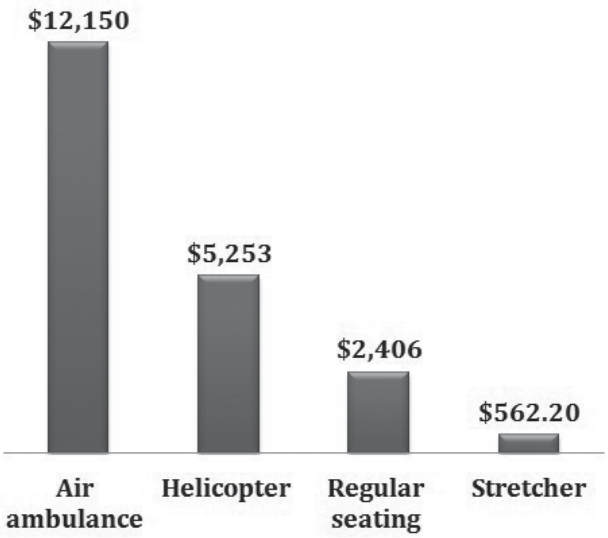


Figure 6: *Type of aircraft in air ambulance cases (n = 104).*



Note: *Some Helicopter missions were in cooperation with the Ministry of Public Health of Thailand (discounted cost).*

Figure 7: *The cost per flight hour of transported cases.*

Table 2: The cost per flight minute and flight hour.

Type	Cost per minute (US)	Cost per hour (US)
Air ambulance	202.50	12,150.00
Helicopter	87.55	5,253.00
A stretcher in a scheduled aircraft	40.10	2,406.00
A scheduled aircraft with regular seating	9.37	562.20

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Discussion

As the demand for medical air transportation is likely to continue to go up in the future due to increased globe trotting and medical tourism,[3] skilled physicians and nurses must be available at all times. Monitoring devices (ECG, blood pressure, pulse oximetry, capnography), defibrillators, pacing devices, ventilators, aeronautical oxygen systems, infusion devices, mattresses, medication including resuscitation drugs must be available 24 hours a day.[2] All equipment must be certified for aeronautical use, and a permanent logistics team ensures its preventive maintenance.[6] Cost-effectiveness is likely to be of the utmost importance for insurance companies and health care systems when determining the appropriate form of air transportation. The flight physician has to determine that the patients not only receive quality medical care but the mode of transportation is most effective in terms of safety, time and cost-effectiveness, even though the most appropriate medical response should be the main factor in the selection of an appropriate form of air transportation. Patients with neurologic conditions need even more timely and careful aeromedical transport than those with other diseases.[7]

From our data, neurologic diseases comprised 25% of the patients that required medical transportation. Most cases of evacuation were transported by helicopter or air ambulance and flight time was about one hour; most cases of repatriation were transported by stretcher or regular seat in commercial aircraft. Most evacuation sites were in Thailand and Indochina countries such as Myanmar and Cambodia. The diagnosis of cases varied from diseases to trauma but most cases (n = 99, 33%) were from accident and trauma, with multiple or severe injuries that needed surgery.

By comparing the costs per flight time, we showed that a stretcher in a scheduled aircraft is significantly cheaper than air ambulance and a scheduled aircraft with regular seating (first, business and economy class) was cheapest. The data also showed that the helicopter was significantly cheaper than air ambulance especially in the context of air evacuation within one hour.

Limitation: Data was collected from only one aviation medical center in the year 2011.

Conclusion

Transport of patients with various diseases or trauma, either by air ambulance or commercial flights, can only be safely performed by well-trained medical escorts and with comprehensive logistic arrangements. Medical air transportation is very costly, and continuing the trend of the last decade, its frequency is likely to further increase. The physician who is in charge of transport planning must communicate effectively with the patient, with the physician on-site, with the patients' relatives and with the patients' insurance company to determine and evaluate needs and determine the most suitable mode of air medical transport.

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Accuracy of Stress Echocardiography in Detecting Ischemic Heart Disease, Experience at the Bangkok Heart Hospital 2012

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OBJECTIVES: Stress echocardiography is a good test for detecting ischemic heart disease. The sensitivity, specificity and accuracy should be verified. This test was compared to standard coronary angiographic results. This is the first study by Bangkok Heart Hospital's echocardiography lab to verify the effectiveness of stress echocardiography.

MATERIAL AND METHODS: This study was a retrospective study that reviewed data from records. The 149 selected cases underwent stress echocardiography and a coronary angiogram (within 2 months after the stress echocardiography) between 1st January and 31st December 2012. The sensitivity, specificity and accuracy were assessed.

RESULTS: The overall sensitivity, specificity, and accuracy were 81.98%, 42.10%, and 71.81% respectively. There was a variation of sensitivity, specificity and accuracy in each day of the week. There were many factors such as number of cases, reporting physicians, technically poor studies (including poor echogenicity of subject), technician experience, abnormal wall motion at rest, atrial fibrillation and bundle branch block. The sensitivity ranged from 57.14 % to 92.3%. The specificity ranged from 16.67% to 70%. The accuracy ranged from 50.0 % to 86.67 %.

CONCLUSION: Stress echocardiography is a good test for evaluating ischemic heart disease. Our echo lab had lower sensitivity, specificity and accuracy than other previous studies. The limitation of this study was that it was a retrospective study. But it showed our routine work. We hope this will help our echo lab to improve the quality of its stress echocardiography testing.

Stress testing is the most frequent investigation to diagnose ischemic heart disease. The most common technique is electrocardiography during a treadmill stress period. Electrocardiography has limitations because there are many artifacts from movement. There are many techniques to improve the detection of ischemic heart disease, such as magnetic resonance imaging (MRI), thallium scintigraphy,[1] radionuclide ventriculography and echocardiography. The dobutamine and exercise stress echocardiography test were shown to detect coronary artery disease.[2-4]

In the Bangkok Heart Hospital, we use treadmill or dobutamine in this test depending on the patient's status. The dobutamine is used in patients who cannot exercise. We often use echocardiography as a technique to diagnose ischemia.

This study retrospectively shows the clinical use of stress echocardiography for diagnosis of coronary artery disease to detect ischemia in patients with known or suspected ischemic heart

disease. This study will show the sensitivity, specificity, and accuracy of stress echocardiography in our non-invasive department. It will help us to improve the quality of stress echocardiography in our echo lab.

Materials and Methods

Case studies: The patients underwent a stress echocardiography test in the non-invasive department of the Bangkok Heart Hospital between 1st January and 31st December 2012. There were 2,035 patients who underwent stress echocardiography. Their ages ranged from 17 to 96 years. There were 1,284 (63.1 %) men and 751 (36.9 %) women. There were 149 cases that had undergone stress echocardiography testing before undergoing a coronary angiogram (CAG) within 2 months. These patients were the subject of this study. All cases were reviewed retrospectively from data recorded.

A coronary angiogram was performed within 2 months after the stress echocardiography testing. Significant narrowing was determined as ≥ 50 % diameter stenosis of the major coronary artery or its major branch.

Stress echocardiography protocols: Sixty-six cases performed the treadmill stress echocardiography testing. The treadmill was used with Bruce protocol. Patients walked at least 85% of predicted heart rate. If they could not reach 85% of predicted heart rate (the test was labeled as an inadequate test), they were excluded. Echocardiographic images were scanned before and after the treadmill test. Electrocardiogram and blood pressure were monitored during exercise.

Eighty-three cases received dobutamine stress echocardiography. Dobutamine was step infused at the doses of 10, 20, 30, 40 μg/kg/min every 2 minutes and every 1 minute to capture echocardiography images. The test was stopped when a new wall motion presented or reached 85% of predicted heart rate. If a 40 μg/kg/min dose could not achieve the target heart rate, atropine was injected and an image was captured at 85% of predicted heart rate or higher.[5]

Echocardiography: 2D echocardiography was recorded with a parasternal short axis, apical 4 chamber 2 chamber, and 3 chamber views. The echocardiographic machines used were GE vivid 7 and vivid E9. The transducer frequency range was 1.5-2.3 MHz. Echocardiographic wall motion was graded as normal, hypokinesia, akinesia or dyskinesia. A 16-segment model (Figure 1) was used for grading wall motion.

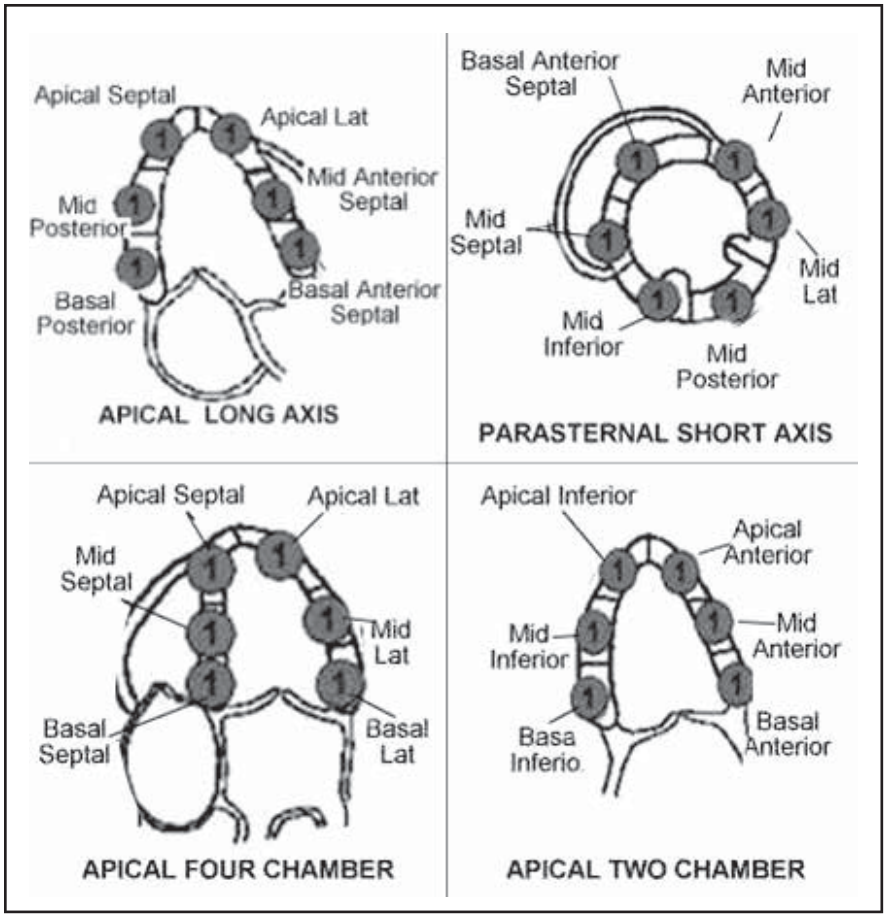

***Figure 1**: 16-segment model.*

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Results

Coronary angiogram results: the positive angiogram was defined as ≥ 50% diameter stenosis. Coronary artery disease was present in 111 patients. Thirty-eight cases were single vessel disease. There were 73 cases with multivessel disease. The left main lesion was defined as multivessel disease.

Exercise (treadmill) stress echocardiography was used in 66 cases. Dobutamine stress echocardiography was used in 83 cases. Positive stress echocardiography was found in 113 cases, 91 cases were true positive and 22 cases were false positive. There were 36 cases with negative stress echocardiography and 16 cases were true negative and 20 cases were false negative (Table 1).

$$\text{Sensitivity was calculated by} \frac{\text{(true positive)}}{\text{(true positive + false negative)}}$$

$$\text{Specificity was calculated by} \frac{\text{(true negative)}}{\text{(true negative + false positive)}}$$

$$\text{Accuracy was defined by} \frac{\text{(true positive + true negative)}}{\text{(total cases)}}$$

$$\text{Positive predictive value was} \frac{\text{(true positive)}}{\text{(true positive + false positive)}}$$

$$\text{Negative predictive value was} \frac{\text{(true negative)}}{\text{(true negative + false negative)}}$$

The calculated values shown in Table 2 detail each day of the week for a week. The sensitivity of this echo lab was 81.98%. The specificity was 42.1%. The accuracy was 71.81%. There were no cases of true negative on Day 3, so the specificity and negative predictive value was 0 (presented as NA) (Table 2).

Discussion

Stress echocardiography has an advantage over stress electrocardiography (ECG). This test evaluated baseline echocardiography before the stress test. Left ventricle (LV) function, regional wall motion, heart valves, chambers and other abnormalities were detected before the stress test. The indication of stress echocardiography is an evaluation of chest pain, diagnosis of coronary artery disease, detection of viable myocardium, preoperative evaluation, and evaluation of status of coronary revascularization. Sensitivity varied from 54% to 96% and specificity varied from 50% to 100% [6-8] in previous studies.

In this study, the overall sensitivity was 81.98%, and this was lower than previous studies.[6-9] The reason might be that this study was retrospective. But this might reflect real life, and routine work. The specificity was very low because there were more false positive cases than true negative cases. Perhaps there was a bias on the part of the physician wanting to recommend that the patient should have an angiogram which resulted in more false positive cases. Some cases did not have an angiogram when there was a negative stress echocardiography, especially on Day 3 (no true negative test). Because of the low true negative and high false positive, the accuracy was too low.

Table 1: Comparision of Stress Echocardiography and Coronary Angiogram.

Stress echocardiography	Coronary Angiogram	
	Positive	Negative
Positive	91 (true positive)	22 (false positive)
Negative	20 (false negative)	16 (true negative)

Table 2: The calculated values show sensitivity, specificity, and accuracy for each day of the week (Unordered).

	n	Sensitivity	Specificity	Accuracy	PPV	NPV
All	149	81.98%	42.10%	71.81%	80.53%	44.44%
Day 1	30	92.0%	60.0%	86.67%	92.0%	60.0%
Day 2	32	72.73%	70.0%	71.87%	84.2%	53.85%
Day 3	13	70.0%	NA	53.85%	70.0%	NA
Day 4	15	72.73%	50.0%	66.67%	80.0%	40.0%
Day 5	10	57.14%	33.33%	50.0%	66.67%	25.0%
Day 6	32	92.30%	16.67%	78.12%	82.76%	33.33%
Day 7	17	90.0%	28.57%	64.70%	64.28%	66.67%

NA = not available , because there was no true negative case on Wednesday.
Bold = highest, Underlined = lowest, PPV = positive predictive value, NPV = negative predictive value

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There was variation in the sensitivity, specificity and accuracy on each day of the week examined. The most sensitive day was Day 6. The most specific day was Day 2. The most accurate day was Day 1. There were many factors that influenced sensitivity, specificity and accuracy. For example, the number of cases, the reporting physician, technically poor studies (including poor echogenicity of subject), technician experience, abnormal wall motion at rest, atrial fibrillation and bundle branch block were important factors that had an effect on each day.

Limitation

This study was a retrospective study. There was some bias from the physician, these results are not randomized. There were many cases that underwent a stress echocardiography test but only selected cases had an angiogram.

There was a subjective interpretation that depends on the reporter's experience. The lack of quantitative evaluation reduced the accuracy, sensitivity, and specificity of the test. Especially in the case of abnormal wall motion at rest, atrial fibrillation, and bundle branch block. The quantitative evaluation was suggested but this is time consuming, and requires good technical studies (good images, good equipment, good views, good operators) and needs experienced reporters.

Conclusion

Stress echocardiography is a good test to evaluate ischemic heart disease but it needs good technical studies and experienced reporters. This study was a retrospective study that showed the routine work of our echo lab. This study showed low sensitivity, specificity and accuracy in our lab compared to previous studies (from another site). This study had limitations but it has shown an opportunity to improve the accuracy, sensitivity, and specificity of the test in the lab. There are many quantitative evaluations, hardware, and software to help. The accuracy, sensitivity, and specificity of stress echocardiography will continue to improve.

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LightCycler® MRSA Advanced Test for Rapid MRSA Detection in Referral Patients Admitted to Intensive Care Units

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OBJECTIVE: We studied the prevalence of Methicillin Resistant Staphylococcus Aureus (MRSA) nasal carrier in patients who were transferred and admitted to the intensive care unit (ICU).

MATERIALS AND METHOD: By using LightCycler® MRSA advanced test for the direct detection of MRSA DNA in nasal colonization by polymerase chain reaction (PCR) and comparing to standard MRSA isolated from plate culture media.

RESULTS: From December 2010 to May 2011, 100 patients were enrolled. They were referred to be admitted in ICUs of Bangkok Hospital Medical Center (BMC) (87), Samitivej Hospital Sukhumvit (12) and Bangkok Hospital Pattaya (1). Seventeen patients were excluded from the study. Of 83 patients, the LightCycler® MRSA test detected MRSA from an anterior nasal swab in 12 (14.5%) patients while concomitant plate culture grew MRSA in 10 (12.1%) (Kappa = 0.7913, 95% confidence interval (CI) = 0.594-0.988).

CONCLUSION: The LightCycler® MRSA advanced test is a diagnostic test for rapid MRSA detection. The test aids in the detection of hospital infection and in the control of MRSA infections by rapid detection, therefore identifying the appropiate and isolated patient whom has MRSA colonization particularly in high risk patients.

Methicillin Resistant Staphylococcus Aureus (MRSA) is now more acknowledged as an important in serious bacterial infection both in healthcare and community acquired settings.

Healthcare-associated MRSA(HA-MRSA) infection is defined as MRSA infection occuring following hospitalization or previously attended healthcare facility (e.g. dialysis, residence in a long terms care setting) within 12 months.[1] The prevalence of HA-MRSA was reported as high with up to 60% among Staphylococcus aureus infections in the ICU.[2]

Community-associated MRSA (CA-MRSA) is defined as MRSA infection occuring in the absence of healthcare exposure. Most case reports of CA-MRSA are associated with skin and soft tissue infection in young adults.[3]

Transmission of the MRSA strain commonly occurs by transiently contaminated hands of healthcare workers or environmental contamination. Persons with MRSA colonization might have a higher risk of MRSA infection than those without and also serve as a reservoir for transmission.[2]

The HA-MRSA strain tends to carry the mecA gene.[4,5] This encode of the penicillin binding protein (PBP2A) permits the organism to be resistant to methicillin and other beta-lactam antibiotics.

The mecA gene is located on a mobile genetic element called Staphylococcal chromosome cassette (SCCmec). Most HA-MRSA clones are associated with SCCmec type I, II and III which are multidrug resistant[6] while CA-MRSA strains have SCCmec type IV and V which are formerly susceptible to other antibiotics.[7] The aim is to prevent and control MRSA infection in hospitals by preventing MRSA cross-infection. Active surveillance culture to detect patients with MRSA colonization would benefit early isolation precautions particularly in high risk settings of MRSA infection, such as patients in ICUs, immuno-compromised patients, patients on hemodialysis and patients in long-term care units.[8,9] Standard plate culture media for bacterial detection and identification usually takes 2-3 days. The LightCycler® MRSA advanced test is a qualitative in vitro diagnostic test for the direct detection of nasal colonization with MRSA by polymerase chain reaction (PCR) with amplified MRSA DNA and a fluorogenic target specific hybrodization probe for the detection of amplified DNA. The test takes under 2 hours of laboratory time.[10]

Our study is to find the prevalence of MRSA nasal carriers of patients whom were referred to our ICUs by using the rapid advanced MRSA test for rapid MRSA detection and comparing this to the bacterial isolation by standard plate culture media.

Materials and Methods

The study was carried out prospectively at three study sites under the Bangkok Hospital Group, i.e., BMC, Samitivej Hospital Sukhumvit and Bangkok Hospital Pattaya. The study included patients who were transferred to be admitted to ICUs at the study sites. They were screened for study eligibility. The eligible patients were patients whose age was > 18 years, who had been hospitalized in transferring hospitals for more than 24 hours prior to the transfer, and provided written informed consent to participate in the study.

For each patient, two nasal swabs were performed for MRSA identification using a standard plate culture for MRSA isolation and the LightCycler® MRSA advanced test, a real-time PCR based diagnostic testing for MRSA DNA. Both laboratory diagnostic tests were done by **"N- Health"**, the certified laboratory center of this study.

Clinical information of the enrolled patients was recorded in separate case record forms.

Laboratory Procedure

- Culture and susceptibility testing for MRSA

Standard plate culture and susceptibility tests for MRSA identification were performed according to standard microbiology laboratory manual references of the National Committee on Clinical Laboratory Standards.

- LightCycler® MRSA advanced test

LightCycler® MRSA advanced test was performed according to the manufacturer's instructions. The test comprised 3 processes as follows:

i. Specimen preparation. The nasal swab was processed though mechanical lysis by using the LightCycler® Advanced Lysis Kit and the MagNA Lyser Instrument.
ii. PCR amplification and specific hybridization probes The lyse specimen was transferred to LightCycler® 2.0 Instrument (manufactured by Roche Molecular System, Inc., Branchburg, NS08876 USA) for PCR amplification of targeted DNA and hybridization probes for detection of the targeted DNA.
iii. Automated result generation. After meeting peak analysis, the PCR result was interpreted and reported by LightCycler® Software 4.05 as negative (i.e., no MRSA DNA detected), positive (i.e., MRSA DNA detected), or invalid (i.e., no internal control detected).

Statistical analysis

The estimated sample size of the study population was 71, which was calculated by following formulation.

$$n = \frac{Z^2_{a/2} P\,(1 - P)}{e^2}$$

Based on previous surveillance data of MRSA, the proportion of MRSA nasal colonization among patients transferred to BMC (p) was 0.015. The precision of the estimate (e) was 0.03 and the dropout rate was 0.1.

All case record forms were transferred to Bangkok Dusit Medical Service (BDMS) Research Center for data management and data analysis. The Statistical Package for Social Service (SPSS) Software version 19 was used for statistical analysis. The agreement of positive and negative results between the LightCycler® MRSA advanced test and the standard plate culture for MRSA isolation were determined by Cohen's kappa coefficient. Risk factors associated with MRSA nasal colonization were determined by the chi-square test and t-test of which p-value ≤ 0.05 was considered statistically significant.

Results

From December 2010 to May 2011, a total of 100 patients were transfered to be admitted to ICUs of the 3 clinical study sites. These were in the ICU of BMC (87), Samitivej Hospital Sukhumvit (12) and Bangkok Hospital Pattaya (1). Seventeen (17%) patients excluded from the study were due to were the exclusion criteria of having been admitted less than

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24 hours before (6), age less than 18 year old (4), specimen for PCR test was not valid (3), admission outside ICU and no informed consent for specimen collection (2).

The total of 83 patients were eligible for the study, 60 (72.3%) male and 23 (27.7%) female. Their mean age was 62.7±17.7 years. Fifty-eight (69.9%) are of Thai Nationality. While 25 (30.1%) patients are foreigners (Europeans 13, middle eastern patients 4 and Asian patients 8), 11 patients were transferred directly from other countries. Sixty-nine (83.1%) had underlying diseases. Most common diseases are hypertension 65.1%, diabetes mallitus 37.3%, coronary heart disease 21.7%, and chronic renal failure 19.3% (Table 1).

The results of nasal MRSA colonization tested by the LightCycler® MRSA advanced test and the standard plate culture isolation are presented in Table 2.

Table 1: Summary of clinical characteristics of enrolled patients.

Characteristic	n (%)
Total	83 (100)
Male	60 (72.3)
Female	23 (27.7)
Age Mean	62.7±17.7
Nationality	
Thai	58 (69.9)
Foreigner	25 (30.1)
Underlying disease	
Present	69 (83.1)
No	14 (16.9)
Location of referral hospital	
Thailand	72 (86.7)
Other countries	11 (13.3)
Medical treatment before transfer	
Previous infection	
No	43 (51.8)
Yes	40 (48.2)
Previous surgery	
No	66 (79.5)
Yes	17 (20.5)
Clinical active infection on arrival	
No	35 (42.2)
Yes	48 (57.8)
Medical device	
Present	62 (74.7)
None	21 (25.3)

The results showed good correlation between the LightCycler® MRSA advanced test and the standard plate culture. The advance MRSA test detected up to 12 patients (14.5%) while the plate culture isolated MRSA detected 10 patients (12.1%), (Table 3) (Kapp = 0.791, 95% CI = 0.594-0.988).

The risk factors for MRSA colonization of these referred patients were significantly related to the history of previous infections from those hospitals (Table 4).

Table 2: Results of the LightCycler® MRSA advanced test and Standard plate culture.

Prevalence of MRSA	Positive n (%)	Negative n (%)	Total n (%)
MRSA plate culture	10(12.1)	73(87.9)	83(100)
MRSA Advanced test	12(14.5)	71(85.5)	83(100)

Table 3: Correlation between results of the LightCycler® MRSA advanced test and Standard plate culture.

LightCycler® MRSA advanced test	Plate culture		Total
	MRSA +ve	MRSA -ve	
MRSA +ve	9	3	12
MRSA -ve	1	70	71
Total	10	73	83

Kapp 0.791, 95% CI = 0.594-0.988

Table 4: Risk factor for MRSA colonization in referral patients.

History	Result of plate culture		*p* value
	MRSA +ve n (%)	MRSA –ve n (%)	
Previous infection			
No	1(10.0)	42(57.5)	0.006*
Yes	9(90.0)	31(42.5)	
Previous surgery			
No	8(80.0)	58(±9.5)	0.968*
Yes	2(20.2)	15(20.5)	
Length of stay in previous hospital (days)	10.6±58	12.2±29.6	0.866**
Medical device insertion before			
No	1(10.0)	20(27.4)	0.235*
Yes	9(90.0)	53(72.6)	

* Chi-square test ** t-test

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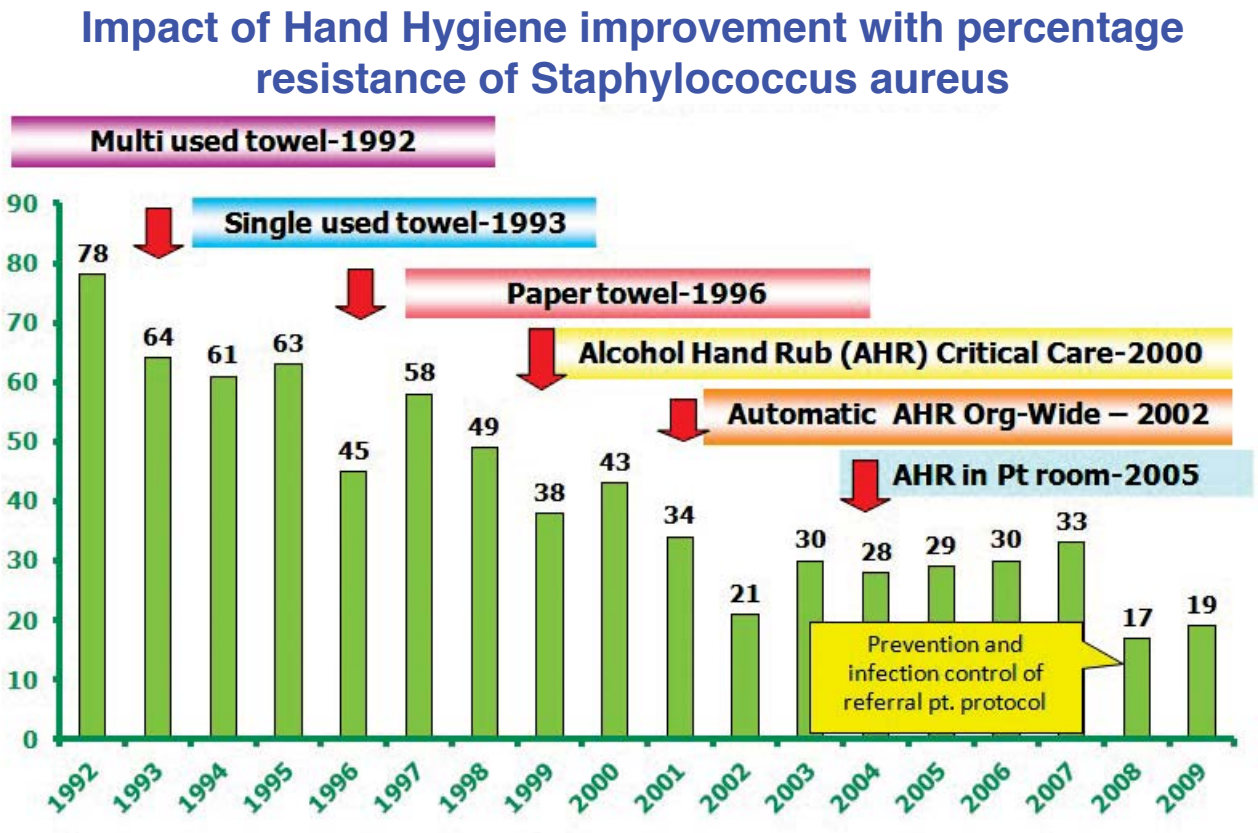

***Figure 1**: Impact of Hand Hygiene.*

Discussion

Our experience of controlling MRSA in hospitals[11] requires a multi-strategy approach to good infection control practices including hand hygiene, patient isolation and preventive transmission activities particularly by improving hand washing compliance methods. The improvement of hand hygiene by supplying more equipment for hand washing and the introduction of alcohol hand rub alternatives for hand hygiene that is easily accessible is important. We found that the prevalence of MRSA gradually declined (Figure 1).

Active surveillance culture of MRSA is a method to identify the patient who has MRSA colonization or infection before entering the hospital. The benefit of active surveillance culture appears to be useful in the setting of outbreaks in hospitals and in certain patients at high risk for MRSA infection such as patients in intensive care units, immunocompromised patients, long term care facility patients and patients on chronic hemodialysis.[8,9] Thompson RL[12] reports MRSA could be controlled over a 12-month period after the implementation of an active surveillance culture to detect and control a strain of MRSA outbreak.

The limitation of an active surveillance culture is the required timing of at least 24-48 hours wait for the culture result. During this period the patient should be placed in isolation as a precaution.

However, the effectiveness to perform universal active surveillance culture is limited, to certain countries where MRSA has a low prevalence e.g. many European countries, for example the Netherlands, Finland and France.[12-16] They found that universal active surveillance culture is successful in controlling MRSA but studies involved multi strategies beside universal active surveillance culture, such as contact isolation, screening for healthcare workers with decolonization, closing units and comprehensive cleaning. Therefore, which intervention or which combination of interventions is most beneficial?

The LightCycler® MRSA advance test is a rapid test tool for direct detection of nasal colonization with MRSA. The test has a short turnaround time of testing of about 2 hours in which the patient will be given appropriate isolation care to reduce transmission and infection in health care settings. It also reduces unnecessary costs for isolation.

Peterson et al.[16] evaluated the use of the LightCycler® MRSA advanced test as a rapid tool for detection of MRSA by nasal surveillance swabs. The test showed relative sensitivity and specificity of 95.2% (95%Cl = 91.1% - 97.8%) and 96.4% (95%Cl = 91.7% - 98.1%) respectively. In comparing with BD gene Ohm assay, for discrepancy analysis, the LightCycler® MRSA Advanced test demonstrated significantly more specificity.

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Our study found the high prevalence of MRSA colonization in critically ill patients up to 12.1 percent who were transferred to our ICUs.

Most of the patients (90%) have had a history of previous infection before admission.

The LightCycler® MRSA advanced test detects the MRSA gene in up to 14.5% of cases. The result showed good correlation with MRSA isolation by plate culture (Kappa = 0791, 95%Cl = 0.594-0.988).

Our study demonstrated that the LightCycler® MRSA advanced test is a useful rapid screening test to detect MRSA colonization. Future study should evaluate the cost benefit and cost effectiveness of the test for MRSA detection and infection control of MRSA infection in hospitals.

Conclusion

We studied the prevalence of MRSA colonization in critically ill patients who were transferred to the ICU in the Bangkok hospital group. The prevalence of MRSA colonization was found up to 12.1%. The LightCycler® MRSA advanced test showed good results and correlation with standard plate culture. The test might be useful for rapid detection MRSA colonization especially in high risk patients. This will be extremely useful in controlling MRSA infection.

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Original Article

The Success of Stroke Fast Track at Bangkok Hospital Medical Center: 5 Years' Experience

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OBJECTIVE: To study the outcomes of intravenous recombinant tissue plasminogen activator (rt-PA) therapy in acute ischemic stroke patients at Bangkok Hospital Medical Center (BMC).

MATERIALS AND METHODS: A retrospective review was performed on acute ischemic stroke patients who arrived at the hospital within three hours of symptom onset and entered the stroke pathway, from 2008 to 2012. The success of the stroke fast track was determined using the National Institute of Health Stroke Scale (NIHSS), Barthel Index (BI), and modified Rankin Scale (mRS) scores.

RESULTS: All 1,548 patients were enrolled in the stroke pathway at BMC from 2008 to 2012. There were 182 acute ischemic stroke patients who arrived at the hospital within 3 hours from the onset of symptoms, and 25 of them were eligible for intravenous rt-PA therapy. The patients who received rt-PA therapy demonstrated a significant reduction in NIHSS and mRS scores, as well as a significant increase in BI scores on the discharge day ($p < 0.01$).

CONCLUSION: Our data suggests favorable clinical outcomes in acute ischemic stroke patients who received rt-PA therapy, as well as the success of the stroke pathway administration system at BMC.

Time is critical for the brain, especially within the first few hours of stroke symptom onset, because nervous tissue is rapidly lost after the occlusion of cerebral arteries. According to the Ministry of Public Health and the World Health Organization, stroke ranks first amongst causes of death in women, and second in men. Stroke is also associated with high disability rates.[1] Acute stroke patients must be promptly evaluated because some of them may be candidates for thrombolytic treatment with intravenous recombinant tissue plasminogen activator (rt-PA) or alteplase, if they present to the hospital within three hours after symptom onset. This FDA-approved treatment has been shown to reduce long-term disability in ischemic stroke patients.[2-4]

There are currently several clinical practice guidelines for acute ischemic stroke patients; however, the rate of rt-PA utilization remains low, and many hospitals do not have enough capacity to administer this medication, due to their limitations in personnel, radiology and laboratory departments, as well as intensive care and inpatient units. The Brain Center of the BMC developed a Clinical Pathway for Acute Stroke Patients, so that our patients receive international standards of care. This pathway classifies stroke patients who arrive within the three-hour window, and makes sure that they receive rt-PA therapy if deemed eligible. The pathway also ensures that the patients receive international standard treatment within the first week from the multi-disciplinary team in our stroke

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unit. This can both reduce the death and disability rates and improve patients' quality of life.[5]

Materials and Methods

A retrospective review was performed on medical records of patients with the diagnosis of acute ischemic stroke having arrived at the hospital within the 3 hours window and having entered the stroke pathway program. The patients had to be at least 18 years old, with documented National Institute of Health Stroke Scale (NIHSS), Barthel Index (BI), and modified Rankin Scale (mRS) scores at day 0 and day 7. The stroke checklists of these patients according to the Clinical Care Program Certification (CCPC) in ischemic stroke by the Joint Commission International (JCI) are determined as: time of onset, time of arrival, time to first doctor, time to neurologist, time to CT brain, time to CT reading, time to laboratory report (blood sugar, INR, and platelet counts), and time to the bolus dose of rt-PA.[6]

Statistical Analysis: SPSS (Statistical Package for Social Science) version 18.0

Demographic data including gender, age, risk factors, the number of patients, the time for intravenous rt-PA administration were analyzed using descriptive statistics, such as frequency, percentage, mean and standard deviation. The comparison of intravenous rt-PA outcomes between the admission day 0 and day 7 with NIHSS, BI, and mRS scores was performed using paired sample t-test analysis.

Results

All 1,548 patients were enrolled in the stroke pathway at BMC, Bangkok, Thailand, from 2008 to 2012. Of these, 1,249 were acute ischemic stroke patients, and 182 of them presented to the hospital within 3 hours after symptom onset. Twenty-five of 182 patients were eligible for intravenous rt-PA therapy and their NIHSS, mRS, and BI were determined on admission day 0 and day 7. The data of these patients are characterized as follows:

- Table 1 demonstrates the demographic information of all 1,548 patients who were enrolled into the stroke pathway. 1,249 patients (80.7%) had ischemic stroke. The majority of acute ischemic stroke patients were men (61.4%). The median age was 67 years (range: 24 years to 94 years). Significant risk factors include hypertension, which presented in 74.7% of the patients followed by diabetes mellitus in 32.0%, and dyslipidemia in 24.4%. There were 182 acute stroke (11.8%) patients who arrived at the hospital within the three-hour window, and only 25 (2%) of the Acute Ischemic Stroke patients received intravenous rt-PA administration.

Table 1: Characteristics of patients enrolled in the Stroke Pathway (n = 1,548).

Parameters	Year				
	2008	2009	2010	2011	2012
n (%)	262 (17)	291 (19)	327 (21)	360 (23)	308 (20)
Type of stroke					
Ischemic stroke	240 (19)	244 (20)	255 (20)	284 (23)	226 (18)
Hemorrhagic stroke	22 (8)	47 (16)	72 (24)	76 (25)	82 (27)
Gender					
Male	149 (16)	182 (19)	185 (19)	239 (25)	196 (21)
Female	113 (19)	109 (18)	142 (24)	121 (20)	112 (19)
Age					
Median (range)	69 (33-100)	67 (24-94)	67 (27-99)	65 (21-96)	65 (24-93)
Risk factor					
Hypertension	190 (16)	216 (19)	247 (21)	270 (24)	233 (20)
Diabetes mellitus	94 (19)	82 (17)	102 (21)	118 (23)	100 (10)
Ischemic heart disease	47 (24)	34 (17)	55 (28)	39 (19)	24 (12)
Atrial fibrillation	35 (16)	50 (24)	37 (18)	56 (26)	33 (16)
Smoking	41 (16)	50 (19)	53 (20)	74 (28)	45 (17)
Valvular heart disease	7 (28)	7 (28)	3 (11)	6 (21)	5 (18)
Hypercholesterolemia	0	0	0	223 (59)	155 (41)
Alcohol	0	0	0	59 (64)	33 (36)
Genetic disease	0	0	0	27 (63)	16 (37)
No risk factor	33 (22)	36 (24)	44 (30)	15 (10)	20 (14)
Onset time within 3 hours	39 (21)	36 (20)	38 (21)	38 (21)	31 (17)
IV rt-PA administration	6 (24)	2 (8)	4 (16)	6 (24)	7 (28)

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- Table 2 demonstrates the key timing of each process for intravenous rt-PA administration according to JCI standards. Compared with the target time, the **'door to stroke team'** and the **'door to lab results'** were longer than the standard in the first year of the stroke pathway administration system, but decreased continuously as the stroke team realized and solved organizational problems. The **'door to needle'** time was more than the target in 2011 and 2012, due to delayed decision-making by patients' families, but overall the patients who entered the stroke pathway received intravenous rt-PA therapy within a three-hour window.

- Table 3 demonstrates the outcomes of acute ischemic stroke patients who received rt-PA treatments. The NIHSS and mRS scores reduced significantly; whereas the BI score has significantly increased, suggesting improved outcomes in stroke patients at day 7.

Table 2: Indicators of intravenous rt-PA administration for patients enrolled to Stroke Fast Track.

Indicators	Year									
	2008 (n=6)		2009 (n=2)		2010 (n=4)		2011 (n=6)		2012 (n=7)	
	n* (%)	Mean±SD	n* (%)	Mean±SD	n* (%)	Mean±SD	n* (%)	Mean±SD	n* (%)	Mean±SD
Door to first doctor (Target 10 Minutes)	5 (83.3)	5.5±4.8	2 (100)	2.5±3.5	4 (100)	0.3±0.5	6 (100)	1.8±4.0	7 (100)	0
Door to Stroke team (Target 15 Minutes)	3 (50.0)	24.8±33.0	2 (100)	8.0±4.2	4 (100)	7.0±1.6	5 (83.3)	8.5±10.6	7 (100)	3.6±5.6
Door to CT read (Target 45 Minutes)	6 (100)	29.5± 8.9	1 (50.0)	33.0±19.8	4 (100)	18.8±8.5	4 (66.7)	39.0±21.6	7 (100)	30.9±10.0
Door to lab result (Target 45 Minutes)	4 (66.7)	49.5±36.8	2 (100)	42.5±3.5	4 (100)	19.8±7.6	5 (83.3)	29.2±14.4	4 (57.1)	55.3±48.5
Door to needle (Target 60 Minutes)	5 (83.3)	56.2±28.8	2 (100)	51.0±4.2	3 (75.0)	52.5±19.8	4 (66.7)	64.7±31.2	3 (42.9)	87.6±50.6

n* = Achieve Target cases

Table 3: Clinical outcome measurement using Paired t-test.

Clinical Outcomes Measures**	Year						
	2008 (n=6)	2009 (n=2)	2010 (n=4)	2011 (n=6)	2012 (n=7)	t	*p* value
NIHSS (mean)							
- Day 0	6	7	13	7	15	4.68	0.0001*
- Day 7	2	3	6	4	14		
Modified Rankin Scale (mean)							
- Day 0	3	3	4	4	4	4.51	0.0002*
- Day 7	1	2	2	3	4		
Barthel Index (mean)							
- Day 0	70	50	40	50	30	-3.46	0.0025*
- Day 7	90	75	50	60	60		

**p* value ≤ 0.01

**NIHSS was measured to initial stroke severity; Mild stroke (NIHSS ≤ 7), Moderate stroke (NIHSS 8-20) and Severe stroke (NIHSS >20).
-Modified Rankin Scale (mRS) used scale for measuring the degree of disability or dependence in daily activities; 0 - No symptoms, 1 - No significant disability, 2 - Slight disability, 3 - Moderate disability, 4 - Moderately severe disability, 5 - Severe disability and 6 - Dead
-Barthel Index (BI) used to measure performance in activities of daily living (ADL); Very severe disability (0-20), Severe disability (25-45), Moderate disability (50-70), Mild disability (75-95) and Physically independent (100).

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Discussion

According to our study, the most common vascular risk factors are hypertension, diabetes mellitus and dyslipidemia respectively. In addition, a lot of our stroke patients were active smokers. These are modifiable risk factors, and lifestyle changes can help improve the risk of stroke in this group of patients.[7]

Our study found that only 11.8% of acute stroke patients arrived at the hospital within the 3 hours window, and only 2.0% of acute ischemic stroke patients received rt-PA therapy. Although the rt-PA utilization rate at BMC appears low, this is comparable to the Thai Stroke Registry; a multi-center study in governmental hospitals of Thailand during 2008-2010, revealed that only 3.8% of the acute ischemic stroke patients receive rt-PA.[8] In addition, a study in JCAHO-accredited Hospital in Michigan also shows a low rt-PA utilization rate of 3.8%.[9] The reasons for not using rt-PA in our institution are as follows: rapid improvement of stroke symptoms in 68 patients (43.3%), intracerebral hemorrhage on CT brain in 29 patients (18.4%), unclear onset time in 15 patients (9.5%) and family refused rt-PA in 10 patients (6.3%) respectively.

The low rate of rt-PA utilization is a major problem worldwide despite its clear benefits, as demonstrated in the study by The National Institute of Neurological Disorders and Stroke (NINDS) and the Zurich Thrombolytic Registry, which show that acute ischemic stroke patients have better clinical outcomes and quality of life at 3 months follow up.[10,11] This is probably due to one of the risks of rt-PA, namely intracranial hemorrhage which can be seen in 6.4% of subjects.[10] However, according to Saver, most patients who developed intracranial hemorrhage were destined anyway for poor clinical outcomes.[12]

Conclusion

This study suggests favorable clinical outcomes in acute ischemic stroke patients who received rt-PA treatments and who arrived at hospital within 3 hours from the onset of symptoms.

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Case Report

Atheroma and Coronary Artery Spasm

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Case Report # 1

A 47-year-old man, a heavy smoker, developed chest pain in the morning. A few minutes before arrival at our center, he collapsed in the taxi. Ventricular fibrillation (VF) was documented at the emergency room. After successful cardiopulmonary resuscitation (CPR), Electrocardiogram (ECG) showed inferior ST segment elevation (STE) so he was transferred to the cardiac catheterization laboratory. Coronary angiogram showed no significant lesion in the left main (LM), anterior descending (LAD) and circumflex (Cx) arteries. The dominant right coronary artery (RCA) had a severe vasospam (> 90% luminal diameter stenosis) in the proximal part (Figure-1A). After administration of intracoronary nitroglycerine (NTG) 300 mcg, the vasospasm disappeared (Figure 1B). The lumen of RCA was enlarged and the smooth border was suggestive of insignificant plaque burden. The inferior ST elevation pattern was also normalized without Q wave. He was pain free and discharged home on aspirin and calcium antagonist. He did well but later discontinued follow-up.

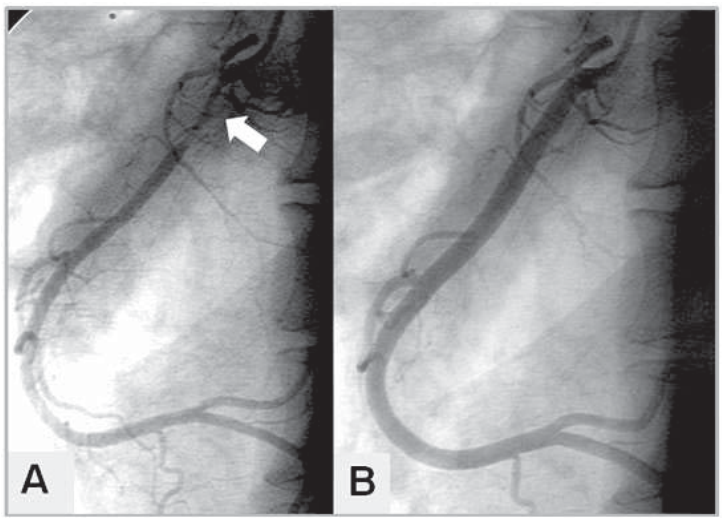

Figure 1: *A. Coronary angiogram of the right coronary artery (RCA) showed severe spasm of proximal part (white arrow). B. After administration of nitroglycerine, the vasospasm disappeared. The smooth, enlarged RCA angiogram suggested no significant plaque burden.*

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Case Report # 2

A 54-year-old man experienced crescendo angina for a month. Chest pain started every morning, right after minimal exertion, and lasted three minutes. His known coronary risk factors included impaired fasting glucose, untreated dyslipidemia (LDL-cholesterol of 170 mg/dl) and hypertension. He had stopped smoking cigarettes 10 years before and did not use any illicit drugs.

The physical examination was unremarkable, BP was 122/88 mmHg, HR was 72 beats per minutes. Baseline ECG showed a normal sinus rhythm without ST-T changes. The echocardiogram revealed mild concentric left ventricular hypertrophy with well-preserved systolic function, ejection fraction of 0.55. Trace mitral regurgitation and mild diastolic dysfunction (grade 1) were also observed.

The Bruce protocol exercise stress test was performed. After walking three minutes, chest pain occurred. It was associated with 2-3 mm ST segment elevation (STE) in leads V1-3, aVR and 2 mm ST depression in leads II,III,F (Figure 2). These findings suggested a critical stenosis in at least one or more major coronary arteries.

A coronary angiography was then performed and showed no significant lesion in the LM trunk, Cx and RCA. There was a modest lesion (50-60% luminal stenosis) in the mid part of the LAD artery at the origin of an unobstructed diagonal branch. The lumen of mid-distal LAD artery was rather small (Figure 3A).

Since this moderate lesion could not entirely explain an ischemic exercise response at low workload, we decided to assess the functional status of this lesion. A pressure wire (St. Jude Medical Company) was passed across the lesion into the distal LAD artery. After obtaining maximal hyperemia by an intracoronary injection of Adenosine 60 cc, the measured fractional flow reserved (FFR) was in the borderline normal zone, 0.76. However, after intracoronary administration of NTG 400 mcg, FFR increased to the normal range, 0.89-0.92, therefore coronary intervention was deferred. The repeat angiogram showed a significantly enlarged luminal diameter of the whole LAD artery (Figure 3B-C) suggestive of coronary vasospasm. The mid LAD lesion persisted in the range of 50% luminal stenosis.

To study the patho-anatomy of atheromatous plaque, we examined this lesion with intravascular ultrasound (IVUS) catheter (Eagle Eye Gold, Volcano Cooperation, US). Despite the normal appearing angiogram, crescentic plaques were noted in the left main (Figure 4A) and proximal LAD (Figure 4B) arteries with an area stenosis of 30% and 54.9% respectively. The mid LAD lesion had an elliptical lumen surrounded by fibro-lipid plaque causing an area stenosis of 55.6 - 67% (Figure 4C-E). There was no significant atheroma observed in the distal LAD segment (Figure 4F). All of these findings suggested a non-hemodynamic significant plaque burden so medical treatment was administered with verapamil SR 240 mg, aspirin (300 mg/day), clopidogrel (75 mg/day) and simvastatin (40 mg/day).

After treatment, the patient had no more pain and was able to walk around as usual. The repeat exercise test after two weeks of medication showed no inducible ischemia. He walked through 9 minutes (10 mets) on standard Bruce protocol with a maximal heart rate of 130 bpm (80% of age predicted maximal heart rate), a maximal BP of 160/79 mmHg. There was no significant ST elevation observed as shown in Figure 5.

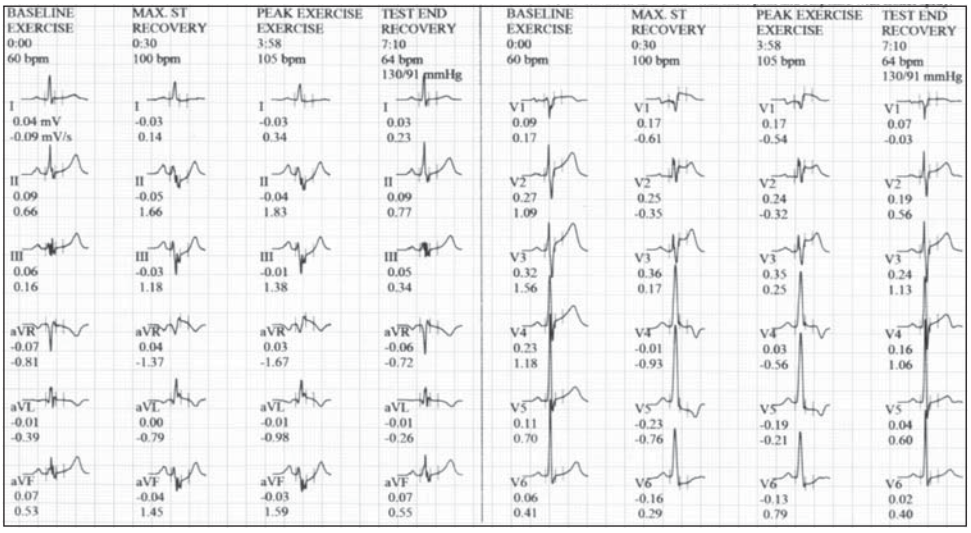

Figure 2: *ST segment elevation in leads V1-3, aVL , aVR and ST depression in leads II, III, aVF, V4-6 were documented during chest pain after exercise for 3 minutes. The maximal heart rate was only 105 bpm. His angina and ST deviation disappeared within 4 minutes.*

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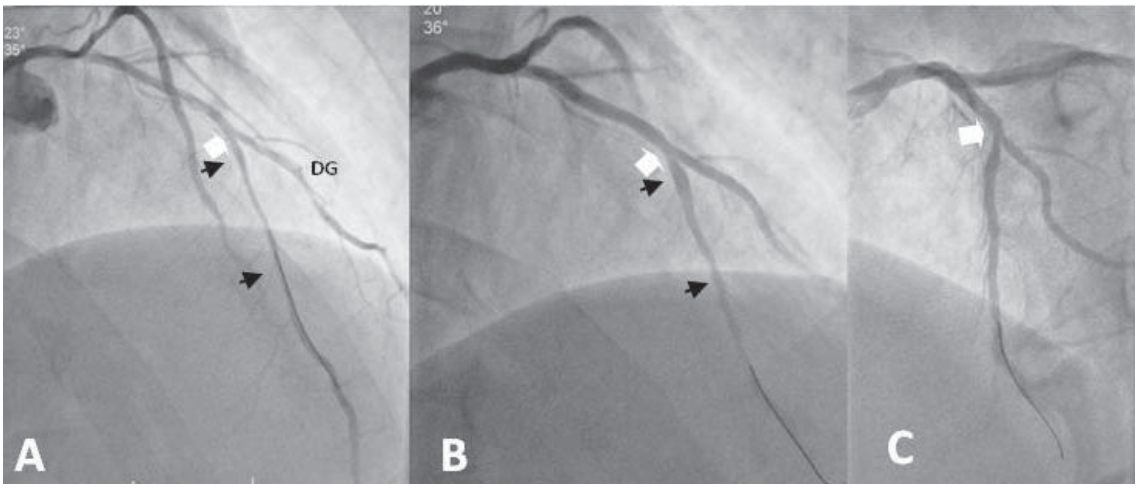

Figure 3: *A: The left coronary angiogram revealed a moderate lesion localized in the mid LAD segment (white arrow, A-C), close to the origin of an unobstructed diagonal branch (DG). The mid LAD segment had diffuse severe stenosis (black arrow).*
B-C: After administration of intra-coronary nitroglycerine, the whole LAD diameter was enlarged but the mid LAD lesion (black arrow) remained in 50-60% diameter stenosis (white arrow B,C). FFR, performed after intracoronary administration of adenosine 60 cc and 400 microgram of NTG, was in the normal range, 0.89-0.95, indicative of a non-hemodynamic significant lesion, so coronary intervention was deferred.

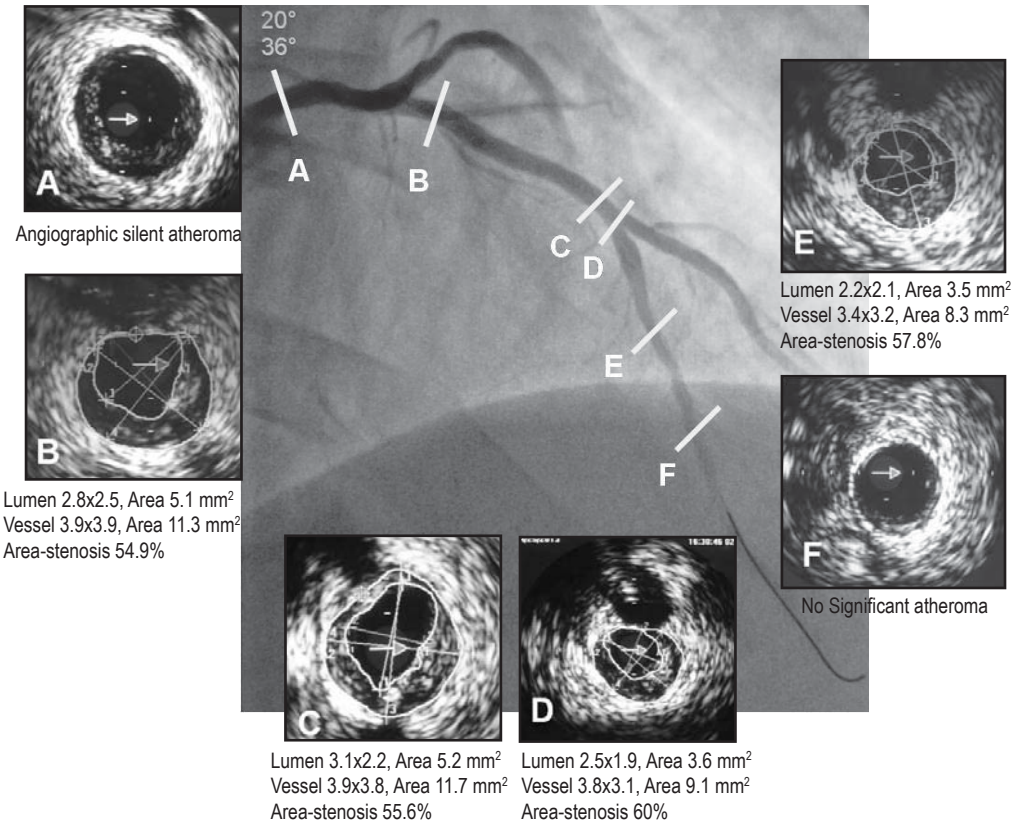

Figure 4: *Intravascular ultrasound imaging showed an angiographic silent atheroma from 2 to 12 o'clock in the left main, (A) and proximal LAD artery (B). At the mid LAD segment, the lumen (arrow sign) shape was elliptical since it was surrounded by an eccentric fibro-lipid atheroma, causing an area stenosis of 55.6% and 60% (C &D). A similar lesion was observed along the vaso-spastic segment (E). However, there was no significant plaque burden in the distal LAD (F).*

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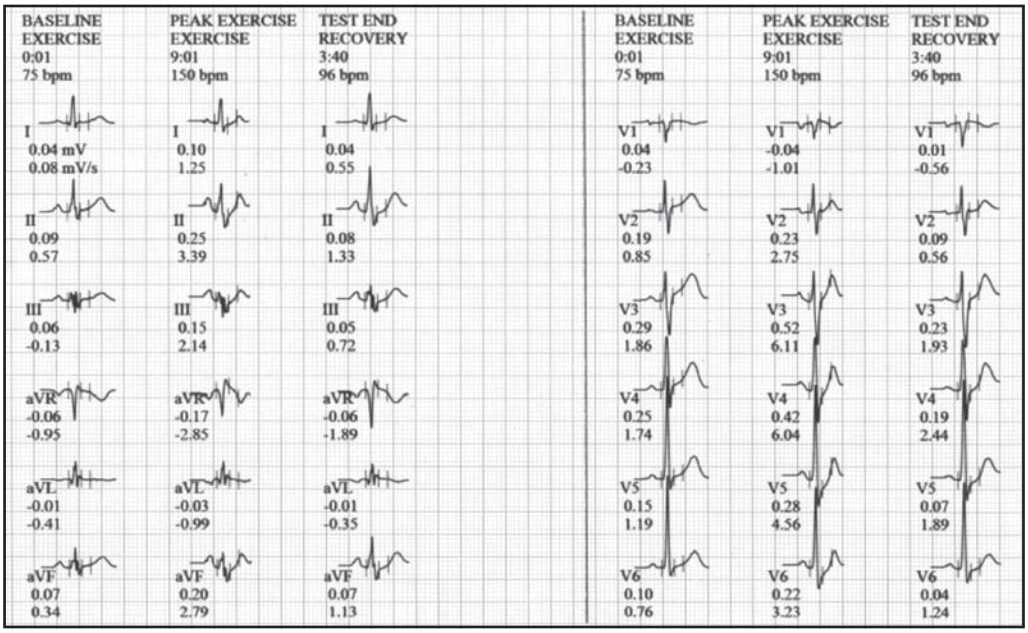

Figure 5: *After administration of slow release verapamil 240 mg for two weeks, the repeat exercise stress test showed no reproducible chest pain after walking 9 minutes on Bruce protocol (10 mets achieved). There was mild STE in aVR and J point ST depression in leads V4-6 and II, aVF but the patient had no symptoms.*

Discussion

Spectrum of coronary artery spasm

Coronary artery spasm or coronary vasospasm is defined as a transient abnormal vasoconstriction of one or more epicardial coronary arteries which results in compromising coronary blood flow and myocardial ischemia. The clinical spectrum largely depends on the degree of coronary spasm, for example in complete arterial occlusion cases, transmural myocardial ischemia, myocardial infarction (MI) and ST segment elevation (STE) would be expected.[1] If occlusion were incomplete, then the patient might have angina from subendocardial ischemia and display ST depression[1]. Historically, Prinzmetal and colleagues were the first group who linked rest angina and spontaneous STE in 1959.[2] In 1962, the angiographic evidence of reversible coronary spasm was delineated by Gensini and colleagues in one patient during an angina attack as well as in animal studies.[3] In general, coronary spasm could occur either spontaneously[1-3] or after exposure to various active substances such as cocaine, marijuana, amphetamine, alcohol, anti-migraine, chemotherapeutic agents and antibiotics.[4-8] During coronary intervention, vasospasm was found in 1-5%[9] and, on rare occasions, has led to cardiogenic shock.[10] Currently, spontaneous coronary vasospasm is widely recognized as a potential cause of acute coronary syndrome (ACS) i.e. unstable angina, STE MI, non-STE-MI,[11,12] exertional angina,[13] silent myocardial ischemia with life-threatening ventricular arrhythmias,[14] advanced AV block and sudden cardiac death.[1,15,16] Although the underlying mechanism remains unclear, a recent study suggested that hyper-reactivity of the smooth muscle cell might be the pathogenic basis of coronary vasospasm.[9,18] The role of post-receptor alterations, gene mutations, autonomic triggers and vasoconstrictive stimuli has been extensively reviewed by Lanza GA and colleagues.[18] The prevalence of coronary vasospasm in the Japanese population is higher than in westerners and genetic factors are involved. For example, polymorphism of the gene associated with endothelium nitric oxide synthase (e-NOS) has been reported.[1,9,18]

Clinical presentation and risk profile

Like formerly reported cases,[14,15] the first patient presented with VF arrest on arrival. After successful defibrillation, transient inferior STE was documented before catheterization. Spasm of proximal RCA disappeared after intra-coronary administration of NTG and the RCA angiogram was completely normal (Figure 1B-C). Thus spontaneous coronary vasospasm was likely the cause of ischemic VF arrest in this particular case. In addition, smoking was the only risk he had and is a well recognized risk factor in the majority of vasospastic cases.[1,19-21] McKenna et al studied 10 cases of young (< 40 years) myocardial infarction (MI) victims who had normal coronary angiograms.[19] Interestingly, they found only one associated risk factor, heavy cigarette smoking. Sugiishi and Fumimaro compared all risk factors of 175 proven coronary spasm cases who had

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near normal angiogram (< 25% diameter stenosis) with the control group, comprising 176 non-vasospasm cases with normal angiogram[20]. Again, cigarette smoking was the only significant associated risk factor with the odd ratio (by multivariate logistic regression analysis) of 2.41 (95%CI = 1.5-3.8, $p < 0.05$).[20] How smoking contributed to vasospasm in the non-significant coronary stenosis was not entirely clear. Several vasoactive substances in cigarettes, such as nicotine and carbon monoxide, potentially produce lipid peroxidation products causing low grade inflammation, pro-thrombotic states and smooth muscle cell spasm.[22] In fact, high levels of the inflammatory marker, C-reactive protein, has been reported in vasospastic cases during the active phase,[23] therefore, smoking cessation is mandatory.

In contrast, the second patient presented with unstable angina (increased frequency of attack on minimal exertion) which was also the common manifestation in coronary spasm cases.[1,9,12] Although he had quit smoking for more than ten years, he had all other known major coronary risk profiles: impaired fasting glucose, hypertension and a high LDL cholesterol level. Thus, it was not surprising that he had diffuse atheroma with area stenosis of 30-60%, starting from the left main to mid LAD arteries (Figure 4A-E). Similar findings were observed in McKenna's report: 30 young MI cases with obstructive coronary angiograms also had multiple risk factors.[19]

Vasospasm and lesion severity

Recent studies have focused on the hypersensitive vascular smooth muscle as a basic common mechanism in vaso-spastic cases.[17,18] While the vascular smooth muscle was scarcely left in advanced atheroma,[24] it was better preserved in mild to moderate atherosclerotic lession as reflected by mild to moderate (< 50%) stenosis or even near normal angiograms. Therefore, it was likely possible that these types of lesions (normal or no disease segment) might be the main site of the vasospasm. There was some direct and indirect evidence from both angiographic and necropsy studies to support this hypothesis. Firstly, the prevalence of acute MI victims with a normal coronary artery (by means of coronary angiographic study, necropsy or both) increased from 4-7% in the general population to almost four times in younger patients.[24-26] It suggested that either coronary spasm or other non-atherosclerotic disease could be the cause of MI in the young. Second, Ong and colleagues studied ACS patients and found that 30% of rest angina patients had a non-obstructive coronary angiogram. Nearly half of this particular group had abnormal vasoconstriction by acetylcholine test.[12] Third, in a necropsy study of 10 fatal myocardial infarction (MI) cases by Elliot et al, 60% of them had no coronary artery stenosis and the rest had only mild to moderate (< 50%) stenotic lesions.[25] In addition, McKenna et al described two fatal MI cases from coronary thrombosis in whom no atheromatous disease was found.[19] Fourth, the link between coronary spasm and subsequent thrombosis was reported in one post-mortem case and other two angiographic studies by Maseri and colleagues.[27] Recently, Reynolds et al studied multi-modalities of cardiac imaging in MI women who had non-obstructive lesions (< 50% diameter stenosis by angiogram). Half of the patients had either normal (30%) or minimal lesions (median diameter stenosis of only 20%) on angiogram. By intravascular ultrasound study (IVUS) imaging, plaque disruption was detected in 38% of the study group.[28] Although our first patient did not have an IVUS examination, it was less likely that he would have significant atheroma as evidenced by his absolutely normal angiogram. In addition, the distal LAD segment of our second case, which also contributed to vasospasm (Figure 3A), was free of atheroma by IVUS, (Figure 4F). All of this evidence suggests that severe fatal coronary spasm required an active muscle cell located in the non-obstructive lesion where the vascular media was well preserved. Severe vasospasm could lead to plaque rupture and fatal coronary thrombosis.

Vasospasm and more advanced atheroma

To study lesion characteristics requires more sophisticated tools than the angiogram, which reflects only the silhouette of contrast filling lumen, so-called luminogram. In fact, the angiogram provides no detail of the arterial wall where the atheroma originated. In contrast, IVUS imaging delineates the cross sectional anatomy of the arterial lumen and its wall component. Thus, in angiographically normal segments, like in the LM and proximal LAD artery of the second case, the silent atheroma was depicted by IVUS images, (Figure 4A-B). By IVUS imaging, various stages of atheroma had been shown at the site of the vasospasm.[1] In contrast to minimal lesions, more advanced atheroma have been reported in fatal vasospastic cases.[16,29,30] As shown in the mid LAD of our second patient (Figure 4D-E), the more advanced atherosclerotic plaques after bifurcation were mostly eccentric in distribution (lumen was out of center).[29,30] In necropsy cases, the disease-free segment (opposite to the plaque) was observed between 2.3 - 32% and vascular media in this segment remained intact.[30] Since the media behind the advanced atherosclerotic wall was thin or absent, it has been postulated that this spared segment might be the responsible site of vasospasm in this type of lesion.[29, 30] How the plaque severity contributes to various degrees of vasospasm remains unknown at the present time and further study is mandatory.

Another way to assess functional severity of the stenotic lesion is by measuring blood flow within the coronary artery by Fractional Flow Reserve (FFR) technique. FFR refers to the proportion of achievable blood flow through the stenotic lesion at baseline compared with the flow during maximal hyperemia.[31] Since the resistant vessels were maximally dilated, the flow and pressure were well-correlated in a linear curve. This technique had been clinically validated in functional assessments of intermediate coronary lesions and the acceptable ratio was 0.75-0.80.[32] In a DEFER study,

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coronary disease patients who had a FFR > 0.75 had the same rate of cardiac death or acute MI between the medical therapy group and the coronary intervention arm.[32] Owing to the normal FFR, 0.76 (baseline) and 0.92 (after adenosine and NTG), coronary intervention was then deferred.

Therapeutic options

The prevention of angina attacks with calcium antagonists and long-acting nitrates has been well established in coronary vasospasm cases[1,9] and both patients responded well to slow release Verapamil. After two weeks of treatment, the second patient walked through 9 minutes (10 mets) without chest pain or STE. Smoking cessation and control of all risk factors were mandatory in all cases[1,9] Lowering cholesterol with statin has been favorably reported in vasospastic cases after withdrawal of the calcium antagonist.[33] Aspirin must be continued to reduce thromboxane A2 production from activated platelets.[9,34] Deficiency of magnesium[1,35] and vitamin E[36-38] had been reported in vasospasm cases and replacement of both agents were recommended in Japanese guidelines.[1] Infrequently, alcohol could induce vasospastic angina but the mechanism remained unknown.[5] It is postulated that alcohol might induce dieresis and magnesium loss, so in this particular case, alcohol restriction is mandatory.[1] In medically refractory vasospasm, coronary stent implantation[39] and coronary bypass graft surgery[40] has been performed with favorable outcomes. In aborted VF victims, the implant of a cardiovertor defibrillator had effectively prevented recurrent sudden cardiac death.[41]

Conclusion

We reported two coronary vasospasm cases with different clinical manifestations, one with VF arrest and another with unstable angina. The correlative pathology and vasospasm were discussed. Severe intense spasm was likely occur in patients who have minor disease or a normal coronary artery, like the first case. The relative young age and cigarette smoking were quite common in this group. In more advanced atheroma, less functional vascular media was left behind so it was postulated that the disease- free segment might be the site of the vasoactive spasm. This latter group, as represented by our second case, was older and had multiple risk factors. Both cases responded well to a long-acting calcium antagonist. To date, it remains unclear how the different types of atheromatous plaque contribute to vasospasm. Thus, further study is mandatory.

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The Survival of an Old Lady with ALCAPA

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The coronary artery system is composed of two major systems, the left and right coronary artery system. Both left and right coronary arteries originate from the aortic left and right coronary cusp respectively. The left anterior descending artery (LAD), the main vessel of the left coronary artery system, is considered to be the most important of the coronary artery system. The LAD supplies the left ventricular anterior wall that plays the main role in the left ventricular pumping function. The right coronary artery system is also considered to be the second most important system that mainly supplies the left ventricular inferior wall. The balance of myocardium blood supply demands an adequate coronary artery blood supply from both systems. If the blood supply to some portion of the myocardium is entirely blocked or the energy demand is much higher than the supply, severe myocardium injury or sudden cardiac death may occur. Total blocking of the left main coronary artery (LMA) and proximal LAD vessel is the main cause of death. **How does a person survive with a total absence of arterial blood supply from the left coronary artery system?**

ALCAPA syndrome is an example of a congenital abnormal condition where a person stays alive even in the absence of blood supply from the left coronary artery system. ALCAPA stands for "**A**nomalous origin of the **L**eft **C**oronary **A**rtery from the **P**ulmonary **A**rtery".[1] ALCAPA is also called **Bland-White-Garland syndrome** because it was described by Bland and colleagues in 1933 during an autopsy.[1] By definition, the main key abnormality of the ALCAPA syndrome is the origination of the left coronary artery system coming from the main pulmonary artery instead of the aortic coronary sinus. ALCAPA is a rare condition and the incidence accounts for 0.25-0.5% of all congenital heart disease cases.[2] This abnormal condition develops during the period of embryogenesis and it may be due to the abnormal septation of the conotruncus into the aorta and pulmonary artery or the persistence of the pulmonary buds together with involution of the aortic buds that form the coronary arteries.[2] The left coronary system is retrogradely supplied by the collaterals from the right to left. ALCAPA syndrome results in coronary artery steal phenomena and a left to right blood shunting which occurs after birth. Coronary steal phenomena and left to right blood shunting are caused by the entering of the blood in the LAD lumen (artery) into the low resistant pulmonary artery trunk (venous). The pulmonary artery steals the blood from the heart, hence, the left ventricular myocardium is underperfused.[3,4] ALCAPA syndrome has two types, the infant type and adult type. In the infant type, about 90% die within the first year of life due to myocardial infarction and heart failure. The development of a collateral system between the RCA to LAD also appears after birth and it is the **key to life**, if a collateral system does not develop well enough on time, 90% of patients die during

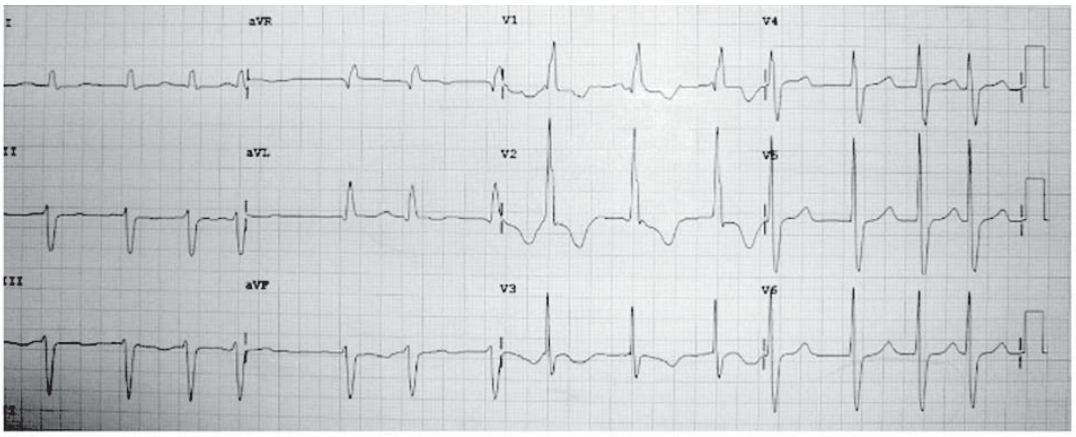

Figure 1: *ECG on admission showed atrial fibrillation, RBBB with secondary ST-T changes.*

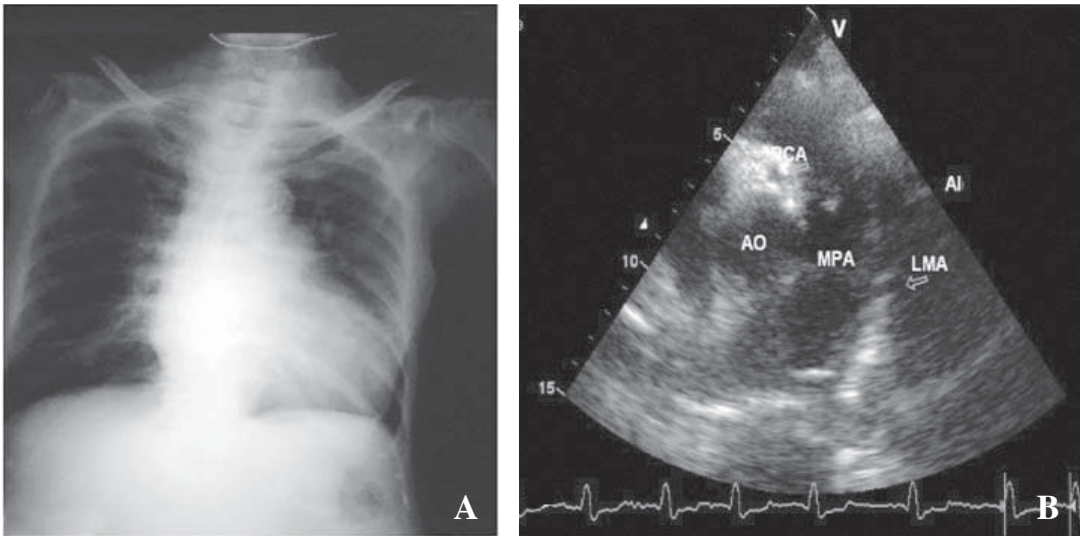

Figure 2: *Left: Chest film five months before this event showed cardiomegaly and prominent pulmonary trunk (A). Right: short axis view of the aortic root and pulmonary trunk that showed origin of RCA and LMA.*

infancy shortly after birth from congestive heart failure and myocardial infarction[4] because the collateral system is the only transport pathway to bring arterial blood from the right coronary artery to the left coronary artery. The ALCAPA patient who outgrows death in the young, may be asymptomatic or present with myocardial ischemia, heart failure, chronic mitral regurgitation and sudden death.[5] Although most ALCAPA patients die young, the survival rate and prognosis can be improved by early detection using noninvasive methods such as echocardiography.[6] Surgical correction should be considered soon after verification of the diagnosis.[5]

Case Report

A 79-year-old Thai lady, had a known history of diabetes mellitus, hypothyroidism, chronic atrial fibrillation and suffered from right sided ischemic stroke for over ten years, presented in May 2011 with pulmonary edema. Physical findings of the left heart failure correlated well with the chest film. Pan systolic murmur grade 2/6 was audible at the apical area. ECG showed atrial fibrillation with moderate ventricular rate response, complete right bundle branch block (RBBB) and precordial ST-T segment depression, (Figure 1). Echocardiography revealed an enlarged left ventricle, dilated left atrium, anterior mitral valve prolapsed causing moderate to severe mitral regurgitation, globally decreased LV systolic function, EF of 0.44 with antero-apical hypokinesia and elevated pulmonary artery pressure, 60 mmHg. With medication, she was successfully extubated, transferred to an intermediate unit for a few days and had recurrent pulmonary congestion requiring re-intubation. Similar events repeatedly occurred three times so it was decided to exclude coronary stenosis by conventional angiography (CAG). CAG images (Figure 2A-B) revealed no left main artery originated from the aortic root. A huge single right coronary artery supplied the whole ventricle and transeptally filled the left coronary (LCA). It was suspicious that the left main (LM) might originate from

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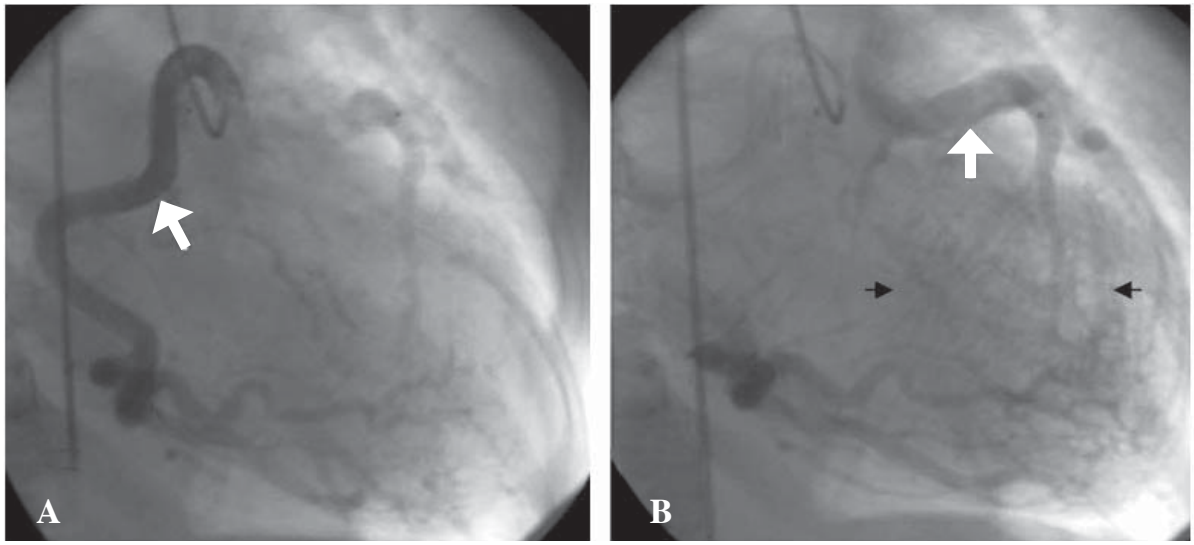

Figure 3: *Left heart CAG images revealed (A) the RCA which was in the right position (A) with no show of the left coronary artery origin at the left cusp sinus , (B) the left coronary arteries (white arrow) were supplied by the right to left collaterals (black arrow).*

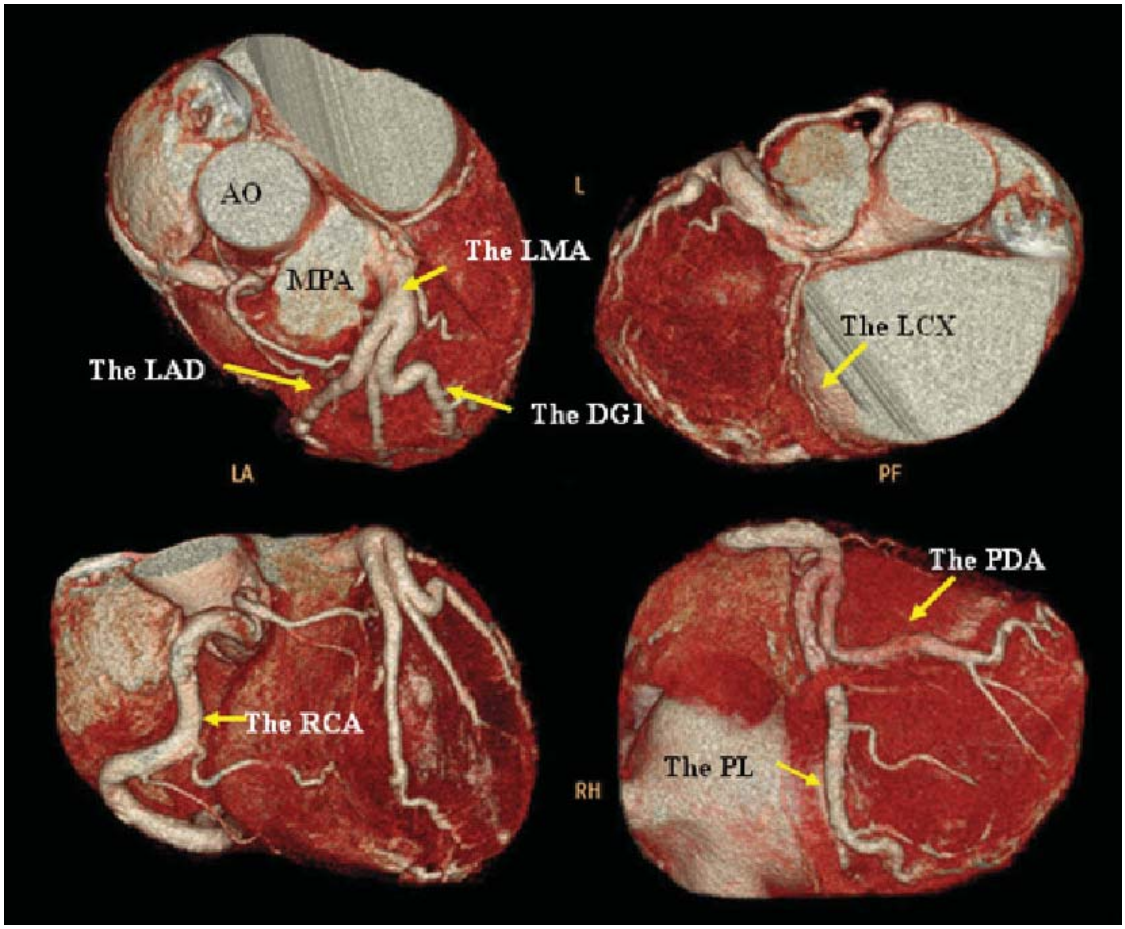

Figure 4: *Volume rendering images of the 256- slice MDCT revealed the large RCA which originated from the right cusp and the LMA originated from the MPA (ALCAPA).*

AO= Aorta *MPA= Main pulmonary artery* *LMA = Left main artery*
LAD = Left descending coronary artery *LCX= Left circumflex coronary artery*
RCA = Right coronary artery *PL= Posterior lateral artery*
PDA = Posterior descending artery

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the main pulmonary artery so she was referred for a multi-detector computerized tomography (MDCT) study. A 256 detector CT scanning with iodinated contrast injection was requested to define the diagnosis and it showed an enlarged RCA took off from the right aortic cusp as shown in Figure 3. The RCA gave the long postero-lateral (PL) and the posterior descending (PDA) branches, supplying the lateral and the posterior wall of the left ventricle, retrogradely filled the left anterior descending (LAD) and the LM arteries. Contrast phase image of MDCT scan confirmed the abnormal origin of the LM trunk that originated from the main pulmonary artery and supplied the small left circumflex (LCx) artery. The course of the LAD and the LCx arteries were still running along the inter-ventricular and the atrio-ventricular groove respectively. Based upon the above MDCT findings, the final diagnosis was ALCAPA syndrome. In ALCAPA cases, besides a prominent pulmonary trunk in the chest film, an echocardiogram may provide some diagnostic clue. In the short axis view of the aortic root, there was no left main origin (see Figure 2B). By color Doppler echocardiography, the pulmonary artery shows the retrograde flow in the pulmonary artery and systolic-diastolic flow through the septal collaterals which indicated that the blood supply to the left main artery and the LAD was through the pulmonary artery (Figure 3). The ECG gated MDCT offers a direct visualization of both the origin of the RCA and LCA, and provides a definitive diagnosis (Figure 4). In our case, the flourish right to left collateral supply noted in conventional angiogram and MDCT images explained why she had been living well through to her 8th decade. The significant mitral regurgitation, either resulted from anterior mitral valve prolapse, combining with dilated ventricle secondary from ischemic cardiomyopathy or both, created a high LVEDP and LA pressure and contributed to recurrent CHF. In addition, the high PAP, 60 mmHg, further compromised myocardial perfusion since the LCA received the reverse flow from RCA. After an uneventful tracheostomy, she was clinically stable and had avoided heart failure for months. The family decided to treat her conservatively.

Discussion

The diagnosis was easily overlooked by routine and non-invasive examinations. The echocardiograms might not have provided a definite diagnostic. The coronary angiogram provided a clue but does not always show a precise abnormal origin of the LM artery. MDCT can be used as a first diagnostic or a complimentary noninvasive technique since it displays the origin of both arteries, the course and other associate diseases i.e. patent ductus arteriosus (PDA), tetralogy of fallot (TOF), ventricular septal defect (VSD) and atrial septal defect (ASD). In a low calcium scoring patient, MDCT can be a one-stop tool for a definitive diagnosis before surgical planning.

Conclusion

Although ALCAPA syndrome is a very rare condition it can be accidentally found in everyday practice. This article illustrated a surviving case in her 8th decade before succumbing to heart failure from multiple causes. It is very rare for ALCAPA patients to survive to their sixth or even seventh decades of life.[7] The key to the survival of this patient is the well developed collaterals from the right to left. Awareness of this condition may prevent complications and may improve survival rates and prognosis.

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Hirayama's Disease

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Hirayama's disease, also known as juvenile non-progressive cervical amyotrophy or monomelic amyotrophy is a rare focal motor neuron disease that primarily affects young Asian males (15-25 years old). The first case was reported by Hirayama in 1959. The patient often has insidious and slowly progressive weakness, followed by a spontaneous arrest within several years. Even though its etiology has not been clearly identified, the hypothesis of dynamically chronic compression of cervical spinal cord was proposed. This is demonstrated by magnetic resonance imaging (MRI) of the cervical spine which shows forward displacement of the posterior wall of the lower cervical dural canal. It leads to marked, often asymmetric, flattening of the lower cervical cord. Early diagnosis is key to successful management. Surgical decompression in some cases and physical therapy are the treatment options.[1-3] This is a report of a young Thai adult, presenting as a classic case of Hirayama disease.

Case Report

A 20-year-old man presented with two years' history of weakness and tremor in both hands (more severe on the right side). The symptoms progressed slowly over the years and seemed to accelerate for a period of six months. He also noticed mild tremor of both hands while holding objects or using his hand in fine motor tasks. There was no sensory or bulbar symptoms, accident or other preceding illnesses. Neurological examination showed mild atrophy and weakness of the right triceps, both forearm and hand muscles which were more affected on the right side (Figure 1). The hand grip was also mildly weak on both sides. Rare fasciculations were found at the right forearm. Irregular and coarse postural tremors, especially with finger extension, were present on both sides. Cranial nerve, sensations and reflexes were normal.

Nerve conduction studies revealed normal median, ulnar and radial nerves, in both motor and sensory components. Electromyography (EMG) showed few positive sharp waves and fibrillation potentials at the right triceps, extensor digitorum communis and first dorsal interosseous muscles. Several very large and polyphasic motor units with reduced interference pattern (more severe at distal muscles on the right side) were found at the right biceps, both EDC, right FCR, both FDI, both triceps. The abnormalities were more severe on the right side. Magnetic resonance imaging (MRI) of the cervical spine, in an initial neutral position revealed a focal atrophic change at the spinal cord at C4/5 to C6/7 levels, without an abnormal signal at the spinal cord. On the flexion sagittal view, the study showed enlargement and a crescent of high signal intensity of T2WI of the posterior epidural space at C3-C6/7 levels, with an epidural flow void in this space (Figure 2).

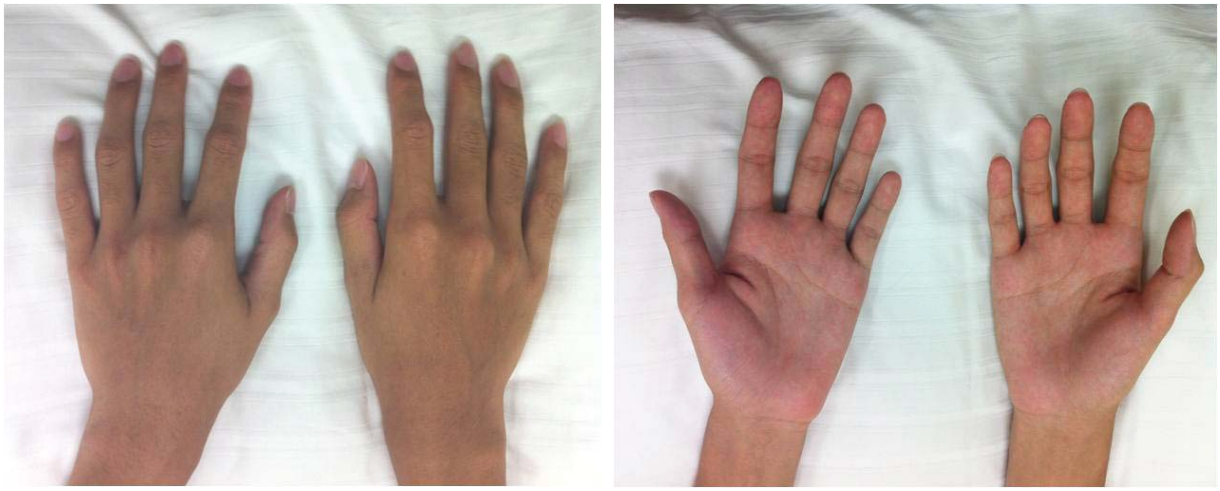

Figure 1: *Atrophy of bilateral intrinsic hand muscles. It was more prominent on the ulnar side and more severe on the right side.*

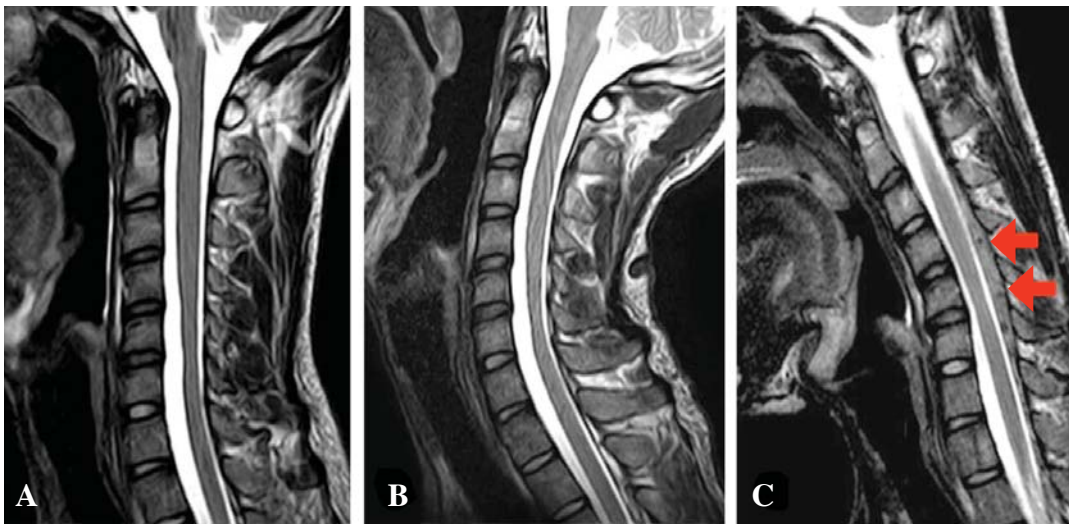

Figure 2: *A, B: Neutral position the sagittal T2-weighted MR image shows spinal cord atrophy at the C4/5 to C6/7 vertebral body, without enlargement of the posterior epidural space. C: The flexion MR image sagittal T2-weighted image, the study shows anterior widening of the posterior epidural space about C3-C6/7 level (red arrows) with a few flow void signals inside.*

The diagnosis of Hirayama's disease was made at that time, based on typical clinical characteristics and classic MRI findings on the flexion position. Propranolol was prescribed for relieving tremors. At the three-month follow up, the tremors had significantly improved. The atrophy and weakness of his forearm and hands had not progressed. A repeated MRI study revealed an unchanged widening of the posterior epidural space in the flexion position, with increased intensity enhanced after a Gadolinium injection (Figure 3).

Discussion

This case demonstrated the typical clinical findings of Hirayama disease. His clinical course was slowly progressive and predominantly involved in the right arm. The symptoms in many reported patients started on one side and spread to the other over several years, hence the term **'monomelic amyotrophy'.** The disease is often benign and does not cause severe disability. The weakness and atrophy are mainly found in muscles which are innervated by the eighth cervical and the first thoracic nerve roots, and less so by the seventh cervical roots. EMG almost always shows chronic denervation change in the affected limbs and sometimes in the asymptomatic limb. Acute or ongoing denervation is often found in active cases. This corresponds to the slow progressive degeneration of the anterior horn cells which leads to functional denervation and loss of motor neuron function. The pathology is limited to the relevant arm segments

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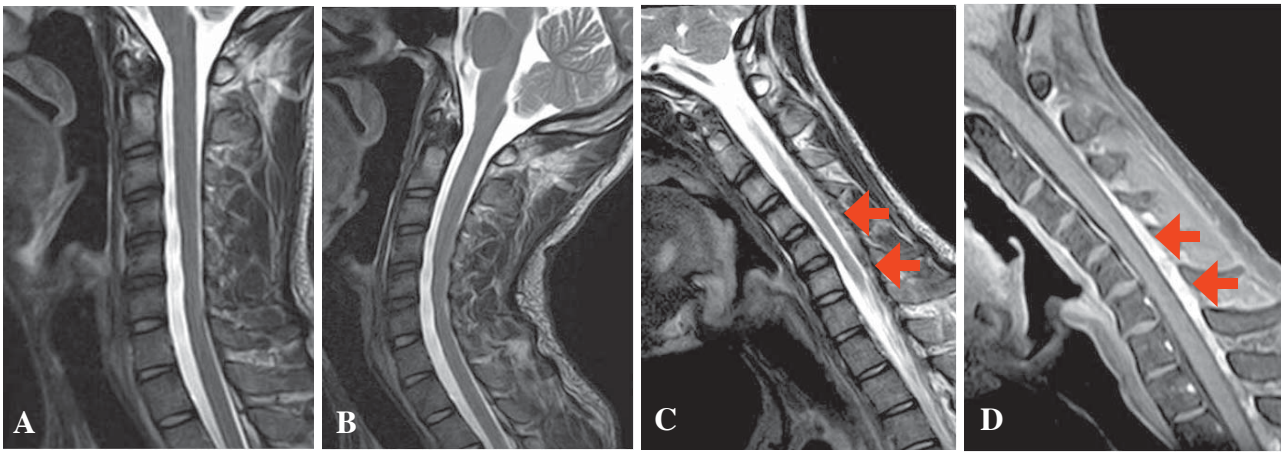

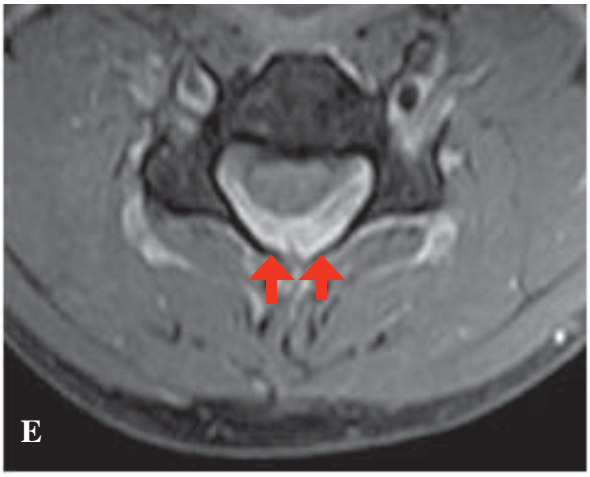

Figure 3: *A, B: Neutral position the sagittal T2-weighted MR image shows an unchanged spinal cord atrophy at the C4/5 to C6/7 vertebral body, without enlargement of the posterior epidural space.*
C- E: Unchanged anterior widening of the posterior epidural space about C3-C6/7 level (red arrows) with a few flow void signals inside on flexion MR image sagittal T2-weighted image and contrast enhancement after supportive treatment after about 3 months.

and both sides are involved. Interestingly, this disease is more prevalent in Asian populations and genetic association studies in Korean patients identifies KIAA1377 and C5orf42 as susceptibility genes for monomelic amyotrophy.[4,5]

The MRI and CT may show muscle atrophy.[1] Spinal cord flattening is an important finding in routine non-flexion MR images and should arouse suspicion. Detection of the focal spinal cord atrophy is another supporting diagnosis found in later stages of the disease.[1,6] Dynamic spinal cord compression at the neck flexion with a forward displacement of the posterior dura is an unequivocal finding in the progressive stage of this disease. The MRI imaging with extension and flexion of the cervical spine showed the relationship of posterior dura mater with the spinal cord and also the reduction in the anteroposterior diameter of the spinal cord.[7] A tight dural canal during flexion of the neck due to the disproportional length between the vertebral and the dural canal is the cause of Hirayama's disease.[6]

These findings are important for the diagnosis of this disease.[3,6-8] Morphologic changes on MR images should be correlated correctly with clinical and electromyographic data. Early diagnosis and supportive treatment is the gold standard to prevent progressive muscular weakness and atrophy.[7,8] However, the clinical course in most cases is benign. The progression of weakness is often stopped and becomes static. Therefore, conservative treatment is preferable. In some cases, a cervical collar may prevent neck flexion and stop disease progression.[9] Anterior cervical decompression and fusion is an option to prevent progressive neurological deficit in rapidly progressive cases and helps the patient to regain a better quality of life.[10]

Conclusion

Hirayama's disease is a juvenile non-progressive segmental spinal muscular atrophy. The correct diagnosis and physical therapy is the effective treatment in case focal atrophy of the spinal cord due to compression. Decompression and fusion is the treatment of choice.

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Noteworthy Cases of Viral Pneumonia

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Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality in all age groups throughout the world. Bacterial pneumonia is the most described, with Streptococcus pneumoniae being the most important pathogen in all age groups. Viruses are also recognised as important of CAP both in children and adults. Viral pneumonia accounts for 13 - 50% of single pathogen diagnosed community-acquired pneumonia cases and 8 -27% of mixed bacterial-viral pneumonia.[1-4]

In the past there were relatively limited ranges of diagnostic tools for viral pneumonia such as antibody detection only, thereby compromising the ability to identify the causative virus in the CAP cases. With the outbreaks of severe acute respiratory syndrome (SARS) and pandemic flu many more studies have focused their attention on the causative viruses in severe viral pneumonias. Developments in diagnostic tests (particularly nucleic acid amplification tests) have improved the ability to detect and clarify the culprit viruses and allow clinicians to understand and characterise the epidemiology of respiratory virus infections better. Significantly, these tests have illustrated how the role of viruses in CAP has been previously underestimated. Influenza virus type A&B are the most common aetiology of viral pneumonia in adults.[4] The other common pathogens are Respiratory syncytial virus (RSV), Adenovirus, Parainfluenza virus (PIV), Coronavirus, and human Metapneumovirus (hMPV). Among these groups the RSV, PIV and hMPV are part of Paramyxoviridae family.

We describe two cases that developed severe viral pneumonia associated with the novel virus in Paramyxoviridae family. These patients were admitted to the intensive care unit (ICU) at Bangkok Hospital Hua Hin because of severe respiratory failure. We hope that these two cases will raise awareness among clinicians to consider other significant causes of viral pneumonia other than Influenza.

Case Report # 1

A 59-year-old Thai man was transferred from the local hospital in Prachuap Khiri Khan Province with worsening respiratory failure. He initially presented to the local hospital with a history of hemoptysis, shortness of breath and low grade fever for 3 days. Five days earlier the only leading symptom was cough. The patient was an ex-smoker. He worked as a civil servant and only drank alcohol occasionally for social purposes. He incorporated a chicken farm into his garden at home. His previous medical history included asthma, hypertension, hypercholesterolemia, benign prostatic hypertrophy and gout. His regular medications were Symbicort, Perindopril, Rosuvastatin, Ezetimibe, Alfuzosin, Aspirin, Allopurinol and Colchicine.

At a local hospital he was treated for community acquired pneumonia with Ceftriaxone and Clarithromycin. Despite treatment with antibiotics, his condition had further deteriorated and he developed respiratory failure.

On arrival at Bangkok Hospital Hua Hin he was in distress with respiratory failure. His lips were dry. He was afebrile at 36.6 ^{o}C, tachypnea at 28 breaths per minute and had a blood pressure of 157/84 mmHg. His pulse rate was normal at 74 beats per minute. His oxygen saturation was 94% despite 10 LPM of oxygen supplement via a non re-breathing mask.

Chest auscultation revealed bilateral crepitation. There was bilateral diffuse patchy infiltration which predominated over the right side on the initial chest x-ray. Completed blood count showed Hb 14 g/dl, WBC 7430 cells/cm^3 (81 % Polymorphonuclear cells and 14% lymphocytes), and platelets 239000/mm^3. Other blood test results were Cr 0.77 mg/dL, ALT 66 U/L, AST 56 U/L, total bilirubin 0.6 mg/dL, total protein 7.29 g/dL, albumin 4.13 g/dL. His prothrombin time was only 13.1 sec. He had a low NT-ProBNP at 108 pg/mL. The anti-HIV antibody was non reactive. The nasopharyngeal swab for influenza type A/B screening test was also negative by Immunofluorescene immunoassay technique. Arterial blood gases analysis was obtained while the patient was on 10 LPM of Oxygen supplement via a non re-breathing mask. The results were pH 7.43, PaO2 83.0 mmHg, PaCO2 42.4 mmHg, HCO3 27.4 mmol/l (PF ratio is 138.3). The sputum gram stain only showed a few white blood cells, gram positive cocci and gram negative bacilli. The sputum acid fast bacilli smear was negative.

Non invasive ventilation (NIV) was initiated and the patient was given Imipenem, Levofloxacin and Oseltamivir while the team waited for the rest of the septic screening results. An echocardiogram was requested and this showed good left ventricular systolic function with left ventricular ejection fraction of 60%. There was no regional wall motion abnormality. Mild mitral regurgitation, trivial aortic regurgitation and trivial tricuspid regurgitation were detected. The estimated right ventricular systolic pressure was 39 mmHg. There was no pericardial effusion. The early and late ventricular filling velocities ratio was 1.15. Inferior Venacava had a normal diameter at 1.6 cm with a caval index of less than 50%.

On the second day following the ICU admission a repeated chest x-ray showed no improvement. A high resolution computerized tomography (HRCT) was arranged within the next 48 hours. In the meantime, a trial of high dose dexamethasone was given. The patient made a transient improvement in his symptoms with the first dose of dexamethasone but not with further doses. The HRCT revealed asymptomatic patchy consolidation which was more prominent at both upper lobes and at the left lower lobe. There was also diffuse ground-glass appearance over both lungs field without pleural effusion. At 96 hours post admission the hemoculture as well as sputum culture results were available and there was no growth on both tests. The polymerase chain reaction (PCR) test for tuberculosis was also negative. The respiratory panel test was carried out and this revealed a positive result for human Metapneumovirus.

Following the respiratory panel test result the antibiotics were stopped after a completion of 7 days course on the basis that a mixed bacterial and viral infection was still a possibility. The patient continued supportive treatment and made a reasonable recovery over the next 7 days of his hospital stay. The patient was discharged after a total of 15 hospital admission days. He came back to the follow up clinics and remained well in himself.

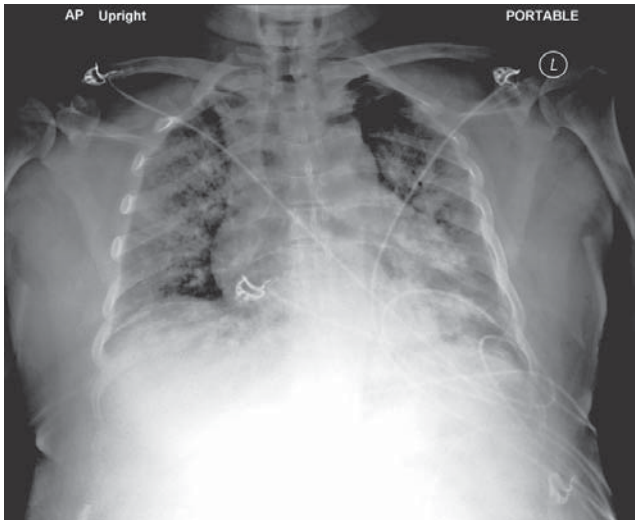

Figure 1: *Day 1, Bilateral diffuse patchy infiltration which predominated the right side.*

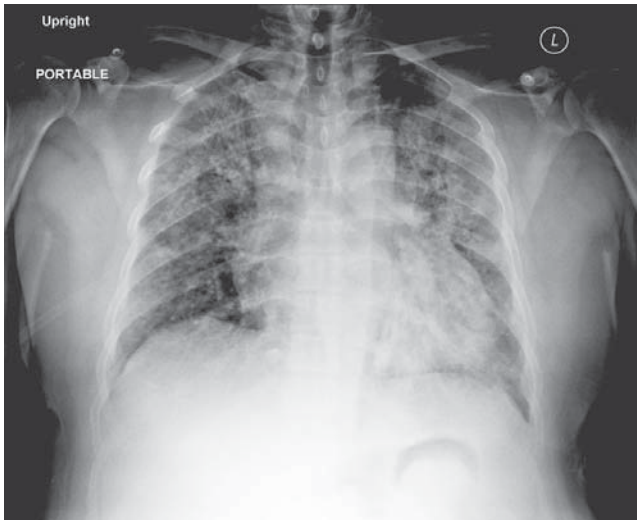

Figure 2: *Day 2, Unchanged infiltration in both lungs.*

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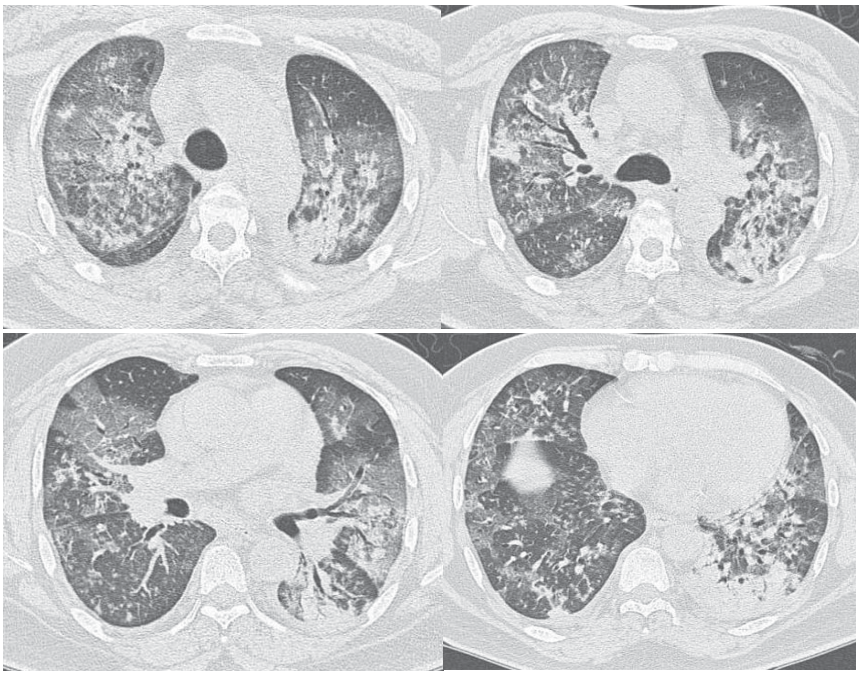

Figure 3: *The high resolution computerized tomography (HRCT) of the chest shows asymmetrical patchy consolidation. The change predominates over both upper lobes and the left lower lobe. There are diffuse ground-glass opacities at both lungs without pleural effusion.*

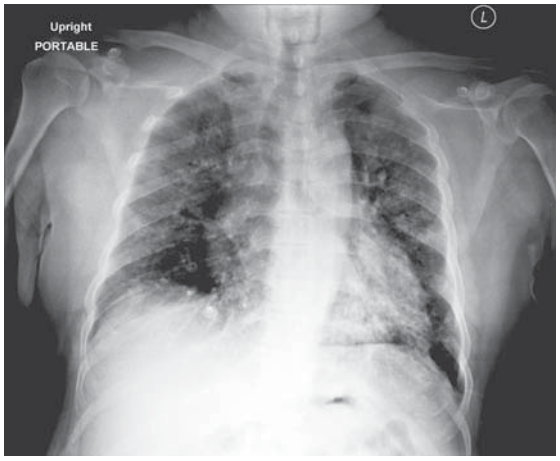

Figure 4: *Day 7, Decreased infiltration in both lungs.*

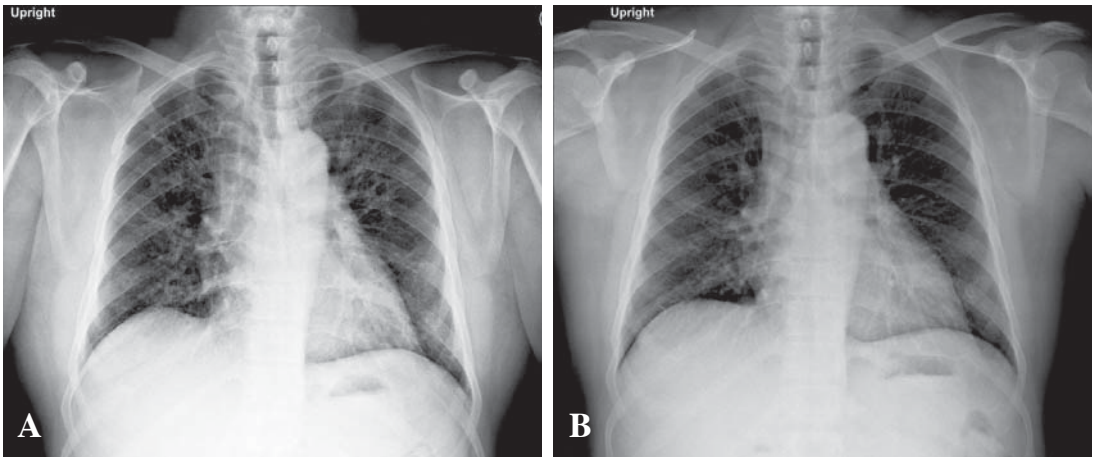

Figure 5: *A. Day 21, Further reduction in bilateral infiltration in comparison to the third chest x-ray. B. Day 50, Significant improvement of both lung fields in comparison with previous chest x-rays.*

Case Report # 2

A 66-year-old British man presented to the emergency room with shortness of breath for 2 days. The patient had been travelling in Thailand for a month before developing unusual chesty symptoms. He described fever, rigor, productive cough with greenish yellow sputum and difficulty in breathing for 48 hours before attending the hospital. His medical background included hypertension, chronic hypersensitivity pneumonitis with pulmonary fibrosis which was diagnosed in 2001. Prior to his trip he had fitness to fly test in the United Kingdom (UK). His baseline oxygen saturation in room air was 96% and he was prescribed an oxygen supplement to be used in the cabin during the flight.

The patient was an ex-smoker with only a 5 pack a year history. He only drank alcohol occasionally for social events. His regular medications were Bendroflumethiazide, Valsartan, Aspirin, and Simvastatin.

On examination the patient was significantly dyspnea with a respiratory rate of 44 breaths per minute. He had a fever of 38.5 ^{o}C. His blood pressure and heart rate were stable at 161/91 mmHg and 75 beats per minute consequently. His oxygen saturation was 97% despite 10 LPM of oxygen supplement via a non re-breathing mask. His chest x-ray revealed bilateral diffuse patchy infiltration. Complete blood count showed Hb 13.9 g/dL, WBC 8120 cells/cm3 (83.4 % Polymorphonuclear cells and 12.3% lymphocytes), and platelets 192000/mm^3. Other blood test were Cr 0.96 mg/dL, ALT 20 U/L, AST 25 U/L, total bilirubin 0.8 mg/dL, total protein 7.43 g/dL, albumin 4.21 g/dL, NT-ProBNP 251 pg/mL, Procalcitonin 0.06 ng/ml. The nasopharyngeal swab for influenza type A/B screening test was also negative by Immunofluorescene immunoassay technique. The sputum gram stain showed a moderate amount of white blood cells, few gram positive cocci and a very small number of gram negative bacilli.

Non invasive ventilation (NIV) was initiated and the patient was given Ceftazidime and Levofloxacin. The patient was transferred to ICU for close monitoring. Bedside echocardiogram revealed good left ventricular systolic function with a left ventricular ejection fraction of 72%. There was no regional wall motion abnormality. Trivial tricuspid regurgitation was detected. The estimated right ventricular systolic pressure was 41 mmHg. There was no pericardial effusion.

The early and late ventricular filling velocities ratio was 0.96. Inferior Venacava had a normal diameter at 1.56 cm with a caval index of less than 50%.

On the grounds of interstitial lung disease the patient was given dexamethasone in parallel with a broad antibiotic regime. The patient made a remarkable recovery despite a transient atrial fibrillation episode. He was weaned off the NIV within 48 hours of admission and became oxygen independent within 3 days. His hemoculture and sputum culture were reported as no growth. The respiratory panel test revealed a positive result for human Metapneumovirus.

The patient was safely discharged from the hospital on the fifth day of hospital admission. The patient returned to our follow-up clinic at day 10 and appeared to be very well in himself. The follow-up chest x-ray demonstrated a significant improvement of the bilateral infiltration in comparison to the first chest x-ray on admission.

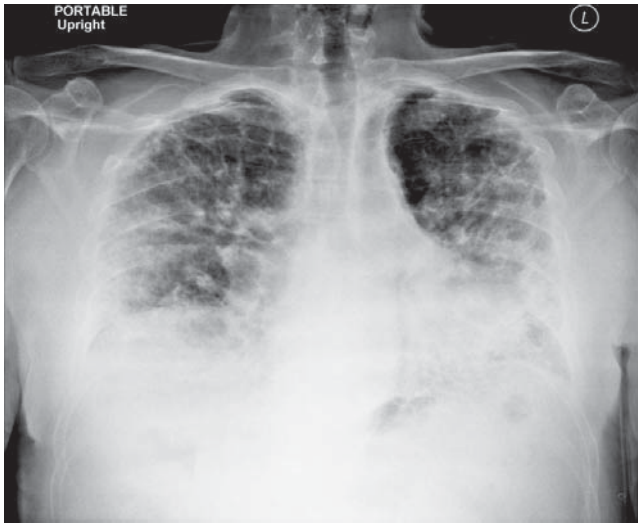

Figure 6: *Day 1, Bilateral diffuse patchy infiltrations which predominate over both lower lungs zone.*

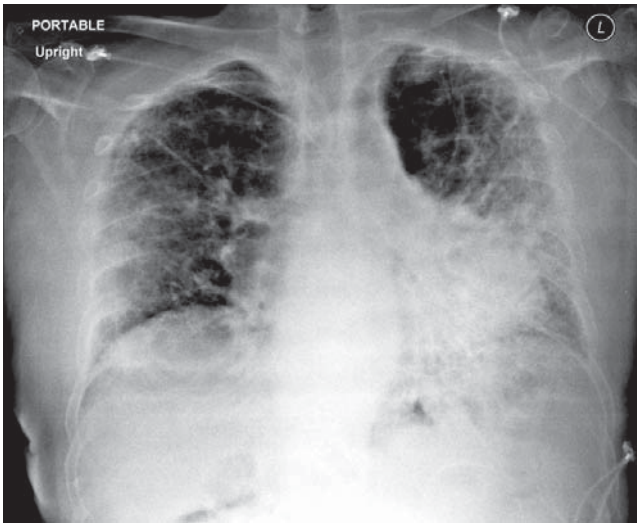

Figure 7: *On day 2, Unchanged bilateral infiltration appearance.*

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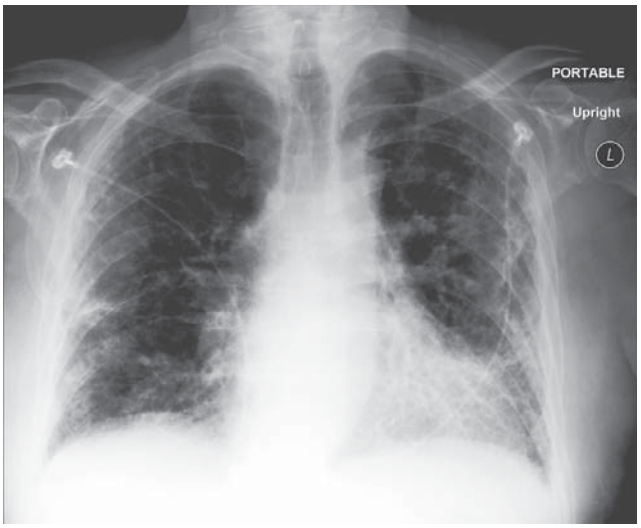

Figure 8: *Day 3, Decreased infiltration of both lungs in comparison to the previous films.*

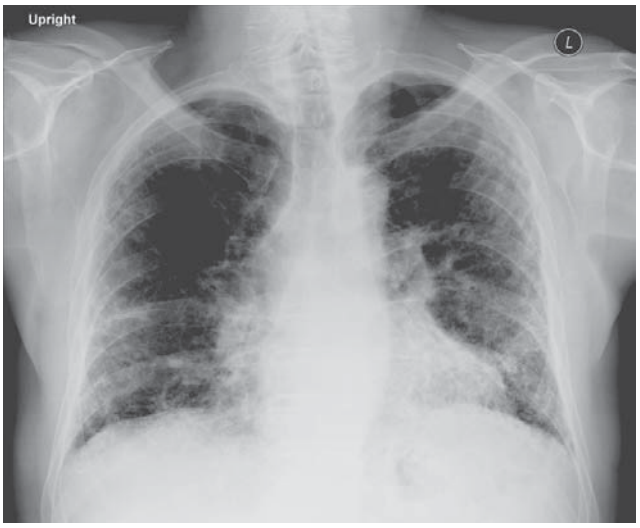

Figure 9: *Day 10, Further improvement in both lung fields.*

Discussion

Human Metapneumovirus (hMPV) was first discovered in the Netherlands in 2001. The virus is classified as the first human member of the Metapneumovirus genus in the subfamily Pneumovirinae of the family Paramyxoviridae. Retrospective serologic studies demonstrated the presence of hMPV antibodies in humans more than 50 years earlier.[5] In their initial 2001 report, van den Hoogen et al demonstrated 100% seropositivity by age 10 years in 28 young children in the Netherlands. Similar studies worldwide have confirmed this high rate of seroprevalence in early childhood.[6, 7]

hMPV is distributed worldwide and there is extensive evidence of previous exposure to the virus from various studies around the world. Although there is a high prevalence of antibodies against the virus in all age groups the peak incidence is found in pediatric and elderly patients. hMPV is the second most common cause of lower respiratory tract infection in young children after RSV. However it is worth nothing that the group of patients with chronic pulmonary disease such as COPD tend to develop more severe features of hMPV infection.[8-10] The cases of severe respiratory failure or even death from hMPV are reported.

hMPV is genetically most similar to the virus in the Pneumoviridae subfamily, of which RSV is a prominent member. hMPV has an identical gene order to the avian pneumovirus (aMPV), which also belongs to the Metapneumovirus genus in Pneumoviridae subfamily.[5] The virus was therefore named human Metapneumovirus after its close relatives in birds. It is an enveloped, negative single-strand RNA virus. Phylogenetic analysis identified two subgroups of hMPV, subgroup A and B. Both subtypes can co-circulate simultaneously, but during an epidemic one subtype usually dominates. hMPV also has a seasonal distribution comparable to that of the influenza virus which tends to strike in the late winter and early spring.[11]

Like many other viruses, hMPV infection produces incomplete immunity therefore re-infection is not uncommon and can occur at all ages. Transmission is by direct or close contact with contaminated secretions, which may involve saliva, droplets, or large particle aerosols. The incubation period is approximately 3 to 6 days.[12]

The signs and symptoms of hMPV infection are generally indistinguishable from those caused by RSV. Like RSV, hMPV has a tropism for the respiratory epithelium. The patient may be asymptomatic. The symptoms may range from mild upper RTI symptoms to severe pneumonia. Most patients present with cough, dyspnea, and fever. Some studies also described a symptom of mononucleosis-like illness. Other symptoms such as productive cough, sore throat, conjunctivitis, and otitis media are also reported.[13] Interestingly RSV or Influenza-infected adults are likely to experience fever more than adults with hMPV infection. In contrast, the patients with hMPV infection are more likely to experience hoarseness and wheezing symptoms than the other 2 viruses.[10] However compared to RSV and influenza, adults with hMPV infection have similar rates of ICU admission, mechanical ventilation, length of stay for hospitalization and length of stay in ICU.

A general respiratory virus culture obtained by nasal wash or nasopharyngeal swab should be performed in concerned patients with clinical symptoms of LRTI.

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Virus culture, however, is relatively difficult, because hMPV grows slowly in conventional cell culture.[14] The rapid culture technique known as shell vial amplification can produce results within 72 hours. The other detection techniques that have been developed include identification by reverse transcriptase-polymerase chain reaction (RT-PCR) assay, enzyme immunoassay (EIA), and enzyme-linked immunosorbent assay (ELISA). Among the antigen detection test RT-PCR is the most sensitive method for diagnosis of hMPV infection.

Conclusion

In summary, hMPV tends to cause only mild illnesses which are self-limiting, but the infections can be severe in high risk groups (elderly patients over 65 years, patients with cardiac or pulmonary diseases and immunocompromised patients). hMPV infection has been increasingly more acknowledged over the last few years; this virus should be considered as a causative agent in patients with respiratory failure in the ICU.

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Extracorporeal Membrane Oxygenator (ECMO) for Life Support in Fulminant Myocarditis

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Keywords: extracorporeal membrane oxygenator, ECMO, renal replacement therapy, myocarditis, enterovirus 71, renal failure, children

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Fulminant myocarditis refers to acute myocarditis with abrupt onset of severe cardiogenic shock and circulatory collapse. Once regarded as a disease with uniformly high mortality, fulminant myocarditis is now a potentially treatable condition, thanks to advances in intensive care and mechanical circulatory support. We report our first pediatric case of fulminant myocarditis rescued by extracorporeal membrane oxygenator (ECMO) and continuous renal replacement therapy (CRRT).

Case Report

A 3-year-old boy presented to the outpatient department (OPD) at Bangkok Hospital with high fever, malaise and vomiting for 2 days prior to admission. He had no underlying disease except for a history of cow milk allergy. His brother was diagnosed with hand foot and mouth disease 1 week prior to the admission.

Physical examination

A well nourished male patient, febrile, good consciousness but appeared tired:

- Body weight: 14 Kilograms (kg).
- Vital signs: Blood pressure (BP) 118/88 mmHg, Heart rate (HR) 163 beats per minute (bpm), Respiratory rate (RR) 26 breaths per minute, Body temperature 37.7 °C.
- Head, Eyes, Ears, Nose, Throat (HEENT) examination: not pale, no icteric sclera, pharynx not injected.
- Heart: tachycardia, no murmur, no gallop.
- Lungs: no retraction, good air entry.
- Abdomen: soft, no hepatosplenomagaly.
- Skin: small area of blisters at plantar area.
- Other: no cervical lymph nodes detected.
- Neurosigns: stiff neck negative.

Investigations on admission

- Complete blood count (CBC): White blood cell (WBC) 21,120 cells/mm3 (Neutrophils 71.3%, Lymphocytes 24.4%, Monocytes 3.9% Eosinophils 0% Basophils 0.4%), Hemoglobin (Hb) 14.1 g/dL, Platelet 529000/mm3
- Urea Nitrogen (BUN) 17 mg/dL (8-20), Creatinine (Cr) 1.36 mg/dL (0.6-1.5), Electrolytes; Sodium (Na+) 130 mmol/L, Potassium (K+) 4.69 mmol/L, Chlorine (Cl-) 90 mmol/L, Total CO2 15.1 mmol/L, Aspartate Aminotransferase (AST) 153 U/L (0-40), Alanine Aminotransferase (ALT) 72 U/L (0-40), Albumin 3.89 g/dL, Creatine phosphokinase (CPK) 440 U/L (15-220), Creatine Kinase-MB (CK-MB) 18.37 ng/ml (0-3), Troponin-T 2,233 ng/L (0-100), Lactate 14 mmol/L (0.5-2.2)
- Echocardiogram (Echo) showed left ventricular ejection fraction (EF) of 30% in the OPD.

Hospital course

The patient developed cardiac arrest at the OPD after intravenous fluid was given. After cardiopulmonary resuscitation (CPR), he was transferred to the pediatric intensive care unit (PICU) with continuous intravenous inotropic drugs (Adrenaline 2 microgram per kilogram per minute (mcg/kg/min), Dopamine 20 mcg/kg/min and Dobutamine 20 mcg/kg/min). Bedside echocardiogram revealed in the PICU showed further deterioration of left ventricular EF to 12%. Although adrenaline, dopamine and dobutamine were continuously administered, a second episode of cardiac arrest followed admission to the PICU and the patient was resuscitated for another 5 minutes. Physical examination showed marked tachycardia (HR 220 /bpm, sinus tachycardia) and frank pulmonary edema. Electrocardiogram (EKG) revealed sinus tachycardia with no other significant abnormality (Figure 1). Chest x-ray revealed the normal size heart and pulmonary edema (Figure 2A). Elevated troponin-T at 2,233 ng/L (normal 0-100) and CPK at 8.37 ng/ml (normal 0-5) were found and fulminant myocarditis was diagnosed. Because of continuing deterioration, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was placed 12 hours after admission. Rotaflow centrifugal pump and Quadrox iD oxygenator (Maquet Inc, Rastatt, Germany) were used in this case.

Blood and secretions were sent for viral studies. Blood test for Enterovirus 71 (EV71) IgM was positive. Lumbar puncture was not done due to the unstable clinical status. Intravenous immunoglobulin (2 g/kg) and broad-spectrum antibiotics were given. Supportive treatment was continued. Troponin-T was 4,469 and 3,301 ng/L (0-100) at 48 and 72 hours after admission, respectively. Serum AST and ALT increased to 5,651 and 2,281 U/L at 48 hours after admission. The patient developed acute renal failure with rising blood urea nitrogen (BUN = 88.3 mg/dL) and creatinine (3.6 mg/dL) on the 3rd day of admission. Continuous renal replacement therapy (CRRT) as a continuous venovenous hemofiltration (CVVH) modality with simultaneous pre and post-dilution fluid replacement modes by Prismaflex® machine (GAMBRO company, Sweden) was incorporated into the ECMO circuit by connecting a CRRT inlet line after the centrifugal pump and its outlet line before the oxygenator (Figure 3).

Both machines functioned adequately and there were no significant changes in the pressures of the ECMO circuit after the introduction of the CRRT device, thus achieving the preset negative fluid balances and normalization of the serum BUN and creatinine. We ran both machines for three days and stopped the CRRT one day before weaning the patient off the ECMO. Milrinone and sodium nitroprusside were administrated during the circulatory assisted period. Weaning of ECMO was started after improvement of the EF to 30% and successful decannulation and removal of ECMO was performed on the 7 day of admission with stable hemodynamic status. The echocardiogram demonstrated further improvement of the left ventricular EF to 65% during the next 7 days. Serial chest x-rays showed resolution of pulmonary edema (Figure 2B-D). Serum AST, ALT and creatinine also improved to 46 U/L, 145 U/L and 0.38 mg/dL, respectively on the 10th day of admission. The patient was fully awake and had good cognitive function after the treatment although he developed central apnea and could not be weaned off the ventilator support. Brain stem injury from the EV71 virus was suspected. The patient was transferred to Chulalongkorn hospital for long-term respiratory management. The patient was discharged 3 and half months after the initial admission with tracheostomy (no home ventilator). The left ventricular EF was normal at the time of discharge.

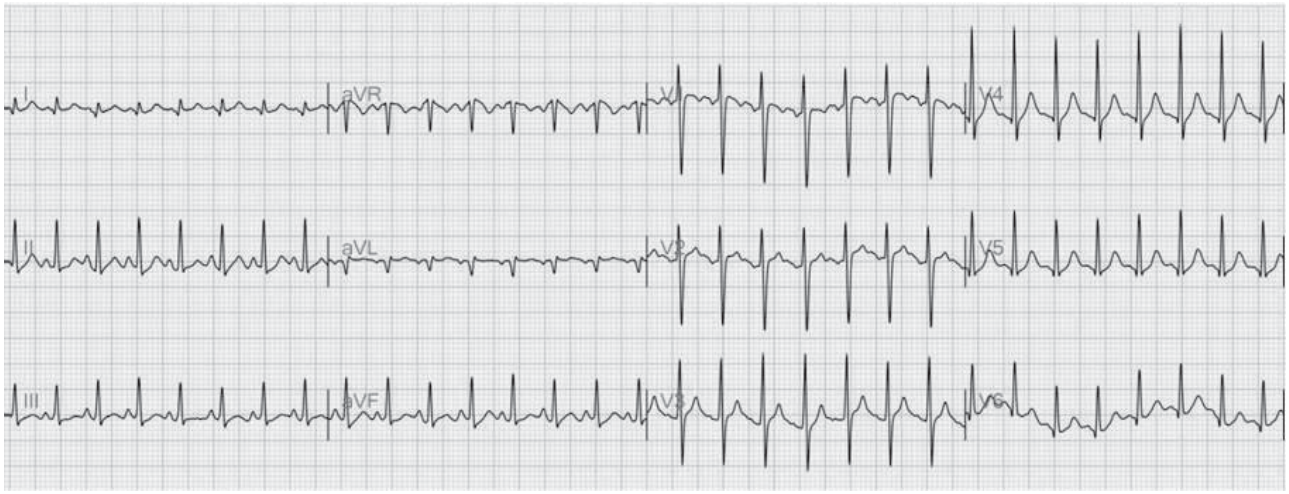

Figure 1: *Electrocardiogram on admission shows sinus tachycardia.*

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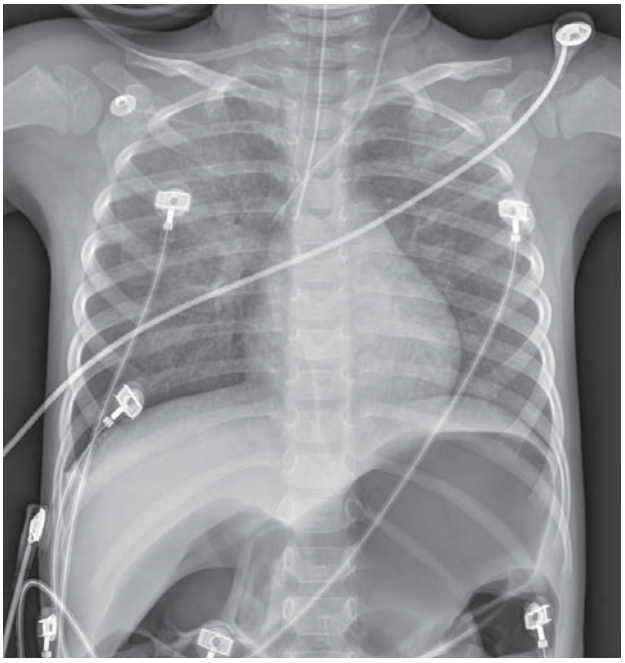

Figure 2A: *On January 20, 2013 at 15:21, a chest x-ray AP supine position reveals early pumonary edema. Heart appeared normal. The tip of the catheter was in SVC, endobroncheal tube is in place.*

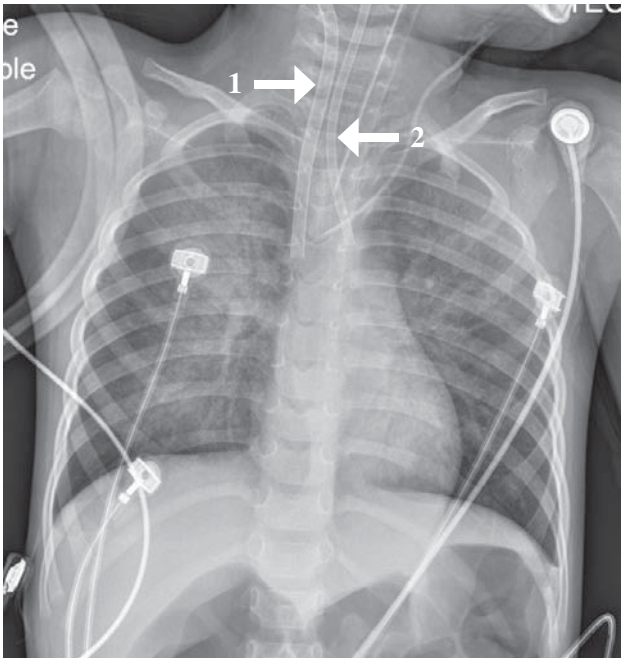

Figure 2B: *On January 23, 2013 at 21:41, a chest x-ray AP supine position and ECMO venous to arterial connection. The tip of catheter 1 is in SVC. The tip of catheter 2 is in the aortic arch. Progressive pulmonary edema developed.*

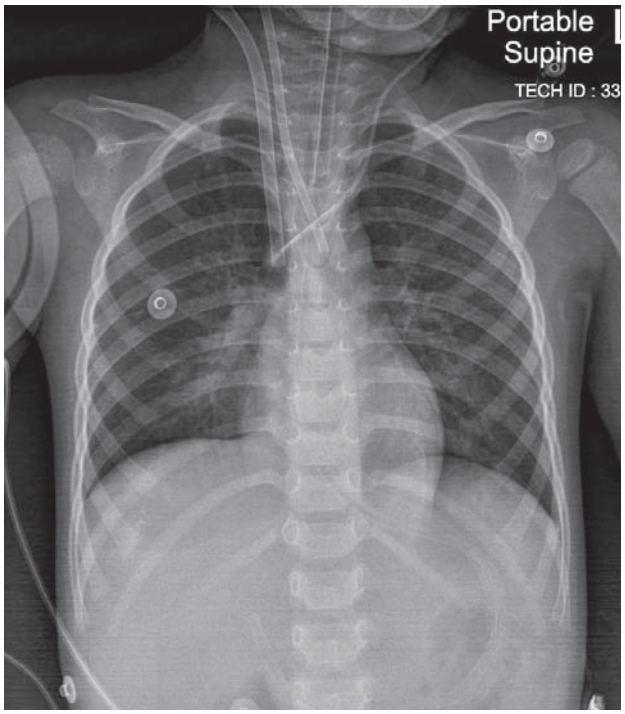

Figure 2C: *On January 24, 2013 at 15:38, a chest x-ray AP supine position reveals improvement of pulmonary edema.*

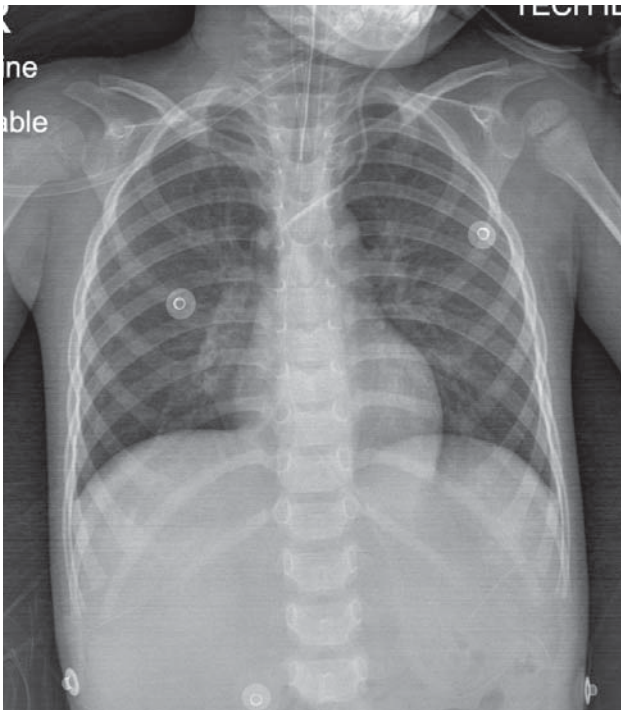

Figure 2D: *On January 27, 2013 at 5:30, a chest x-ray AP supine position and post removal ECMO reveals heart and lung appear normal.*

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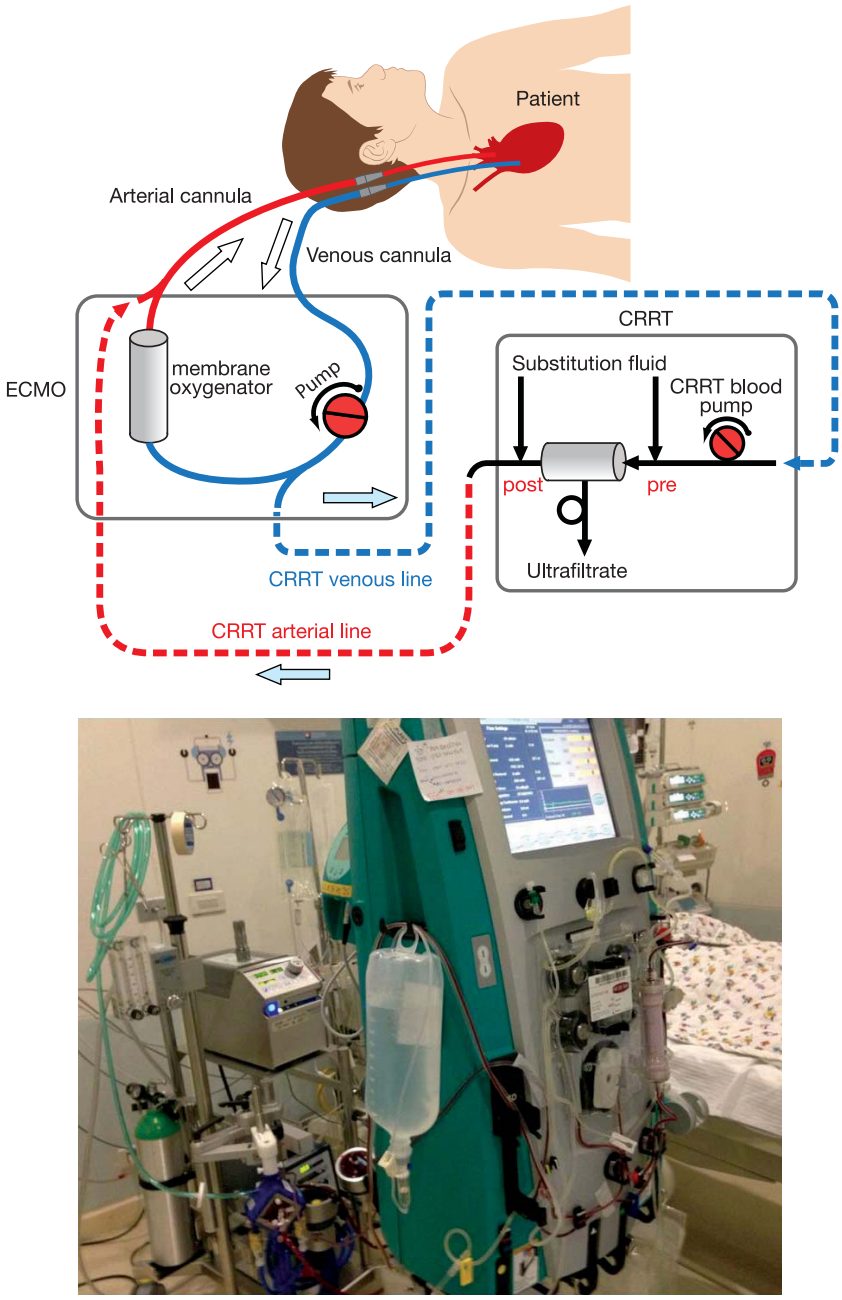

Figure 3: *Diagram of venous-arterial connection with continuous renal replacement therapy (CRRT) incorporated into the circuit.*

Discussion

Hand-foot-and-mouth disease (HFMD) is caused by a group of enteroviruses, most commonly coxsackievirus A 16 (CA16) and enterovirus 71 (EV71). In general, the disease is mild and self-limited except in the case of EV71 infections, which may result in serious complications such as myocarditis and encephalitis.[1] In Thailand, the prevalence of EV71 was high during 2008-2009 and has been increasing since 2011.[2] There are currently no approved vaccines or antiviral therapies for the prevention or treatment of EV71 infection. Acute viral myocarditis is caused by viral induced infiltration of inflammatory cells into the myocardium. Fulminant myocarditis is characterized by rapid onset of pump failure that sometimes leads to death by cardiogenic shock.[3] In our patient, rapid progression of hemodynamic instabilities was observed after admission despite maximal medical therapy necessitating a rescue by ECMO. Laboratory studies confirmed the EV71 infection in addition to history of recent HFMD in his brother.

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The overall survival rate for children with acute myocarditis is about 73% and is lower in patients with fulminant myocarditis.[4] A number of reports suggest that mechanical circulatory support may be used to successfully bridge children with acute fulminant myocarditis to recovery or transplantation.[4-7] The survival rate in patients with fulminant myocarditis undergoing ECMO support are 67-82%.[5-7] In this patient, progressive reduction of EF and hemodynamic instability were observed despite maximal medical treatment. Laboratory investigations also showed severe metabolic acidosis, increased cardiac enzymes levels and decreased renal function. Venoarterial ECMO was then used to successfully salvage the patient despite multiple organ failure. End-organ dysfunction is associated with increased mortality in pediatric cardiac patients requiring extracorporeal support.[6]

Acute renal failure while on ECMO is associated with a decreased risk for survival in pediatric cardiac patients.[6,8] In the absence of primary renal disease, this is usually transient and would not progress to chronic renal failure after concurrent use of CRRT with ECMO.[9] In our patient, the renal function recovered and his serum creatinine was normal before transfer. No complication such as circuit clotting was detected and only one filter was used during CRRT with ECMO. One study reported that the introduction of a CRRT device into the ECMO circuit, similar to what we used in our patient, was safe and effective.[10]

Brainstem encephalitis caused by EV71 in children is a serious complication. Magnetic resonance imaging (MRI) scans can provide important information for clinical evaluation and treatment.[11] In our case, the patient was also affected by central respiratory failure from brainstem encephalitis and required prolonged mechanical ventilation.

Conclusion

Viral myocarditis is an important cause of cardiogenic shock in children outside of the neonatal period and can be fatal if left untreated. No specific treatment is available at this time and supportive treatment is the standard treatment to support the circulation while waiting for a spontaneous recovery. Application of ECMO with or without renal support in selected patients can be life-saving in children who develop refractory shock despite maximal medical treatments.

Acknowledgement

We would like to thank Dr Anthony Chang (Children Hospital Orange County, California, USA) and Anthony Rossi (Miami Children Hospital, Florida, USA) and Dr Kriengkri Tantivongsekosi (Siriraj Hospital, Bangkok, Thailand) for their advice in the management of pediatric ECMO in this patient.

Contributors

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Case Report

Combination of adult and pediatric fiberoptic bronchoscopy in bronchial cleaning in smoke inhalation-induced respiratory distress syndrome

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In the practice of medicine, new technologies are developed and old models are improved upon. As new technologies are integrated into standard practices, further innovation occurs to meet situational demands when patients have critical needs; what follows illustrates such an adaptation using modern bronchoscopic instruments.

Smoke inhalation-induced respiratory distress has been known to cause high mortality among victims of fire accidents, especially for those who have been trapped inside burning buildings. In the aftermath of a fire accident, several victims died as a result of smoke inhalation-induced respiratory distress. We have effectively saved fire victims by scrubbing their bronchial airways using a fiberoptic bronchoscope to improve ventilation and oxygenation.

However, with a standard-sized bronchoscope it is not possible to reach smaller bronchi, so we combined the use of a pediatric bronchoscopy to the procedure in order to better clean the debris and secretions.

A successful case is reported below:

A 28-year-old patient, male, was admitted due to smoke inhalation and consequently developed pneumonia and conjunctivitis. Upon initial assessment, the patient presented with difficulty in breathing, chemical corneal burn of both eyes, coryza with mucus discharge and black ash debris in the pharynx. No wheezing was noted.

The patient was admitted to the Intensive Care Unit. Initial x-rays revealed diffuse interstitial opacity in both lungs, likely indicating pneumonia. Mild cardiomegaly was noted and was probably related to suboptimal inspiration. Subsequent x-rays revealed increased infiltration of the lungs as in Acute Respiratory Distress Syndrome (ARDS). The patient was intubated. Fiberoptic bronchoscopy was suggested to enable further investigation. The initial bronchoscopic visualization via endotracheal tube revealed burned nasal cavity and epiglottis, burned bronchial mucosa and thick secretions in every single airway. Debris and pus were removed through bronchial washing. Due to the narrowed condition of the bronchi, an innovative technique combining the use of an adult and pediatric fiberoptic bronchoscopy was performed in order to reach through the deeper areas of the lungs thus thoroughly cleaning out pus and debris. This helped to improve the patient's oxygenation. Cefditoren was administered to control the infection.

Subsequent bronchoscopy procedures were done with the goal of removing debris and secretions inside the burned lungs, to decrease infiltration, to improve the patient's breathing and to prevent further complications.

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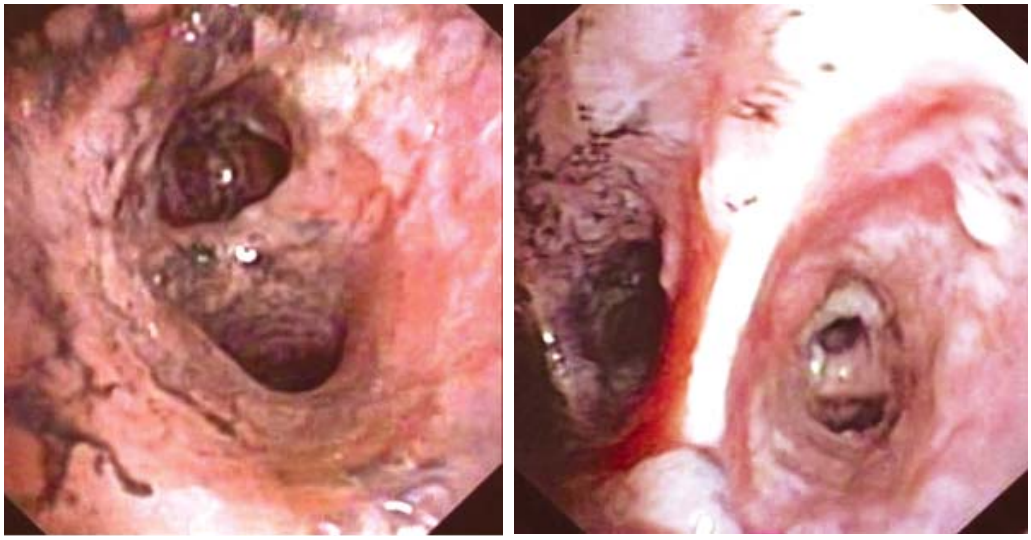

Figure 1 and 2: *View of patient's lungs during first session of fiberoptic bronchoscopy.*

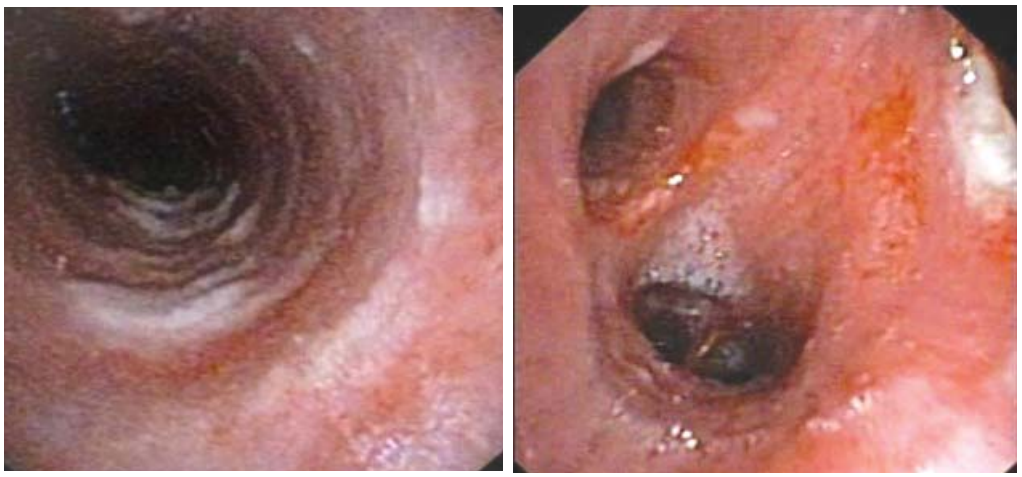

Figure 3: *View of patient's lungs after first session of fiberoptic bronchoscopy.*

Figure 4: *Bronchoscopic view of patient's lungs after fifth consecutive FOB session.*

Upon the fifth consecutive day of performing this bronchoscopic procedure, the patient went through visualization and washing without desaturating. Extubation was done without complications.

Discussion

In the USA, more than 1 million burn injuries occur every year. Although the survival rates from burn injuries has increased in recent years with the development of effective fluid resuscitation management and early surgical excision of burned tissue, the mortality rates of burn injury cases is still high. In these fire victims, progressive pulmonary failure and cardiovascular dysfunction are important determinants of morbidity and mortality. The morbidity and mortality increases when the burn injury is associated with smoke inhalation.[1]

In 2000, Alpard et al.[2] developed a predictable, dose-dependent, clinically relevant model of severe respiratory failure associated with a 40% total body surface area, full-thickness (third-degree) cutaneous flame burn and smoke inhalation injury in adult sheep. Development of respiratory distress syndrome (RDS) by smoke and cutaneous flame burn injury depends on the smoke inhalation dose. A combination of 36 breaths of smoke and a 40% total body surface area (third-degree) cutaneous flame burn injury can induce severe RDS (PaO2/FIO2 < 200) within 40 - 48 hours. All animals developed RDS in 24 - 30 hours, and none survived the experimental period. When all other techniques fail to remove secretions, the use of a fiberoptic bronchoscope has proven to be of benefit. In addition to its diagnostic functions, bronchoscopy retains important therapeutic applications. Copious secretions encountered

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in patients with inhalation injuries may require repeated bronchoscopic procedures when more conservative methods are unsuccessful. The modern fiberoptic bronchoscope is small in diameter, flexible, and has a steerable tip which can be maneuvered into the fourth or fifth generation.

Conclusion

This case is likely to be the first reported use of the combined adult and pediatric fiberoptic brochoscopy technique to effectively remove debris inside a burned lung airway. A combination of further controlled experimental studies, as well as anecdotal evidence from the frontline of emergency rooms and pulmonary centers will serve to continue the development of innovative techniques. This in turn will drive the need for technological advances in medical instruments and the integration of the resulting methodologies into standard treatment procedures.

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Transjugular Intrahepatic Portosystemic Shunt (TIPS)

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Surgery for portal hypertension began in 1877, with Nicolai Vladirmirovich who performed the first portacaval anastomosis. There was little clinical success until Blakemore and Whipple between the 1920's and 1940's: the mortality rate ranged from 25-40%. Hepatic encephalopathy was a clinical problem. In 1960, Warren and collegues performed a distal splenorenal shunt, which reduced the incidence of hepatic encephalopathy to an acceptable level.[1] Other complications after undergoing successful portacaval anastomosis included ammonia toxicity, responsible for the neuropsychiatric changers seen in patients with impending hepatic coma[2] and progressive hypersplenism, inducing thrombocytopenia and leucopenia which can become life-threatening after a shunt procedure.[3] Transjugular intrahepatic portosystemic shunt (TIPS) is a less invasive, non-surgical procedure basis which minimizes complications in the treatment of portal hypertension.[4] The procedure is mostly performed by Interventional Radiologists (IR) and is effective in selected cases of cirrhosis and portal hypertension.

Case Report

A 51-year-old man, a known case of alcoholic cirrhosis, was hepatitis B virus (HBV), hepatitis C virus (HCV), human immuno-deficiency virus (HIV) positive with CD4 normal, and gastric varices. The abdomen showed a small liver with ascites. There was evidence of gastric varices. Previous operations included gastric surgery. He underwent glue injections on more than one occasion. The computed tomography (CT) of the whole abdomen showed liver cirrhosis with multiple varices postop multiple glue injections of gastric varices (Figure 1). It showed patency of hepatic vein, portal vein and inferior vena cava (IVC). There was evidence of splenomegaly and large amount of ascites, as well as multiple gallstones and some sand stones. The patient was referred to IR for consideration to undergo TIPS to correct previous failures to control upper gastrointestinal bleeding and refractory ascites. TIPS was performed under digitalsubtraction angiography (DSA) via the right internal jugular accesswith 12-F introducer sheath. After identifying the right branch ofthe hepatic vein, the venography was done with the wedge injection technique to demonstrate both right hepatic vein and right portal veins. Using the Rosch-Uchida needle system, the branch of the right portal vein was punctured after multiple attempts. Finally, the portal vein was reached by the guide wire and a new tract between the hepatic vein and portal vein was created. Balloon dilatation wasdone using the Angioplasty balloon, 10 mm diameter and 6 cms long. Then the wall stent (Nitinol endoprosthesis, 12x90 mm) was inserted.Post stenting, balloon dilatation was done again. The venographywas done through the newly created shunt and showed bloodflow from the main portal vein via the shunt into the hepatic vein and systemic circulation with no delay or obstruction. The patient tolerated the procedure well.

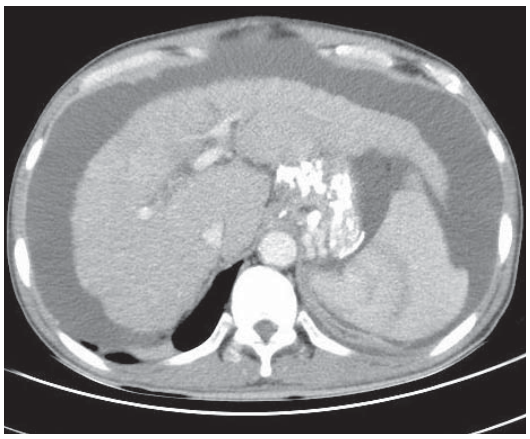

Figure 1: *CT of the whole abdomen shows liver cirrhosis with multiple gastric varices post multiple glue injections.*

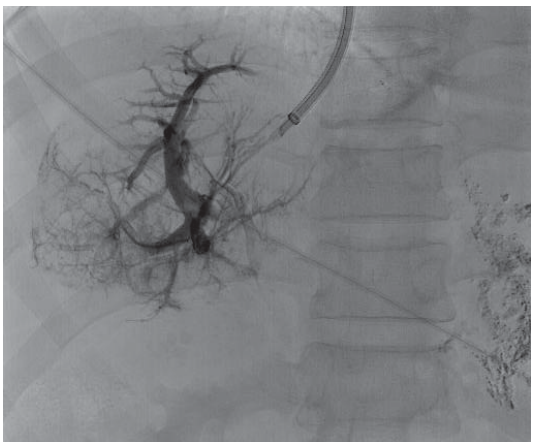

Figure 2: *Transjugular to the right atrium, the catheter tip is in the right middle hepatic vein. Well demonstrated right middle hepatic vein and its distribution.*

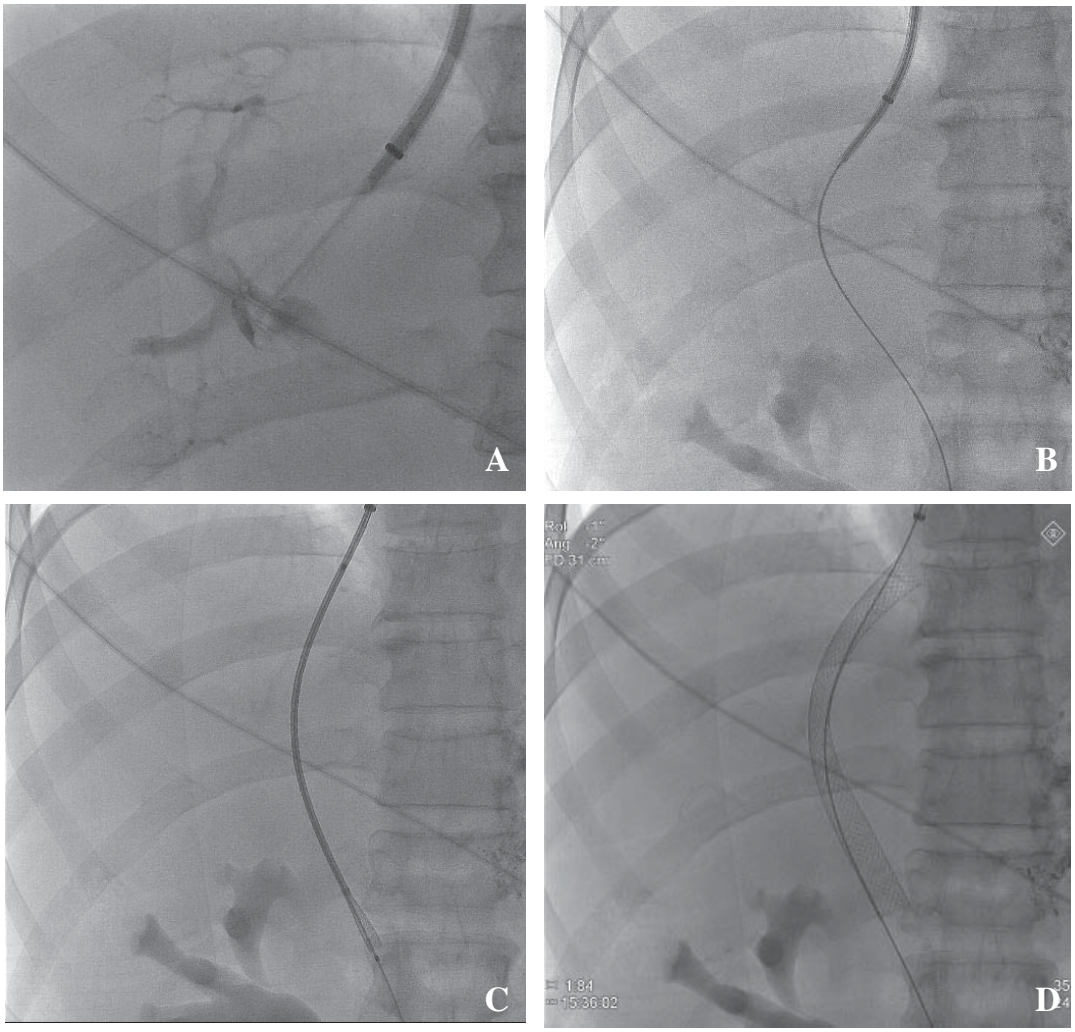

Figure 3: *A. Needle punctured the hepatic vein and tipped in branch of portal vein. Venogram of intrahepatic portal veins are well visualized.*
B. The guide wire passed through the catheter under fluoroscopy. The guide wire passed into the portal vein.
C. The intraluminal stent is inserted then the catheter and distal end of the stent is in the portal vein. The proximal end is in the right middle hepatic vein.
E. The 12 mm diameter stent is deployed in the proper position after balloon angioplasty was done.

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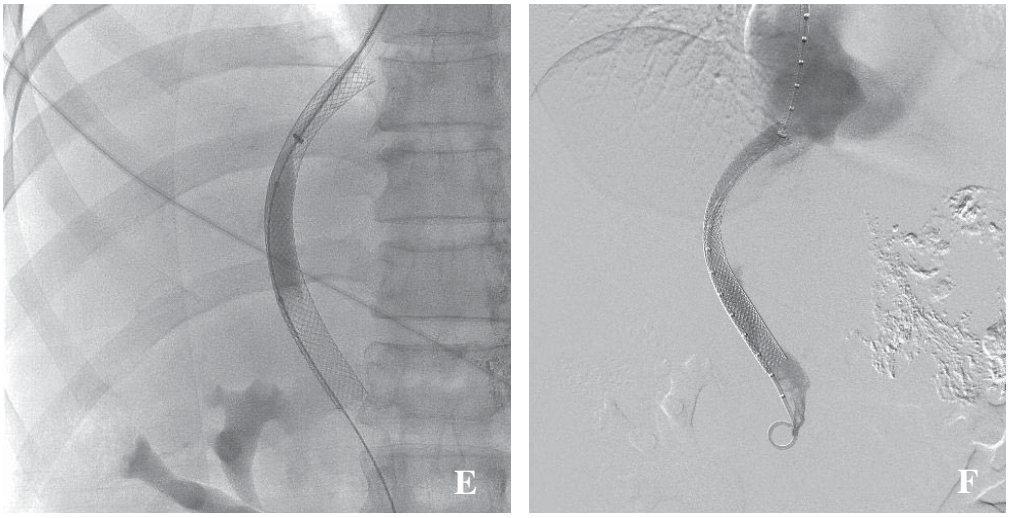

Figure 3: *E. The stent is again expanded using 10 mm balloon dilatation.*
F. The contrast of the whole stent is well visualized.
The contrast flows through the portal vein with well visualized opacities in the right atrium.

Discussion

Portal hypertension is a serious complication of liver disease leading to the troublesome complication of bleeding esophageal varices. Portacaval anastomosis was the treatment of choice in the past with ammonia toxicity the untoward side effect of surgery. TIPS is a less invasive management which reduces such complications. The qualified interventional radiologist is able to correct the problems with a satisfactory result.

This procedure is a minimaly invasive technique to reduce the portal pressure by creating a connection between the portal and systemic circulation via percutaneous approach, in the majority of cases we perform via the transjugular vein. The shunt patency is maintained by placing an expandable metal stent. In 1969, Rosch created the connection between the portal vein and the hepatic vein via the jugular vein to create a functional shunt using a silicone tube and a silastic stent. But results were poor due to stent occlusion within a short period of time, until Gore via tips were approved by the Food and Drug Administration (FDA) which expanded polytera-fluoroethylene graft lining. These reduce occlusion by the prevention of bile and mucin penetration and growth of the tissue into endoprosthesis.

Indications

1. Uncontrolled acute varices or recurrent bleeding after medical treatment and sclerotherapy.
2. In case of liver hepatoma;
   i. Reduction of intrahepatic morbidity.
   ii. On waiting list for liver transplantation.
3. For palliative treatments to prolong life in case of inoperable and non-nourished vascular lesser degree neovascular or hepatic tumors.

Contraindication

1. Severe hepatic encephalopathy or liver failure.
2. Repeat hepatic failure.
3. Portal vein thrombosis.
4. Polycystic hepatic disease.

Patient preparation

1. Blood examination for coagulopathy. Platelets are routinely administered when platelet counts are less than 50000 mm^3, fresh frozen plasma is used as well.
2. Prophylactic broad-spectrum antibiotics are given.
3. Anatomical structures of liver vascular apply. Both portal vein and hepatic vein are established. The patency of the portal vein is essential and doppler ultrasound should study portal flow end pressure.

MRI of the liver should be performed to evaluate the hepatic vein, portal vein and biliary tract.

Technique

1. Anesthesia by short acting sedation or general anesthesia.
2. Special tips commercial sets are available.
3. In the majority of cases, right jugular vein approach by using ultrasound guidance is recommended.
4. A 5F catheter is wedged in a peripheral branch of the right or middle hepatic vein and carbon dioxide (CO2) gas to opacity portal vein.

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5. Under biplane fluoroscopy, use the hepatic venogram images as a guide.

The colapinto needle is advanced through the right atrium, hepatic vein (right or middle branch) and directed in an anteroinferior direction after penetration of the wall of the hepatic vein into the portal vein (right or middle branches). The catheter in the right hepatic vein lies supero-posterior to the portal vein. The needle is aimed anteromedially and advanced 3-4 cm in the liver caudally, after entrance into the portal vein, the guide wire and catheter are advanced into the portal vein. Then the portal vein is visualized. Precaution should be taken not to hit the portal vein at the extrahepatic portion, which can cause life-threatening hemorrhage. The portosystemic gradient pressure should be more than 12 mmHg, then the TIPS procedure will be effective. The porto-hepatic shunt should be a dilated shunt of 8-12 mm. After stent replacement is performed, the portosystemic shunt pressure should decrease and good flow demonstrated. The puncture site into the portal vein should be the intrahepatic portion proximal to the portal bifurcation by at least 1 cm.

Complications

1. Cardiac arrhythmia.
2. Injury to hepatic artery and/or bile duct.
3. Life-threatening hemorrhage due to capsular tear from portal venous puncture into extrahepatic portion.
4. Hepatic encephalopathy may develop case of child class, or portosystemic gradient reduction.
5. After TIPS procedure, deterioration of hemodynamic return may cause congestive heart failure to develop.

Clinical results

The success rate depends on an operation experience success rate of more than 90%. The portosystemic shunt gradient is less than 12 mmHg. The varices tend not to bleed. Improvement may occur within 1 month after the procedure. Stenosis may develop later. Follow up doppler ultrasound should be performed within 24 hours.

Conclusion

TIPS is an effective procedure to reduce portal pressure in cases of acute or recurrent variceal bleeding and uncontrolled medical treatment or sclerotic therapy. The success rate will be improved by operator experience. Complications of the procedure and hepatic encephalopathy may develop later dependent on liver status and the change in portosystemic circulation.

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Simvastatin-Induced Acute Pancreatitis: A rare side effect of a statin

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Keywords: acute pancreatitis, simvastatin, statin, HMG-CoA, side effect, drug induced pancreatitis

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Acute Pancreatitis is defined as the abrupt nonbacterial inflammation of the pancreas. Typical symptoms comprise abdominal pain located in the epigastrium and radiating to the back. In the majority of cases, the progression of acute pancreatitis is mild and self-limited. Albeit, one fifth of patients may deteriorate and develop multiple organ dysfunction syndrome (MODS) which eventually enhances mortality rate.[1,2] The first and second most common etiologies, accounting for approximately 75% of cases in most developed countries, are gallstones and alcohol respectively.[3] Less common causes include pancreatitis occurring after endoscopic retrograde cholangiopancreatography (ERCP), abdominal trauma, familial hypertriglyceridemia, hypercalcemia, autoimmune disease, toxins, etc.[4,5] Drug-induced pancreatitis is a relatively rare occurrence, accounting for approximately 1.2-2% of cases.[6-8] Of those, acute pancreatitis caused by the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, often referred to as statins, has been reported rarely.[9] We reported a case experiencing the very rare side effect of simvastatin-associated acute pancreatitis. This information should increase awareness of physicians and pharmacists not to overlook the etiology particularly in any patients diagnosed with idiopathic pancreatitis.

Case Report

An 84-year-old Thai man was admitted to hospital outside Bangkok on April 15, 2013 (Day 1) due to acute epigastric pain radiating to the middle of the back, without nausea or vomiting. The attack occurred after dinner and lasted for 10 hours prior to admission. He had underlying diseases of hypertension (HT), coronary artery disease (CAD), and hypertrophy of the prostate gland and these conditions were well-controlled by oral medications including simvastatin (40 mg once daily), aspirin (81 mg once daily), amlodipine (5 mg once daily), trimetazidine hydrochloride (35 mg twice a day), and alfuzosin (10 mg once daily). He had been taking these medications since diagnoses were made in 2007. Alcohol consumption was stopped more than 10 years previously.

On physical examination, the patient was alert. Vital signs: BP 120/70 mmHg, HR 80/min, T 37.8°C, RR 22/min. Body mass index was 26.1 kg/m^2. The cardiopulmonary system was unremarkable. Abdominal examination revealed no guarding but with generalized rebound tenderness; hepatosplenomegaly could not be detected. There was no cutaneous sign of chronic liver disease.

Hematologic studies revealed the following findings: pancreatic amylase (P-amylase) 2,598 U/L (normal: 8-53 U/L), no lipase level performed before transfer, total bilirubin 2.8 mg/dL (normal: 0-1.5 mg/dL), direct bilirubin 2.1 mg/dL (normal: 0-0.5 mg/dL), aspartate aminotransferase (AST) 136 U/L (normal: 0-40 U/L), alanine

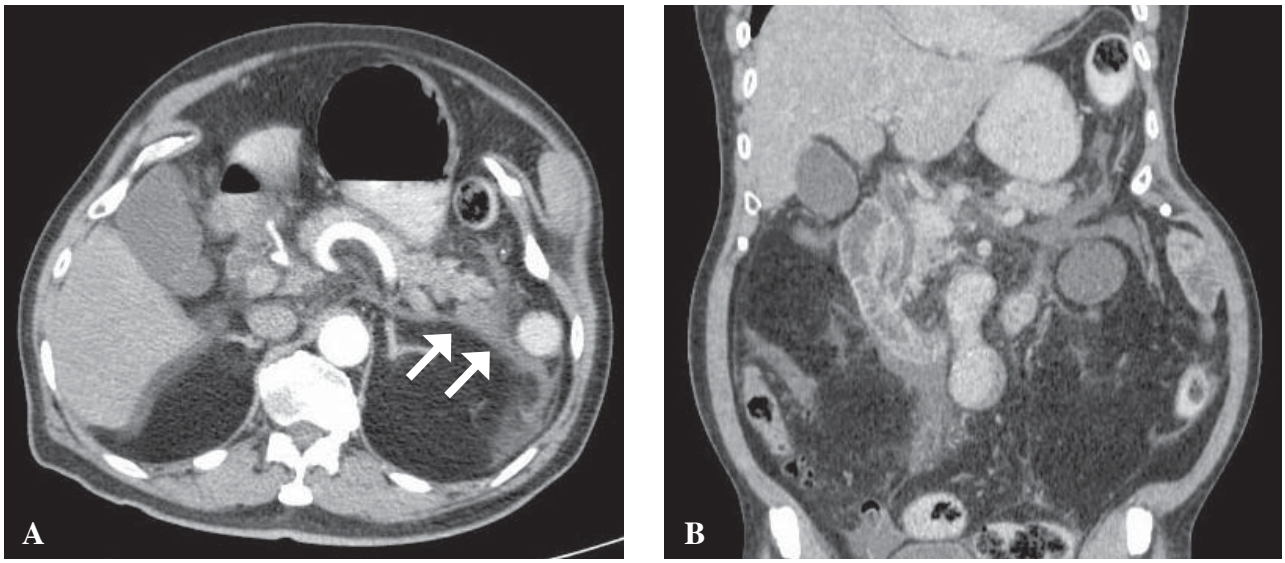

Figure 1: *MDCT of the upper abdomen with contrast enhancement, axial section reveals:*
A. infiltration of the peripancreatic fat planes (see arrows) central, dorsal and left anterior renal fascia, while the pancreas itself appears unremarkable.
B. normal gallbladder and common bile duct.

aminotransferase (ALT) 112 U/L (normal: 0-40 U/L), cholesterol 112 mg/dL (normal: < 200 mg/dL), triglyceride 49 mg/dL (normal: < 150 mg/dL), troponin-T 0.006 ng/mL (normal: 0-0.014 ng/mL), carcinoembryonic antigen (CEA) 1.85 ng/mL (normal: 0-3.8 ng/mL), CA 19-9 (digestive tract) 26.41 U/mL (normal: 0-37 U/mL). Complete blood count, alkaline phosphatase (ALP), and hepatitis serologies were unremarkable. Blood culture was taken.

Multidetector computed tomography (MDCT) of the whole abdomen demonstrated diffuse enlargement of the pancreas with fluid infiltrating along peripancreatic and bilateral anterior pararenal spaces; dilatation of the intrahepatic bile ducts down to the common bile duct, 11 mm in maximal diameter with suspected thickening of the periampullary region. The gallbladder was well-distended without gallstones. These findings were compatible with acute non-necrotizing pancreatitis. (Figure 1)

Symptomatic and supportive treatments were provided including adequate hydration and nutrition, pain management using meperidine hydrochloride (Pethidine®), maintaining equilibrium of body fluid and electrolytes. Due to fever and since infectious causes could not be entirely excluded, empirical antibiotics (ceftriaxone and metrodinazole) were administered. With regard to drug - associated acute pancreatitis, all regular medications had been withheld since admission to the referring hospital prior to his arrival at BMC.

On Day 3 of admission, patient was clinically improved: no fever, increased appetite, and disappearance of abdominal symptoms and signs. Blood culture showed no organism growth within 72 hours, therefore antibiotics were discontinued. Blood tests showed decrement of P-amylase levels (401 U/L), AST (38 U/L), and ALT (60 U/L). Blood for lipase showed a high level of 259 U/L (normal: 0-190 U/L). However, to avoid comorbidities that could be caused by underlying diseases of HT and CAD, all withheld oral medications- except simvastatin - were restarted on that day.

On Day 5, two days after restarting these medications, blood tests for both P-amylase and lipase showed normal values of 96 and 74 U/L respectively.

On Day 7 with normal level of P-amylase of 86 U/L, patient was discharged. Simvastatin was not prescribed.

On Day 12, five days after discharge, at follow up, he was clinically well without abdominal pain or jaundice. Serum P-amylase was followed and was found to be normal.

Discussion

The diagnosis of acute pancreatitis, according to the guidelines of the American College of Gastroenterology, requires at least two from three of the following criteria: 1) characteristic abdominal pain, 2) elevation level of serum amylase and/or lipase (≥ 3 times the upper normal limit), and 3) characteristic findings of acute pancreatitis on CT scan. Our patient had clinically and radiographically fulfilled the diagnostic criteria: classic abdominal pain, high serum level of amylase more than 3 times of upper limits, and MDCT (which is the best imaging technique for diagnosis of acute pancreatitis) which displayed typical findings comprising of enlargement of the pancreas with diffuse edema with peripancreatic fluid collections.[1, 10-12]

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Table 1: Series of blood tests from admission to hospital discharge and follow up visit.

Test / DAY	Normal range	DAY 1 (Admission)	DAY 3* (Restarted medictions)	DAY 5	DAY 7 (Discharge)	DAY 12 (Follow up)
P-Amylase	28-100 Unit/L	2598	401	96	86	80
Lipase	0-190 Unit/L	N/A**	259	74	N/A	N/A
Total Bilirubin	0-1.5 mg/dL	2.8	N/A	N/A	N/A	N/A
Direct Bilirubin	0-0.5 mg/dL	2.1	N/A	N/A	N/A	N/A
AST	0-40 Unit/L	136	38	30	N/A	N/A
ALT	0-40 Unit/L	112	60	34	N/A	N/A

*DAY 3 = Day of restart withheld medications except simvastatin; **N/A = not applicable.

Table 2: Classification system of medication-associated acute pancreatitis.[13]

Categories	Definition
Class Ia	Medications at least one case report Evidence of a positive rechallenge Exclusion of other causes of acute pancreatitis
Class Ib	Similar to class Ia but other causes of acute pancreatitis could not be excluded
Class II	Medications at least four case reports Consistent latency period for at least 75% of the cases
Class III	Medications at least two case reports Do not have rechallenge data or a consistent latency period
Class IV	Medications have one case report without rechallenge data

Specifying the etiology of acute pancreatitis is crucial. Due to common causes e.g. gallstones, alcohol, a history of ERCP, hypertriglyceridemia, autoimmune having been excluded, there was thus a suspicion of medication-associated pancreatitis. Some medical literature has reported and listed a panel of drug-induced acute pancreatitis.[7,8, 13-17] Looking at the regular medications used by our patient, aspirin,[14,18] amlodipine,[14,18] and simvastatin[13,14,18,19] have all been identified as causes of acute pancreatitis. After carefully determining risks and advantages between underlying diseases and restart of medications, all withheld drugs but simvastatin were re-challenged. Patient was closely observed and monitored and revealed clinical improvement and serum P-amylase returned to normal. According to this information, pancreatitis induced by aspirin, amlodipine, trimetazidine hydrochloride, and alfuzosin were ruled out. Therefore, by exclusion of other possible medications, the etiology of simvastatin-induced acute pancreatitis was confirmed.

Drug-associated acute pancreatitis has been classified into five categories: Ia, Ib, II, III, and IV based on the number of case reports, available rechallenge data, consistent latency period, and ability to exclude other causes of acute pancreatitis (Table 2). Statins or HMG-CoA reductase inhibitors have been suggested as a class effect, and they are categorized as class Ia, Ib, III, and IV.[13, 20]

Until recently, the mechanism of action for statin-associated acute pancreatitis was limited and not quite clear. It had been reported as both dose-independent and unpredictable.[21] Because of lacking a consistent latency period, statins are possibly directly toxic to the pancreas causing accumulation of a toxic metabolite that eventually induces acute pancreatitis.[19-21] Other mechanisms are reckoned to be associated with drug interactions through CYP3A4, and/or related to rhabdomyolysis or myalgia that occurred before development of acute pancreatitis.[21, 22] Onset of symptoms can develop from hours to years after commencing statins.[23-26] Similar to our patient, symptoms of acute pancreatitis developed only after taking simvastatin for approximately 7 years.

Regarding prognosis, fortunately the progression of acute pancreatitis in the majority of cases is mild and self-limited.[1] The overall mortality in acute pancreatitis is 5% (3% in interstitial pancreatitis, 17% in necrotizing pancreatitis).[27-46] However, the mortality rate is close to 0 among patients who develop acute pancreatitis but no multiple organ dysfunction syndrome (MODS).[31, 38, 47, 48]

Conclusion

It is a great challenge for physicians and pharmacists to declare the diagnosis of drug-induced acute pancreatitis. Even if common etiologies of pancreatitis such as gallstones, alcohol, history of ERCP, hypertriglyceridemia, toxin, etc. have already been excluded, **'idiopathic'** (an undiscovered, underlying etiology) pancreatitis should not be finalized unless such a very rare side effect of medications can be excluded. An HMG-CoA reductase inhibitor such as simvastatin is commonly prescribed not only for patients with hyperlipidemia but also for patients with CAD. This medication should be considered as a possible cause of statin-associated acute pancreatitis even if the abovementioned side effect is infrequently reported.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Case Report

Imaging of A Single Malignant Osseous Involvement by F-18 NaF PET/CT

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Since the introduction of Tc-99m methylene diphosphonate (Tc-99m MDP) for bone imaging in 1971 by Subramanian and McAfee, bone scans have become one of the most widely used investigations in nuclear medicine for malignant osseous involvement.[1] After its introduction by Blau et al in 1962, F-18 NaF was recognized as an excellent radiopharmaceutical for skeletal imaging, several decades before the introduction of the PET system.[2,3]

In the early 1990s, Phelp et al used F-18 NaF as a model for the development of whole body PET because of the favorable skeletal kinetics of F-18 NaF.[3] It was reported that F-18 NaF PET/CT improved the clinician's ability to identify the presence and extent of bone metastases.[3] We report our first experience using this technique in localizing a single skeletal metastasis at Siriraj Hospital.

Case Report

A 34-year-old female with previous history of breast cancer was sent for a bone scan because of her complaint of lower back pain. A previous plain radiograph of the lumbar spine appeared unremarkable (Figure 1A). The whole body bone images were obtained at 3 hours after the intravenous administration of 20 mCi of Tc-99m MDP using a dual-head gamma camera (Infinia Hawk Eye: GE Healthcare). The study showed increased radioactivity uptake at the left aspect of L4 (Figure 1B) with suspicion of osseous metastasis.

One week after the bone scan, PET/CT images were performed at 60 minutes after the intravenous administration of 10 mCi of F-18 NaF using a Discovery PET/CT system (GE Healthcare). Low-dose CT acquisition was performed first with 140 kV, 80 mA, 0.8 seconds per CT rotation, a pitch of 6 and a table speed of 22.5 mm/second. A PET emission scan was performed immediately after acquisition of the CT without changing the patient's positioning. Six bed positions were performed with an acquisition time of 3 minutes per bed from vertex to mid thigh. PET images were reconstructed using an ordered-subsets expectation maximization algorithm. CT data were used for attenuation correction. Studies were interpreted on a Xeleris workstation. PET image clearly showed abnormal activity at the left lateral aspect of the vertebral body of L4 (Figure 1C). CT part of the PET/CT images showed an osseous destruction at the corresponding site of abnormal activity, indicating an osseous metastasis.

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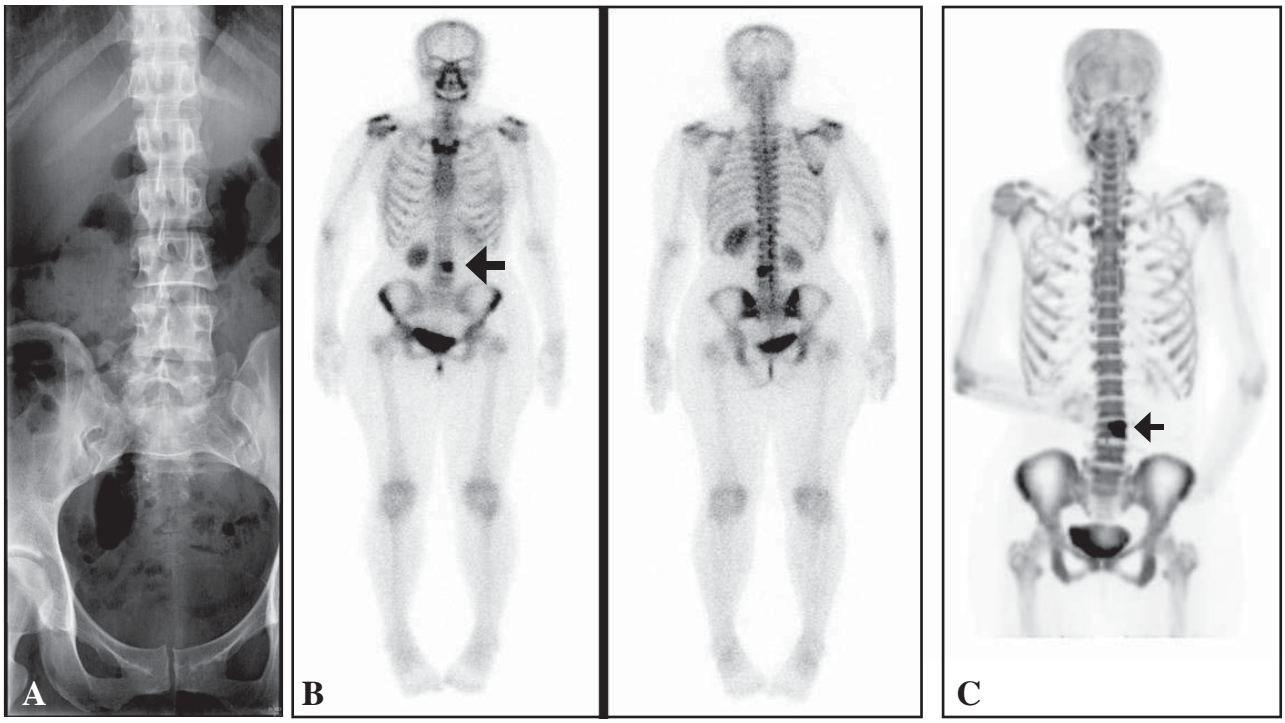

Figure 1*: A. Radiograph of lumbar spine shows unremarkable findings.*
B. Anterior and posterior whole body bone scan (Tc-99m MDP) show increased radioactivity uptake at left aspect of L4 (arrow).
C. Anterior whole body PET/CT (F-18) shows increased radioactivity uptake at left aspect of L4 (arrow).

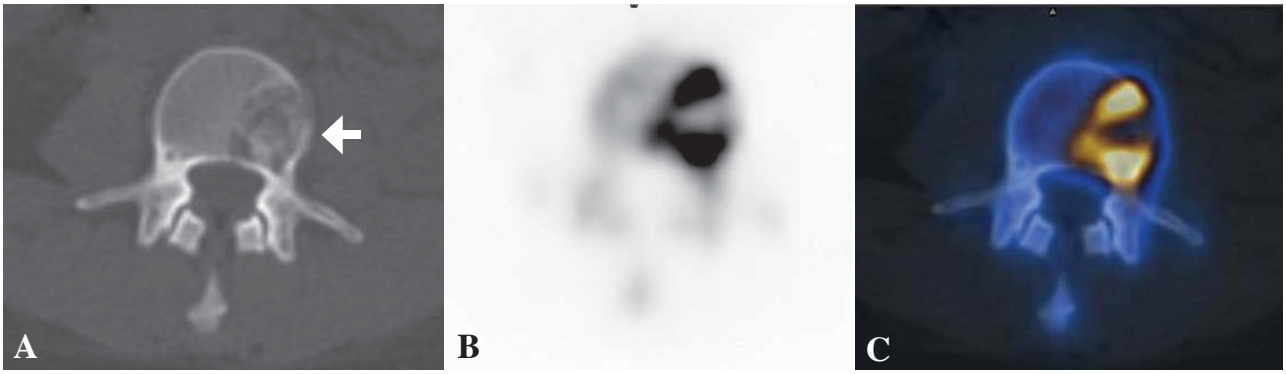

Figure 2: *A. CT part of PET/CT image shows osseous destruction at vertebral body of L4 (arrow) (Same patient as fig. 1C).*
B. PET scan shows abnormal activity at the corresponding osseous destruction.
C. Fusion PET/CT of the osseous metastasis.

Discussion

Schirrmeister, et al.[4] reported 80-90% sensitivity of the planar bone scan for the detection of peripheral skeletal metastases, however the sensitivity for detection of vertebral metastases is only 20-40%. Because the planar bone scan has variable sensitivity and low specificity, there is a recommendation to perform SPECT of the entire spinal column in patients at high risk for bone metastases.[4] The major advantages of SPECT are that it allows direct correlation with anatomic lesions, improves interpreter confidence and diagnostic accuracy.[5] The major drawback of bone SPECT is the long acquisition time (25 to 30 minutes per field of view). PET/CT technique can offer whole body tomographic images so it provides higher spatial resolution and improves anatomic detail. In our patient, F-18 NaF PET/CT accurately characterized a single osseous metastasis even though this lesion was indeterminate on the planar bone scan and not demonstrated by plain radiograph. Last but not least, this technique uses a shorter imaging time (one hour) as compared to Tc-99m MDP bone scan (3-4 hours) so it may

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be more convenient for the patient, who will experience less emotional and physical stress due to a long wait.

F-18 NaF PET/CT may be an alternative technique for characterizing benign and malignant disease of the skeleton as it can provide higher quality imaging, increase clinical accuracy and provide greater convenience to the patients.

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Mesenchymal Stem Cells

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Stem cells are a special type of cell, which can be found in almost all types of tissue and through the entire life span of multicellular organisms. Their main function is to provide tissue development, homeostasis and to repair tissue damage. Stem cells are characterised as cells that have the capacity to self renew, multipotency/pluriopotency, clonality, and are divided into embryonic stem cells and adult stem cells.

Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells (MSCs) are a group of adult stem cells occurring naturally in the body. Adult stem cells are undifferentiated cells found in numerous tissues throughout the body that divide to replenish dying cells and to regenerate damaged tissues. To date, other than bone marrow stem cells, MSCs have been identified in a variety of tissues,[1-3] such as adipose tissue, peripheral blood, spleen, brain, synovial fluid, dermis, muscle, dental pulp, umbilical cord, placenta, skin, liver, pancreas and intestines that are differentiated along several mesenchymal lineages. On the other hand, there are significant differences in the proliferation and their differentiation abilities, and in harvesting procedures among these MSCs.

In 2007, The International Society for Cellular Therapy (ISCT) agreed that a MSC should adhere to plastic in standard culture conditions; and express (≥ 95%+) CD105, CD73, CD90 and not express (≤ 2%+) CD45, CD34, CD14 or CD11b, CD79a or CD19, HLA-DR and should give at least three differentiated lineages: osteoblastic, adipogenic, chondroblastic (this needs to be demonstrated by staining of in vitro differentiated cell cultures).[4] However, the isolation of stem cells remains a major obstacle because of the lack of universally accepted markers. There are still controversies in obtaining reproducible results by the published methods, especially where differentiation protocols are concerned.[5-9] Meanwhile, different isolation methods cause striking impacts on the differentiation potential of adult stem cells.[10,11] There is a limited number of studies comparing the differentiation capacity of stem cells obtained from various sources using the same differentiation protocols.[12-17] Since there is no consistency between the established protocols of different labs, it is also quite challenging to interpret previously reported data.

MSCs have generated considerable biomedical interest since their multi-lineage potential was first identified in 1999.[18] MSCs can differentiate several cell types and produce important growth factors and cytokines.[19,20] MSCs have the ability to modify the response of immune cells thereby associating with immune-related disorders, especially autoimmune diseases.[21,22] Despite the wide distribution of MSCs in the body, the bone marrow remains the principal source for most MSC-based pre-clinical and clinical studies where MSCs have mainly been characterized after isolation.[19] Actually, MSCs are a rare population in bone marrow aspirates.

The frequency of MSCs is approximately 1/10^6 nucleated cells in adult bone marrow and 1/10^4 nucleated cells in umbilical cord.[23] The number of MSCs has been noted to decrease with age.[24] Later on, more primitive MSCs were discovered. Immunomagnetically separated cells were named mesodermal progemitor cells (MPCs) or multipotent adult progenitor cells (MAPCs).[25,26]

Expansion of Mesenchymal Stem Cells

The expansion of MSCs is a necessity for clinical use. MSCs are rare in the human body but can be expanded in vitro to hundreds of millions of cells, isolated from the other cells by adherence to plastic and consecutive passaging. MSCs proliferate to spindle-shaped cells in confluent cultures. Although homogeneous by light microscopy, even single cell–derived colonies form a molecularly heterogeneous population of cells that vary to some extent in their differentiative capacity. Even if MSCs rapidly expand 1 billion-fold, individual cells in a culture exhibit a highly variable expansion potential. Furthermore, the cell yield after expansion varies with the age and condition of the donor and with the harvesting techniques used. Naturally, differences in isolation techniques, culture conditions, media additives, and sub-culturing techniques greatly affect cell yield and possibly also the phenotype of the expanded cell product. The gene expression/proteomics of MSCs that have been culture-expanded depend on the culture conditions, passage, species, and other factors which may or may not reflect in vivo events. Moderate subcultivation will not change the karyotype or telomerase activity of MSCs, but if the cells are cultured, many passages, and signs of senescence and apoptosis appear.[27]

Mesenchymal Stem Cells from Bone Marrow (Figure 1)

MSCs were fist identified in the stromal compartment of bone marrow by Friedenstein and colleagues in 1960s.[28-31] MSCs are conventionally extracted from bone marrow sources as a cellular therapy for inflammatory associated conditions. Specifically, the most advanced clinical trials in the area of regenerative medicine have been performed by the company Osiris, whose main product is a **'universal donor'** MSC, termed **'Prochymal'**. This cellular product has entered Phase III trials in graft versus host disease, and is currently being tested for heart failure.[32] Other bone marrow derived MSC-like products are in clinical trials, for example, Mesoblast is in Phase III assessing its Mesenchymal Precursor Cell for efficacy in post hematopoietic transplant graft failure, as well as in Phase II for heart failure.[33] Therapeutic advantages of MSC include their ability to migrate to injured tissue, in part via detections of hypoxia through the CXCR4-SDF-1 axis differentiation activity into multiple tissues release of trophic factors inhibition of apoptosis stimulation of angiogenesis, inhibition of inflammation, and stimulation of Treg activity.[34-44] Despite the advantages of the current approaches, bone marrow contains relatively small numbers of MSC, thus, as previously mentioned, therapeutics with bone marrow for systemic applications requires ex vivo expansion.

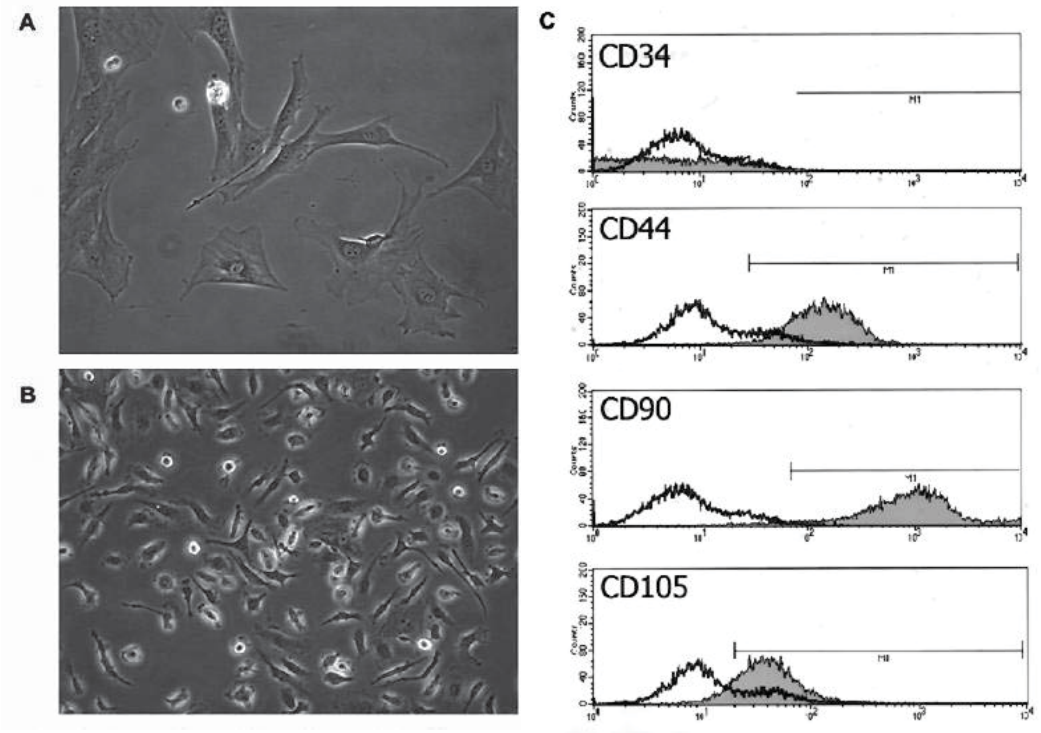

Figure 1: *A. CD34-/CD45- cells show fibroblastic morphology typical of MSCs.*
B. CD34+/CD45+ cells show spherical morphology consistent with lymphohematopoietic cells.
C. FACS analysis of murine MSCs. Cells were uniformly negative for CD34 and positive for CD44 (95+0.6%), CD90 (99.1+0.1%), and CD105 (89+2.1%), markers associated with MSCs.

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Figure 2: *Stromal Vascular Fraction (SVF) extracted from adipose tissue.*

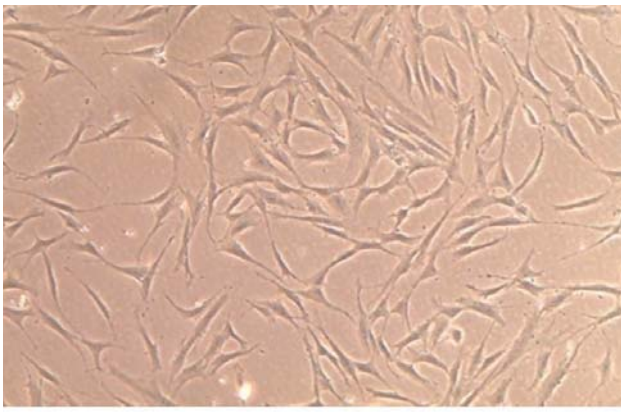

Figure 3: *Mesenchymal Stem Cells derived from adipose tissue.*

Mesenchymal Stem Cells from Adipose Tissue

Adipose tissue contains approximately 100-1000 fold higher MSC concentrations, or approximately 50-100,000 MSC per ml.[45] Given the relative ease of extracting 500 ml of lipoaspirate, it is conceptually feasible to generate a 25-50 million cell dose of MSC, which is close to the systemic doses of MSC that are typically used in clinical trials of allogeneic expanded cells (e.g. 50-100 million cells in various clinical trials).[46] Conceptually, given that the MSC present in the stromal vascular fraction (SVF, Figure 2) are autologous, one could envision higher therapeutic potential due to the lack of allo-immune clearance when compared to allogeneic MSC, although this needs to be assessed experimentally.

Adipose MSCs (Figure 3) contain several similarities and differences when compared to bone marrow derived MSC, although this area is still considered to be controversial. Specifically, in animal cardiac infarct models, it has been demonstrated that expanded adipose MSCs are superior to bone marrow MSC in terms of stimulating angiogenesis, decreasing cardiac pathology, and stimulating VEGF and FGF secretion.[47] Using an in vivo lentiviral-labeled system, it was demonstrated that adipose-derived MSC (ASC) have a superior ability to BM derived MSC (BDSC) to integrate into cardiac muscle after injury, as well as to restore function.[48] In addition to specific propensities for differentiation, adipose tissue-derived MSC appear to be superior to bone marrow in terms of proliferative potential without loss of telomere length. Vidal et al.[49] demonstrated that adipose MSC could multiply almost twice as many cell passages without undergoing senescence when compared to bone marrow MSC.

A much simpler procedure, for which adipose tissue is uniquely suited, is the administration of autologous, non-expanded cellular fraction. The rationale behind this derives from observations that: a) adipose tissue contains substantially higher numbers of MSC compared to bone marrow[50] b) MSC from adipose tissue do not appear to decrease in number as a result of age.[51,52] It has also been reported that the expression level of 5 chemokine receptors (CCR1, CXCR4, CCR7, CXCR6, and CXCR3) is higher in ASC than BDSC, which indicates ASC might show a better migration and homing capacity following transplantation.[53] These distinct characteristics will determine the strategy for cell-based therapy.

Thus it appears that the MSC component of adipose tissue possesses numerous preclinical and clinical therapeutic properties and may be an important component of the SVF cell population that is responsible for therapeutic effects observed after administration. Patients received the indicated amount of cells by intravenous injection ($2x10^6$ cells per ml diluted in Saline solution), intra-articular injection ($2.5x10^6$ cells per ml in each injured joint, diluted in Saline solution and the patient's own serum). Multiple injections of cells were given to increase the therapeutic efficacy. Follow-ups were performed for all patients at 1, 3, 6 and 12 months. SVF cells were isolated and prepared under the guidelines of Good Tissue Practices 21 CFR 1271 as related to sample screening and processing in the sterile flow hood, inside of a class 10,000 clean room.[54] Thirteen patients with rheumatoid arthritis were treated with 38-148 million SVF cells intravenously and intra-articularly. Although no hematopoietic or biological abnormalities were noted, one of the patients reported facial flushing, fever and myalgia after a third of four injections. These symptoms all resolved spontaneously.

Mesenchymal Stem Cells from Dental Pulp (DPSC)

Dental pulp (DP) is a well defined compartment of soft tissue, which keeps a primitive structure similar to the gelatinous tissue of the umbilical cord. Dental pulp represents a well delimited separated compartment from other tissues, which retains a unique histological structure and a stem cell niche. Since there are two sources for dental pulp development (dental mesenchyme of neural crest origin and vascular mesenchyme (Figure 4)) there are two different lines of DPSCs inside the DP. DPSCs can be isolated from two DP compartments. Jakub Suchánek

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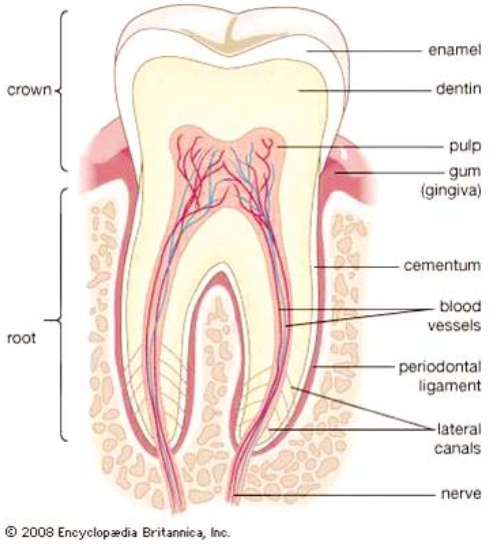

Credit: Encyclopædia Britannica, Inc.
http://www.britannica.com/EBchecked/media/112882/Cross-section-of-an-adult-human-molar

Figure 4: *Tooth; cross section of an adult human.*

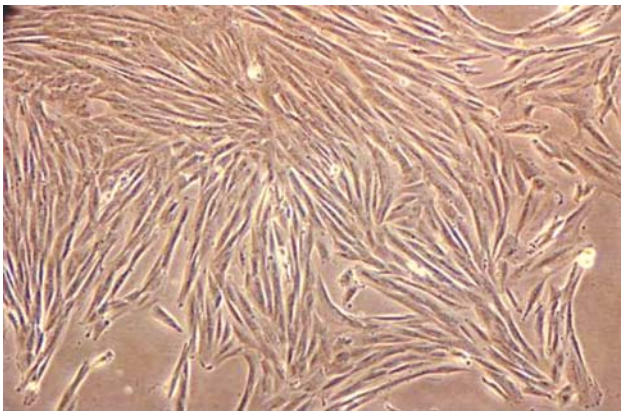

Figure 5: *Mesenchymal stem cells derived from human exfoliated deciduous teeth (SHED) Cells with the ability to develop into a wide range of tissues.*

and co-workers[55] named these compartments according to their localization within the DP- subodontoblastic compartment (inner surface of tooth and outer part of DP; SOc) and perivascular compartment (the inner part of DP;PVc). DPSCs isolated from PVc were spindle-shaped with long processes. Conversely, DPSCs from SOc were more rounded.

In the year 2000, Gronthos and co-workers[56] isolated stem cells from the human dental pulp (DPSCs). The pulp tissue was extracted from impacted third molars. In the year 2003, Miura et al[57] isolated stem cells from human exfoliated deciduous teeth (SHED; Figure 5). DPSCs can be cultivated for a long time, over 60 population doublings in cultivation media designed for bone marrow MPCs.[55] After reaching Hayflick's limit, they still have a normal karyotype. Initial doubling time of the cultures was from 12 to 50 hours for the first 40 population doublings, after reaching 50 population doublings, doubling time had increased to 60–90 hours. Regression analysis of the unaccumulated population doublings proved a tight dependence of population doublings on passage number and slow decrease of proliferation potential. In comparison with bone marrow MPCs, DPSCs share similar biological characteristics and stem cell properties. The results of our experiments proved that both DPSCs and MPCs are highly proliferative; clonogenic cells that can be expanded beyond Hayflick's limit and remain cytogenetically stable. Moreover two different populations of DPSCs can be isolated. These DPSCs lines differed from one another in morphology. Because of their high proliferative and differentiation potential, DPSCs can become a more attractive, easily accessible source of adult stem cells for therapeutic purposes.

Cultivated DPSCs and SHED were highly proliferative and cytogenetically stable stem cells. Morphological differences of cells isolated from both defined compartments were not related to changes in proliferation potential. Over the entire cultivation period, Jakub Suchánek and co-workers[55] did not observe any changes in cell viability and cells remained undifferentiated. Dental pulp has represented an alternative and easily accessible source for obtaining tissue-specific stem cells which are histocompatible with tissues of the individual patient. In comparison with bone marrow MPCs, DPSCs share similar biological characteristics and stem cell properties. DNA analysis proved that DPSCs have more cells in S-G2 phase than bone marrow MPCs.[55] A higher proliferation activity of DPSCs was confirmed by DT trend analysis. In addition, any signs of spontaneous differentiation were not observed during DPSCs long term cultivation.

Stem cells from human exfoliated deciduous teeth show higher proliferation rates and increased population doubling time than stem cells from human permanent teeth pulp.[9,57] Apart from deciduous teeth, the umbilical cord is another postnatal organ discarded after birth and the collection of cells does not require an invasive procedure with ethical concerns. Stromal cells, as the dominant cells of this fetus-derived tissue, possess multipotent properties between embryonic stem cells and adult stem cells. They bear a relatively higher proliferation rate and self-renewal capacity.[58] The suitable cells should be chosen for specific tissue engineering trials. The most reliable cell source for dental tissue engineering is that of autologous pulp stem/progenitor cells isolated from deciduous teeth, which have been exfoliated naturally.

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The Potential Clinical Use of Mesenchymal Stem Cells

A significant improvement in understanding MSC biology in recent years has paved the way for their potential clinical use. A new era has begun in the treatment of diseases with the discovery of stem cells from diverse organs and tissues. Increasing evidence suggests that one mechanism of action by which cells provide tissue protection and repair may involve paracrine factors, including cytokines and growth factors, released from transplanted stem cells into the surrounding tissue.[59] There is increasing evidence that stem cells themselves, specifically MSCs, secrete a variety of pro-inflammatory and anti-inflammatory cytokines. MSCs represent an advantageous cell type for allogeneic transplantation as well because MSCs are immune-privileged with low major histocompatibility complex I (MHC I) and no MHC II expression, therefore possessing a reduced risk of allogeneic transplant rejection.[19]

Different tissue-originated MSCs may have variance in their differentiation capacity even if cultured in exactly the same microenvironment. While investigators report studies of MSCs using different methods to isolate the cells and using different approaches to characterize the cells, the considerable therapeutic potential of human MSCs has generated markedly increasing interest in a wide variety of biomedical disciplines. Thus it is increasingly difficult to compare study outcomes, which hinders progress in the field. Obviously, it is critical to have an acknowledged standard to evaluate the characteristics of MSCs.

Cardiovascular therapeutic potential

The cardiovascular therapeutic potential of bone marrow mesenchymal stromal/stem cells (MSCs) is largely mediated by paracrine effects. The traditional preparation of MSC has involved plastic adherence-isolation. In contrast, prospective immunoselection aims to improve cell isolation by enriching mesenchymal precursor cells (MPC) of higher purity. This study compared the biological characteristics and cardiovascular trophic activity of plastic adherence-isolated MSC (PA-MSC) and MPC prepared from the same human donors by immunoselection for stromal precursor antigen-1 (STRO-1). Compared to PA-MSC, STRO-1-MPC displayed greater (1) clonogenicity, proliferative capacity, multilineage differentiation potential, and mRNA expression of mesenchymal stem cell-related transcripts. In vitro assays demonstrated that conditioned medium from STRO-1-MPC had greater paracrine activity than PA-MSC, with respect to cardiac cell proliferation and migration and endothelial cell migration and tube formation. Enrichment for STRO-1 is also accompanied by increased expression of cardiovascular-relevant cytokines and enhanced trophic activity.[60] Over the last decade, cellular therapy has emerged as a potential adjunct in the management of ischemic heart disease and congestive heart failure.[61] Preclinical and clinical studies have shown that bone marrow (BM)-derived MSC are capable of mediating cardiovascular reparative effects, predominantly through indirect, paracrine mechanisms that target endogenous cardiomyocytes and vascular cells.[62-65] The field of MSC research remains hindered by a lack of uniformity in the methods used for cell isolation, culture, and characterization. Until now, the majority of in vitro and in vivo cardiovascular studies have utilized BM MSC prepared by plastic adherence-isolation.[18,66] However, this non-selective technique is limited both by the low frequency of clonogenic colony forming units-fibroblastic (CFU-F) in adult human BM and the contamination of immature mesenchymal precursor cells (MPC) with more mature stromal and non-mesenchymal cell types.[67] Prospective immunoselection has been advocated as an alternative strategy for isolating pure populations of immature MPC, based on their expression of cell surface antigens to which specific monoclonal antibodies (mAb) may be directed. One such example is the murine IgM mAb that identifies stromal precursor antigen-1 (STRO-1). The STRO-1 antigen is expressed on the surface of approximately 10–20% of adult human BM that includes all CFU-F, Glycophorin-A$^+$ nucleated red cells, and a small subset of CD19$^+$ B-cells, but is not expressed on hematopoietic stem and progenitor cells (HSC).[68] STRO-1 is widely regarded as a marker of early mesenchymal/stromal precursor cells, because it has been strongly linked to mesenchymal cell clonogenicity, plasticity, and other progenitor cell characteristics.[69-74] This study also presents new findings to show that the presence of STRO-1$^+$ precursors is an important indicator of the cardiovascular paracrine properties of mesenchymal cells. Many of the limitations of MSC therapy for cardiovascular disease arise from the inadequate engraftment and transdifferentiation of transplanted cells in recipient myocardium.[75] Crucially, by comparison to plastic adherence-isolation, the expanded progeny of STRO-1-MPC displays biological characteristics indicative of a higher retention of immature precursor cells supporting the notion that improving the precision and quality of STRO-1-MPC isolation is an important consideration in optimizing mesenchymal cell biology and repair.

Novel wound-healing promotion therapy

Chronic wounds are difficult to heal, and little improvement has been made in preventing the associated morbidity and disability over the past few decades.[76] The best available treatment for chronic wounds achieves only a 50% healing rate. Therefore innovative treatments to enhance wound healing and regeneration are needed. The major goal of wound-healing biology is to discover how skin can be induced to reconstruct damaged parts more perfectly.[77]

SHED and hMSCs (human mesenchymal stem cells) can enhance wound healing by promoting re-epithelialization and the relationship with the extracellular matrix, especially HA.[78] Treatments using MSCs would be effective, but the number, proliferation and differentiation

potential of MSCs decline with increasing age.[79] On the other hand, SHED can be obtained without any invasion and could be a substitute for MSCs.[57] SHED significantly promotes wound healing compared with Fibro and control groups.[78] Deciduous teeth, which are considered to be medical waste, could provide novel therapeutic approaches for the treatment of wounds and novel stem-cell sources for wound healing.[78]

Implications of the immunoregulatory functions of mesenchymal stem cells in the treatment of human liver diseases

The transplantation of mesenchymal stem cells (MSCs) has been recently studied in animal models, and in clinical trials of patients with fulminant hepatic failure, end-stage liver diseases and inherited metabolic disorders. Modulatory cytokines produced by MSCs can inhibit immunocyte proliferation and migration to the liver, thereby attenuating inflammatory injury and reducing hepatocyte apoptosis. In addition, MSCs play an important role in regressing liver fibrosis and in supporting the function, proliferation and differentiation of endogenous hepatocytes under appropriate conditions.[80] These findings indicate that MSC treatment is promising in the therapy of liver diseases, and although remarkable progress has been achieved in basic and clinical MSC studies, optimal therapeutic regimens for the clinical application of MSCs, such as optimal doses, transplantation routines and interval periods for transplantation, need to be examined in more detail.

Anti-inflammatory and anti-tumor effects

It has been demonstrated that MSC exhibit innate anti-tumor effects against PANC-1 cells and can serve as delivery vehicles for IFN-β for the treatment of pancreatic cancer. However, these beneficial effects may be lost in therapies combining MSC with anti-inflammatory agents.[81] It is now clear that trophic modulation of inflammation, cell death, fibrosis, and tissue repair are the main mechanisms of MSC therapy. Delivery of growth factors, cytokines, and other signaling molecules secreted by MSCs is often sufficient to obtain therapeutic effects.[82]

Other diseases

It has been shown that the transplantation of MSCs could be an effective therapy for many diseases,[83-103] including blood disease, diabetes type 1 and 2, osteoarthritis, lung disease, spinal cord injury, liver injury, stroke, myocardial infarction, amyotrophic lateral sclerosis, parkinson's disease, neural disease, acute graft-versus-host-disease (GVHD), systemic lupus erythematosus (SLE), kidney disease and cancers. To date, hundreds of clinical trials using MSCs have been registered in the database (http://www.clinicaltrials.gov/) of the US national institutes of health. However, it is essential to find the specific adult stem cell with the greatest potential for tissue engineering and transplantation, those which require good survival rates and stable hemodynamic behavior. In addition, the difference between gene and protein expressions in different adult stem cells has to be determined first. The success of stem cell-based therapy will depend on cell availability, the potential to differentiate between specific cell lineage, inflammation response after transplantation, etc. Mesenchymal stem cell types from different sources could partly fulfill the criteria of being a suitable candidate for a specific lineage, which in turn is very important in regenerative cell therapies.

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Review Article

The new wave of Carpal Tunnel Syndrome (CTS) Surgery

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Carpal tunnel syndrome (CTS) is the most common hand disease. The clinical prevalence in the general population is 3.8%.[1] From a study of Australian population, people younger than 25 had a 2.4% prevalence compared to an extremely high prevalence in 45 to 65 year-olds who had a 45.5% prevalence.[2] In all carpal tunnel syndrome cases, in patients who developed numbness, and experienced symptoms for more than 6 months or did not receive adequate conservative treatment needed further treatment of surgery (Figure 1). The incidence of surgery is high: up to 31% to 40% of patients with carpal tunnel syndrome.[3,4] If the patients had severe compression and develop thenar muscle atrophy, the treatment has to be performed and urgent decompression is necessary to enable potential full recovery.[5] Because carpal tunnel syndrome is the most common hand disease with the highest functional recovery of treatments, patients need to know and look for an update on treatment information. Nowadays, surgical treatment had been in continuous development in terms of minimal invasive surgery. There has been a great paradigm shift from standard large open surgery to minimal invasive surgery based on patients benefit and recovery. Also CTS is one of the beneficial changes with the concept of minimal incision because of minimal dissection of highly sensitive numerous nerve areas, minimal trauma, rapid recovery and less complications.

Carpal tunnel syndrome (CTS) is a condition of the compressed median nerve in the carpal tunnel of the wrist area. Although the exact cause of this common disease remains unknown, there are correlations with certain risk factors. However, in literature reviews there is a correlation with the elderly, hormones, arthritis, synovitis, repetitive work, and vibration related work.[6,7] The most common idiopathic group is 40 to 60 year-old women (four times more than men)[1] who had symptoms of numbness in the redial side of hand in the morning. The numbness is reduced by shaking the affected hands or putting hands in a warm water bath. Specific signs include: Tinel's sign, Phalen's test and Durkan's compression test. These are all used to confirm a diagnosis of CTS. However, thenar muscle atrophy indicates severe compression and a need to perform decompression urgently.

Currently, CTS has treatment guidelines that are based on severity, progression and duration of symptoms. In cases of early and mild compression, patients can show good responses to conservative treatments such as medication to reduce inflammation and also warming up hands in a warm water bath for 10 to 15 minutes every day. In moderate compression cases, numbness will progress as often as 2-3 times a week and these cases clinically might not respond to medication and the warming up of the affected hand in a warm water bath. Corticosteroid injections or surgery may be considered to treat moderate compression. However, the effectiveness of corti-

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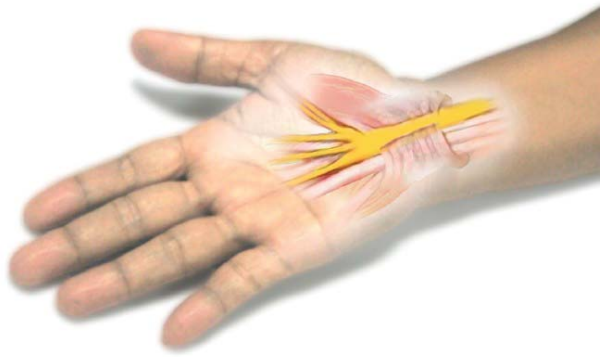

***Figure 1**: Carpal tunnel release.*

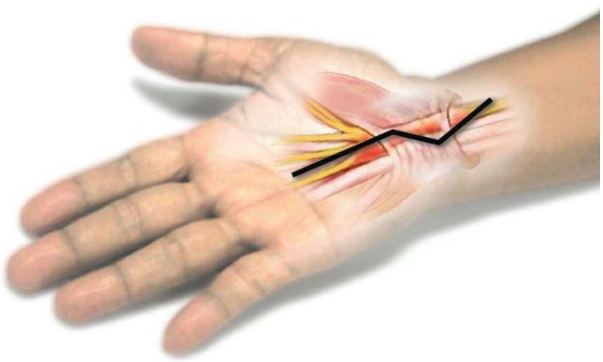

***Figure 2**: Standard carpal tunnel release 3-5 cm incision.*

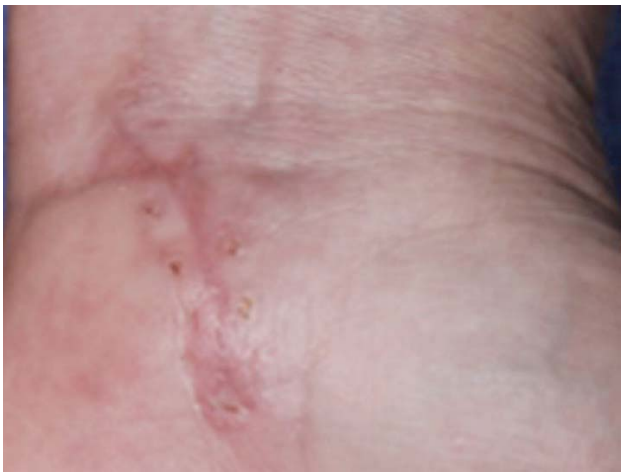

***Figure 3**: Wound complications and painful scars.*

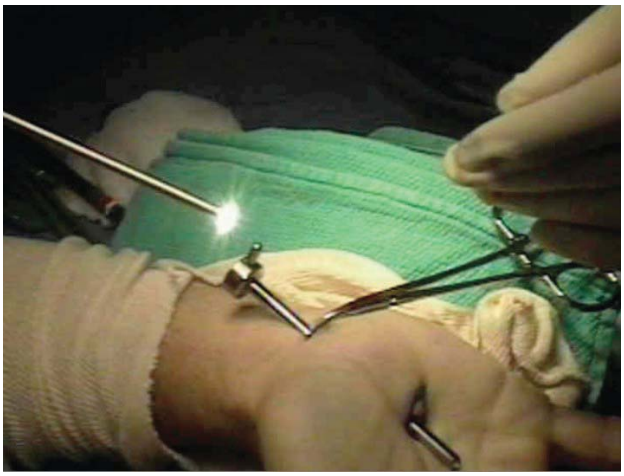

***Figure 4**: Wound complications and painful scars.*

costeroid injection cannot be proven yet.[8] In serious cases, the risk of complete median nerve damage by injection is related to the experience of physicians and the anatomical distortion of each case. This is because the injection landmark is close to the median nerve. By contrast, a new method of minimal invasive carpal tunnel release has had promising results and reduced complications of previous surgical techniques. The minimal invasive carpal tunnel releases has had many benefits not only with the severe compression group but also with the moderate compression group. This is because of less complications compared to serious permanent nerve damage after corticosteroid injections.

In the past, a standard carpal tunnel release treatment consisted of a long 3-5 cm wound incision (Figure 2). Because of the long incision and wide dissection, surgeries have to be operated under adequate general or regional anesthesia. The surgeries also had high levels of wound complications such as wound dehiscence, wound infection and painful scars (Figure 3). In 1989, the minimal invasive carpal tunnel release procedure using an endoscopic instrument was introduced and reduced prior wound complications.[9,10] Furthermore, wound complications had been diminishing by using the endoscopic technique but there are others problems. These include: difficult surgical techniques, difficult endoscope insertion and visualization of transverse retinaculum identification. In some literature, the endoscope had a higher incidence of incomplete release and nerve damage during the insertion of the endoscope (Figure 4).[11,12] A subsequent and better carpal tunnel release technique is the semi blind technique using a special knife such as the Indiana Tome (Biomet, Warsaw, USA), the KnifeLight (Stryker Instruments, Kalamazoo, Michigan, USA) and the **'Safeguard'** system (KMI, Inc., San Diego, USA). This not only reduces wound size but is more convenient to use. This change has reduced the operative time and the cost of anesthesia replaced by local anesthesia. However, the question of visualization makes the widespread use of the surgical knife very limited. To eliminate the weak points of the limitation of visualization, a novel minimal invasive enhancing visualization tool was proved to see 4.77 cm further than the 2.85 cm of the transverse carpal ligament.[13] Following the bright idea of visualization using a minimal invasive carpal tunnel release technique, MiniSure has developed a complete set for viewing and cutting. MiniSure view was designed to be used as the superficial scope. MiniSure cut was designed to be used as the retinaculum cutting knife.

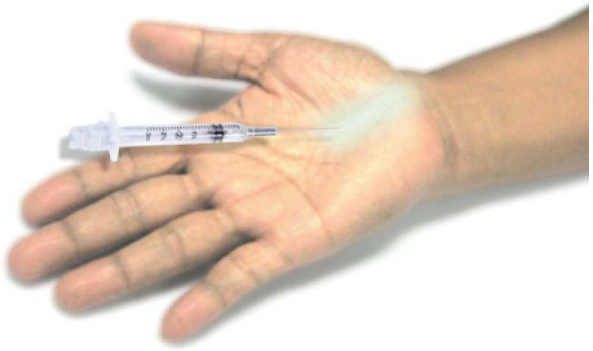

***Figure 5**: Local anesthesia.*

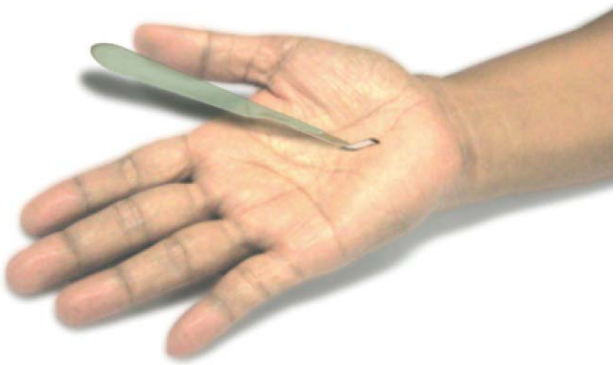

***Figure 6**: Open incision.*

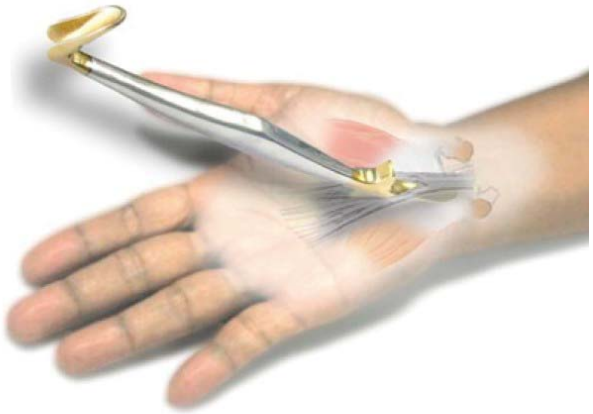

***Figure 7**: Insert navigator tip.*

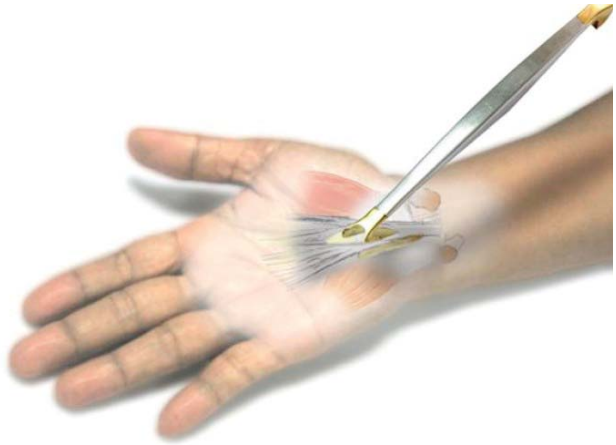

***Figure 8**: Insert visual tube.*

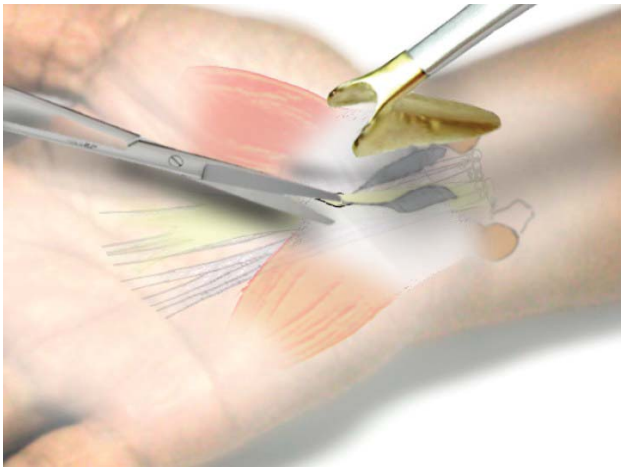

***Figure 9**: TCL release.*

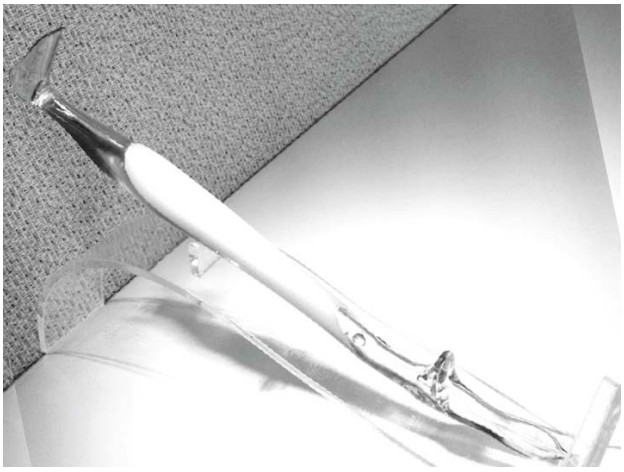

***Figure 10**: MiniSure view.*

For the new method of using the concept of minimal invasive enhancing visualization, Wongsiri developed a simplified 5 steps protocol of surgical techniques.[14] Wongsiri techniques is composed of: 1). Local anesthesia (Figure 5), 2). Open incision (Figure 6), 3). Insert navigator tip (Figure 7), 4). Insert visual tube (Figure 8) and 5). TCL release (Figure 9). Because of this simplified steps approach, the surgeon can improve operative time to under 10 minutes. The volar wrist sensation is supplied from the cutaneous nerve plexus of the volar wrist, supplied from the median nerve and the ulnar nerve. These must be avoided to prevent injury during surgery.[15] Beneath the Palmaris longus and Above Retinaculum (BPLAR) is a good approach to protect and avoid the tiny plexus of the median cutaneous nerve by approaching beneath the Palmaris longus and the cutaneous nerve. BPLAR is a safe approach because it stays on top and above the transverse reticulum. This is the proper way to perform carpal tunnel

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***Figure 11**: MiniSure cut.*

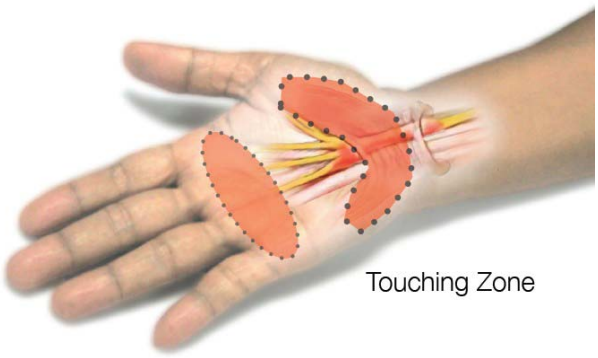

***Figure 12**: Touching zone.*

Table 1: Comparisons of different carpal tunnel release techniques.

Results	Open Technique	Endoscopic Technique	Limited Technique	Wongsiri Technique
1. Quick service, no hospital admission, saves operative time				
2. Reduces wound size				
3. Reduces pain and complications				
4. Less staff & tools (anesthetist, assistants, anesthetic & surgical tools)				
5. Less surgical cost				
6. Short recovery time				

release. The visual field is enhanced during BPLAR by approaching with MiniSure view (Figure 10). Then carpal tunnel decompression can be performed under a special knife named MiniSure Cut (Figure 11). In the preliminary report at the 11th Triennial Congress of the IFSSH, Korea, the new equipment and surgical techniques were introduced and compared to the standard approach.[16]

From Table 1, Carpal tunnel release techniques were compared and showed that the Wongsiri techniques have more benefits. Firstly, fast surgery and quick service; the Wongsiri techniques have simplified the surgical steps with user-friendly new surgical tools. Moreover, minimal invasive surgery leads the way for out-patients services. Patients can be discharged after surgery in less than an hour. This saves time, not only for surgeons but patients too. Because of the minimal incision, Wongsiri techniques have a better outcome of pain reduction and less complications especially with wound problems. Most patients complained of wound problems, especially those that involve quality of life during work, painful scars and pillar pain of the volar wrist area, these effects are commonly reported after open techniques. Even though some surgeons try to use minimal incisions without the proper assisted tool, most of them use the volar incision of touching the area of the volar wrist zone, that makes the complex of cutaneous nerve more susceptible to injury and triggers neuropatic pain (Figure 12). Wongsiri techniques are more distal to avoid the complex cutaneous nerve that is correlated to less pillar pain and less painful scars.

Nowadays, several approaches also change the incision to be more distal and have reduced pain problems also.[17] However, these approaches still had the limitation of visualization because of the lack of a proper visualization tool. The risks of nerve injury during the insertion of the tool in the blind spot area are increased. The minisure view has been designed for the purpose of visualization and for better safety standards during surgery. Even though the endoscopic carpal tunnel release technique uses the concept of minimal invasive surgery with the internal visualization during surgery, visualization still can be a major problem in terms of clear vision. In fact, the transverse carpal ligament is not suitable for a clear internal observation because of the all around coverage of synovitis. Not surprisingly, the results from the latest literature show a higher incidence of recurrence and incomplete release in the endoscopic group and also in the less experienced group of surgeons. Moreover, serious complications when using the endoscope include injury of the median nerve that occurs during the insertion of the endoscopic tools. The recommendation to use an endoscope is not advised for surgeons if they feel any tightness during the insertion of tools because over compression of the endoscope tool against the nerve might occur. Finally, the new development of MiniSure and Wongsiri techniques has been reducing the problem of over compression of the median nerve and painful scars. MiniSure and Wongsiri techniques had better and more promising outcomes with early recovery and fewer complications.

Because MiniSure and Wongsiri techniques use minimal resources of assistants and equipment, costs can be saved, including hospital stay costs, anesthesia costs, operating room costs and medication. Compared to the other operations of carpal tunnel release, MiniSure and Wongsiri techniques can be safer. Health care systems in the USA spend more than USD 2 billion a year on carpal tunnel release.[18] In the same way, Thailand has spent a lot of resources and money on the old carpal tunnel release system. Thailand can benefit from medical tourism, and offer a new technique of carpal tunnel release with MiniSure at Bangkok Hospital branches. This could become one of the most internationally popular surgeries. The Bangkok Hospital disposes of world class surgeons and facilities including well trained orthopedists and surgeons who are familiar with a new surgical technique using an innovative tool.

In conclusion, CTS is a common disease and is easily treatable and cured. Initial and early stages of carpal tunnel syndrome can be treated with medications and a warm bath. However, with moderate to severe cases, there is a need to perform surgery. The most developed techniques of minimal invasive carpal tunnel release, the Wongsiri Technique with MiniSure, has had promising results: helping to minimize complications, saving time and costs (Figure 13).

Please look out for the next article on surgical tips and the Wongsiri techniques of minimal invasive carpal tunnel release in the future volumes of the Bangkok Medical Journal.

***Figure 13**: Minimal invasive carpal tunnel release performed on 15 hands in 2 hours with minimal resources of equipment and nurses team.*

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Review Article

Hospital Care for the Elderly

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Older adults are at disproportionate risk of becoming seriously ill and requiring hospital care, whether it is in an emergency department, on a medical or surgical ward, or in a critical-care unit. Adults aged 60 and above account for 35% of acute-care hospital admissions and nearly 50% of hospital expenditure for all adults.[1,2] While many principles of acute hospital care are the same for all age groups, the elderly patient population is at increased risk of comorbidities and accompanying medications, functional decline and cognitive impairment. Therefore, there are several issues related to the hospital admission, stay and discharge that deserve specific attention when considering the care of the geriatric population. The care of hospitalized elders requires a systematic approach to the evaluation and management of commonly seen geriatric conditions and perhaps implementation of structural changes specifically designed to address the needs of an often medically complex and potentially vulnerable population.[3,4]

Hospital Admission

Reason for Admission for Geriatric Patients

The major diagnoses for which older adults are hospitalized are related to chronic diseases, particularly cardiovascular and respiratory conditions. The five most common conditions, accounting for 24% of hospital admission diagnoses, are listed in Table 1. Also common and important to recognize, but less likely to be reported as the reason for admission, are conditions more likely to occur in older adults such as failure to thrive, falls, adverse drug effects, or change in mental status. In addition, older adults may be admitted with an atypical presentation of another condition, such as when change in mental status is due to urinary tract infection. Often the reported diagnosis for a hospitalized older patient may not fully capture the underlying reasons that necessitated the admission and does not explain the hospital course and subsequent health status of the patient. In addition to the primary problems that led to the admission, the effect of comorbid chronic diseases must be considered. Over 60% of elderly patients have two or more major chronic diseases. Comorbid chronic diseases have several consequences for the hospitalized elder and for the clinician. Multiple diseases often mean multiple outpatient physicians and multiple medications. Multiple medications, can result in confusion about medications, difficulty with medication reconciliation and drug adherence, and adverse drug events.[5] In older adults, especially those 75 years and older, common conditions such as vision or hearing impairment, mobility impairment and fall risk, poor nutrition, incontinence, depression, cognitive impairment and functional impairment often occur in conjunction with the major chronic diseases that lead to the hospital admissions.

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Conditions commonly seen in older patients are often labeled as **'geriatric'** and can contribute to the need for acute admission, and will substantially influence the hospital course and discharge plans. Cognitive impairment, one such geriatric condition, is a major risk for delirium, which is associated with longer hospital length of stay, greater functional disability and increased mortality following hospitalization.[3]

Admission screening

At the time of admission, much of the focus is on evaluation and management of a disease-specific, perhaps life-threatening illness. However, elderly patients should be screened for issues of importance in the care, particularly issues that are likely to affect the course, treatment and prognosis of the illness that precipitated the hospitalization.[6]

Medication reconciliation

Hospital admission is an important time for medication review. Clarification of the patient's medications, often prescribed by multiple physicians, and identification of potential adverse drug reactions (ADR) are two important aspects of medication review. ADR lead to one-third of the hospital admission in the elderly. Aging is not the only predictor of ADRs: polypharmacy is also an important factor. There are certain medications or classes of medication that have been identified by expert consensus panels as being high risk for ADRs in elderly patients; Tables 2-6 list the Beers criteria. These high risk medications such as sedatives, psychoactive drugs and analgesics should be avoided if possible.[7]

Identify Frailty

There are not precise definitions of frailty; many studies have shown that patients of advanced age, 80 and above or with functional impairments are the most vulnerable and should be considered **'frail'**. Frailty puts patients at risk for further functional and cognitive decline, delirium and prolonged hospital stay, increased costs and mortality. Identification of frailty at admission should alert the physician to the need to further evaluate for dementia and other geriatric conditions.[3]

Functional screen

Functional measures are strong predictors of mortality and contribute more to prognosis in hospitalized older patients than comorbid illness, disease severity and diagnosis. Assessing activities of daily living (ADLs) and instrumental activities of daily living (IADLs) are well-known measures of functional impairment. Any documented mobility of ADL impairment should trigger physical therapy and /or occupational therapy assessment and should signal the need to institute early mobilization.[8]

Dementia screening

Screening for dementia is particularly important in the elderly patient who is losing weight, noncompliant with mediations and readmitted to the hospital. Impaired judgment can impact a patient's ability to make sensible health decisions. While diagnosis of dementia is based on DSM-IV criteria, two common screening tools are Mini-Mental Status Examination (Table 7) and the Mini-Cog Screening (Table 8). Impairments on either test should result in active planning for cognitive stimulation and comprehensive discharge planning.

Hospital Stay

Hospitalization presents many hazards for older patients. The elderly are at five times increased risk for iatrogenic complications during hospitalization. Older patients have an average 35% risk of functional decline during acute hospitalization. In addition, they are at increased risk for the development of delirium. Thus, considerable attention must be given to creating a systematic approach to preventing and treating common hospital complications in the geriatric population.

Common problems in hospitalized elderly patients

Delirium

Delirium is an acute confusional state marked by inattention and a fluctuating course. The confusion assessment method is frequently used to diagnose delirium (Table 9).[9] The incidence of delirium in hospitalized older patients is as high as 50% and is associated with increased mortality and hospital length of stay. Delirium in elderly patients can be present atypically, such as in the hypoactive form where it often goes unrecognized by physicians and nurses. Many aspects of hospitalization promote delirium for the older patient. The change in environment is disruptive to the patient's daily routine. Pain, interruption of sleep patterns, and several classes of medications as listed in Beer's criteria are important risk factors for delirium. Effective measures to prevent delirium include orientation protocols, environmental modification, early mobilization, use of visual and hearing aids, adequate pain treatment and reduction in polypharmacy.

Immobility and Falls

Older hospitalized adults are at greater risk of falling due to the effects of acute illness along with unfamiliar environment and side effects of treatment. While all elderly patients are at risk for falling, the risk of falls increases with age. Multiple factors that can identify patients at the highest risk (Table 10).[10] Several strategies can help prevent falls in the hospital setting, such as avoiding medications that might increase the fall

risk and close supervision with ambulation for patients who are at risk for fall. Time out of bed throughout the day should be encouraged in order to prevent orthostatic hypotension associated with prolonged immobility; intravenous lines and urinary catheters should be discontinued as early as possible.[11]

Infections

Older patients have an increasing rate of nocosomial infections due to underlying health conditions, poor nutritional status and severity of illness. Atypical presentations are quite common, hence fever may not be present in older adults with active infection. Commonly seen infections in older hospitalized patients include:

Pneumonia - Hospital-acquired pneumonia (HAP) is pneumonia that occurs 48 hours or more after admission. The most significant risk factor for HAP is mechanical ventilation. Patient with advanced dementia, severe Parkinson's disease, or stroke, are also at high risk for aspiration pneumonia. Preventive measures include avoidance of acid-blocking medications, attention to oral hygiene, and feeding in an upright position.

Urinary Tract infections - Urinary tract infection associated with urinary catheters are the leading cause of secondary nocosomial bacteremia, which is associated with high mortality. The most effective strategies to reduce urinary infections are avoidance of unnecessary catheterization and catheter removal when this is no longer indicated.

Standard precautions are recommended in the care of all hospitalized patients to reduce the risk of infection transmission between patients and healthcare workers. Precautions include hand hygiene before and after every patient contact; use of gloves, gowns, and eye protection for situations in which there is exposure to body fluid.

Malnutrition

Poor nutrition for older hospitalized patients may result from several factors such as impaired cognition, poor appetite, restriction of movement, difficulty in self-feeding and restricted diet orders. In-patient assessment by a nutritionist can identify nutritional deficiencies in older patients, and combined with subsequent nutritional follow-up following discharge, may decrease mortality. In malnourished geriatric patients, providing liquid diet supplements may improve survival rates.[12]

Pressure Ulcers

Several host and environmental factors increase the risk of developing pressure ulcers during hospitalization in older patients, including poor nutritional status, incontinence, immobility and neurologic impairment. Optimizing nutritional status and limiting the time spent in one position can help prevent pressure ulcers. Patients who are bed-bound should be repositioned at least every two hours and pressure-reducing products for patients at increased risk of ulcers should also be used.

Hospital-Wide Interventions

Although limitations in the physiologic reserve for older patients are largely not modifiable, there are several strategies that can improve outcomes for older adults when implemented on a hospital–wide basis.

Multidisciplinary team - Multidisciplinary teams strive to integrate all care providers into the daily assessment and plan of care for older patients. Including input from the attending physician, geriatrician, nursing staff, physical therapists and dietician, can enhance the quality of care provided to the complex, frail elderly patients. The benefits of multidisciplinary care have been demonstrated in shorter length of stays, lower rate of complications and reduced hospital cost.[13-15]

Since not all hospitals have the resources to provide specialized units for older patients, some programs have attempted to re-create the core elements of multidisciplinary care units for hospitalized older persons who are not located in a single unit. Some hospitals have combined hospitalist-directed care with mobile geriatric care teams to provide enhanced care to older patients throughout the hospital. In a trial comparing hospitalized patients age > 75 assigned to an intervention involving an interdisciplinary geriatric team or usual care, patients who were assigned the intervention were associated with a lower rate of adverse events, shorter hospital stays and better satisfaction.[16,17]

Checklists and order sets - Checklists can improve the quality of care for older patients by integrating reminders into everyday care to ensure practice standards are met. Checklists can be tailored to remind staff about specific geriatric issues such as daily patient mobilization, readdressing the need for catheters, and assessing for the presence of delirium.

Early mobilization programs - It is important to ensure that patients are mobilized early and often during their hospitalization. Mobilization can help prevent falls. Observational studies find that increased mobility in the hospital is associated with less functional decline during hospitalization and shorter lengths of stay.[18-20]

Conclusion

Older adults represent a large and growing segment of hospitalized patients and are at high risk of complications

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during hospitalization, including falls, delirium, adverse drug events, infections, and death. The assessment of older hospitalized adults should extend beyond the traditional history and physical to include: assessment of physical function and cognition; social support; living situation; as well as an evaluation for possible polypharmacy. Many adverse outcomes encountered by older adults during hospitalization can be prevented. Some hospital-wide strategies are associated with improved outcomes for older adults, including care involving multidisciplinary teams, checklists, and early mobilization programs.

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Appendix

Table 1: Most frequent conditions causing hospitalization among older patients, 2003.

Rank	Principle diagnosis	% of all hospitalizations in older adults
1	Heart failure	6.3
2	Pneumonia	5.8
3	Coronary atherosclerosis	5.1
4	Cardiac dysthymias	3.7
5	Acute myocardial infarction	3.4

Source: AHRQ, Center for delivery, Organization and Markets, Healthcare cost and utilization project, Nationwide Inpatient sample 2003

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Table 2: 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.

Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Anticholinergics (excludes TCAs)					
− Doxylamine − Hydroxyzine − Promethazine − Triprolidine	Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate.				
Antiparkinson agents − Benztropine (oral) − Trihexyphenidyl	Not recommended for prevention of extra-pyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease.	Avoid	Moderate	Strong	Rudolph 2008
Antispasmodics - Belladonna alkaloids - Clidinium-chlordiazepoxide - Dicyclomine - Hyoscyamine - Propantheline - Scopolamine	Highly anticholinergic, uncertain effectiveness.	Avoid except in short-term palliative care to decrease oral secretions.	Moderate	Strong	Lechevallier-Michel 2005
Antithrombotics					
Dipyridamole, oral short-acting* (does not apply to the extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing.	Avoid	Moderate	Strong	De Schryver 2010 Dipyridamole Package Insert
Ticlopidine*	Safer, effective alternatives available.	Avoid	Moderate	Strong	Ticlopidine Package Insert
Anti-infective					
Nitrofurantoin	Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl <60 mL/min due to inadequate drug concentration in the urine.	Avoid for long-term suppression; avoid in patients with CrCl <60 mL/min.	Moderate	Strong	Felts 1971 Hardak 2010 Holmberg 1980
Cardiovascular					
Alpha1 blockers • Doxazosin • Prazosin • Terazosin	High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile.	Avoid use as an antihypertensive.	Moderate	Strong	ALLHAT 2000 Aronow 2011
Alpha blockers, central - Clonidine - Guanabenz* - Guanfacine* - Methyldopa* - Reserpine (>0.1 mg/day)*	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension.	Avoid clonidine as a first-line antihypertensive. Avoid others as listed.	Low	Strong	Aronow 2011 Methyldopa Package Insert Reserpine Package Insert

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Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Antiarrhythmic drugs (Class Ia, Ic, III) - Amiodarone - Dofetilide - Dronedarone - Flecainide - Ibutilide - Procainamide - Propafenone - Quinidine - Sotalol	Data suggest that rate control yields better balance of benefits and harms than rhythm control for most older adults.	Amiodarone is associated with multiple toxicities, including thyroid disease, pulmonary disorders, and QT interval prolongation. Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation.	High	Strong	Roy 2008 Doyle 2009 Fuster 2006 Van Gelder 2002 Wann 2011a Wyse 2002
Disopyramide*	Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred.	Avoid	Low	Strong	Fuster 2006 Disopyramide Package Insert
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or heart failure. In general, rate control is preferred over rhythm control for atrial fibrillation.	Avoid in patients with permanent atrial fibrillation or heart failure	Moderate	Strong	Connolly 2011 FDA Drug Safety 2011 Hohnloser 2009 Korber 2008 Dronedarone Package Insert – revised Dec 2011
Digoxin >0.125 mg/day	In heart failure, higher dosages associated with no additional benefit and may increase risk of toxicity; decreased renal clearance may lead to increased risk of toxic effects.	Avoid	Moderate	Strong	Adams 2002 Ahmed 2007 Rathore 2003
Nifedipine, immediate release*	Potential for hypotension; risk of precipitating myocardial ischemia.	Avoid	High	Strong	Furberg 1995 Nifedipine Package Insert Pahor1995 Psaty1995a Psaty1995b
Spironolactone >25 mg/day	In heart failure, the risk of hyperkalemia is higher in older adults if taking >25 mg/day.	Avoid in patients with heart failure or with a CrCl <30 mL/min.	Moderate	Strong	Juurlink 2004
Central Nervous System					
Tertiary TCAs, alone or in combination: - Amitriptyline - Chlordiazepoxide-amitriptyline - Clomipramine - Doxepin >6 mg/day - Imipramine - Perphenazine-amitriptyline - Trimipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; the safety profile of low-dose doxepin (≤6 mg/day) is comparable to that of placebo.	Avoid	High	Strong	Coupland 2011 Nelson 2011 Scharf 2008

Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Antipsychotics, first- (conventional) and second- (atypical) generation (see Table 5 for full list)	Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia.	Avoid use for behavioral problems of dementia unless non-pharmacologic options have failed and patient is threat to self or others.	Moderate	Strong	Dore 2009 Maher 2011 Schneider 2005 Schneider 2006a Schneider 2006b Vigen 2011
Thioridazine Mesoridazine	Highly anticholinergic and greater risk of QT-interval prolongation.	Avoid	Moderate	Strong	Goldstein 1974 Ray 2001 Stollberger 2005
Barbiturates - Amobarbital* - Butabarbital* - Butalbital - Mephobarbital* - Pentobarbital* - Phenobarbital - Secobarbital*	High rate of physical dependence; tolerance to sleep benefits; greater risk of overdose at low dosages.	Avoid	High	Strong	Cumbo 2010 McLean 2000 Messina 2005
Benzodiazepines Short- and intermediate-acting: - Alprazolam - Estazolam - Lorazepam - Oxazepam - Temazepam - Triazolam Long-acting: - Chlorazepate - Chlordiazepoxide - Chlordiazepoxide-amitriptyline - Clidinium-chlordiazepoxide - Clonazepam - Diazepam - Flurazepam - Quazepam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults. May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anesthesia, end-of-life care.	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium.	High	Strong	Allain 2005 Cotroneo 2007 Finkle 2011 Paterniti 2002
Chloral hydrate*	Tolerance occurs within 10 days and risk outweighs the benefits in light of overdose with doses only 3 times the recommended dose.	Avoid	Low	Strong	Bain 2006 Goldstein 1978 Miller 1979
Meprobamate	High rate of physical dependence; very sedating.	Avoid	Moderate	Strong	Keston 1974 Rhalimi 2009
Nonbenzodiazepine hypnotics • Eszopiclone • Zolpidem • Zaleplon	Benzodiazepine-receptor agonists that have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); minimal improvement in sleep latency and duration.	Avoid chronic use (>90 days)	Moderate	Strong	Allain 2005 Cotroneo 2007 Finkle 2011 McCrae 2007 Orriols 2011 Rhalimi 2009 Wang 2001b Yang 2011

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Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Ergot mesylates* Isoxsuprine*	Lack of efficacy.	Avoid	High	Strong	Isoxsuprine Package Insert
Endocrine					
Androgens • Methyltestosterone* • Testosterone	Potential for cardiac problems and contra-indicated in men with prostate cancer.	Avoid unless indicated for moderate to severe hypogonadism.	Moderate	Weak	Basaria 2010 Jones 2011
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available.	Avoid	Low	Strong	Baskin2002 Rees-Jones 1977 Rees-Jones 1980 Sawin 1978 Sawin 1989
Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women. Evidence that vaginal estrogens for treatment of vaginal dryness is safe and effective in women with breast cancer, especially at dosages of estradiol <25 mcg twice weekly.	Avoid oral and topical patch. Topical vaginal cream: Acceptable to use low-dose intravaginal estrogen for the management of dyspareunia, lower urinary tract infections, and other vaginal symptoms.	Oral and patch: high Topical: moderate	Oral and patch: strong Topical: weak	Bath 2005 Cho 2005 Epp 2010 Hendrix 2005 Perrotta 2008 Sare 2008
Growth hormone	Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose.	Avoid, except as hormone replacement following pituitary gland removal.	High	Strong	Liu 2007
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting.	Avoid	Moderate	Strong	Queale 1997
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults.	Avoid	Moderate	Strong	Bodenner 2007 Reuben 2005 Simmons 2005 Yeh 2000
Sulfonylureas, long-duration • Chlorpropamide • Glyburide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes SIADH Glyburide: higher risk of severe prolonged hypoglycemia in older adults.	Avoid	High	Strong	Clarke 1975 Gangji 2007 Shorr 1996

Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Gastrointestinal					
Metoclopramide	Can cause extrapyramidal effects including tardive dyskinesia; risk may be further increased in frail older adults.	Avoid, unless for gastroparesis.	Moderate	Strong	Bateman 1985 Ganzini 1993 Miller 1989
Mineral oil, given orally	Potential for aspiration and adverse effects; safer alternatives available.	Avoid	Moderate	Strong	Marchiori 2010a Marchiori 2010b Meltzer 2006 Simmons 2007
Trimethobenzamide	One of the least effective antiemetic drugs; can cause extrapyramidal adverse effects.	Avoid	Moderate	Strong	Bardfeld 1966 Moertel 1963
Pain Medications					
Meperidine	Not an effective oral analgesic in dosages commonly used; may cause neurotoxicity; safer alternatives available.	Avoid	High	Strong	Kaiko 1982 Szeto 1977 Meperidine Package Insert
Non-COX-selective NSAIDs, oral • Aspirin > 325 mg/day • Diclofenac • Diflunisal • Etodolac • Fenoprofen • Ibuprofen • Ketoprofen • Meclofenamate • Mefenamic acid • Meloxicam • Nabumetone • Naproxen • Oxaprocin • Piroxicam • Sulindac • Tolmetin	Increases risk of GI bleeding/peptic ulcer disease in high-risk groups, including those >75 years old or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents. Use of proton pump inhibitor or misoprostol reduces but does not eliminate risk. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2%–4% of patients treated for 1 year. These trends continue with longer duration of use.	Avoid chronic use unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol).	All others: moderate	Strong	AGS Pain Guideline 2009 Langman 1994 Lanas 2006 Llorente Melero 2002 Pilotto 2003 Piper 1991
Indomethacin Ketorolac, includes parenteral	Increases risk of GI bleeding/peptic ulcer disease in high-risk groups (See above Non-COX selective NSAIDs). Of all the NSAIDs, indomethacin has most adverse effects.	Avoid	Indomethacin: moderate Ketorolac: high;	Strong	Onder 2004

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Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Pentazocine*	Opioid analgesic that causes CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs; is also a mixed agonist and antagonist; safer alternatives available.	Avoid	Low	Strong	AGS Pain Guideline 2009 Pentazocine Package Insert
Skeletal muscle relaxants • Carisoprodol • Chlorzoxazone • Cyclobenzaprine • Metaxalone • Methocarbamol • Orphenadrine	Most muscle relaxants poorly tolerated by older adults, because of anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults is questionable.	Avoid	Moderate	Strong	Billups 2011 Rudolph 2008

*Infrequently used drugs

Abbreviations: ACEI, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CNS, central nervous system; COX, cyclooxygenase; CrCl, creatinine clearance; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TCAs, tricyclic antidepressants

The primary target audience is the practicing clinician. The intentions of the criteria include: 1) improving the selection of prescription drugs by clinicians and patients; 2) evaluating patterns of drug use within populations; 3) educating clinicians and patients on proper drug usage; and 4) evaluating health-outcome, quality of care, cost, and utilization data.

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Table 3: 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome.

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Cardiovascular						
Heart failure	NSAIDs and COX-2 inhibitors Nondihydropyridine CCBs (avoid only for systolic heart failure) • Diltiazem • Verapamil Pioglitazone, rosiglitazone Cilostazol Dronedarone	Potential to promote fluid retention and/or exacerbate heart failure.	Avoid	NSAIDs: moderate; CCBs: moderate; Thiazolidinediones (glitazones): high; Cilostazol: low; Dronedarone: moderate	Strong	Cilostazol Package Insert Connolly 2011 Dronedarone Package Insert – revised Dec2011 Heerdink 1998 Goldstein 1991 Jessup 2009 Korber 2009 Loke 2011 Pioglitazone Package Insert Rosiglitazone Package Insert
Syncope	Acetylcholinesterase inhibitors (AChEIs) Peripheral alpha blockers • Doxazosin • Prazosin • Terazosin Tertiary TCAs Chlorpromazine, thioridazine, and olanzapine	Increases risk of orthostatic hypotension or bradycardia.	Avoid	AChEIs and alpha blockers: high TCAs and antipsychotics: Moderate AChEIs and TCAs: strong	Alpha blockers and antipsychotics: weak	Bordier 2005 Davidson1989 French 2006 Gaggioli1997 Gill 2009 Kim 2011 Litvinenko 2008 Nickel 2008 Schneider 2006a Schneider 2006b Wild 2010
Central Nervous System						
Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	Lowers seizure threshold; may be acceptable in patients with well-controlled seizures in whom alternative agents have not been effective.	Avoid	Moderate	Strong	Pisani 2002
Delirium	All TCAs Anticholinergics (see Table 6 for full list) Benzodiazepines Chlorpromazine Corticosteroids H2 -receptor antagonist Meperidine Sedative hypnotics Thioridazine	Avoid in older adults with or at high risk of delirium because of inducing or worsening delirium in older adults; if discontinuing drugs used chronically, taper to avoid withdrawal symptoms.	Avoid	Moderate	Strong	Clegg 2011 Gaudreau 2005 Laurila 2008 Marcantonio 1994 Moore 1999 Morrison 2003 Ozbolt 2008 Panharipande 2006 Rudolph 2008 Stockl 2010

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Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Dementia and cognitive impairment	Anticholinergics (see Table 6 for full list) Benzodiazepines H2-receptor antagonists Zolpidem Antipsychotics, chronic and as-needed use	Avoid due to adverse CNS effects. Avoid antipsychotics for behavioral problems of dementia unless non-pharmacologic options have failed and patient is a threat to themselves or others. Antipsychotics are associated increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia.	Avoid	High	Strong	Boustani 2007 Hanlon2004 Finkle 2011 Frey 2011 Paterniti 2002 Rasmussen 1999 Rudolph 2008 Schneider 2005 Schneider 2006a Schneider 2006b Seitz 2011 Vigen 2011 Wright 2009
History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Nonbenzodiazepine hypnotics • Eszopiclone • Zaleplon • Zolpidem TCAs/SSRIs	Ability to produce ataxia, impaired psychomotor function, syncope, and additional falls; shorter-acting benzodiazepines are not safer than long-acting ones.	Avoid unless safer alternatives are not available; avoid anticonvulsants except for seizure	High	Strong	Allain 2005 Berdot 2009 Deandrea 2010 Ensrud 2003 Hartikainen 2007 Jalbert 2010 Liperoti 2007 Mets 2010 Sterke 2008 Turner 2011 van der Hooft 2008 Vestergaard 2008 Wagner 2004 Wang 2001a Wang 2001b Zint 2010
Insomnia	Oral decongestants • Pseudoephedrine • Phenylephrine Stimulants • Amphetamine • Methylphenidate • Pemoline Theobromines • Theophylline • Caffeine	CNS stimulant effects	Avoid	Moderate	Strong	Foral 2011
Parkinson disease	All antipsychotics (see Table 5 for full list, except for quetiapine and clozapine) Antiemetics • Metoclopramide • Prochlorperazine • Promethazine	Dopamine receptor antagonists with potential to worsen parkinsonian symptoms. Quetiapine and clozapine appear to be less likely to precipitate worsening of Parkinson disease.	Avoid	Moderate	Strong	Bateman 1985 Dore 2009 Ganzini 1993 Morgan 2005 Thanvi 2009

Disease or Syndrome	Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Gastrointestinal						
Chronic constipation	Oral antimuscarinics for urinary incontinence • Darifenacin • Fesoterodine • Oxybutynin (oral)	Ability to worsen constipation; agents for urinary incontinence: antimuscarinics overall differ in effectiveness	Avoid unless no other alternatives	For urinary incontinence: high All others: Moderate/low	Weak	Glass 2008 Meek 2011 Murray 1995 Perazella 1999 Schneider 2006 Sica 1989 Winkelmayer 2008
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen)	Aggravation of incontinence.	Avoid in women	High	Strong	Dew 2003 Epp 2010 Grodstein 2004 Hartmann 2009 Hendrix 2005 Perrotta 2008 Ruby 2010
Lower urinary tract symptoms, benign prostatic hyperplasia	Inhaled anticholinergic agents Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table 9 for complete list).	May decrease urinary flow and cause urinary retention.	Avoid in men	Moderate	Inhaled agents: strong All others: weak	Afonso 2011 Athanasopoulos 2003 Barkin 2004 Blake-James 2006 Chapple 2005 Griebling 2009 Kaplan 2006 Kraus 2010 Malone-Lee 2001 Martin Merino 2009 Spigset 1999 Uher 2009 Verhamme 2008 Wuerstle 2011
Stress or mixed urinary incontinence	Alpha-blockers • Doxazosin • Prazosin • Terazosin	Aggravation of incontinence.	Avoid in women	Moderate	Strong	Marshall 1996 Ruby 2010

Abbreviations: CCBs, calcium channel blockers; AChEIs, acetylcholinesterase inhibitors; CNS, central nervous system; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants

The primary target audience is the practicing clinician. The intentions of the criteria include: 1) improving the selection of prescription drugs by clinicians and patients; 2) evaluating patterns of drug use within populations; 3) educating clinicians and patients on proper drug usage; and 4) evaluating health-outcome, quality of care, cost, and utilization data.

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Table 4: 2012 AGS Beers Criteria for Potentially Inappropriate Medications to Be Used with Caution in Older Adults.

Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Aspirin for primary prevention of cardiac events	Lack of evidence of benefit versus risk in individuals ≥80 years old.	Use with caution in adults ≥80 years old.	Low	Weak	McQuaid 2006 Wolff 2009
Dabigatran	Increased risk of bleeding compared with warfarin in adults ≥75 years old; lack of evidence for efficacy and safety in patients with CrCl <30 mL/min	Use with caution in adults ≥75 years old or if CrCl <30 mL/ min.	Moderate	Weak	Connolly 2009 Diener 2010 Eikelboom 2011 Legrand 2011 Wann 2011b Dabigatran Package Insert
Prasugrel	Increased risk of bleeding in older adults; risk may be offset by benefit in highest-risk older patients (eg, those with prior myocardial infarction or diabetes).	Use with caution in adults ≥75 years old.	Moderate	Weak	Hochholzer 2011 Wiviott 2007 Prasugrel Package Insert
Antipsychotics Carbamazepine Carboplatin Cisplatin Mirtazapine SNRIs SSRIs TCAs Vincristine	May exacerbate or cause SIADH or hyponatremia; need to monitor sodium level closely when starting or changing dosages in older adults due to increased risk.	Use with caution.	Moderate	Strong	Bouman 1998 Coupland 2011 Liamis 2008 Liu 1996
Vasodilators	May exacerbate episodes of syncope in individuals with history of syncope.	Use with caution.	Moderate	Weak	Davidson 1989 Gaggioli 1997

Abbreviations: CrCl, creatinine clearance; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants

The primary target audience is the practicing clinician. The intentions of the criteria include: 1) improving the selection of prescription drugs by clinicians and patients; 2) evaluating patterns of drug use within populations; 3) educating clinicians and patients on proper drug usage; and 4) evaluating health-outcome, quality of care, cost, and utilization data.

Table 5: First- and Second-Generation Antipsychotics.

First-Generation (Conventional) Agents	Second-Generation (Atypical) Agents
Chlorpromazine	Aripiprazole
Fluphenazine	Asenapine
Haloperidol	Clozapine
Loxapine	Iloperidone
Molindone	Lurasidone
Perphenazine	Olanzapine
Pimozide	Paliperidone
Thioridazine	Quetiapine
Thiothixene	Risperidone
Trifluoperazine	Ziprasidone
Trifluoporazine	

Table 6: Drugs with Strong Anticholinergic Properties.

Antihistamines • Brompheniramine • Carbinoxamine • Chlorpheniramine • Clemastine • Cyproheptadine • Dimenhydrinate • Diphenhydramine • Hydroxyzine • Loratadin • Meclizine	Antiparkinson agents • Benztropine • Trihexyphenidyl	Skeletal Muscle Relaxants • Carisoprodol • Cyclobenzaprine • Orphenadrine • Tizanidine
Antidepressants • Amitriptyline • Amoxapine • Clomipramine • Desipramine • Doxepin • Imipramine • Nortriptyline • Paroxetine • Protriptyline • Trimipramine	Antipsychotics • Chlorpromazine • Clozapine • Fluphenazine • Loxapine • Olanzapine • Perphenazine • Pimozide • Prochlorperazine • Promethazine • Thioridazine • Thiothixene • Trifluoperazine	
Antimuscarinics (urinary incontinence) • Darifenacin • Fesoterodine • Flavoxate • Oxybutynin • Solifenacin • Tolterodine • Trospium	Antispasmodics • Atropine products • Belladonna alkaloids • Dicyclomine • Homatropine • Hyoscyamine products • Loperamide • Propantheline • Scopolamine	

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Table 7: Mini-Mental State Examination.[21]

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

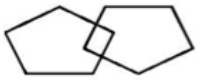
Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Table 8: Mini-Cog screening.[22]

The Mini-Cog scoring algorithm. The Mini-Cog users a three-item recall tests for memory and the intuitive clock-drawing test. The latter servers as an 'information distractor,' helping to clarify scores when the memory recall score is intermediate.

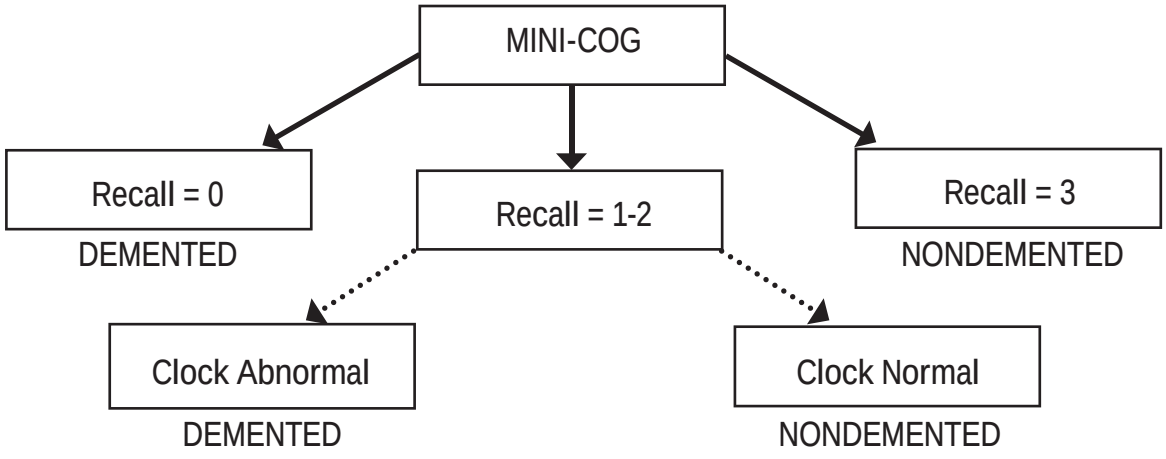


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Table 9: Confusion Assessment Method (CAM) screening.[23]

CONFUSION ASSESSMENT METHOD (CAM) SHORTENED VERSION WORKSHEET

EVALUATOR: DATE:

1. ACUTE ONSET AND FLUCTUATING COURSE

BOX 1

– Is there evidence of an acute change in mental status from the patient's baseline? No ____ Yes ____

– Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity? No ____ Yes ____

2. INATTENTION

Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said? No ____ Yes ____

3. DISORGANIZED THINKING

BOX 2

Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject? No ____ Yes ____

4. ALTERED LEVEL OF CONSCIOUSNESS

Overall, how would you rate the patient's level of consciousness?

– Alert (normal)

- Vigilant (hyperalert)
- Lethargic (drowsy, easily aroused)
- Stupor (difficult to arouse)
- Coma (unarousable)

Do any checks appear in this box? No ____ Yes ____

If all items in BOX 1 are checked and at least one item in BOX 2 is checked a diagnosis of delirium is suggested.

Table 10: Fall risk factors and associated relative risk.[24]

Risk factor	Mean relative risk ratio (range)
Muscle weakness	4.4 (1.5-10.3)
History of falls	3.0 (1.7-7.0)
Gait deficit	2.9 (1.3-5.6)
Balance deficit	2.9 (1.6-5.4)
Use of assistive device	2.6 (1.2-4.6)
Visual deficit	2.5 (1.6-3.5)
Arthritis	2.4 (1.9-2.9)
Impaired activities of daily living	2.3 (1.5-3.1)
Depression	2.2 (1.7-2.5)
Cognitive impairment	1.8 (1.0-2.3)
Age 80 and older	1.7 (1.1-2.5)

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Demonstration of a Complete Tear of the Pancreatic Duct by Magnetic Resonance Cholangiopancreatography (MRCP)

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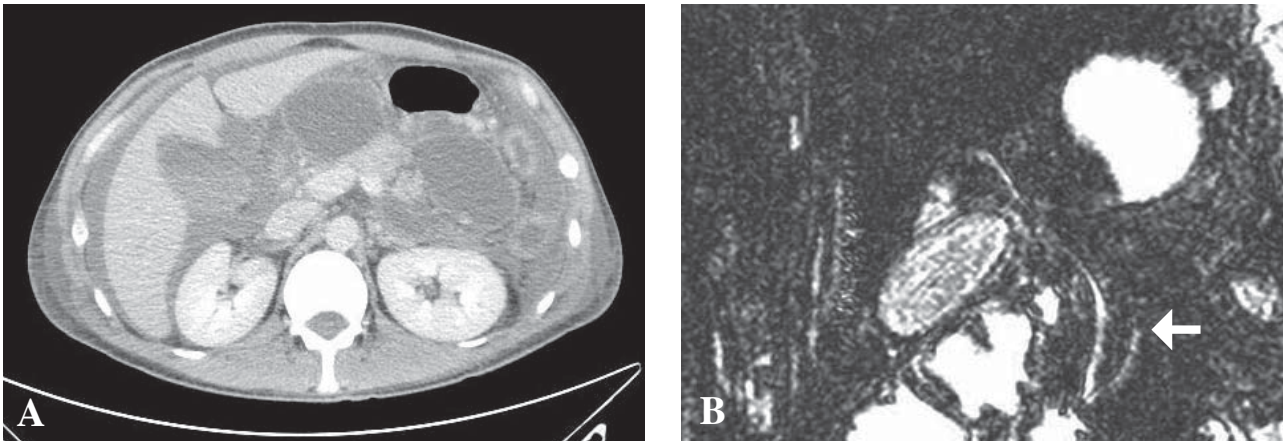

A 31-year-old man was involved in a motorcycle accident whilst riding and sustained a blunt abdominal injury. He was treated conservatively at a local hospital for 5 days before transferring to the Bangkok Hospital.

A whole abdomen CT showed a transverse tear at the body of the pancreas (Figure A) with hematoma at the anterior compartment of the retroperitoneum. The magnetic resonance cholangiopancreatography (MRCP) showed a good visualization of the common bile duct (CBD) and a distended gall bladder. Only the proximal of the pancreatic duct is visualized (see arrow Figure B). The findings suggested a complete tear of the pancreatic duct at the level of the body of the pancreas. The patient underwent an exploratory laparotomy. There was evidence of 2,000 ml of bloody fluid in the peritoneal cavity. A distal pancreatectomy was performed with drainage. He had an uneventful post operative course.

It is an art to handle a conservative management of pancreatic trauma. Previously observed cases of pancreatic injury resulted in high mortality rates. Today, we have CT scans and MRI which enables us to verify the extent of pancreatic tissue and pancreatic duct injury or the evidence of pancreatic cysts.[1] A CT of the abdomen is essential to properly evaluate the site of the organ injury. This is in order to verify the extent of internal organ trauma of the penetrated abdominal injury and to determine if the patient requires emergency surgery. In this case, a CT established laceration of the pancreas. Our hospital CT and MRI units are located close together. We are able to perform MRCP immediately. The total scan time for MRCP takes about 15 minutes using HASTE technique because this technique is performed during normal breathing and produces a 3D reconstruction.[2] The site of the pancreatic duct tear is well demonstrated. This is useful information for surgeons to make decisions and to minimize the operative time.

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Special Feature

Update of Inpatient Management of Polytrauma Patients

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Inpatient care of polytrauma victims requires careful attention to detail, and meticulous treatment of ongoing injuries and complications after the immediate resuscitation and damage control surgery. This discussion provides an update on the management of coagulopathy, respiratory failure, and prevention and treatment of venous thromboembolism in polytrauma victims. Specifically, the role of thromboelastography, ratios of blood product transfusions, newer modes of respiratory support including airway pressure release ventilation and veno-venous extracorporeal membrane oxygenation, and the use of mechanical and chemoprophylaxis for prophylaxis and management of venous thromboembolism are addressed.

Inpatient and intensive care of polytrauma patients requires careful attention to detail and frequent reassessment after transfer from the emergency department or operating room. Immediate concerns include evaluation and management of shock, control of bleeding, support of the respiratory system, prevention of complications, and correction of coagulopathy that may contribute to morbidity and mortality. A complete review of the management of polytrauma patients is beyond the scope of this paper, and a number of good reviews have been written to address this subject.[1,2] The goal of this discussion therefore, will be to provide an update on the management of coagulopathy, respiratory failure, and prevention and treatment of venous thromboembolism in polytrauma victims.

Initial management of shock in patients who have suffered polytrauma is aimed at damage control resuscitation with transfusions of blood products and fluids as the mainstay of therapy, and should be guided by repeated physical and laboratory examinations.[2] The goal of damage control resuscitation is to restore systolic blood pressure only to 80-90 mmHg (100 mmHg in patients with traumatic brain injury) to minimize bleeding from relative hypertension.[3] In general, intravascular volume should be repleted with blood products rather than isotonic fluids, and component therapy should be used to correct coagulopathy.[1] It is also critical to recognize that ongoing bleeding may be occult.

Many patients who are initially stabilized in the emergency department or operating room require delayed definitive treatment of other known injuries only when their conditions allow. It is important to avoid pitfalls in the care of trauma victims, including under-estimated bleeding from pelvic fractures, development of compartment syndrome, and missed injuries. Missed injuries are common in polytrauma patients, and have been reported in 1.5-39% of patients. Although most missed injuries are not life threatening, as many as 6.5% of trauma-related deaths are due to undiagnosed injuries. Most missed injuries involve the extremities, and most

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missed injuries are associated with an injury severity score ≥ 16 and a Glasgow coma scale < 8.

Coagulopathy

Coagulopathy often contributes to ongoing blood loss and shock from both missed and recognized injuries, and may be extremely difficult to manage. The damage control model of resuscitation relies on empiric ratios of transfusion products and includes goal directed hemostatic resuscitation with serial measurements of generally accepted measures of coagulation. Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio, fibrinogen levels and platelet counts guide therapy but are grossly inadequate measures of coagulopathy. Thus, the ideal transfusion ratio of red cells to plasma to platelets remains unclear, and is being addressed by the Pragmatic Randomized Optimum Platelet and Plasma Ratio (PROPPR) trial, an ongoing multicenter, prospective, randomized study that will evaluate different blood product ratios to be administered to trauma patients in need of > 10 U of PRBCs in the first 24 hours (http://ccctsp.sph.uth.tmc.edu/proppr_trial/SitePages/Home.aspx, accessed March 25, 2013).

Coagulopathy in polytrauma victims may be caused by a variety of factors, including acidosis, hemodilution, hypothermia, traumatic brain injury and the release of brain thromboplastin, disseminated intravascular coagulation, and the **"acute traumatic coagulopathy"** characterized by the activation of the thrombomodulin-Protein C system.[4,5] Routine tests of coagulation may be inadequate to accurately assess specific deficiencies in clotting mechanisms, and thromboelastography may be useful to guide goal-directed treatment of life-threatening coagulopathy with specific coagulation factors. Although thromboelastography was first described in 1948, it is not widely available, but it has recently been recognized as a useful tool to manage bleeding disorders from a variety of causes.

Thromboelastography is a functional assay that assesses the viscoelastic properties of clot formation and synthesizes information obtained from the PT, PTT, thrombin time, fibrinogen level and platelet counts. It then provides information regarding clot formation, clot strength, and fibrinolysis and may be used to guide therapy as well as to monitor the progress or resolution of an existing coagulopathy after trauma.[6]

Rapid thromboelastography provides data in real time[7] and is particularly useful in the operating room and intensive care units where ongoing life-threatening bleeding may occur. The data generated can then be used to direct which blood products are needed to treat ongoing hemorrhage - platelets, plasma, cryoprecipitate, desmopressin, aminocaproic acid, or specific clotting factors. Use of thromboelastography has been shown to decrease the transfusion of blood products and may improve outcomes in critically injured polytrauma victims.[4]

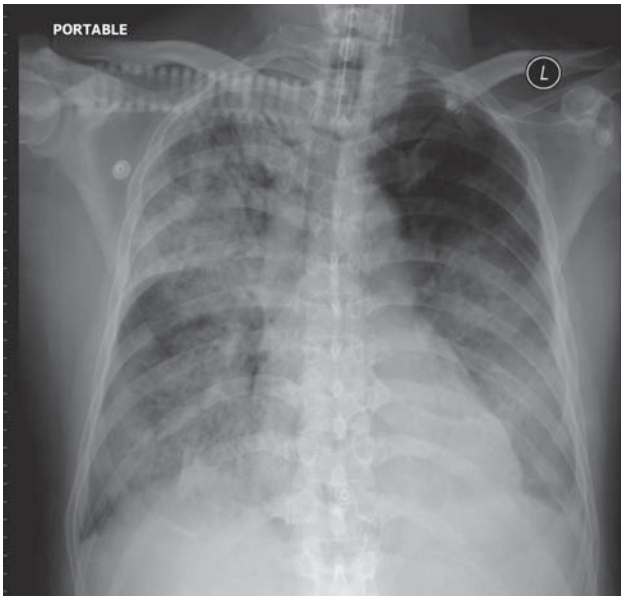
In the absence of thromboelastography, treatment of coagulopathy with blood products and clotting factors based on clinical data is the norm. In addition, tranexamic acid has been shown to be associated with decreased mortality when given within 3 hours of injury.[8] Tranexamic acid is a synthetic lysine derivative that inhibits lysine binding sites on plasminogen, blocking conversion of plasminogen to plasmin. It also inhibits the proteolytic action of plasmin on fibrin clot and platelet receptors and is an effective antifibrinolytic.

Recombinant activated factor VII is another effective procoagulant therapy. It acts locally at the site of tissue injury by binding to exposed tissue factor at the site of tissue injury. It increases thrombin generation and generates a tight fibrin hemostatic plug, thereby decreasing blood loss.[9] In spite of this, however, it has not been shown to alter mortality in trauma victims and it is extremely expensive.

Likewise, prothrombin complex concentrate containing factors II, VII, IX, and X is also capable of decreasing blood loss and may be useful in trauma,[9] but it is also expensive and more studies are needed to determine its role in the treatment of polytrauma victims.

Respiratory failure

Respiratory failure is common in severely injured patients, and results not only from pulmonary contusions or other trauma to the lungs or chest, but may also be caused by the development of the acute respiratory distress syndrome, transfusion related acute lung injury, or transfusion associated circulatory overload (Figure 1).



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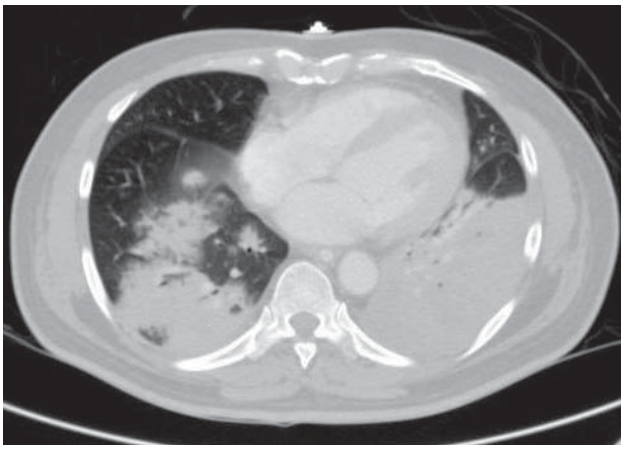

Figure 2: *CT of chest axial section reveals bilateral confluent ground-glass appearance.*

The goals of respiratory support are to ensure adequate oxygenation and ventilation and to prevent ventilator associated lung injury. Positive end expiratory pressure should be used with caution as high levels may impair venous return, especially in patients with inadequately restored intravascular volume, and the effects of lung or chest injury must be taken into consideration. Transfusion associated lung injury or circulatory overload may also affect the need for and manner of providing respiratory support.

The mainstay of respiratory support is lung protective ventilation with low (6 ml/kg predicted body weight) tidal volumes and limitation of airway plateau pressures (≤ 30 cm H_2O pressure). In patients with the acute respiratory distress syndrome this remains the single therapy that has been demonstrated to reduce mortality.[10] Newer modes of ventilatory support including airway pressure release ventilation (APRV), high frequency oscillatory ventilation, and veno-venous extracorporeal membrane oxygenation (ECMO) have been used in these patients with increasing success, and further studies are needed to determine whether these modes of support will ultimately improve outcomes in trauma patients with respiratory failure. Noninvasive modes of ventilation may also be used to avoid intubation and mechanical ventilation in select, less severely injured patients, and may be useful in some spinal cord injured patients. Because of increasing interest in APRV and ECMO, these modalities will be discussed in more detail.

Airway pressure release ventilation is a form of inverse ratio ventilation whereby a sustained level of increased positive airway pressure (P-high) is interrupted periodically and very briefly to a much lower level (P-low). The sustained positive pressure is intended to improve alveolar recruitment and thus improve oxygenation, which is dependent on both the amount of pressure delivered at P-high, and the amount of time (T-high) spent at P-high. Carbon dioxide elimination is achieved during P-low, and is dependent in part on the duration (T-low) of the reduced pressure. Patients can be ventilated with APRV whether they are ventilating spontaneously or not, and weaning is achieved by incrementally reducing T-high and P-high, and by increasing T-low and P-low. (For tutorials on the use of APRV and other ventilation strategies, see www.ccmtutorials.com/rs/mv.) Purported advantages of APRV include improved alveolar recruitment, especially in dependent lung zones, decreased peak airway pressures, and minimal hemodynamic effects. In a small study of trauma patients with acute lung injury, those patients ventilated with APRV required less sedation and neuromuscular blockade, less time on mechanical ventilation, and less time in the intensive care unit.[11] In spite of these advantages however, mortality was not improved in this study. APRV must be used with caution in patients with significant airflow obstruction, as significant pulmonary hyperinflation may occur, potentially resulting in impaired venous return and decreased cardiac function.

Veno-venous extracorporeal membrane oxygenation (ECMO) has been increasingly used in trauma patients with respiratory failure, although there have been no large-scale trials to substantiate its benefit. Accepted indications for ECMO include severe hypoxemia or respiratory acidosis in spite of maximal conventional support. Relative contraindications include irreversible lung injury, contraindications to anticoagulation, and respiratory failure requiring mechanical ventilation for longer than a week. In contrast to venoarterial ECMO, veno-venous ECMO provides respiratory but not hemodynamic support. In veno-venous ECMO, blood is extracted from the vena cava or right atrium and is returned to the right atrium. Cannulae are usually placed into the right common femoral vein (for drainage) and right internal jugular vein (for infusion), although double lumen cannulae are now available for placement in the internal jugular vein. The advantages of the use of a double lumen internal jugular cannula include the necessity for only a single venipuncture site, and increased mobility of the patient during recovery. A retrospective study showed that 20 of 28 consecutive trauma patients referred for ECMO survived, suggesting a possible role of ECMO in trauma patients with acute respiratory failure. (Cordell-Smith, Injury 2006) Small case reports have also suggested ECMO as a viable treatment option for respiratory failure in polytrauma victims.[12,13] More studies are needed, however, before recommendations can be made regarding the use of ECMO in this population.

Pulmonary embolism

Concomitant with ongoing evaluation and definitive treatment of injuries in polytrauma victims, avoidance of complications is crucial. Pulmonary embolism (PE) is common and may range in severity from trivial and incidentally discovered to massive and ultimately fatal.

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Polytrauma victims are at increased risk for PE because of immobilization due to spinal cord injury, long bone or pelvic fractures, and major surgery. Vascular injuries and the increasing use of central venous catheters also contribute to the risk.

The hemodynamic consequences of PE include right ventricular strain or even failure from vascular obstruction and vasoconstriction. In patients with massive PE, right ventricular failure and circulatory collapse is the primary cause of death. The pulmonary consequences of PE include inequality in the ratio of ventilation to perfusion as blood flow is redistributed. Blood flow is decreased distal to the embolic obstruction and normal regions of the lungs are subsequently over-perfused. Alveolar dead space increases and mixed venous oxygen saturation decreases. Atelectasis may occur distal to the embolic obstruction as a result of surfactant loss and alveolar hemorrhage, thereby worsening hypoxemia.

To prevent this complication, prophylaxis must be initiated as soon as possible, ideally with a combination of mechanical and chemoprophylaxis. Ongoing bleeding, severe head trauma, or lower extremity fractures may preclude the use of anticoagulants or sequential compression devices however.

Recommendations from the American College of Chest Physicians for prophylaxis in nonorthopedic surgical patients at moderate (approximately 3%) risk for deep venous thrombosis or PE include low molecular weight heparin or low dose unfractionated heparin in patients who are not at high risk for major bleeding, or mechanical prophylaxis with intermittent pneumatic compression devices.[14] Patients at higher risk (approximately 6%) for thromboembolism should receive a combination of low molecular weight or unfractionated heparin and mechanical prophylaxis. Recommendations for orthopedic surgery patients are similar but also include the possible use of anti-Factor Xia drugs, direct thrombin inhibitors, or other anticoagulant therapy.[15] Although the use of vena cava filters has become more widespread, particularly since the advent of removable filters, these devices are not recommended as primary prevention.

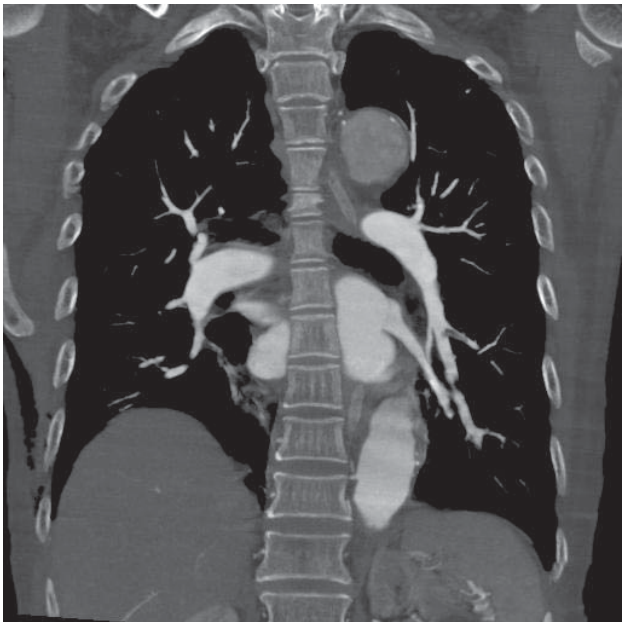

Figure 3: *CT pulmonary angiogram reveals small pulmonary embolism at descending branches of pulmonary arteries.*

Diagnosis of symptomatic pulmonary embolism is typically with CT angiogram (Figure 3), although conventional pulmonary angiogram and ventilation/perfusion scans are done preferentially in some centers. In patients with contraindications to radiocontrast agents, a presumptive diagnosis of PE can be made by demonstrating deep venous thrombosis using ultrasound, although there is a high false negative rate using this technique.[16]

Treatment of acute PE or deep venous thrombosis is typically with parenteral anticoagulation, and massive PE resulting in hemodynamic compromise requires thrombolytic therapy unless contraindicated by high risk or recent injury.[17] Patients with small incidentally-discovered PE may not always require therapy.

In a prospective study of 90 moderately to severely injured trauma victims with an Injury Severity Score of ≥ 9, 22 (24%) were found to have asymptomatic PE detected by CT scanning.[18] Of these,[17] patients had only minor clot burden (segmental and/or subsegmental clots only) and were not treated for thromboembolism. There were no deaths in the untreated group.

Conclusion

In patients who have suffered polytrauma, resuscitation continues after initial damage control resuscitation and surgery. Circulatory support is paramount and is typically best accomplished with blood product transfusions rather than crystalloids, but the proper ratio of blood products for transfusion remains unclear. Coagulopathy is common in polytrauma victims and has many causes including acidosis, hemodilution, hypothermia, traumatic brain injury, disseminated intravascular coagulation, and activation of the thrombomodulin-Protein C system. Correction of coagulopathy should be guided by laboratory studies and by ongoing clinical assessment, and may be aided by the use of thromboelastography where available.

Respiratory failure is also common, particularly in patients with chest trauma, and is best treated with lung protective ventilation using low tidal volumes and limited airway plateau pressures, but other modes such as APRV

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or even ECMO may have a role. Pulmonary embolism is a potentially fatal complication of polytrauma, so prevention is paramount. Although prophylaxis is ideally achieved with a combination of mechanical and chemoprophylaxis, the extent and nature of injuries may limit prophylactic options. Appropriate therapy for PE is typically with systemic anticoagulation, but depends on the clinical situation.

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Emergency Medicine: Clinical Essentials

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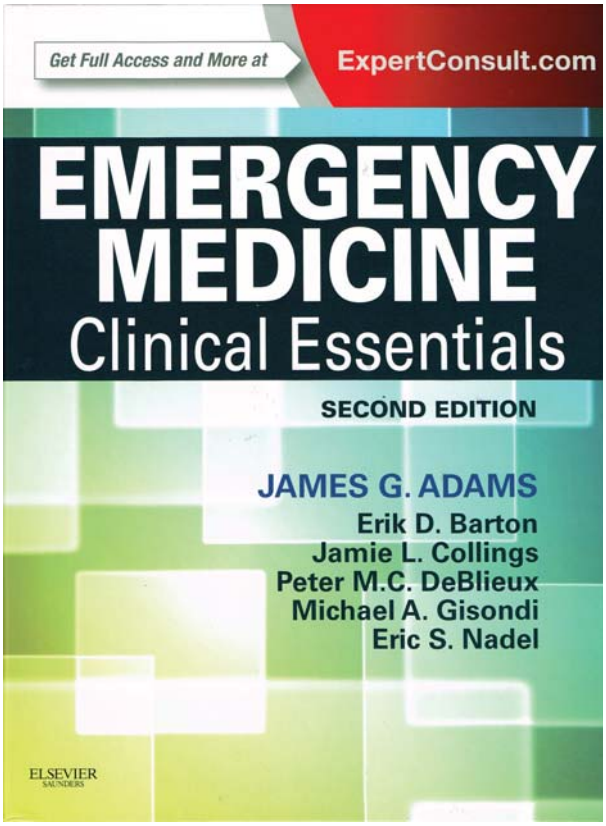

The Emergency Medicine Clinical Essentials 2nd Edition written by James G. Adams and his colleagues gives an up to date and comprehensive review of emergency medicine, including a thorough description and brief physiology review for every topic. With a specially designed format, the book has several tool boxes with summarized critical information such as key points, facts and formulas, red flags etc. that make this book very accessible; useful not only for the emergency physician but also for others needing a quick, consistent reference.

All recommendations provide essential information covering all patient care processes. The documentation guide is especially useful. The illustrations, clinical photographs and diagrams are clear. The descriptions are concise and use straightforward language. Though the book does not provide every detail in emergency medicine, it has all the essential elements that make it suitable as a quick guide in daily practice. The second edition also has new chapters covering such topics as Hemophilia and clotting disorders, antibiotic recommendations and patient centered care.

I give Adams full credit and highly recommend this book as a teaching tool and a practice guideline for emergency physicians and others who work in the emergency field.