Myanmar Medical Association

Training Centre

MYANMAR MEDICAL ASSOCIATION

MMA CME Book 2020

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MMA CME Book 2020

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Foreword

In many countries nowadays doctors do continuing medical education because it is compulsory to maintain their license to practice.

However, whether or not CME is compulsory it is required for the practising physician for the following reasons -

- Medicine advances all the time. New understandings of disease, new drugs and treatment regimens are being introduced all the time, more so in the past few decades along with scientific developments.
- If we are to provide the best treatment for the patient we need to be familiar with all the advancements that are available today. We should also be able to advise the patient about the best treatments available.
- CME will enable a physician to practise “patient safety.”
- CME ensures that a physician will remain competent continually. It will maintain his knowledge and skill in the practice of medicine.
- There could be less patient dissatisfaction and the consequences that could follow this e.g. litigation.

The term CME mainly focuses on medical knowledge. However, physicians also need to have skills other than medical knowledge such as social skills, personal skills, managerial and leadership skills. In addition physicians will need to know about research and they will be involved in teaching as well. If all these are put into the continuing education programme this will be known as continuing professional development or CPD. All these skills will ultimately affect the patient directly or indirectly. So nowadays we talk of CPD rather than CME only.

CPD is a process of lifelong learning and to ensure that all physicians are doing the best practice for all patients CPD has been made compulsory in many countries. Doctors need CPD points to renew their license to practice.

To achieve the ultimate aim of CPD this will have to be made accessible to all doctors. Traditionally this has been in the form of attending live lectures. However, medical journals publications, treatment guidelines and books are also useful for CPD. Myanmar Medical Association has been publishing a medical journal – the Myanmar Medical Journal – every 3 months regularly. Treatment guidelines and books have also been published by specialty societies of MMA. We are now introducing a CME book every year at the annual medical conference. We will be also providing an online CME programme very soon and we are also working with the World Medical Association to provide a CME platform which will be accessible to all doctors in Myanmar.

To maintain standards, legitimacy and credibility all CME/CPD programmes will need to be accredited and we are working with the Myanmar Medical Council to achieve this.

Myanmar Medical Association has been providing CME/CPD ever since it was founded. Now we are doing this more extensively and we will be expanding our services to all doctors so that when CME/CPD becomes compulsory, and the Ministry of Health and Sports has stated that this will be so in the near future, we will all be ready.

Meanwhile we should engage in CME/CPD because it is beneficial for us, it is beneficial for the patients.

Rai Mra

Professor Rai Mra
President
Myanmar Medical Association
January 2020

Droplet and Air-Borne Transmission

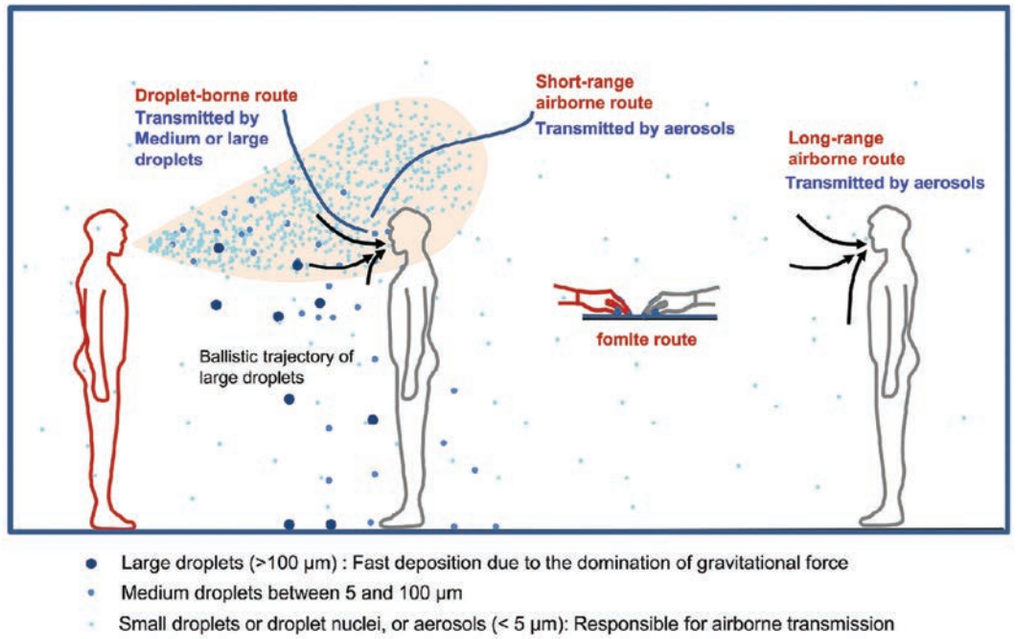
Microbiology Society

Airborne diseases

- Diseases caused by pathogens that small enough to be discharged from an infected person in a form of tiny droplets that are < 5 µm in diameter (called aerosols or droplet nuclei)
- The pathogen containing droplet nuclei suspended in air and disperse.

The term *airborne* means spread by aerosols that are transported by air currents over long time periods (minutes) and large distances (> 1 m). Thus, small aerosols contribute to the **airborne infection mode**, while larger aerosols (which settle out quickly) contribute to the **droplet infection mode**.

Examples of microorganisms that are spread by droplet transmission are: influenza, colds, respiratory syncytial virus (RSV) and some organisms causing pneumonia. There are 2 air-borne routes: short ranged air-borne route and long-ranged airborne route.



Droplets infections are caused by ingestion or aspiration of droplets carrying pathogens. Droplets are respiratory secretions, larger than aerosols (> 5 µm in diameter) that produced during laughing, talking, coughing or sneezing (Some accepted > 20 µm or > 60 µm) and don't remain airborne for long. They fall into the ground or onto surface shortly after being expelled. Droplets travel short distances, less than 3 feet (1 meter) from one person to another.

Some examples of microorganisms that are transmitted by the airborne route are: *M. tuberculosis*, rubella, varicella and hantaviruses.

Airborne and droplets infectious diseases

Airborne	Droplet
Influenza - both*	SARS - both*
Varicella (Chickenpox)	Pertussis
Measles	Strep throat
Anthrax	Ebola
Tuberculosis	Norovirus - both*

Generation of aerosols

Aerosols can be generated and released by human expiratory actions (speech, coughing, and sneezing), skin shedding, or re-suspension from surfaces.
Three droplet size distribution modes have been proposed:

Source	Activity	Droplet size
the bronchiolar fluid film	droplets produced during normal breathing	$d \leq 1$ µm
the laryngeal	most active during voicing and coughing	$d \geq 1$ µm
the oral cavity	active during speech and coughing	≥ 100 µm

Activity and number of droplet produced

Activity	Numbers of droplets produced
Exhalation	1-320 droplets/liter of Exhale air
Coughing	600 droplets
Speaking	4-600 droplets

Spread of droplets (Large droplets)

Activity	Velocity	Distance
Sneezing	50 m/s	6 meters
Coughing	10 m/s	2 meters
Breathing	1 m/s	< 1 meter

Duration of suspending

Size of droplet	Time to suspend or fall down
1-3 µm	Remain suspended indefinitely
10 µm	Took 15 minutes to fall 3 meter to the floor
20 µm	Took 4 minutes to fall 3 meter to the floor
100 µm	Took 10 second to fall 0.049 meter to the floor

Table of Survival Times of Microorganisms on Hard Inanimate Surfaces (BMC Infectious Diseases 2006: 6: 130)

Organism	Survival Time
Adenovirus	Up to 3 months
Clostridium difficile	Up to 5 months
Coronovirus	3 hours
E. coli	Up to 16 months
Influenza	1-2 days
MRSA	Up to 7 months
M. tuberculosis	Up to 4 months
Norovirus	Up to 7 days
RSV	Up to 6 hours

Relevance to Infection Control

involves blocking any stage of the infection pathway. For airborne transmission, this can mean reducing the generation of pathogens from an infectious person, using disinfection techniques to kill pathogens released to the air, or simply isolating infectious people in special rooms.

Controls generally fall into three categories: administrative, personal protection, and environmental and engineering.

Administrative controls aim to keep infectious people away from vulnerable people (infection detection, triage, communication, and education) and ensure that technical controls (e.g., engineering and personal protection) are used correctly. For the airborne transmission pathway, personal protection consists of some form of mask or respirator to prevent either the distribution or inhalation of pathogens. Engineering and environmental controls primarily intervene after pathogens leave the breathing zone from one person before they enter the breathing zone of another. (Advances in preventive medicine)

Respiratory infection could be reduced or eliminated by interruptions in 3 phases: release of pathogen at the source, transport of pathogen by air or by surface touch, and protection of the susceptible person.

Prevention of droplet release at origin by saline inhalation

A study found that delivering approximately 1 g of isotonic saline orally via nebulized aerosols (droplets 5.6 µm in diameter) reduced the total amount of expired aerosols (among super-producing individuals) by approximately 72% over a 6 hour period.

Use of masks for infected individuals and for susceptible individuals

Two reviews highlight the limited evidence base supporting the efficacy of face masks in reducing influenza virus transmission. They suggested that surgical masks may reduce infectiousness, rather than protect against infection, especially when airborne transmission is important. Influenza viruses (with sizes in the 80- to 120- nm range) and other viruses of similar size are capable of penetrating the mask in either direction. The N95 respirators are efficient in removing very fine droplet nuclei, but face masks are not. However, face masks, if worn by an infected person, can suppress the expired jets and reduce the close contact transmission via both the droplet-borne and short-range airborne routes.

Environmental ventilation for the long-range airborne route

A multidisciplinary systematic review suggested that ventilation rate and airflow patterns contribute directly to the airborne spread of infectious agents; however, the minimum ventilation rate for effective airborne transmission control is unknown at present.

The current minimum requirement is 12 air changes per hour for negative-pressure airborne isolation rooms. Natural ventilation may offer a low-cost alternative.

Because deposition is the main mechanism for removing large droplets, floor cleaning in hospitals is absolutely necessary.

Personalized ventilation for the short-range airborne route

This may be a less well-known technology in the infection control community. Its principle is based on detectable jets of air with a high momentum directed at a person's face. It may not be effective when the mobility of the subject is considered. An air supply pillow was suggested for hospital use. The personalized ventilation (PV) system can be supplemented with a general ventilation system in the room. Experiments with PV, together with vertical ventilation from ceiling-mounted terminals, show increased efficiency of personal protection by a factor of up to 35. A combination of PV and the personalized exhaust method was suggested.

Components of Respiratory Hygiene/Cough Etiquette Program

1. Posted signs/alerts to patients and family members
2. Covering mouth/nose when coughing with tissues or masks
3. Hand hygiene after contact with respiratory secretions
4. Spatial separation (ideally > 3 feet) of persons with respiratory infections, whenever possible
5. Droplet precautions for healthcare workers who provide care to patients with possible respiratory infections

Contact Precautions (CDC, 2007)

- Hand hygiene
- Gloves and gowns for all patient contacts
- Dedicated noncritical patient-care items, when possible
- Private room or cohort
- Limit patient movement/transport to essential purposes only

Droplet Precautions (CDC, 2007)

- Private room or cohort
- No special ventilation requirements; door may remain open
- Use of mask when providing direct care or within 3 feet of patient

Airborne Precautions (CDC, 2007)

- Private room with monitored negative air pressure
- 6 - 12 air changes per hour
- High efficiency particulate air (HEPA) filtration for re-circulated air
- HCWs wear respirators (minimum N95)
- Limit patient movement/transport to essential purposes only

Droplet transmitted diseases and length of isolation (CDC, 2007)

- Pharyngeal Diphtheria - until 2 sets of cultures are negative 24 hours apart
- Epiglottis from H. influenzae type B - 24 hours
- Seasonal influenza - 5 days
- Pandemic influenza - 5 days from onset of symptoms
- **H1N1 - 7 days from onset or 24 hours after symptoms resolve *whichever is longer**
  - Meningitis (H. influenzae type B) - 24 hours
- Meningitis (Neisseria Meningitidis) - 24 hours
- Meningococcal disease; sepsis, pneumonia, or meningitis - 24 hours
- Mumps - 9 days
- Mycoplasma pnuemonia
- Parvovirus B19 - up to 7 days in immunocompromised patients with chronic conditions
  - Pertussis (Whooping cough) - 5 days
  - Yersinia Pestis (Pneumonic) - 48 hours
- Pneumonia (Adenovirus) - duration of illness
- Pneumonia (H. Influenzae type B) infants and children - 24 hours
- Pneumonia (Streptococcus type A) adults and children - 24 hours
- Rhinovirus - duration of illness
- Rubella (German measles) - 7 days after onset of rash
- Severe Acute Respiratory Syndrome (SARS) - duration of illness plus 10 days

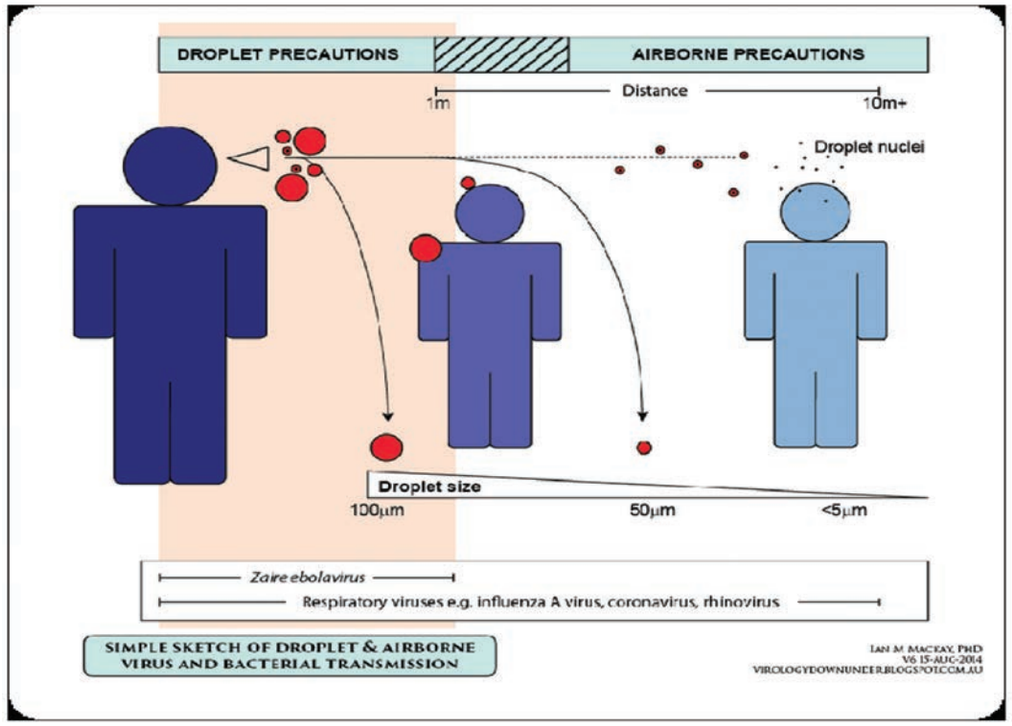
Airborne diseases and duration of isolation (CDC, 2007)

- Herpes Zoster (Shingles, Chickenpox) - duration of illness from unvaccinated healthcare personnel
- Measles (Rubella) - 4 days after onset of rash, duration of illness from for immuno-compromised people
- Monkeypox - until confirmed and small pox excluded
- Severe Acute Respiratory Syndrome (SARS) - duration of illness plus 10 days after resolution of illness
- Smallpox - duration of illness
- Tuberculosis (Extra-pulmonary with draining lesion, pulmonary or laryngeal confirmed or suspected) - until clinically improving or 3 consecutive negative wound cultures. For confirmed pulmonary or laryngeal, 3 negative AFB smears collected 8-24 hours apart.

Vaccine Preventable Aerosol Transmitted Disease (CDC, 2007)

- Diphtheria; Measles/Mumps/Rubella (MMR); Influenza; Pneumonia
- Varicella; Pertussis; Meningococcal infection; H1N1

Droplet Transmission	Airborne Transmission
• Contact with mucous membranes or conjunctivae with infected large particles **(> 5 µm in size)** • Requires **close contact** • Travel short distances (< 3 feet) • **Do not remain suspended in the air** • No special air handling or ventilation is required	• Small particle residue (< 5 µm in size) • Dissemination of droplet nuclei, evaporated droplets, or dust particles • Dispersed widely by air currents • Inhaled • Special air handling and ventilation **is required** (CDC, 1996)
Droplet Precautions • Used to prevent transmission of pathogens spread through close respiratory contact or mucous membrane contact with infected respiratory secretions • **Not infectious over long distances** • Single patient rooms are preferred • **Masks are worn upon entry to patient room** • If patient needs to be transported, the patient wears a mask (CDC, 2007)	**Airborne Precautions** • Used to prevent transmission of infectious agents that **remain infectious over long distances when suspended in the air** • Single-patient, negative pressure room • **Wear a mask or respirator (N95 mask or higher) prior to entry** • Non-immune healthcare workers should not care for patients with vaccine-preventable airborne diseases (CDC, 2007)



References

- Centers for Disease Control and Prevention. Guidelines for Isolation Precautions in Hospitals Hospital Infection Control Advisory Committee (1996). Retreived from: *https://wonder.cdc.gov/wonder/prevguid/p0000419/p0000419.asp*
- Centers for Disease Control and Prevention. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (2007). Retrieved from: *https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html*
- Centers for Disease Control and Prevention. Respiratory Hygiene/Cough Etiquette in Healthcare Settings (2009). Retrieved from: *http://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm*
- Centers for Disease Control and Prevention. Vaccines and preventable diseases (2010). Retrieved from: *http://www.cdc.gov/vaccines/vpd-vac/default.htm*
- Gold D. The Cal/OSHA aerosol transmissible disease regulation (2010).Retrieved from: http://www.cdph.ca.gov/programs/ohb/Documents/HCRespATDStandard.pdf
- World Health Organization. Standard precautions in health care (2007). Retrieved from: *http://www.who.int/csr/resources/publications/EPR_AM2_E7.pdf*
- Wei J and Li Y. Airborne spread of infectious agents in the indoor environment. *American Journal of Infection Control* (2016); 44 (9): S102-S108.
- Pearson ML. Basics of Airborne Infection Control, CDC, 2010.

Collection and Transport of Clinical Specimens

Microbiology Society

I. GENERAL INSTRUCTIONS

- All specimens for culture must be taken before institution of antimicrobial therapy.
- Collect adequate amount of the specimen from site where the organisms are most likely to be found and at a stage when the organisms may be found maximally.
- Apply strict aseptic techniques throughout the procedure.
- Give clear and correct instructions to the patient for collection of specimens as for example urine and sputum.

Sterile containers

- All specimens for culture should be collected in appropriate sterile containers.
- The containers must be provided with tightly fitted caps or lids to prevent leakage or contamination during transport.
- The container must be properly labeled with patient's name, site, date and time of collection.
- Outside of containers or laboratory forms should never be soiled with the specimens. If the outside of containers is contaminated by the specimen, it should be cleaned with disinfectants to prevent transfer of infection to those handling the container.

Specimen Requisition

The requisition should contain as much information as possible. A complete requisition should include the following:

- Patient's name
- Age
- Sex
- Registration number
- Address/Ward
- Collection date and time
- Source and type of specimen
- Tests requested
- Probable diagnosis/Clinical details
- Antimicrobial therapy

Transport of clinical specimens

- Transport specimens to the laboratory within 30 minutes of collection, or refrigerate immediately (except CSF, blood, specimens for anaerobes).
- Refrigerated specimens should be cultured within 2 to 3 hours.
- **Blood cultures should be incubated and never refrigerated.**

II. COLLECTION OF CLINICAL SPECIMENS FOR ROUTINE CULTURE

BLOOD

- Whenever possible, blood should be taken before antibiotics are administered.
- The best time is when the patient is expected to have chills or a temperature spike.
- Skin antisepsis is extremely important to reduce the risk of introducing contaminants into the blood culture media.

Method of Collection

- Using 70% alcohol, the skin over the venipuncture site is cleaned in a circle approximately 5 cm in diameter by rubbing vigorously.
- 2% tincture of iodine or 10% povidone iodine or chlorhexidine (0.5% in 70% alcohol) are applied in circles and left for 1-2 minutes to dry.
- Iodine is removed by a 70% alcohol wash.
- If the site must again be palpated after the iodine-alcohol preparation, the finger must be disinfected or sterile gloves worn.

Number and Timing

- It is recommended that two or preferably three blood cultures be obtained, separated by intervals of approximately 1 hour (or less if treatment cannot be delayed).
- The strategy depends upon the clinical condition and the degree of urgency to start antimicrobial treatment.

Volume of Blood to be collected

- Adults - 10 ml
- Children - 2-5 ml
- Infants and neonates - 1-2 ml

Immediately after collection of blood

- The top of the blood culture bottle is cleaned with ethanol swab and blood is injected into the bottle aseptically. If a patient has an existing IV line, blood should be drawn below the existing line. Blood drawn above the line will be diluted by the fluid being infused.
- *Note:* blood culture bottles should be stored at 4°C when not in use and pre-warmed to room temperature (25°C) or 37°C before inoculation.
- Blood culture bottles are available in a variety of sizes and volumes for adult and pediatric collections depending on the blood culture system used.
- Different broth formulations are available as are unique bottles for automated blood culture systems.
- All blood culture bottles must have their tops disinfected prior to collection using the manufacturer recommendations.

- After inoculation, swirl the bottle several times to mix and transport to a microbiology laboratory immediately
- If immediate transport to a microbiology laboratory is not feasible, place the inoculated blood culture bottle in an incubator at 35-37°C or at room temperature
- Inoculated blood culture bottles should not be placed in the refrigerator.

CEREBROSPINAL FLUID (CSF)

- CSF examination is done for the laboratory diagnosis of suspected meningitis and CNS infections. The specimen is collected aseptically only by a trained doctor/physician. The following important precautions need to be taken for CSF collections and transportation.
- CSF should be collected before administration of antibiotics as far as possible.
- 3-10 ml of CSF should be collected in 3-4 sterile screw capped containers for microbiological and chemical studies.
- It should be delivered immediately to the laboratory.
- Specimens should never be refrigerated.
- If CSF cannot be processed immediately it should be incubated at 37°C or left at room temperature.

SPUTUM

- Sputum is processed in the laboratory for diagnosis of bacterial and fungal infections of the lower respiratory tract. It is of utmost importance in the diagnosis of bronchopneumonia and pulmonary tuberculosis.
- If possible sputum should be collected before any antibiotic therapy is begun.
- Sputum should be collected in a sterile wide mouthed container, preferably disposable and leak proof to prevent leakage or contamination during transport.
- Early morning sputum samples should be obtained as they contain pooled overnight secretions.
- The patients should be instructed, to inhale deeply 2-3 times, cough up deeply from the chest and spit in the specimen container by bringing it close to the mouth.
- It is essential that sputum, containing purulent material or destroyed tissue brought by a deep cough and not saliva, be collected.
- Place about 5 to 10 ml of coughed up specimen into a sterile screw cap bottle.
- Send specimen to the laboratory within 30 minutes of collection.
- If delay in transport, refrigerate and send within 1 to 3 hours.

URINE

- All areas of the urinary tract above the urethra in a healthy human are sterile. The urethra and genitalia are normally colonized by bacteria many of which may cause urinary tract infection (UTI).
- Urine should be collected prior to antibiotic therapy.

- First morning sample is ideal and if this is not possible then collection should be done after holding the urine for atleast 3 hrs. For microbiological examination 5-10 ml urine should be collected as **clean catch midstream** urine specimen.

The patients are instructed to collect "clean catch midstream" specimens as follows:

1. Thoroughly cleanse the genitalia with soap and water (under supervision, if a child), and wipe with a clean, dry cloth.
2. Collect urine (after voiding and discarding an initial small amount) directly into a sterile wide-mouthed, screw-capped bottle.

- In a catheterized patient the soft rubber connector between the catheter and the collecting tube is cleaned vigorously with 70% ethanol and urine aspirated by a sterile syringe. Specimen should not be obtained from the collecting bag.
- Suprapubic aspiration is done for neonates and small children by disinfecting the skin over the bladder. Urine is aspirated by a 18 gauge short bevel spinal needle.
- Specimen should be processed within 2 hrs.
- In case of delay the specimen can be refrigerated for upto 6 hrs.

STOOL

- Stool for routine examination should be collected during the acute phase of diarrhoea.
- Specimen should be collected in a clean, dry, disinfectant free suitable wide mouthed container covered with a tight fitting lid. The container need not be sterile. Contamination with urine should be avoided.
- Volume of stool to be collected liquid - 1 tsp (5 ml), Formed stool pea sized (2 gm).
- Specimen should be delivered to the laboratory within 2 hours.
- In case of delay, specimen should be transported in transport media.

RECTAL SWABS

- Rectal swabs are used only if it is not possible to obtain faeces.
- Used for collecting samples in newborns or in severely debilitated patients.
- Swab should be inserted just beyond the anal sphincter and placed in transport medium, immediately to avoid drying.
- **When cholera is suspected**: A rectal catheter could be used to collect watery stool and should be sent in alkaline transport medium i.e. alkaline peptone water

WOUND, SKIN AND DEEP SEPSIS

- Pus or exudate should be aspirated from the depths of wounds and abscesses with a sterile needle and syringe.
- Specimen should be transferred to a small sterile leak proof bottle or a firmly stoppered tube or sealed capillary tube.
- If material cannot be obtained with a needle and syringe, then a swab must be used.

Two swabs one for direct microscopy and one for culture are taken from the depths of the wound or lesion and should be loaded well with the material.

- Specimen should be transported to the lab as soon as possible.
- In case of delay they should be transported in Amies transport medium.

THROAT SWAB

- Throat swabs are used for collecting samples from cases of pharyngitis and tonsillitis.
- For bacteriological sampling, albumin coated or charcoal coated or plain cotton wool swabs should be used.
- A bright light should be focused into the oral cavity.
- The patient is instructed to tilt his or her head back and breathe deeply. The tongue is gently depressed with a tongue depressor tovisualise the tonsillar fossae and posterior pharynx. The patient is asked to make the sound 'ah' which serves to lift the uvula and helps prevent gagging.
- The inflamed areas of the throat, tonsils and then the pharynx are swabbed, taking care not to touch the lateral walls of the buccal cavity or the tongue to minimise contamination with commensal bacteria.
- The swabs are placed in a sterile test tube.
- Swabs should be sent to the laboratory within 4 hrs.
- In case of delay they should be refrigerated or sent in a transport media.

GENITAL TRACT SPECIMENS

Uretheral discharge

From male patients

- If possible collect the early morning sample before the patient passes urine or collection done atleast 1 hour after urination.
- Clean around the uretheral opening usingsterile swab moisten with sterile saline.
- Apply gentle pressure on the penis so that a drop of pus appears at the meatus.
- If no pus appears, gently massage the urethra from above downwards.
- If material is scanty, collect by inserting a narrow diameter cotton swab 2 cm into the anterior urethra.
- Collect two swabs, one for direct microscopy and the second for culture.

From Female Patient

- The specimen should be collected by a doctor or trained nurse with the aid of a speculum.
- Observe all the precautions as for collection of specimens in male and collect two swabs, as mentioned above.
- Send it to the laboratory immediately. Do not refrigerate specimens sent for GC culture

VAGINAL SPECIMENS

- For examination of yeasts, *Trichomonas vaginalis* and bacterial vaginosis - A high vaginal swab (HVS) is collected.
- The specimen should be collected by a doctor or trained nurse with the aid of a speculum.
- Samples may be collected from the posterior fornix of the vagina using a sterile swab.
- Make a smear on a slide for gram staining.

GENITAL ULCER

- Wear protective gloves for this procedure.
- Clean the ulcer with a sterile gauze pad soaked in saline. Collect the exudate from the ulcer base with a sterile cotton swab.
- If there is no obvious serous fluid scrape the edge of the ulcer with a sterile flat edge of a scalpel blade till some blood is expressed.
- Blot the blood and then compress the ulcer gently with a gauze pad.
- Collect the exudate immediately on the slide and apply a coverslip.
- Transport should be done within 12 hrs.

EAR & EYE SPECIMENS

Ear specimens

- Collection of specimens should be done by trained personnel
- Collect the aspirate or swab in to a sterile leak proof container
- Transfer to laboratory as soon as possible. If delay is anticipated send the specimen inStuart's transport medium.

Eye specimens

- Collection of specimens should be done by trained personnel
- Use a dry sterile cotton swab for collection and transfer to laboratory immediately. If delay is anticipated send the specimen inStuart's transport medium.
- If fungal infection is suspected send a corneal scraping collected by the ophthalmologist.

Further Readings

1. Bailey & Scott's Diagnostic Microbiology Eds: Betty A. Forbes, Daniel F.Sahm, Alice S. Weissfeld, 12th edition Mosby 2007.
2. Color Atlas and Text Book of Diagnostic Microbiology. Eds: Elmer W. Koneman, Stephen D. Allen, William H. Janda, Paul C. Schreckenberger, Wahington C. Winn Jr. 6th edition, Lippincott Williams & Wilkin 2006.
3. Basic Laboratory procedures in clinical bacteriology. World Health Organization,Geneva, 2nd edition, 2003.

Principle of Fracture Management for General Practitioner

Myanmar Orthopaedic Society

Fracture management can be divided into non-operative and operative techniques. The non-operative approach consists of a closed reduction if required, followed by a period of immobilization with casting or splinting. Closed reduction is needed if the fracture is significantly displaced or angulated. Pediatric fractures are generally much more tolerant of non-operative management, owing to their significant remodeling potential.

Indications for surgical intervention include the following:

- Failed non-operative (closed) management
- Unstable fractures that cannot be adequately maintained in a reduced position
- Displaced intra-articular fractures (> 2 mm)
- Patients with fractures that are known to heal poorly following non-operative management (eg, femoral neck fractures)
- Large avulsion fractures that disrupt the muscle-tendon or ligamentous function of an affected joint (eg, patella fracture)
- Impending pathologic fractures
- Multiple traumatic injuries with fractures involving the pelvis, femur, or vertebrae
- Unstable open fractures, any type II or type III open fracture
- Fractures in individuals who would poorly tolerate prolonged immobilization required for non-operative management (eg, elderly patients with proximal femur fractures)
- Fractures in growth areas in skeletally immature individuals that have increased risk for growth arrest (eg, Salter-Harris types III-V)
- Non-unions or mal-unions that have failed to respond to non-operative treatment

Contra-indications to surgical reconstruction are as follows:

- Active infection (local or systemic) or osteomyelitis
- Soft tissues that compromise the overlying fracture or the surgical approach because of poor soft-tissue quality due to soft-tissue injury or burns, excessive swelling, previous surgical scars, or active infection
- Medical conditions that contraindicate surgery or anesthesia (eg, recent myocardial infarction)
- Cases in which amputation, rather than attempted fracture fixation, would better serve the limb and the patient

Non-displaced fractures all require a period of healing that may or may not involve cast care. In this time of aggressive operative treatment, only simple non-displaced fractures of long bones or joints may be treated with non-operative cast care; the rest are treated with emergency operative care so as to allow for early motion to prevent stiffness of adjacent joints.

Elements of Initial Fracture Management

The most important factors in fracture healing are blood supply and soft-tissue health, and initial management of an injured limb should have the goal of maintaining or improving these.

The initial management of fractures consists of realignment of the broken limb segment (if grossly deformed) and then immobilizing the fractured extremity in a splint. The distal neurologic and vascular status must be clinically assessed and documented before and after realignment and splinting. If a patient sustains an open fracture, achieving hemostasis as rapidly as possible at the injury site is essential; this can be achieved by placing a sterile pressure dressing over the injury site.

Splinting is critical in providing symptomatic relief for the patient, as well as in preventing potential neurologic and vascular injury and further injury to the local soft tissues. Patients should receive adequate analgesics in the form of acetaminophen or opiates, if necessary.

Open fractures

The treatment goals for open fractures are as follows:

- To prevent infection
- To allow the fracture to heal
- To restore function in the injured limb

Once the initial assessment, evaluation, and management of any life-threatening injury are completed, the open fracture is treated. Hemostasis should be obtained if there is significant ongoing bleeding, though bone bleeding is best reduced by anatomic reduction. Gross contaminants can be removed if possible and the soft-tissue wound can be covered by a sterile dressing moistened with normal saline. Harsher adjuncts, such as iodine solutions, are not recommended, because of their cytotoxic effects. Tetanus immunization should be provided if the patient does not have current immunity.

Bhandari's Evidence-Based Orthopedics provides an excellent overview of current best evidence for open fracture management. Time to antibiotic administration has been shown to be the most important factor in reduction of infection risk in open fractures; therefore, antibiotics should be given immediately.

For type I and type II fracture injuries, a first generation cephalosporin (eg, cefazolin) is adequate. If the wound is severely contaminated (type III), an aminoglycoside (eg, gentamicin, tobramycin) is commonly added to complement treatment. If the injury is a "barnyard injury" (contaminated with soil) or water-type injury, penicillin may also be added to provide prophylaxis against Clostridium perfringens and other anaerobes.

Rodriguez *et al* reported on the use of an evidence-based antibiotic protocol based on open fracture grade, in which patients with grade I or II fractures received cefazolin

(clindamycin in the case of allergy) and those with grade III fractures received ceftriaxone (clindamycin and aztreonam in the case of allergy) for 48 hours; aminoglycosides, vancomycin, and penicillin were excluded from the protocol. Implementation of this protocol for open fracture antibiotic prophylaxis led to significantly reduced use of aminoglycoside and glycopeptide antibiotics without increasing rates of in skin and soft-tissue infection.

Prophylactic use of quinolones is not appropriate, both because of the rapid development of resistant staphylococci and because quinolones are important drugs in the treatment of implant related infections.

There is little evidence available to guide the decision of appropriate duration to continue antibiotic administration, but general practice in North America is to provide 24 hours of coverage after definitive wound closure.

The traditional teaching of open fracture management was that urgent irrigation and debridement (I & D) of the wound in the operating room (OR) is mandatory within 6 hours and that open fractures are considered orthopedic emergencies. More recent data, such as the findings from the Lower Extremity Assessment Program (LEAP) suggested that surgical I & D within 24 hours of injury is sufficient. For type II and type III injuries, serial I & Ds are recommended every 24-48 hours after the initial debridement until a clean surgical wound is ensured and no necrotic tissue persists.

Debridement must be carried out by the most senior clinician available because experience has been proved to enhance infection prevention. All dead and devitalized tissue is removed, including all skin, bone, muscle, tendon, adipose, vessels, and nerves that are not viable and without blood supply. The best way of determining with assurance that a type of tissue is alive is to see if it bleeds.

A tumor-type resection is performed to ensure that all dead tissue is removed. Thorough irrigation is then carried out. If the wound is not too dirty, a single debridement may be satisfactory, but if there is any doubt as to the efficacy of the debridement, a second or third debridement should be planned. At this time, any tissues that were at all questionable with regard to survival will have declared themselves and either will be salvageable or will be best treated with excision.

There is some controversy with regard to the most appropriate type of irrigation fluid, the optimal volume, and the preferred degree of pressure. Antisepsis must be balanced against the cytotoxic effect on the native tissues. Bhandari *et al* advocated the use of simple normal saline for irrigation via a low-pressure delivery system. A widely accepted approach is to use a minimum of 3 L of irrigation for a type I fracture, 6 L for a type II fracture, and 9 L for a type III fracture.

The wound is closed when it is clean, ideally within 3-7 days of the initial injury; the risk of infection and flap failure rise precipitously when closure of type III fractures occurs more than 7 days after injury. Plastic surgery colleagues may need to be involved in the wound closure.

Management of the open fracture depends on the site of injury and type of open fracture. The wound is subsequently stabilized either temporarily or definitively. If soft-tissue coverage over the injury is inadequate between debridements, wet-to-dry dressings or negative pressure wound therapy (eg, vacuum-assisted closure [VAC] dressings) may be used. If the fracture reduction cannot be maintained between debridements, an external fixator may be used, with the pin sites well outside the zone of injury.

Non-operative Therapy

Early fracture management is generally aimed at controlling hemorrhage, providing pain relief, preventing ischemia-reperfusion injury, and removing potential sources of contamination (foreign body and nonviable tissues). Once these tasks are accomplished, the fracture should be reduced and the reduction should be maintained, which will optimize the conditions for fracture union and minimize potential complications.

The ultimate goal of fracture management is to ensure that the involved limb segment, when healed, has returned to its maximal possible function. This is accomplished by obtaining and subsequently maintaining a reduction of the fracture with an immobilization technique that allows the fracture to heal and, at the same time, provides the patient with functional aftercare. Either non-operative or surgical means may be employed.

Non-operative (closed) therapy consists of casting and traction (skin and skeletal traction).

Casting

Closed reduction should be performed initially for any fracture that is displaced, shortened, or angulated. This is achieved by applying traction to the long axis of the injured limb, reversing the mechanism of injury/fracture, and finally immobilizing the limb through casting or splinting. Splints and casts can be made from fiberglass or plaster of Paris. Barriers to accomplishing reduction include soft-tissue interposition at the fracture site and hematoma formation that create tension in the soft tissues.

Closed reduction is contraindicated in the following circumstances:

- If there is no displacement
- If displacement exists but is not relevant to functional outcome (eg, humeral shaft fracture where the shoulder and elbow motion can compensate for residual angulation)
- If reduction is impossible (severely comminuted fracture)
- If the reduction, when achieved, cannot be maintained
- If the fracture has been produced by traction forces (eg, displaced patellar fracture)

Traction

For hundreds of years, traction has been used for the management of fractures and dislocations that cannot be treated by means of casting. With the advancement

of orthopedic implant technology and operative techniques, traction is rarely used for definitive fracture/dislocation management. Two types of traction exist: skin traction and skeletal traction.

Skin traction

In skin traction, traction tapes are attached to the skin of the limb segment that is below the fracture or a foam boot is securely fitted to the patient's foot. In the application of skin traction, or Buck traction, usually 10% of the patient's body weight (up to a maximum of 10 lb) is recommended. At weights greater than 10 lb, superficial skin layers are disrupted and irritated. Because most of the forces created by skin traction are lost and dissipated in the soft tissue structures, skin traction is rarely used as definitive therapy in adults; rather, it is commonly used as a temporary measure until definitive therapy is achieved.

Skeletal traction

In skeletal traction, a pin (eg, a Steinmann pin) is placed through a bone distal to the fracture. Weights are applied to this pin, and the patient is placed in an apparatus to facilitate traction and nursing care. Skeletal traction is most commonly used in femur fractures: A pin is placed in the distal femur (see the image below) or proximal tibia 1-2 cm posterior to the tibial tuberosity. Once the pin is placed, a Thomas splint is used to achieve balanced suspension.

Surgical Therapy

The four AO (Arbeitsgemeinschaft für Osteosynthesefragen [Association for Osteosynthesis]) principles, in their basic form, have governed the society’s approach to fracture management for decades. They are as follows:

- Anatomic reduction of the fracture fragments - For the diaphysis, anatomic alignment ensuring that length, angulation, and rotation are corrected as required; intra-articular fractures demand anatomic reduction of all fragments
- Stable fixation, absolute or relative, to fulfill biomechanical demands
- Preservation of blood supply to the injured area of the extremity and respect for the soft tissues
- Early range of motion (ROM) and rehabilitation

Preparation for operative intervention

Detecting and adequately addressing all other injuries, including co-morbidities and preexisting medical conditions, is essential. If patients have multiple medical problems, consult an internal medicine specialist and/or anesthesiologist before performing any operative intervention.

Prophylactic antibiotics (cefazolin, 1 - 2 g) should be administered prior to incision. If the patient is allergic to penicillin, clindamycin can be administered. Patients with open fractures should be given appropriate antibiotic prophylaxis (see Elements of Initial Fracture Management). There is no evidence to support continuing prophylactic antibiotics beyond 24 hours postoperatively.

Open reduction and internal fixation

The objectives of open reduction and internal fixation (ORIF) include the following:

- Adequately exposing the fracture site
- Minimizing soft-tissue stripping
- Obtaining a reduction of the fracture
- Stabilizing and maintaining the reduction that has been achieved

Kirschner wires

Kirschner wires (K-wires) are commonly used for temporary and definitive treatment of fractures. However, K-wires resist only changes in alignment; they do not resist rotation, and they have poor resistance to torque and bending forces. K-wires are commonly used as adjunctive fixation for screws or plates and screws that involve fractures around joints.

When K-wires are used as the sole form of fixation, they are supplemented by casting or splinting. The wires can be placed percutaneously or through a mini-open mechanism. As stated by Canale, K-wire fixation "is adequate for small fragments in metaphyseal and epiphyseal regions, especially in fractures of the distal foot, wrist, and hand, such as Colles fractures, and in displaced metacarpal and phalangeal fractures after closed reduction. " K-wires are also commonly used as adjunctive therapy for many fractures, including patellar fractures, proximal humerus fractures, olecranon fractures, and calcaneus fractures.

Plates and screws

Plates and screws are commonly used in the management of articular fractures. This use demands an anatomic reduction of the fracture fragments and allows for early ROM of the injured extremity. Plates provide strength and stability to neutralize the forces on the injured limb for functional postoperative aftercare.

Plate designs vary, depending on the anatomic region and size of the bone the plate is used for. All plates should be applied with minimal stripping of the soft tissue.

Plates may be divided into five types on the basis of their main functions, as follows :

- Buttress (anti-glide) plates
- Compression plates
- Neutralization plates

- Tension-band plate
- Bridge plates

Locking plates or fixed-angle devices are also helpful.

Buttress plates encourage compression and counteract the shear forces that commonly occur with fractures that involve the metaphysis and epiphysis. These plates are commonly used with inter fragmentary screw fixation. The buttress plate is always fixed to the larger main fracture fragment but does not necessarily require fixation through the smaller fragment, because the plate buttresses the small fragment into the larger fragment. To achieve this function requires appropriate plate contouring for adequate fixation and support.

Compression plates counteract bending, shear, and torsional forces by providing compression across the fracture site via the eccentrically loaded holes in the plate. These plates are commonly used in the long bones, especially the fibula, radius, and ulna, and in nonunion or malunion surgery.

Neutralization plates are used in combination with inter fragmentary lag-screw fixation. The inter fragmentary compression screws provide compression at the fracture site. This plate function neutralizes bending, shear, and torsional forces on the lag-screw fixation, as well as increases the stability of the construct. Neutralization plates are commonly used for fractures involving the fibula, radius, ulna, and humerus.

Bridge plates are useful in the management of multi-fragmented diaphyseal and metaphyseal fractures. Achieving adequate reduction and stability without disrupting the soft-tissue attachments to the bone fragments may be difficult and requires skill in the use of indirect reduction techniques. Care should be taken to obtain correction of rotation, length, and alignment with bridge plating.

A tension-band plate technique converts tension forces into compressive forces, thereby providing absolute stability. An example of this technique is the use of a tension-band plate for fixation of a transverse olecranon fracture.

A locking plate acts like an internal fixator. There is no need to anatomically contour the plate onto the bone; consequently, bone necrosis is reduced, and a minimally invasive technique is possible. Locking screws directly anchor and lock onto the plate, thereby providing angular and axial stability. These screws are incapable of toggling, sliding, or becoming dislodged, thus reducing the possibility of a secondary loss of reduction, as well as eliminating the possibility of intraoperative overtightening of the screws.

The locking plate is indicated for poor-quality bone (ie, osteoporotic fractures), for short and metaphyseal segment fractures, and for bridging comminuted areas. These plates are also appropriate for metaphyseal areas where subsidence may occur or prostheses are involved. Locking plates can only hold a reduction that has already been obtained.

Intramedullary nails

The use of intramedullary nails over the past half century has been widely accepted. These nails operate like an internal splint that shares the load with the bone and can be flexible or rigid, locked or unlocked, and reamed or un-reamed.

Locked intramedullary nails provide relative stability to maintain bone alignment and length and to limit rotation. Ideally, intramedullary nailing allows for compressive forces at the fracture site, which stimulates bone healing. Intramedullary nails are commonly used for femoral and tibial diaphyseal fractures (see the image below) and, occasionally, humeral diaphyseal fractures. The advantages of intramedullary nails include minimally invasive procedures, early postoperative ambulation, and early ROM. Mid-shaft femur fracture managed with open reduction and internal fixation performed with use of an intramedullary nail.

Reference: Medscape (emidicine.medscape.com)

Allergic Rhinitis and Management Guidelines

Myanmar ORL, Head & Neck Society

Allergic rhinitis is a very common disease in general practice and it affects approximately 30% of population. The economic costs of allergic rhinitis are considerable and largest indirect costs are related to the loss of work and school days annually from the allergy itself and also from the negative side effects of allergic medications, especially antihistamines.

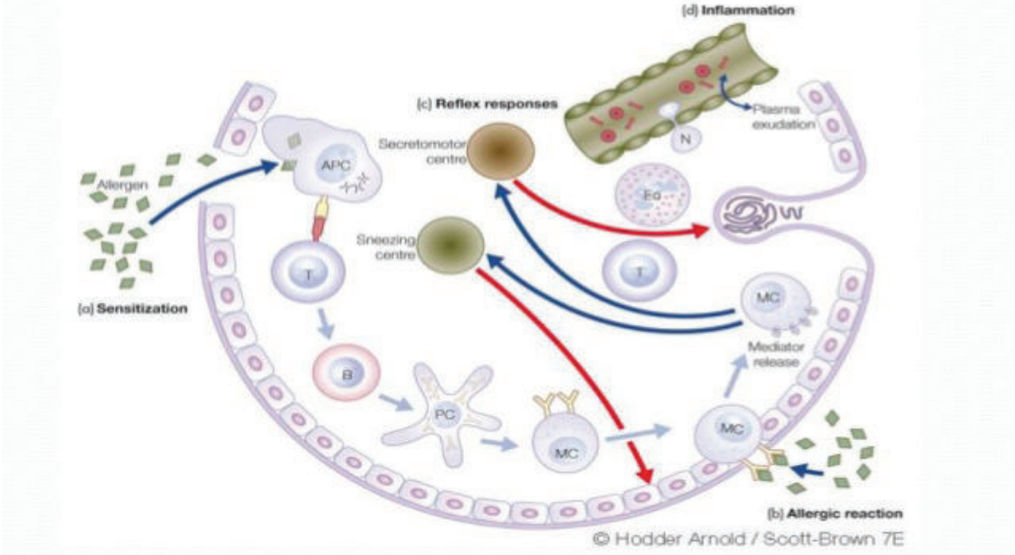
It is an inflammatory condition that affects the nasal mucosa.

Aetiology

Allergic rhinitis is a Ig E mediated type I hypersensitivity reaction in the mucous membranes of the nasal airways. Commonest allergens are highly soluble proteins or glycoproteins. Typical allergens include pollens, moulds, house- dust mite (*Dermatophagoidespteronyssinus* and *D. farinae*) and animal dentures.

Pathogenesis

This figure shows the four phases of allergic reaction in nose.



The allergic response is primarily mediated by a Type I hypersensitivity and it involves the excessive production of specific Ig E antibodies. Allergic cascade has 3 clinical phases that include (1) sensitization phase (2) early phase response (3) late phase response.

The immunoglobulin E is formed by plasma cells which are regulates by T-suppressor lymphocytes and T-helper cells.

Clinical features

The diagnosis of allergic rhinitis is mainly by clinically by patients' history that includes nasal congestion or blockage, clear and watery nasal discharge, post nasal drip, and itching of the nose, throat and eyes.

Electron microscopy of house dust mite and human squame

Thorough allergy history should determine if symptoms are seasonal or perennial. Patients should be asked about the onset, duration, type, progression and severity of their symptoms. Also the impact of their symptoms on the quality of life should be always questioned.

Physical examinations

It must include inspections of the ears, throat and nasal passages after decongestion with topical decongestant and with help of nasendoscope. Typical findings are bluish, pale, boggy turbinates with wet and swollen mucosa. Other abnormalities such as deviated nasal septum, concha bullosa and nasal polyps may be present. Other physical findings may include conjunctivitis, eczema and possibly asthmatic wheezing.

In children allergic shiners, facial grimacing, mouth breathing and nasal salute are common physical findings. Concomitant OME is also a possibility.

Special tests

1. **Allergy testing**

   Allergy testing is performed to establish objective evidence of atopic disease. It can also determine the causative allergens which would then lead to specific therapeutic recommendations. Two major types of testing available for identifying allergen sensitivity: skin testing and in vitro serum assays

Skin testing - it can be epi-cutaneous, intradermal or combination of both.

Skin prick test - It is the most common epi-cutaneous test used. It is quick, specific, safe, and economical test. With new multi-test system available, it is an easy and simple office procedure to perform. When the result is equivocal it is often followed with an intradermal test.

Intradermal testing - used quantitative 1:5 serial dilutions and method of choice for most allergists. It is an excellent quantifier of allergen sensitivity. Today most otolaryngologists use the skin prick test as a screening test prior to performing IDT.

In vitro testing - Allergen specific serum Ig E testing is an easy and accurate method for determining the presence of atopic allergy. This test is safe, specific, cost effective, reproducible and do not require the patient to be free of antihistamines and other medications that may interfere with skin testing. They are also easy and quick and therefore preferred in children and in anxious patients.

Treatment

In general there are three options available for the management of allergic rhinitis (1) avoidance and environmental controls (2) pharmacotherapy (3) immunotherapy.

General guideline is as follows:

- Education / allergen avoidance
- Pharmacotherapy
- Immunotherapy
- Others-nasal douching
- Surgery

Education/allergen avoidance

- Explanation of disease, progress (atopic march), treatments
- Genetics
- Breast feeding
- Parental smoking
- Allergen avoidance - primary/secondary

Pharmacotherapy

The selection of pharmacotherapy for a patient depends on multiple factors

- Symptom profile
- Cost/availability
- Patient compliance/ease of administration
- Response to previous treatment
- Pathophysiology of disease
- Associated medical conditions
- Side effect profile

Pharmacologic agents in the management of allergic rhinitis

Class	Mechanism of action
anti-histamines	Antagonize the H_1 receptor-mediated effects of histamines
decongestants	Act predominantly on α adrenergic receptors of the mucosa of the respiratory tract
Intranasal and oral corticosteroids	Exert a wide range of effects on multiple cell types and mediators
Mast cell stabilizers	Inhibit the release of mediators from mast cells
Anticholinergic agents	Antagonize the action of acetylcholine at muscarinic receptors
Leukotriene modifiers	Antagonize the action of leukotriene receptors or inhibit 5-lipoxygenase and the formation of leukotrienes

Antihistamines

They are used as first line therapy. They block H_1 receptor sites and prevent histamine induced reactions including inhibiting increased vascular permeability, smooth muscle contraction, increased mucous production and pruritus. First generation antihistamines can cause sedation and impair performance. Many have anticholinergic effects and cause dry mouth. Second generation antihistamines have a better safety profile and no anticholinergic activity with rapid onset of action.

Intranasal corticosteroids

Intranasal corticosteroids may be the most effective medications for the overall control of allergic rhinitis symptoms. They relieve sneezing, itching, and rhinorrhea and also nasal congestion. Their effectiveness depends on regular use and an adequate nasal airway for application. They have no systemic side effects with regard to HPSA axis suppression and do not effect long-bone growth in children. Local side effects such as dryness and epistaxis, can be reduced by careful patient instruction on their use and also the regular, concomitant use of intranasal saline.

Systemic corticosteroids

They may be necessary for severe, intractable symptoms. They can be administered either by intramuscular injections or orally with a tapering dose. Systemic steroids act on inflammation and significantly reduce all the symptoms of allergic rhinitis. The repeated dose can cause serious side effects such as HPA axis suppression and other common side effects of steroids.

Decongestants

Decongestants act on α adrenergic receptors of nasal mucosa producing vaso-constriction and reducing turbinate congestion. But they will not relieve rhinorrhea,

pruritus and sneezing. The use of intranasal decongestants can cause rebound nasal congestion and become addictive if used more than 3 - 4 days (rhinitis medica mentosa).

Intranasal anticholinergics

They tend to control only rhinorrhea and no other effects on allergy symptoms.

Intranasal cromolyn

They must be used prior to the onset of symptoms in order to be effective. This medication must be used throughout the entire exposure and considered to be very safe.

Leukotriene inhibitors

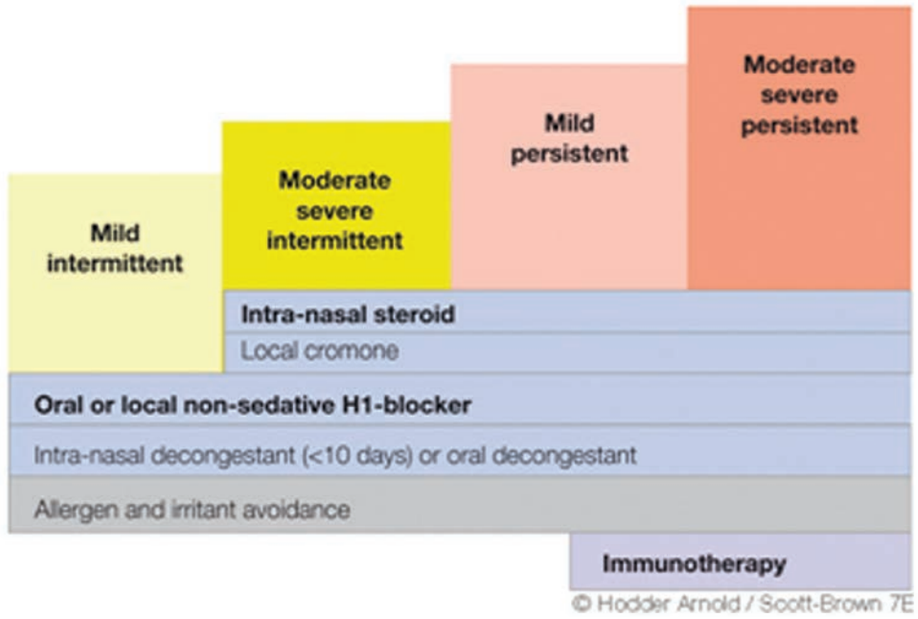
Montelukast is relatively new medication of the treatment of allergic rhinitis. Clinical studies have shown its efficacy to be greater than placebo but less effective than antihistamines and intranasal steroids.

Immunotherapy

It tends to increase the threshold level for the appearance of symptoms after aero allergen exposure.

Indications for immunotherapy include long-term pharmacotherapy for prolonged periods of time, the inadequacy or intolerability of drug therapy and significant allergen sensitivity.

General guidelines for pharmacotherapy



Prior to beginning of immunotherapy, the physician must confirm the actopic diagnosis by testing Ig E specific to the offending allergens. Most immunotherapy administered today is through a gradual increase of the dose of the antigens given until either a mild systemic symptom or a large local reaction at the subcutaneous injection site occurs. In some centers, sublingual immunotherapy is the method of choice. There is no adequate test available to indicate to the patient how long immunotherapy must be continued. A minimum of 2 - 3 years is usually given to avoid a rapid recurrence of symptoms in uncomplicated allergic rhinitis.

Other treatment considering include the first aspect of patients who have no responded well to therapeutic measures. The next steps are to adjust drug dosages, try 1 or 2 other agents and combination therapy. Surgery is mainly treating the sequalae of long standing allergic rhinitis such as inferior turbinoplasy.

Reference

Scadding. G and Stephen D. Allergic rhinitis. Scott-Brown's Otorhinnolaryngology, Head and Neck Surgery, 2008. 7th Edition. Hodder Arnold.Ltd.

Contraceptions

Myanmar Obstetrical and Gynaecological Society

Contraception is the prevention of conception or impregnation through the use of various devices, agents, drugs, sexual practices.

Family Planning

A program to regulate the number and spacing of children in a family through the practice of contraception or other methods of birth control.

Birth Spacing Methods

Hormonal Contraceptive Methods	
1. Oral Contraceptive Pills	Combined Oral Contraceptive Pills (COCs)
	Progestin-Only Pills (POPs)
2. Injectable	Depot medroxyprogesterone acetate (DMPA, Depo-Provera)
	Norethisteroneenanthate (NET-EN)
3. Implants	Jadelle
	Implanon NXT
	Implanex
Barrier Methods	
Condoms	Male Condoms
	Female Condoms
Intrauterine Device (IUD)	
Intrauterine Device (IUD)	Copper-Bearing Intrauterine Device
	Levonorgestrel Intrauterine Device (LNG-IUD)
Permanent Methods	
Sterilization	Female Sterilization
	Male Sterilization
Emergency Methods	
1. Emergency Contraceptive Pills (ECPs)	Progestin Only Pills with Evonorgestrel or Norgestrel
	Combined Oral Contraceptive with oestrogen and progesterone (COC)
	Ulipristal acetate (UPA)
2. Intrauterine Device (IUD)	Copper-Bearing Intrauterine Device
Others	
1. Natural Methods	1. Fertility Awareness Methods 2. Lactational Amenorrhea Method (LAM) 3. Withdrawal
2. Cervical Cap	
3. Diaphragm	
4. Spermicide	

Combined Oral Contraceptive Pills

The Combined Oral Contraceptive Pill (COCP) is a type of birth control that is designed to be taken orally by women. COCP contains a low dose estrogen (ethinyloestradiol in a dose of 15-35 µg) and progestrogen. The types of progestogens are second-generation (levonorgestrel, norethisterone), third-generation (gestodenedesogestrel) and fourth-generation progestogens (drospirenone and dienogest).

When to start COCP

COCP can be started up to and including Day 5 of a natural menstrual cycle without the need for additional contraceptive protection. A woman can start COCP if a high sensitivity urine pregnancy test is negative (i.e, she is sure to be not pregnant) and there was no unprotected sexual intercourse [UPSI] in the last 21 days. It can be started as soon as evacuation of miscarriage.

How to take COCP

Take one pill each day until the pack is empty. When she finishes one pack, she should take the first pill from the next pack on the very next day. When she missed some pills to take, please see missed pill guidelines.

Mechanism of Action

COCPs inhibit follicular development and prevent ovulation by suppressing the release of gonadotrophins. It is a primary mechanism of action.

Effectiveness of COCP

Percentage of women experiencing an unintended pregnancy within the first year of its typical use is 9% and its perfect use is 0.3%.

Contra-indications of COCP

(UK medical eligibility criteria category 4 conditions for use of combined hormonal contraception)

- Breast feeding a baby < 6 months
- Age > 35 years and smoking (≥ 15 cigarettes/day)
- Blood pressure ≥ 160/100 mmHg
- Hypertension with vascular disease
- Serious active liver disease, cirrhosis of liver, liver cancer and symptomatic gall bladder disease
- Diabetes for > 20 year with complication
- Current or past deep vein thrombosis, myocardial infarction, cerebrovascular accident

- Complicated valvular and congenital heart disease with (e.g. pulmonary hypertension, history of subacute bacterial endocarditis), cardiomyopathy with impaired cardiac function and atrial fibrillation
- Connective tissue disorders such as systemic lupus erythematosus (SLE) with positive anti-phospholipid antibodies and anti-phospholipid syndrome
- Known thrombogenic mutations
- Current breast cancer
- Migraine with aura at any age
- Major surgery with prolonged immobilization

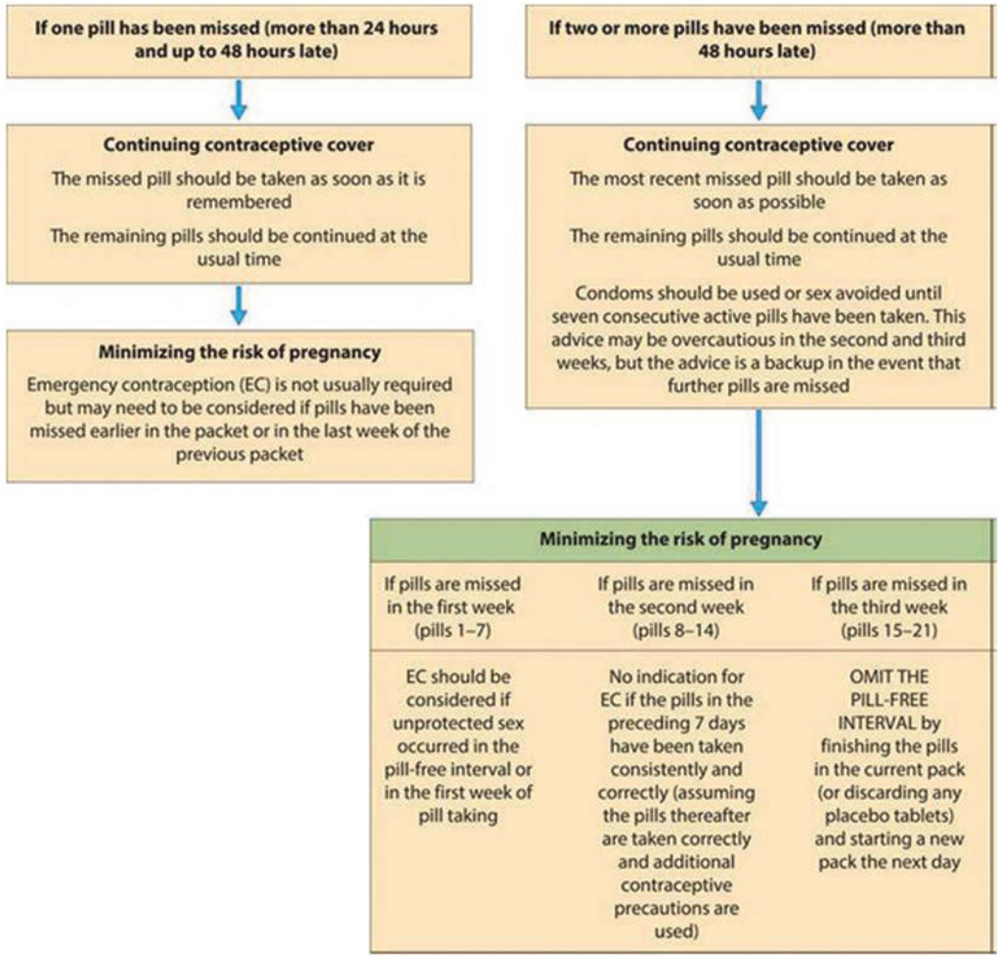
Side effects of COCP

- Cause breakthrough bleeding, weight gain or fluid retention, breast tenderness, nausea and mood change
- Increase cardiovascular disease (CVD) risks (myocardial infarction, stroke)
- Increase risk of breast cancer during use (decreases on stopping and similar risk to never used by 10 years after stopping)

Non contraceptive benefits of COCP

- Reduce risk of colo-rectal cancer, endometrial cancer, and ovarian cancer
- reduce heavy menstrual bleeding (HMB) and menstrual pain and can predict bleeding patterns
- Reduce risk of recurrence of endometriosis after surgical management (particularly continuous regimens)
- Drospirenone containing COC may be beneficial for women with premenstrual syndrome (PMS) and for weight control
- Co-cyprindiol (containing 35 µg ethinylestridiol with cyproterone acetate, an anti-androgen) is indicated for management of moderate to severe acne, hirsutism and management of symptoms of polycystic ovary syndrome (PCOS)

Missed pill guidelines (Adapted from Faculty of Sexual and Reproductive Healthcare, CEU Statement, 2011)



Progestogen-only contraception

The progestogen-only pill (POP or mini-pill) is only used by about 5% of women. Exluton (Lynestrenol 0.5 mg) has safety period of 3 hours and new generation POP, Embevin-28 (Desogestrel 0.075 mg) has safety period of 12 hours.

It is a useful alternative when the COCP is contraindicated because of estrogenic side effects. Precise explanations must be given to a woman commencing the POP. It must be taken at the same time each day, and taken continuously. If a pill is missed by more than 3 hours or 12 hours, a barrier method should be used for at least 7 days. If unprotected intercourse occurs after a missed pill, emergency contraception should be considered.

Mode of action

The POP acts to thicken cervical mucus and prevents sperm penetration. In 56 - 60% of women, ovulation may be inhibited and, in a small proportion, all follicular development may be suppressed, resulting in amenorrhea.

Indications

- During breast-feeding
- Women who are contraindicated for using COC pills
- Women at increased risk of thromboembolism

Side effects

- Irregular bleeding
- Has a relatively short half-life and a slightly increased failure rate

Injectable contraceptives

There are two long-term injectable contraceptive progestogens: depot medroxy-progesterone acetate (DMPA, Depo-Provera) 150 mg IM every 13 weeks, Sayana press (single-dose container with 104 mg medroxyprogesterone acetate in 0.65 ml suspension) subcutaneously every 13 weeks and norethisteroneenanthate (NET-EN) 200 mg IM every 8 weeks.

How to use

- Return for injections regularly and as scheduled. Coming back every 3 months (13 weeks) for DMPA or every 2 months for NET-EN is important for greatest effectiveness.
- Injection can be provided up to 4 weeks late for DMPA, 2 weeks late for NET-EN and 1 week late or early for monthly injectable. Client should come back even if later than scheduled date.
- Return of fertility is often delayed. It takes several months longer on average to become pregnant after stopping progestin only injectable than after stopping other methods.

Health Benefits

Helps protect against:

- Endometrial cancer
- Sickle cell crises among women with sickle cell anemia
- Symptoms of endometriosis (pelvic pain, irregular bleeding)
- Inexpensive, safe and effective
- can be used for breast-feeding mothers
- Particularly for women with poor compliance on other method

Contra-indications

- Patients who have multiple risk factors for CVD (such as smoking, diabetes, hypertension, obesity and dyslipidaemias)
- Ischemic heart diseases, stroke and vascular disease
- Cirrhosis of liver and liver cancer
- Current breast cancer
- Unexplained vaginal bleeding

Side Effects

1. Changes in bleeding patterns including,
   For DMPA users: First 3 months: Irregular/Prolong bleeding
   : At one year: No monthly bleeding, Infrequent/Irregular bleeding
   For NET-EN users: fewer days of bleeding in the first 6 months
   : less likely to have no monthly bleeding after one year than DMPA
2. Others: Weight gain, headaches, dizziness, abdominal bloating and discomfort, mood changes, less sex drive, loss of bone density

Contraceptive implants

Small plastic rods or capsules, each about the size of a matchstick, that release a progestin like the natural hormone progesterone in a woman's body.

Types of Implants:

- Jadelle - 2 rods (each rod contain levonorgestral 75 mg), effective for 5 years;
- Implanon NXT (Nexplanon) - 1 rod containing etonogestrel 68 mg, effective for up to 3 years. (Implanon NXT can be seen on X ray and has an improved insertion device).
- Sino-implant or Levoplant or Implanex (2 rods containing levonorgestrel), effective for up to 4 years of use.

Mechanism of action

Work primarily by thickening cervical mucus (this blocks sperm from meeting an egg) and disrupting the menstrual cycle, including preventing (ovulation).

Who Can Use LARC - Implants
Nearly all women can use implants safely and effectively, including women who:

- Are breast feeding
- Have or have not had children
- Are married or not married
- Are of any age, including adolescents and women over 40 years old
- Have just had an abortion or miscarriage or ectopic pregnancy

- Smoke cigarette - regardless of age and number of cigarette smoked
- Are infected with HIV, whether or not on anti-retroviral therapy

Contra-indications

- Cirrhosis of liver, liver adenoma and liver cancer
- Unexplained vaginal bleeding
- History of breast cancer or current breast cancer
- Current and history of ischaemic heart disease and stroke (history of cerebro-vascular accident, including TIA)

Side Effects
Complications of insertion (Uncommon)

- Infection at insertion site (most infections occur within the first 2 months after insertion)
- Difficult removal (rare if properly inserted and the provider is skilled at removal)
- Expulsion of implant (expulsions most often occur within the first 4 months after insertion)

Changes in bleeding patterns including: First several months:

- Lighter bleeding and fewer days of bleeding
- Prolong bleeding, Irregular bleeding and Infrequent bleeding

After about one year:

- Lighter bleeding and fewer days of bleeding
- Irregular bleeding and Infrequent bleeding

Side effects of progesterone

- Headaches and Dizziness
- Abdominal pain
- Acne (can improve or worsen)
- Weight change, mood changes and nausea
- Breast tenderness

Male Condom

It is a sheath or covering, that fit over a man's erect penis.

Mechanism of action

Prevent pregnancy by creating a physical barrier to the sperm from reaching and fertilizing the egg.

Advantages

Cheap and easy to carry, simple to use, disposable, protection against STDs, no side effects, useful where the coital act is infrequent and irregular, protection against cervical cancer and pelvic inflammatory disease.

Disadvantages

Slip, torn, inadequate sexual pleasure, disposable after one coital act

Contra-indications

Severe allergic reaction among people with latex allergy

Failure rate

2-13 HWY

Explaining how to use

Whenever possible, show clients how to put on a condom. Use a model of a penis, if available, or other item, like a banana, to demonstrate.

Explain the 5 basic steps of using a male condom

1. Using a new condom for each act of sex
2. Before any physical contact, place the condom on the tip of the erect penis with the rolled side out
3. Unrolled the condom all the way to the base of the erect penis
4. Immediately after ejaculation, hold the rim of the condom in place and withdraw the penis while it is still erect
5. Dispose of the use condom safely

Explain emergency contraceptive pills use in case of errors in condom use including not using a condom to help prevent pregnancy.

Copper-bearing intrauterine device (IUD)

The IUD is a long-lasting and highly effective method of contraception. It causes local inflammatory response in the endometrium, interfering with sperm and egg function and inhibiting fertilization and implantation. The duration of effectiveness of IUDs is 5-8 years.

Women who can use IUD

Nearly all women can use IUD safely and effectively, including women who:

- Are not married
- Are of any age, including adolescents and women over 40 years old

- Have just had an abortion or miscarriage (no evidence of infection)
- Are breast feeding
- Do hard physical work
- Have had ectopic pregnancy
- Have treated PID and vaginal infection
- HIV patient who is on anti-retroviral therapy and not immune-compromised

Contra-indications

- A woman who delivered more than 48 hours to less than 4 weeks.
- Immediate septic induced abortion
- Puerperal sepsis
- History of recent gestational trophoblastic disease
- Unexplained vaginal bleeding
- Distorted uterine cavity
- Very high risk of STIs
- Currently with purulent cervicitis, gonorrhea, chlamydia, PID, pelvic tuberculosis
- AIDS patient who is not clinically well/not on ART

When to start providing IUD

A woman can start using IUD anytime or within 5 days of menstrual cycle and any day of menstrual cycle if she is not sexual contact.

Side Effects

Changes in bleeding patterns (especially in the first 3 to 6 months) including:

- Prolonged and heavy monthly bleeding
- Irregular bleeding
- More cramps and pain during monthly bleeding

The levonorgestrel intrauterine System (LNG-IUS)

It is a T-shaped plastic device that steadily releases small amounts of levonorgestrel each day. (Levonorgestrel is a progestin widely used in implants and oral contraceptive pills). It is also called the levonorgestrel-releasing intrauterine system, LNG-IUS or hormonal IUD.

Mechanism of action

- preventing sperm from fertilizing an egg

Non contraceptive benefits

Suitable for women who have heavy menstrual bleeding, endometriosis or endometrial hyperplasia without atypia.

Contra-indications

- Cirrhosis of liver, liver adenoma and liver cancer
- Unexplained vaginal bleeding
- Had breast cancer
- Distorted uterine cavity

Side effects

- Changes in bleeding patterns including: lighter, infrequent bleeding
- Acne, headaches, nausea, dizziness, mood changes, weight gain, breast tenderness or pain
- Perforation of the uterus by the IUD or an instrument used for insertion

Emergency contraception

Emergency contraceptions help a woman avoid pregnancy after she has sex without contraception. Either hormonal contraception or a copper-containing IUCD can be used for emergency contraception within 5 days after unprotected sex.

Types of emergency contraception methods

- Progestin-only pills with levonorgestrel 1.5 mg single oral dose
- Ulipristal acetate (UPA) 30 mg single oral dose
- Copper-bearing IUD

Lactational amenorrhea method

This method based on natural effect of breast feeding on fertility. Provides contraception for the mother and best feeding for the baby.

The lactational amenorrhea method (LAM) requires 3 conditions. All 3 must be met:

1. The mother's monthly bleeding has not returned
2. The baby is fully or nearly fully breast fed and is fed often, day and night
3. The baby is less than 6 months old

Failure rate

2-1 HWY (hundred women per year)

Contra-indications

All breast feeding women can safely use LAM, but a woman in the following circumstances may want to consider other contraceptive methods:

- Using certain medications during breast feeding (including mood altering drugs, reserpine, ergotamine, anti-metabolites, cyclosporine, high doses of corticosteroids, bromocriptine, radioactive drugs, lithium, and certain anticoagulants)
- Newborn has a condition that makes it difficult to breast feed (including being small-for-date or premature and needing intensive neonatal care, unable to digest food normally, or having deformities of the mouth, jaw, or palate)

References

1. Family Planning Guideline for Service Providers (2018). Maternal and Reproductive Health Division, Ministry of Health and Sports.
2. Sharon Camerom (2017). Contraception and Abortion, In Ten Teacher, 20th edition, Gynaecology, Chapter (6), Pg. 99-112.
3. Faculty of Sexual & Reproductive Healthcare (FSRH) Guideline: Combined Hormonal Contraception, January, 2019.
4. Faculty of Sexual & Reproductive Healthcare (FSRH) Guideline, UK Medical Eligibility Criteria For Contraceptive Use, 2017.

Pediatric Headache

Myanmar Pediatric Society

Introduction

Headache is one of the most universally experienced aliments and also common in children affecting as many as 88% of the pediatric and adolescent population[1]. Certain forms of headache in children such as migraine impose not only significant disability due to prolonged periods of pain and school absenteeism but affect quality of life for the entire family. Diseases may include simple conditions such as sinus, ear, or dental problems or more severe disease including brain tumors.

A population-based study done in United States found that 17% of children reported frequent or severe headaches in the past year[2]. A systematic review of pediatric headache burden found that 58% of children experienced headache sometime during childhood[3]. Although most of the headaches are due to primary headache disorders such as migraine or tension-type headaches, in a small population, they may indicate a potentially life-threatening neurological condition. Headache phenotypes may differ between adults and children because childhood and adolescence is an active time of brain development and myelination and complaints may depend on age and developmental status of the child.

Epidemiology

Headaches are common in the pediatric population; however, there is significant variability in the results from studies of the prevalence of migraine and other pediatric headache syndromes[4]. The estimated overall mean prevalence of headache was 54.4% (95% CI 43.1-65.8) and the overall mean prevalence of migraine was 9.1% (95% CI 7.1-11.1)[5]. The prevalence of headache in school-aged children is similar in males and females and it increases more sharply in girls than boys during puberty[3]. In adolescents, 8% of girls and 5% of boys report a migraine and 27% of girls and 20% of boys report frequent or severe headaches within 1 year time period[6].

Phenotypes of headache

Headache phenotypes may be divided into four basic categories: acute, episodic, chronic progressive, chronic non progressive. Episodic and chronic non-progressive headaches are most likely related to a primary headache disorder although secondary causes are possible. However, if headaches are continuing to increase and severity which is chronic progressive in nature, complete testing including neuroimaging and CSF examination should be preceded. It is important to consider other potential causes of headache before making the diagnosis of migraine or simple illness-associated headache[7].

Table 1. Differential diagnosis of headache by pattern

Acute	Acute infection – upper respiratory tract infection, sinusitis, meningitis, encephalitis Hypertension Substance/toxin induced – substance use, medications, intoxications (lead, CO) Increased intracranial pressure (brain tumour, hydrocephalus) Vascular (intracranial haemorrhage, subarachnoid haemorrhage, cerebral venous sinus thrombosis) Migraine (first presentation)
Acute recurrent	Primary headache type – migraine, tension-type headache, autonomic cephalagia Seizures Hypertension Metabolic – hyperthyroidism, electrolyte disturbance Medication induced
Chronic non-progressive	Primary headache type – chronic migraine, chronic TTH Medication overuse headache Post-concussion syndrome
Chronic progressive	Increased intracranial pressure – brain tumour, hydrocephalus, pseudo-tumour cerebri Vascular – vascular malformation, aneurysm, haematoma Medications

Approach to Pediatric headache

To get the diagnosis of pediatric headache, it should be based on thorough headache and medical history, family observations, and examination.

History

The single most important factor in the evaluation of a child with headache is the history. This should include complete characterization of the headache and associated symptoms, past medical history, family history, stressors, sleep, mood, diet, hydration, activity, and triggers[4]. A common challenge that may make headache diagnosis difficult in younger children is the potential inability to self report symptoms. In such cases, headache drawings and asking the caregiver the manner of the child during severe headache period (e.g., photophobia, phonophobia or movement sensitivity) may be useful in distinguishing migraine versus non-migraine etiologies[8].

A series of helpful headache questions has been previously proposed by Rothner[7] and can be seen in Table 2.

Helpful questions	
When did the headache begin?	Chronic headaches are unlikely to reflect intracranial pathology. New onset worsening headaches are more likely to be due to a space-occupying lesion and require neuroimaging.
How did the headache begin?	Look for precipitants, such as head injury or social stresses.
What is the temporal pattern of the headaches?	Intermittent headaches separated by intervals of well-being are most likely to be migraines. Progressively more severe headaches are more likely to reflect pathology and require further investigations. Tension-type headaches (TTH) are usually chronic and non-progressive.
What is the headache frequency?	Migraines typically occur weekly or less often. TTH occur daily or several times per week. Headache syndromes in childhood, such as cluster headache, may have their own unique pattern, occurring in clusters of two to three per week over a few weeks or months, followed by long periods of headache freedom. Headaches due to increased intracranial pressure (ICP) often occur nightly.
How long does the headache typically last?	Migraines are often brief, lasting 30-120 min. Although the International Headache Society criteria define pediatric migraine as lasting upto 72 hrs, few pediatric patients have regular migraines that last this long. TTH often lasts “all day”. Cluster headaches are brief.
Do the headaches happen at any particular time or circumstance?	Headaches that occur at night or in the early morning are more likely to reflect increased ICP, although as many as 25% of migraine episodes occur at night. Children with TTH may describe waking with their headache, although this is typically after the child arises in contrast with increased ICP, which may wake up the child. Occasionally, headaches occur exclusively in one situation or circumstance (e.g., school, when hungry or with changes in weather).
Is there an aura or prodrome?	Children with migraines may be able to describe or draw their aura. If the aura is persistently on the same side, a structural lesion should be excluded. Parents may predict a migraine hours before it occurs because their child may show a prodrome of lethargy, mood change, thirsts or food cravings, yawning, or pallor.
Where is the pain?	Migraine is bifrontal in more than 55%. TTH is usually more diffusely located. The severity of pain is not helpful in identifying serious causes of headaches. An inability to describe the quality of the headache is much more likely to distinguish those with brain tumors or ventriculo peritoneal shunt malfunctions; occipital headaches are more likely to occur in children with brain tumors. Persistent unilateral headaches should be considered to be suspicious.

What is the pain like?	Offering choices helps to determine the quality of the pain. Migraines are typically throbbing, but may be described as heavy or pressing. An inability to describe the pain is more significant than the actual choice of adjective. Historical concepts of throbbing equating to migraine and band-like to TTH are probably inaccurate.
Are there associated symptoms?	Migraines are usually accompanied by nausea, vomiting, anorexia, photophobia, phonophobia, or osmophobia. Vomiting without accompanying nausea is suspicious. Migraine with aura may be associated with aphasia, vertigo, visual, sensory, or other associated symptoms. If symptoms persist beyond the headache or if the associated phenomenon is persistent from one headache to the next, thought should be given to possible underlying pathology.
What do you do during the headache?	What a child does if a headache begins during play is often more informative than asking what they do if a headache begins at school. Those with migraines will usually interrupt their activity to return home. Children with TTH will often watch television or play video games. In comparison, those with migraines usually seek refuge in a quiet and darkened bedroom.
Would I know you had a headache if I saw you?	The child with migraines usually looks ill. Those with TTH usually appear normal.
What makes the headache better and worse?	Details on medication use can provide insight into both the headache and the patient/family's preferences. Many report using large doses of medication despite its lack of benefit. Migraine soften describe benefit from sleep or simple analgesics taken early in the headache course. Aggravating factors in migraine include activity, light, noise, and smells. Those with increased ICP will often find increased discomfort on lying down. Headaches due to low ICP are usually worse on sitting or standing up.
Are there symptoms between headaches?	Patients with migraines or TTH are asymptomatic between headaches. Ongoing symptoms, such as forgetfulness, confusion, or localizing neurological symptoms suggest a structural lesion. Brain tumors may manifest as lethargy, personality changes, or recent school failure. Difficulties with concentration may persist beyond the headaches in those who have suffered a concussion. In the setting of chronic daily headache, co-morbid symptoms of depression may be present. Underlying psychosocial factors are common and may relate to learning difficulties, bullying, parental conflict, grieving reactions, and drug or alcohol abuse. In a population-based study, school-related factors, life style, and mental health were predictive of headaches in adolescence.
Are there any other health problems?	Children with chronic illnesses often feel stressed by their prognosis, they need to attend hospital visits and take medications. Those with hypertension may have “migraine-like” headaches.

Are you taking medications?	Headaches may occur as an adverse effect to medications used to treat other conditions or to treat the headaches themselves. It is important to understand the attitudes of the patient and parents toward medication. Quantifying the child's use of non-prescription analgesics will identify those at risk for rebound analgesic headaches. A medication history may also reveal exposure to medications associated with idiopathic intracranial hypertension, such as oral contraceptives, vitamin A, isotretinoin, tetracycline, and corticosteroids.
Is there a family history of headaches?	Many children with migraine or TTH have first-degree family members with similar headaches. In these families, educational efforts should be directed toward all those in the family with headaches.
What do you think is causing the headaches?	This is usually a very valuable question. Some children will identify a particular stressor of which the parents are often unaware. Both children and parents are also afforded the opportunity to discuss their fears of underlying pathology. A number of families will demonstrate a remarkable misunderstanding of the potential causes of their child's headaches. Many believe the headaches are caused by chronic sinusitis. There is no evidence to support chronic headaches as a result of chronic sinusitis.

Examination

Examination should include measurement of vital signs and a thorough physical examination: palpation of scalp, head, face, neck and shoulders to identify any evidence of limitation of nuchal movement, muscular tenderness, trigger points, occipital neuralgia or allodynia. Dental problems should be evaluated via oral examination with attention to teeth and temporomandibular function. A thorough neurological examination should be performed to screen for evidence of altered mental status as well as abnormalities in speech, vision, eye movements, sensation, strength, reflexes, gait or coordination. Any new focal abnormalities require further evacuation. A fundoscopic examination should be done to screen for evidence of increased intracranial pressure or other abnormalities related to headache.

Secondary Headache

In the pediatric who come to the emergency department for evaluation of headache, several factors have been associated with an intracranial space occupying lesion, including sleep-related headache, absence of family history of migraine, headache fewer than 6 months in duration, confusion, abnormal neurological examination, lack of visual aura symptoms, and vomiting[11]. If there are signs of some other underlying disorder or syndrome, the secondary causes should be considered. These may include infection, endocrinological abnormalities, autoimmune disorders, dental disease, autoimmune disorders, eating disorders, epilepsy, and pregnancy. In addition, medications may be associated with new or worse headache[13]. Headaches due to underlying intracranial disease should be considered if any of the red flag sign warning signs of increased ICP are present.

The followings are red flags of secondary headache[14].

- Age of onset (< 6 year)
- New headache type or progressive increase in severity and frequency of headache
- Exacerbation of headache with straining, sneezing, or coughing
- Sudden onset of severe headache (< 6 months in duration)
- Symptoms of systemic disease, which may include weight loss, night sweats, fever, joint pains, etc.
- Known systemic disorder, including hypercoagulable state, genetic disorder, cancer, rheumatological disorder, immunosuppression
- Abnormal neurological examination, including papilledema, altered mental status, ataxia, or other abnormalities or asymmetries
- Headache that wakes the child from sleep or that is always present in the morning

Neuroimaging

The American Academy of Neurology (AAN) practice parameter for neuroimaging in the evaluation of children and adolescents with recurrent headaches states that:

- Obtaining a neuroimaging study on a routine basis is not indicated in children with recurrent headaches and a normal neurologic examination.
- Neuroimaging should be considered in children with an abnormal neurologic examination, the coexistence of seizures, or both.
- Neuroimaging should be considered in children in whom there are historical features to suggest the recent onset of severe headache, change in the type of headache, or if there are associated features that suggest neurologic dysfunction[15].

Primary Headache Syndromes

There are several primary headache syndromes. Among them, migraine and tension-type headache are common in childhood and adolescents.

Migraine

Migraine is the most common form of primary headache disorder that causes disability in childhood[16] with an overall prevalence of 7.7% (95% CI, 7.6-7.8%)[3].

Diagnostic criteria of migraine without aura[9]

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

Pediatric migraines are usually briefer than adult attacks, often lasting only 30 to 60 minutes. In younger children, photophobia and phonophobia may be inferred from their behavior (eg. the child seeks out a quiet and dark place) and vomiting or vertigo may be the most obvious symptoms of migraine and may be prominent than headache.

Diagnostic criteria of migraine with aura[9]

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:
1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least three of the following six characteristics:
1. at least one aura symptom spreads gradually over 5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5-60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis.

Some children are unable to self report aura symptoms.

Tension-type headache

Tension-type headaches are much more common, usually cause much less disability and seek fewer medical visits than migraine. The pain is mild to moderate and often describes as a band-like pressure around head and can last for hours or days. Precipitating factors include fatigue, illness, and stress (similar to migraine), but can also include muscular discomfort and tension, particularly in the cervical and shoulder region. These headaches may be episodic (< 15 days per month) or chronic (≥ 15 days per month).

Less common primary headache syndromes

Trigeminal autonomic cephalalgias (TAC) such as cluster headaches, paroxysmal hemicranias, primary stabbing headache or ice-pick headache are less common in children.

Treatment of primary headaches

After excluding secondary causes of headache, we are able to establish an appropriate primary headache diagnosis and management can begin. Here we will discuss about treatment of migraine. There are four major domains of headache treatment:
1. lifestyle modification
2. abortive therapy
3. complementary therapies
4. preventive treatment

1. Lifestyle modification

Lifestyle modification is an important part of management. A variety of non-pharmacologic complementary and integrative treatments are utilized in the management of migraine headaches in children and adolescents. Those with migraine should aim to achieve regular and adequate sleep, to eat regular and nutritious meals (including breakfast), to limit caffeine intake to fewer than three servings per week, to maintain good hydration, to appropriately manage stress, and to exercise regularly in appropriate amounts[4].

2. Abortive therapy

Abortive therapy should be used at the onset of symptoms to minimize potential for medication overuse. Delay in acute treatment until migraine intensity peaks can lead to delay relief and decrease medication efficacy. Abortive treatments for migraines in children include the non-steroidal anti-inflammatory agents (NSAIDs), analgesics, and 5-hydroxytryptamine receptor agonists, commonly referred to astriptans. The most commonly used agent as a migraine abortive is the NSAID ibuprofen at a dose of 10 mg/kg/dose. Its onset of action is within 30 min of administration, and ibuprofen results in a significant reduction in head pain at 2 hr in 50-75% of migraine patients given a weight appropriate dose, compared to only 36-53% of patients on placebo[17]. Acetaminophen at a dose of 15 mg/kg results in similar improvement to ibuprofen, possibly with a faster onset of action[17].

If NSAIDs are not effective, one may consider using triptans (5-HT_1 receptor agonists) in appropriate circumstances. Although many different triptans are available for use in adults, only a few triptans have been approved by the US Food and Drug Administration (FDA) for migraine abortive therapy in children, but others have been studied[18]. Rizatrip-

tan has been approved for children age 6 years and older. Almotriptan has been approved for use in adolescents, and a combination of sumatriptan and naproxen was recently approved for use in adolescents[18]. There are some contra-indications to triptans such as cerebrovascular or peripheral vascular diseases, severe hepatic impairment, taking mono-amine oxidase inhibitors, uncontrolled hypertension and hemiplegic migraine.

However, to prevent medication-overuse headaches, abortive therapies should be used no more than 2 to 3 days per week (< 10-15 days per month for NSAIDs and < 8 days per month for triptans or caffeine)[19].

Table 3. Abortive therapies for pediatric migraine[14]

Drug	Usual dosage
Ibuprofen	10 mg/kg q 4-6 hr prn Age > 12 yr to adult: 400-600 mg every 6 hr Max: 2,400 mg/day
Naproxen sodium	5-7 mg/kg q 8-12 hr prn Age > 13 yr to adult: 250-500 mg every 8 hr Max: 1,250 mg/day
Acetaminophen	10-12.5 mg/kg q 4-6 hr prn Age > 13 yr to adult: 650-1,000 mg every 6 hr prn Max: 4,000 mg/day
5-HT$_1$ agonists, triptans	
Rizatriptan	Children < 40 kg: 5 mg oral once Children > 40 kg: 10 mg oral once Adult: 5-10 mg may repeat once in 2 hr oral disintegrating tablet or tablets Max: 30 mg/day (propranolol will increase serum concentration of rizatriptan)
Sumatriptan	Oral Child: 1 mg/kg, max: 50 mg/day Adult: 25-100 mg, max: 200 mg/day
Almotriptan	Age > 12 yr: 6.25-12.5 mg oral, may repeat once in 2 hr Max: 25 mg/day

3. Complementary therapies

Complementary therapies play an important role in the management of chronic or recurrent episodic headache. Biobehavioral techniques that may improve headache disability include cognitive-behavioral therapy, biofeedback therapy, yoga, relaxation techniques, acupuncture, hypnosis. Cognitive-behavioral therapy has the most scientific evidence to support its use for the management of chronic migraine in adolescents[20].

4. Preventive therapies

Preventive medications are indicated for patients who have significant disability related to their headaches. The goals are to reduce frequency, duration and severity of migraine attacks and to improve health-related quality of life and functioning in all spheres of the patient's life. There are no published guidelines when to start migraine preventive therapy in children. But there are some indications such as: ≥ 3-4 headache days per month, poor tolerance of abortive therapy, significant disability from frequent headaches that can be measured using Ped MIDAS[21]. For duration, the general recommendation is to provide treatment through the calendar year then gradually eliminate during summer vacation. Another option is that once headaches are under control for 3 to 6 months, slowly tapering off the daily medication should be done[4].

Table 4. Selective preventive agents used in pediatric migraine[14]

Cyproheptadine	Child: 0.25-1.5 mg/kg per day Adult: 4-8 mg up to 3 times per day (can give once per day at bedtime)
Tricyclic antidepressants	
Amitriptyline	10- 50 mg at bedtime 0.1 to 1 mg/kg/day Max: 50-100 mg for headache
Antiepileptics	
Topiramate	1-2 mg/kg/day for headache Typical adult/teen dose: 50 mg bid
Valproic acid	Child: 20-40 mg/kg/day Adult: 500-1,000 mg/day
Gabapentin	10-40 mg/kg/day Adult: 1,800-2,400 mg/day Max: 3,600 mg/day
Antihypertensives	
Propranolol	2-4 mg/kg/day Adult: 160-240 mg/day
Verapamil	4-8 mg/kg/day divided tid Adult: 240-480 mg/day divided tid

Conclusion

Although 90% of all headaches in pediatric population account for primary headache, it is still important to detect the signs and symptoms of secondary headaches. Primary headache tends to have stereo typed presentations and triggers. In pediatric headache, a stepwise approach (relevant history, examination, individualized investigations) is essential to avoid missing secondary headaches, to make the correct diagnosis as soon as possible, and to develop a multilayered treatment approach. Early and effective abortive therapy with necessary preventive measures will help not only the child but also the whole family.

References

1. Krogh AB, Larsson B, Linde M. Prevalence and disability of headache among Norwegian adolescents: across-sectional school-based study. *Cephalalgia* 2015.
2. Lateef TM, Merikangas KR, He J, *et al*. Headache in a national sample of American children: prevalence and comorbidity. *J Child Neurol*. 2009; **24 (5)**: 536-543.
3. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. *Dev Med Child Neurol*. 2010; **52 (12)**: 1088-1097.
4. Blume HK. Childhood headache: A brief review. *Pediatr Ann*. 2017; **46 (4)**: e155-e165.
5. Wöber-Bingöl C. *Curr Pain Headache Rep* 2013; **17 (341)**: 1-11.
6. Bigal ME, Lipton RB, Winner P, Reed ML, Diamond S, Stewart WF. Migraine in adolescents: association with socioeconomic status and family history. *Neurology*. 2007; **69 (1)**: 16-25.
7. Rothner AD. The evaluation of headaches in children and adolescents. *Semin Pediatr Neurol*. 1995; **2 (2)**: 109-118.
8. Stafstrom CE, Goldenholz SR, Dulli DA. Serial headache drawingsby children with migraine: correlation with clinical headache status. *J Child Neurol*. 2005; **20 (10)**: 809-13.
9. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia*. 2018, **38 (1)**: 1-211.
10. Zanchin G, Fuccaro M, Battistella P, Ermani M, Mainardi F, Maggioni F. A lost track in ICHD 3 beta: a comprehensive reviewon osmophobia. Cephalalgia SAGE Publications Sage UK: London, England. 2016; 8: 033310241667839.
11. Medina LS, Pinter JD, Zurakowski D, Davis RG, Kuban K, Barnes PD. Children with headache: clinical predictors of surgical space-occupying lesions and the role of neuroimaging. *Radiology*. 1997; **202 (3)**: 819-824.
12. Papetti L, Capuano A, Tarantino S, *et al*. Headache as an emergency in children and adolescents. *Curr Pain Headache Rep* 2015; **19 (3)**: 3.
13. Blume HK, Szperka CL. Secondary causes of headaches in children: when it isn't a migraine. *Pediatr Ann*. 2010; **39**: 431-439.
14. Blume HK. Pediatric headache: a review. *Pediatr Rev*. 2012; **33 (12)**: 562-576.

15. Lewis DW, Ashwal S, Dahl G, *et al*. Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Practice parameter: evaluation of children and adolescents with recurrent headaches: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2002; **59 (4)**: 490-498.
16. Abu-Arefeh I, Russell G. Prevalence of headache and migraine in school children. *BMJ*. 1994; **309 (6957)**: 765-769.
17. Hämäläinen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. *Neurology* 1997; **48 (1)**: 103-7.
18. Sakai F. Oral triptans in children and adolescents: an update. *Curr Pain Headache Rep*. 2015; **19 (3)**: 8.
19. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache*. 2008; **48 (8)**: 1157-1168.
20. Powers SW, Kashikar-Zuck SM, Allen JR, *et al*. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. *JAMA*. 2013; **310 (24)**: 2622-2630.
21. Kacperski J, Kabbouche MA, O'Brien HL, Weberding JL. The optimal management of headaches in children and adolescents. *The Adv Neurol Disorder*. 2016; **9 (1)**: 53-68.

Preoperative Fasting Guidelines

Myanmar Society of Anaesthesiologists (MSA)

Pulmonary aspiration of gastric or oropharyngeal contents during anaesthesia is a rare event, but one with significant morbidity and mortality. Fasting guidelines for patients having anaesthesia attempt to reduce the risk of aspiration and severity of the pulmonary effects should aspiration occur.

Pre-anaesthetic fasting guidelines apply to patients having elective surgery and are intended for procedures performed under general anaesthesia, regional anaesthesia and monitored anaesthesia care. Aspiration may occur during all types of anaesthesia in non-fasted patients because anaesthetic and sedative medications reduce or eliminate airway protective reflexes that normally prevent regurgitated gastric contents from entering into lungs.

Fasting recommendations

1. Clear liquids

No clear liquid is allowed within two hours of surgery, which means elective surgery requiring general anaesthesia or sedation. Clear liquids include water, juice without pulp, coffee and tea without milk, carbohydrate drinks, and should not include alcohol.

Clear liquids and gastric secretions move rapidly out of the stomach, 50% emptying time of water is approximately within 12 minutes. Glucose containing fluids initially leave the stomach more slowly, but after 90 minutes, the stomach is empty of clear liquids regardless of type. Gastric residual volume averages about 25 ml in patients fasted overnight prior to surgery. This is unchanged in patients who drink clear liquids, water, clear juices, coffee, tea or carbohydrate drinks up to 2 hours before surgery. Values for pH are also unchanged in patients drinking clear liquids.

2. Other liquids

Breast milk is not allowed within four hours of surgery. Other non-clear liquids such as non-human milk or formula milk and light meals are not allowed within six hours of surgery. Undiluted milk is considered as a solid because it contains variable amount of proteins and fat. Non-clear liquids are felt to empty more slowly from the stomach and may leave residual particulate matter.

3. Solid food

Patient may not eat solid food six hours before elective procedures requiring general anaesthesia or sedation; fasting interval should be increased to at least eight hours following a large or fatty meal.

Solid food takes longer than liquids to empty the stomach. It begins emptying after a delay of about an hour, and then empties in a linear fashion, with a half of the solid food passing into duodenum in about two hours. However, emptying times are quite variable and depend on volume and nutrient content of the meal. Gastric emptying is slowed by increased food weight, caloric density and addition of fat.

ASA Practice Guidelines Recommendations

Recommendations for Preoperative Assessment

Perform a review of pertinent medical records, a physical examination, and interview as a part of preoperative evaluation.

History, examination and interview should include assessment of ASA physical status, age, sex, type of surgery and potential for difficult airway management as well as consideration for GERD, dysphagia symptoms, other GI motility and metabolic disorders (eg. DM) that may increase risk of regurgitation and pulmonary aspiration.

Inform patient of fasting requirement

Verify patient compliance with fasting requirements at the time of their procedure

When these fasting guidelines are not followed, compare the risks and benefits of proceeding, with consideration given to the amount and type of liquid or solids ingested.

Recommendations for Clear Liquids

Clear liquids may be ingested for up to two hours before procedures requiring GA, regional anaesthesia or procedural sedation.

These liquid should not include alcohol.

Recommendations for Breast Milk

Breast milk may be ingested for up to four hours before procedures requiring GA, regional anaesthesia or procedural sedation.

Recommendations for Infant formula

Infant formula may be ingested for up to six hours before procedures requiring GA, regional anaesthesia or procedural sedation.

Recommendations for Solid or Non-human Milk

A light meal or non-human milk may be ingested for up to six hours before procedures requiring GA, regional anaesthesia or procedural sedation.

Additional fasting time (8 hr or more) may be needed in cases of patient intake of fried foods, fatty foods or meat.

Consider both the amount and type of foods ingested when determining appropriate fasting period. Since non-human milk is similar to solid in gastric emptying time, consider amount ingested when determining appropriate fasting period.

Recommendations for GI Stimulants

GI stimulants (Metoclopramide) may be preoperatively administered to patients at increased risk of pulmonary aspiration.

Do not routinely administer preoperative GI stimulants for purpose of reducing risk of pulmonary aspiration in patients with no apparent increased risk of pulmonary aspiration.

Recommendations for Pharmacologic Blockade of Gastric Acid Secretion

Medications that block gastric acid secretion (H2 blockers, PPI) may be pre-operatively administered to patients at increased risk of pulmonary aspiration.

Do not routinely administer preoperative medications that block gastric acid secretion for purpose of reducing risk of pulmonary aspiration in patients with no apparent increased risk of pulmonary aspiration.

Recommendations for Antacids

Antacids (Sodium citrate or magnesium trisilicate) may be preoperatively administered to patients at increased risk of pulmonary aspiration. Only administer non-particulate antacids.

Do not routinely administer preoperative medications that block gastric acid secretion for purpose of reducing risk of pulmonary aspiration in patients with no apparent increased risk of pulmonary aspiration.

Recommendations for Anti-emetics

Anti-emetics (5HT3 antagonists) may be preoperatively administered to patients at increased risk of Postoperative nausea and vomiting (PONV).

Routine preoperative administration of anti-emetics to reduce the risk of PONV is not recommended for patients with no apparent increased risk of pulmonary aspiration.

Recommendations for Anticholinergics

Administration of preoperative anticholinergics (Atropine, Glycopyrrolate) to reduce the risk of pulmonary aspiration is not recommended.

Reference

Practice guidelines for preoperative fasting and use of pharmacologic agents, Anesthesiology, 126, No. 3.

Diagnostic Modalities in Coronary Artery Disease (CAD)

Myanmar Cardiac Society

Aim for Tests in Coronary Artery Disease (CAD)

1. Diagnosis of CAD for chest pain and breathlessness
2. Prognostic Implications for known CAD for risk of MI or sudden cardiac death
3. Risk assessment after MI to detect residual ischaemia and risk of further MI

Diagnosis of CAD

Diagnosis of Angina is mainly clinical and Risk factors and character of chest pain are important.

- **Typical angina (definite)**
  - Substernal chest discomfort with a characteristic quality and duration that is
  - provoked by exertion or emotional stress and
  - relieved by rest or nitroglycerin after 5 mins
- **Atypical angina (probable)**
  - Meets 2 of the above characteristics
- **Noncardiac chest pain**
  - Meets ≤ 1 of the typical angina characteristics

After clinical possibility of diagnosis of angina, further diagnostic modalities are needed to confirm the CAD, to assess severity of CAD and prognosis.

Diagnostic Modalities in CAD

I. Non-invasive Tests

1. Resting ECG
2. Exercise ECG (Exercise Treadmill Test or ETT)
3. Echocardiogram
   - Conventional Echo (transthoracic echo)
   - Tissue Doppler Imaging (TDI) (Strain study)
   - Stress Echo
4. Nuclear Scanning
   - Myocardial Perfusion Scan (MPS)
   - SPECT
5. Computed Tomography (CT)
   - Electron Beam CT (EBCT)
   - CT Coronary Angiogram (CTCA)
6. Cardiac MRI (CMR)

II. Invasive Tests

1. Cardiac catheterization: Coronary angiogram

General approach to diagnose CAD

- Confirm or deny presence of CAD with ETT
- Exclude false positives with perfusion imaging
- Assess extent of CAD with perfusion imaging
- Assess prognosis combining extent of CAD with severity of LV dysfunction: echo/ Nuclear scan
- Cardiac Catheterization only for adverse prognostic indicators
  - refractory symptoms
  - 3VCAD/2VCAD (prox. LAD) plus LV dysfunction (echo or nuclear scan) post MI

Prognostic implication and Risk Stratification: For known CAD and after MI

Noninvasive Testing Markers **(Functional evaluation)**

- Amount of infarcted myocardium
- Amount of jeopardized myocardium
- Degree of jeopardy
- Left ventricular systolic function

Invasive Testing Markers **(Anatomical evaluation)**

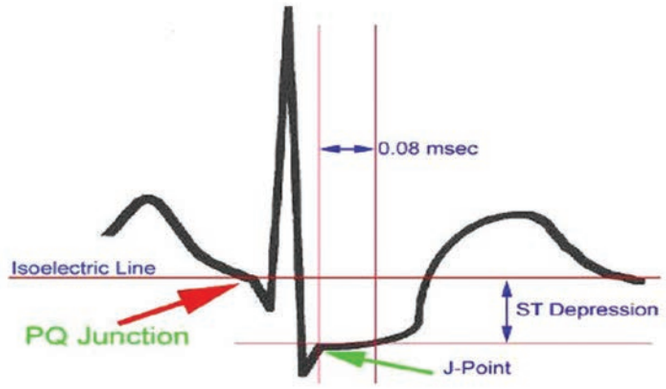
- Number of culprit vessels stenosed
- degree of stenoses
- characteristics of lesions

1. Resting ECG

Normal ECG cannot exclude CAD and ECG changes in CAD are

- ST segment - Elevation/Depression (> 1 mm above or below the isoelectric line)
- Pathological Q waves (> 25% of following R wave)
- T inversion - Shallow/Deep (significant T inversion is > 3 mm and more significant if seen in multiple leads)
- Bundle Branch Block - new onset Left/Right bundle branch block
- Arrhythmias - Atrial fibrillation/VEs & AV Blocks

Fig 1. ECG Analysis



24 hr Holter ECG monitor

Usually not a diagnostic tool and sometime may be useful to detect silent ischaemia and arrhythmia.

Value of resting ECG in diagnosis of CAD

- ECG is not a perfect diagnostic tool (specificity-sensitivity - 50/50)
- Request previous ECG for comparison
- Serial ECGs (and continuous ST-monitoring?) improve sensitivity
- Stress ECG improves sensitivity and specificity

Indications for Stress Testing

- Objective confirmation of ischaemia
- Assessing extent of ischaemia
- Documenting exercise capacity
- Functional assessment of known CAD
- Determining risk and prognosis
- Determining need for angiography
- Assessing response to treatment

Rationale for stress testing in asymptomatic individuals?

Asymptomatic ST Segment depression predicts mortality

Treatment of silent ischemia improves outcomes

2. Exercise ECG (Exercise Stress Test)

- Low sensitivity and specificity for diagnosis of CAD
- Stable obstructive CAD screening has shifted to stress Echo or nuclear scanning.
- Main use of ETT - evaluation of prognosis and gate-way to other imaging modalities.
- Stand-alone testing for CAD diagnosis is reserved for patients with intermediate risk for CAD
- For general population, sensitivity - 68% and specificity - 70%
- Positive Predictive Value for low risk population - 21% and PPV for high risk population - 83%

Probability of CAD

Pre-test Probability of CAD from CASS Trial

	Non-Anginal Chest Pain		Atypical Chest Pain		Typical Angina	
Age	Men	Women	Men	Women	Men	Women
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

Positive results of ETT

- ST segment changes
  ST depression, ST elevation, ST pseudo-normalization
  Increased probability of ischaemia - Number of leads involved, the workload at which the ST depression occurs, angle of slope, magnitude of ST depression
- Arrhythmias and bundle branch blocks
- Longer recovery
- Low BP response
- Symptoms

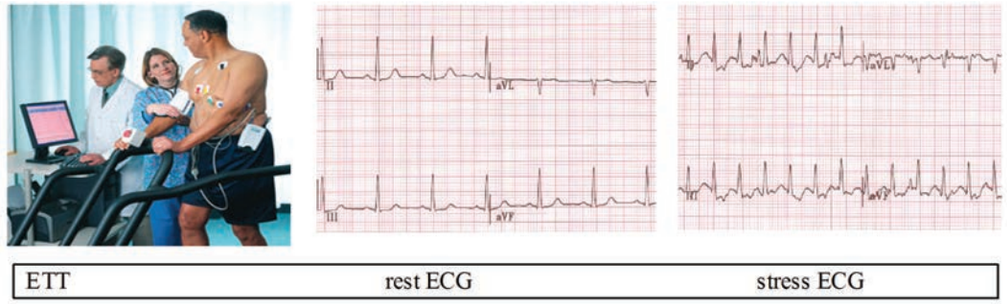
Stress Testing: Safety

- Risk of death or MI about 1 in 10,000
- Test can reasonably be performed by:
  - Physician
  - Nurse, technician, etc. with immediate availability of supervising physician

High Risk Indicators in Exercise Stress Testing

- Early positive - stage I: Mortality > 5%/year
- Strongly positive > 2.5 mm ST depression
- ST elevation > 1 mm in leads without Q waves
- Fall in SBP > 10 mmHg
- Early onset ventricular arrhythmia's
- Chronotropic incompetence Ex HR < 120/min not due to drugs
- Prolonged Ischaemic changes in recovery ST 2 mm lasting > 6 minutes in multiple leads

Fig 2. Exercise stress test



Implication of Baseline ST Abnormalities

o Further changes <u>not</u> diagnostic when baseline changes are due to:
  - Left ventricular hypertrophy
  - Bundle branch block
  - Digoxin

o Further changes may be diagnostic when baseline changes due to CAD

3. Echocardiography

- Conventional Echo (2 D, M mode, Colour doppler)
- Tissue Velocity Imaging
- Stress Echo

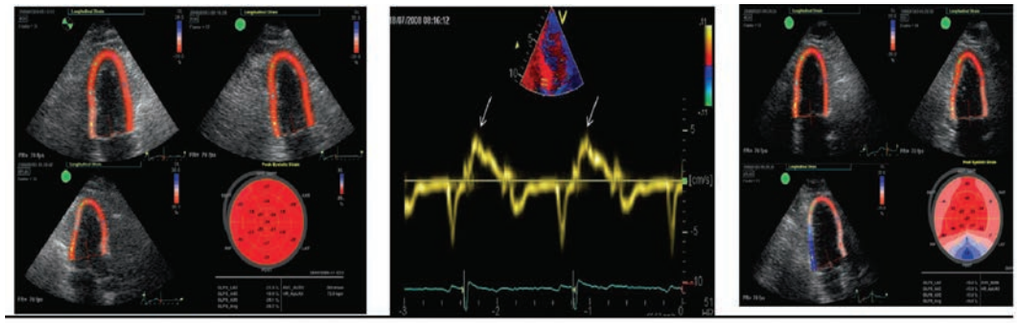
3a. 2D Echo

Conventional 2D Echo is not a routine diagnostic tool for diagnosis of CAD. It is used only to exclude other differential diagnosis of chest pain like significant valvular heart disease or hypertrophic obstructive cardiomyopathy. In patients with prior MI or severe ischaemia, regional wall motion abnormality (RWMI) and reduced systolic function (LV ejection fraction) can be detected.

3b. Tissue Doppler Imaging

- Visual evaluation of wall motion is known to be highly subjective, at times insensitive, and requires significant training and mostly assesses only radial deformation component of the myocardium.
- *TVI, also known as Tissue Doppler Imaging*, is currently accepted as a sensitive and accurate echocardiographic tool for quantitative assessment of cardiac function.
- TVI provides information on the velocity of the myocardial motion in the direction parallel to the ultrasound beam.
- *Myocardial deformation (strain and strain rate)* can be calculated non-invasively for both left and right ventricular or atrial myocardium, providing meaningful information on regional function in a variety of clinical settings.
- From a physical point of view, strain is a dimensionless parameter defined as the relative change in length of a material related to its original length, whereas strain rate describes the temporal change in strain (rate of shortening or lengthening) and it is expressed as a percent.
- While strain is a measurement of deformation relative to a reference state, strain rate is an instantaneous measurement.
- Strain rate seems to be a correlate of rate of change in LV pressure, a parameter that reflects contractility, whereas strain is an analogue of regional ejection fraction
- Among the main advantages of TVI and strain imaging, there are the quantitative assessment of wall motion, and the possibility to measure velocity and acceleration as better descriptors of cardiac motion than classical wall thickening.
- For example, short-lived events (such as isovolumic events) can be detected only by high temporal resolution techniques such as TVI, or detection of post-systolic shortening or thickening (a highly specific marker of dyssynchrony and/or viability)

Fig 3. Tissue doppler imaging and strain study



3c. Stress Echo

- Effective method of evaluating for myocardial ischaemia
- Based on principle that ischaemic myocardium becomes hypokinetic
- Detect stress-induced systolic regional wall motion abnormalities (RWMAs)
- Screening for CAD and identification of the coronary vessels involved
- Can differentiate viable from scarred myocardium
- Safe, relatively inexpensive and rapid
- Sensitivity - 75-92% and specificity - 64% to 100%

Types of stress echocardiography

1. Exercise stress testing
2. Pharmacological stress testing
   - Dobutamine stress testing
   - Vasodilator stress testing - dipyridamole or adenosine

Images are obtained and digitized at rest, before peak, at peak and after peak exercise. Wall motion is subjectively graded as normal, mildly hypokinetic, severely hypokinetic, akinetic or dyskinetic.

Indications for Stress Echo

- Patients in whom exercise test is contraindicated (severe hypertension)
- Patients in whom exercise test is not feasible (intermittent claudication, arthritis/ deformity)
- Patients in whom exercise test was non-diagnostic or yielded ambiguous result
- LBBB or significant resting ECG changes that makes any ECG interpretation during stress difficult.
- Submaximal stress ECG

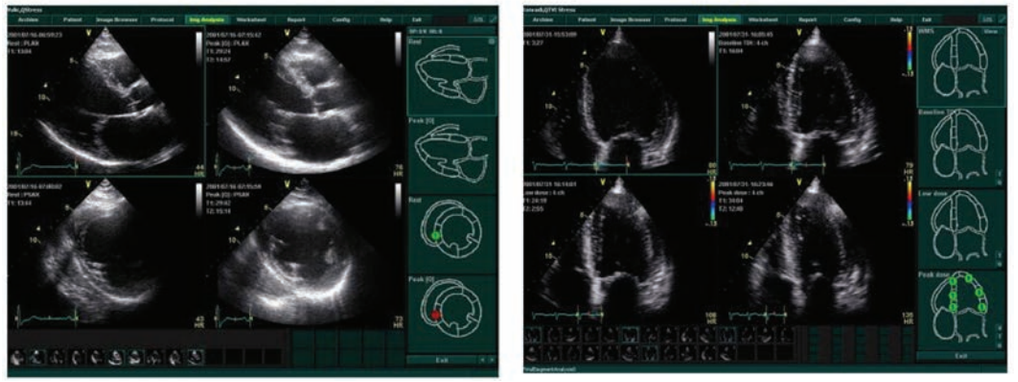
Results of stress echocardiography

1. <u>normal response</u> - increased wall thickness and increased endocardial excursion with stress

2. <u>Resting RWMAs</u> - prior MI or diffuse myopathic processes
   - akinesia and dyskinesia - transmural infarct
   - hypokinesia - partial infarct or viable
3. <u>abnormal response</u> - worsening RWMA with or without decrease in LVEF - specific for ischaemia

	Rest	Stress
Normal	**Normal**	**Hyperkinetic**
Ischemia	**Normal**	**Hypokinetic**
Infarction	**Hypo or Akinetic**	**Unchanged**

Fig 4. Stress Echo study



Stress Echocardiography: Advantages

- Sensitivity and specificity improved over exercise testing alone and comparable to MPI
- Portable
- Immediate results
- Less time and cost investment compared to nuclear imaging
- Provides information regarding valve function, etc.

Stress Echocardiography: Disadvantages

- Interpretation subjective and non-standardized
- Interpretation difficult when resting wall motion abnormalities present
- Technical limitations in obese, emphysematous and other patients

4. Nuclear Imaging

- Assessment of myocardial viability and stratification of risk
- Sensitivity -90%, specificity- 74%

- Indications
  - Screening: Multiple risk factors, Family history
  - Suspected Coronary artery disease (abnormal ECG, nondiagnostic exercise test)
  - assessment of severity of known CAD
  - assessment after therapeutic intervention: medical, intervention, surgery
  - Evaluation of acute chest pain syndromes
  - risk stratification after MI
  - viability assessment before and after cardiac revascularization
  - ischaemia evaluation prior to non-cardiac surgery

4 a. Myocardial Perfusion Imaging

- MPI is a non-invasive nuclear imaging technique that uses radioactive imaging agents to image the heart.
  - Thallium - 201
  - Technetium - 99 m Sestamibi
  - Technetium - 99 m Tetrofosmin
- Performed at rest & stress
- Stress study options
  - o treadmill exercise
  - o pharmacologic stress agents
    - adenosine
    - dipyridamole
    - dobutamine

Results of MPI

- Percentage of LV myocardium receiving decreased perfusion
- Differentiate ischemia from MI
- 24 hour delayed images demonstrate myocardial viability (hibernating)
- Rest-only studies can provide information on acute MI's

In a typical nuclear cardiac imaging exam, the physician reviews:

- Static "Summed Perfusion Images"
- Dynamic "Gated Images"

4 b. ECG-Gated SPECT Imaging

- Allows for assessment of global LVEF, regional wall motion, and regional wall thickening.
- Limitations:
  - Tends to estimate LVEF 5-10% lower vs. echocardiography.
  - Decreased accuracy with irregular HR, low count density, increased extracardiac radiopharmaceutical uptake, and small LVEF.

- Primary uses of test
  - congestive heart failure
  - cardiomyopathy
  - chemo cardiotoxicity

Fig 5. Myocardial perfusion study

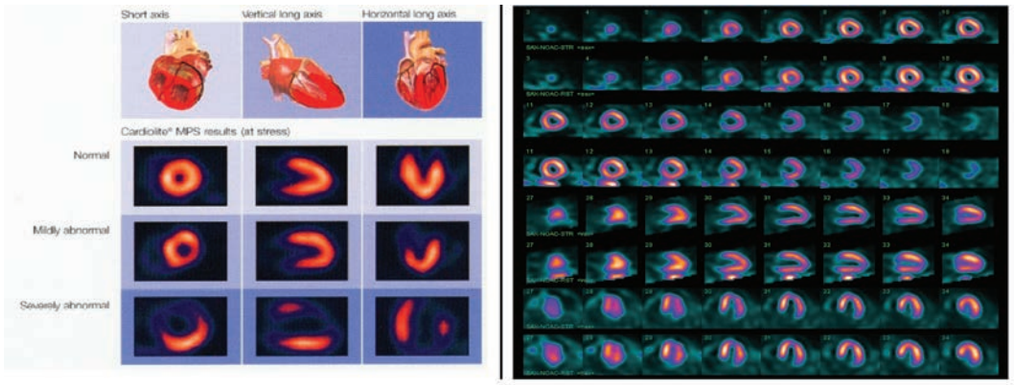
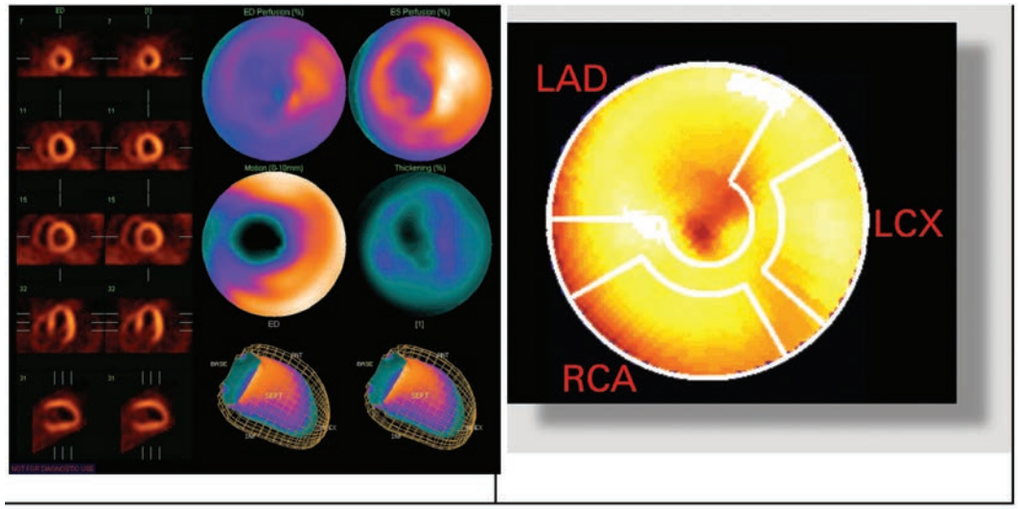


Fig 6. ECG-gated SPECT



Characterization of Defects

- Fixed - scar
- Reversible - ischaemic myocardium
- Partially reversible - mixture of scar and ischaemic myocardium
- Artifacts - breast attenuation and diaphragmatic attenuation

Results of Nuclear scan

- **Normal Scan**
  - no defect during stress

- **Myocardial Infarction**
  - perfusion defect on rest & stress
- **Myocardial Ischemia**
  - perfusion defect on stress only

High-risk perfusion scan

- perfusion defects in more than one vascular distribution
- Large perfusion defects (> 7% of LV)
- increased lung thallium uptake
- Increased pulmonary thallium uptake indicating low CO or elevated LVEDP
- Transient LV dilatation (TID)

Clinical Value of Nuclear scan

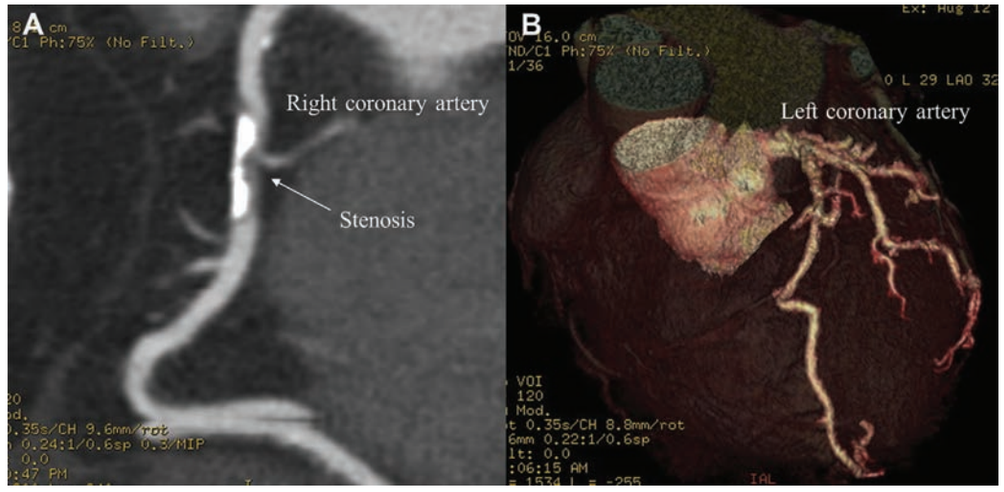
A nuclear stress test provides excellent negative predictive value: Patients from the general population with normal MPI scans have < 1% annual risk of cardiac events.

A gated nuclear stress test is a powerful tool to risk stratify patients for optimal management: It is in effect a "gate-keeper" to the cardiac cath lab.

5. Cardiac CT

- Provide excellent negative predictive value
- Accurate sensitivity to detect coronary arterial luminal narrowing
- Noninvasive and very low risk
- Reveals information on
  - **Coronary Calcium score by Electron beam CT (EBCT)**
    - Quantitate the amount of volume of calcium
      - 1-10 – minimal, 11-100 – mild, 101-400 – moderate, > 400 – severe
    - Negative cannot rule out unstable soft plaque
    - Positive scan - confirm the presence of atherosclerotic plaque
    - Sensitivity - 63% and Specificity - 79%
    - No role for young healthy individuals < 40 years with no risk factors
    - Use a calcium score to screen patients with moderate (intermediate) Framingham risk: positive CAC scans indicate incremental risk, alters therapeutic goal (LDL, BP, etc), identify patients who do not need further cardiac evaluation (scores of zero have a 95-99% negative predictive power)
  - **Coronary artery anatomy (Multi-slices CT)**
    - Sensitivity - 92% and Specificity - 93%
    - When there is an anomalous coronary artery, MSCT is superior to angiogram
  - Cardiac Morphology and function

Fig 7. CT coronary angiogram



Clinical Applications of CTA

- Screening: no application
- Diagnosis of CAD
  - Intermediate likelihood of disease**
  - After equivocal/discordant stress imaging**
  - Coronary anomalies
  - Before valvular surgery
  - Nonischemic vs. ischemic cardiomyopathy
  - Acute chest pain (our ED/Cards starting a pilot study soon)
  - Bypass graft patency/location (images of transplanted arteries and veins are much better)
- Risk stratification (known CAD): After equivocal/discordant stress imaging

Precaution and limitation for Cardiac CT

- Contrast allergy
- Contrast-induced nephropathy
- Heart rate control with beta-blocker (50-70 bpm)
- Radiation exposures (10-15 mSV)
- Heavy coronary calcification

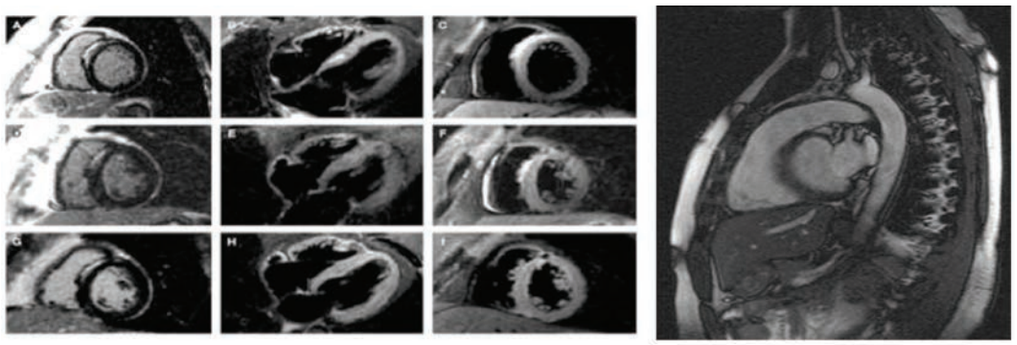
6. Cardiac MRI

- Sensitivity - 90% and Specificity - 92%
- Dobutamine MRI had a sensitivity of 89% and specificity of 94%

Advantages of Cardiac MRI

- No radiation and minimal invasiveness (IV injection)
- 3-dimensional anatomic images (3D coronary artery and myocardial imaging)
- Comprehensive functional imaging: Myocardial perfusion and viability

Fig 8. Cardiac MRI



7. Cardiac Catheterization

The Gold Standard for diagnosis of CAD
Sensitivity and specificity - 100%

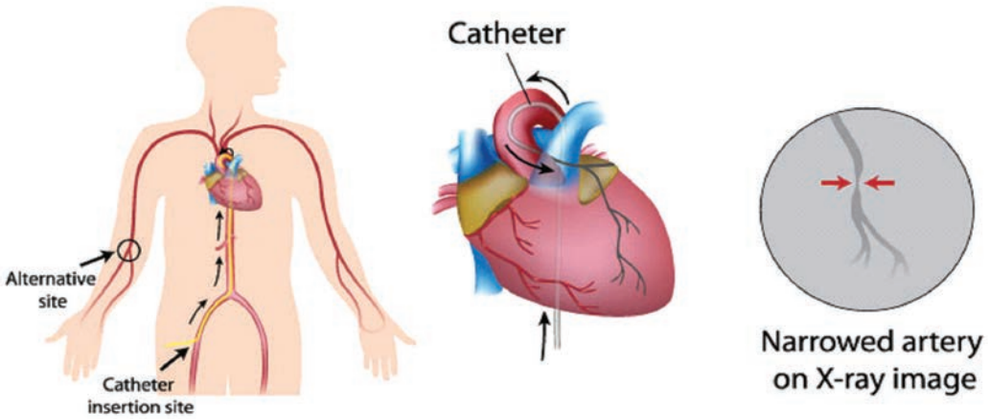
Cardiac Catheterization: Problems

- Cost
- Invasive
  - Complications: 1:1000 risk of death, MI, Stroke, Vascular complications
- Does not provide information on functional significance of CAD

Indications for Coronary Angiography

- High risk stress test: ECG changes, haemodynamic changes
- High risk perfusion study: Multiple defects, Severe perfusion defects, TID
- Ongoing symptoms, Unstable angina and post MI angina
- Vocational indication: such as pilots and truck/bus drivers
- Diagnostic uncertainty

Fig 9. Cardiac MRI



Summary for diagnostic modalities for CAD

Anatomical evaluation of coronary artery stenosis

- Coronary Angiogram
- CT Coronary Angiogram
- Cardiac MRI

Functional evaluation of coronary artery stenosis

- Stress Testing
  - ETT
  - Stress Echo
- Perfusion scan
  - MPS
  - SPECT
- Cardiac MRI

Algorithm for Chest Pain Evaluation

Low Probability of CAD (< 20%)

- Consider no test
- High likelihood false + result

Intermediate Probability of CAD (20-80%)

- ETT
- Perfusion imaging or stress echo
- Non-invasive angiogram: CT or MRI

High Risk Probability of CAD (> 80%)

- Perfusion imaging or stress echo
- Consider invasive angiography

Summary for choice of stress test

- For normal resting ECG patients
  - ETT
- For those with resting ECG abnormalities, alternative testing modalities, perhaps more accurate but more expensive, include:
  - Exercise echocardiography
  - Myocardial perfusion imaging
- In those with functional limitations alternatives tests include:
  - dobutamine stress echocardiography
  - Dipyridamole or adenosine perfusion imaging

The choice of imaging modality in a particular setting depends on several factors including availability, feasibility, expertise and cost considerations.

Comparison of different Screening tests

Imaging modality	Sensitivity (%)	Specificity (%)
CT angiography	91	93
Stress echocardiography	79	87
MPI-SPECT	86	74
MPI-PET	89	90
Stress MR perfusion	91	81
Stress MR wall motion	83	86
MR coronary angiography	73	86
Exercise electrocardiogram	68	77

Anorectal emergencies

Myanmar Colorectal Surgeon Society (MCRSS)

Abstract

Anorectal emergencies refer to anorectal disorders presenting with some alarming symptoms such as acute anal pain and bleeding which might require an immediate management.

Common anorectalemergencies are

1. acutely thrombosed external hemorrhoid,
2. thrombosed or strangulated internal hemorrhoid,
3. bleeding hemorrhoid,
4. anal fissure,
5. irreducible or strangulated rectal prolapse,
6. anorectal abscess,
7. perineal necrotizing fasciitis (Fournier gangrene)
8. retained anorectal foreign bodies and obstructing rectal cancer

A detailed history taking and a careful physical examination, including digital rectal examination and proctoscopy is essential for correct diagnosis and plan of treatment. In some cases, some imaging examinations, such as endoanal ultrasonography and computerized tomography scan of whole abdomen may be required.

Signs and Symptoms

Accurate diagnosis can be a challenging thing to do, as patients are often uncomfortable talking about this part of the body and bowel function. This anxiety results in delays in seeking care. When a patient presents with perianal problems, a careful history should be taken.

Presenting features of painful perianal conditions

	Pain	Mass	Blood	Drainage
Internal Hemorrhoids	no	when prolapsed	yes	no
Thrombosed External Hemorrhoids	yes	yes	no	no
Incarcerated Hemorrhoids	yes	yes	some	no
Anal Fissure	yes	no	some	no
Perianal Abscess	yes	yes	no	when ruptures
Perianal Fistula	no	no	no	yes
Anal Cancer	yes	yes	yes	no
Anal Condyloma	no	yes	no	no
Proctitis	no	no	yes	no

1. Pain

Patients with **thrombosed or incarcerated hemorrhoids** usually present with severe, constant pain that come on suddenly, with episode of severe constipation or lifting heavy objects that preceded the pain.

Anal fissures often present after an episode of severe constipation or anal trauma, and are characterized as a very sharp, cutting or tearing pain, often described as "passing glass" during defecation or having "a sharp knife poking" the anus. It may persist for hours after defecation.

Pain that is constant but comes on gradually over the course of several days is characteristic of a **perianal or perirectal abscess** or **an anal sexually transmitted disease** (i.e., syphilis or herpes). Pain that worsens over many weeks or months is typical of **proctitis and malignancies**.

In general, moderate or mild hemorrhoidal disease is not associated with significant pain.

2. Mass

Patients with the most common types of perirectal abscess, pilonidal abscess, and thrombosed external or incarcerated hemorrhoids will complaint of a new mass or swelling which is tender to touch. Anal fissures can be associated with an anal skin tag (sentinel pile). Patients with intermittent grade II or grade III hemorrhoids can have protrusion of tissue.

Patients with anal condylomamay present with small and multiple lumps.

Anal cancers may present as new emerging lump.

Less commonly, rectal prolapse can also present as a new large mass that can be confused with hemorrhoids.

3. Presence of bleeding

Internal hemorrhoids classically bleed with bowel movements, resulting in blood on the tissue or in the toilet water and coating the stools. Sometimes, the bleeding can be severe enough to cause anemia, though, it is usually mild.

Anal fissures also have a similar bleeding pattern, though these are often associated with pain. Proctitis patients classically will have urgency and frequency and often have frequent, small, bloody bowel movements. The bleeding can be bright or darker red.

Bleeding can occur with **pilonidal disease** if there is a break in the skin, though the bleeding is mild and usually the patient can appreciate the bleeding is not near the anus but at the top of the gluteal crease, not related to bowel movements and frequently just located on the underwear.

Thrombosed external hemorrhoids may have mild bleeding seen on the toilet paper or in the underwear. **Malignancies** often bleed with even gentle touch or manipulation. Occasionally, if a **perianal abscess** has developed into a perianal fistula, the external opening of the fistula can also have mild bleeding.

4. Presence of drainage or opening

The classic draining lesion in the perianal region is a perianal fistula, which produces scanty thick yellow or greenish-tinged discharge.

Abscesses that have burst spontaneously can produce some drainage, which is usually copious at first and rapidly decreases in volume. Prolapsed internal hemorrhoids or rectal prolapse can also produce some drainage, though this tends to be thin, white or clear drainage and occasionally pink-tinged.

5. Other questions?

In general, a range of three bowel movements per day to once every three is considered normal. Additionally, soft but formed stool is the ideal, which should require little to no straining to evacuate. It is also important to inquire about the patients' control of their bowels and any accidents and leakage they may have, as fecal incontinence is a frequent problem in older women due to previous obstetrical injuries during vaginal deliveries.

Weight loss in an older patient may raise concerns of anorectal cancer, especially if associated with change in bowel habits.

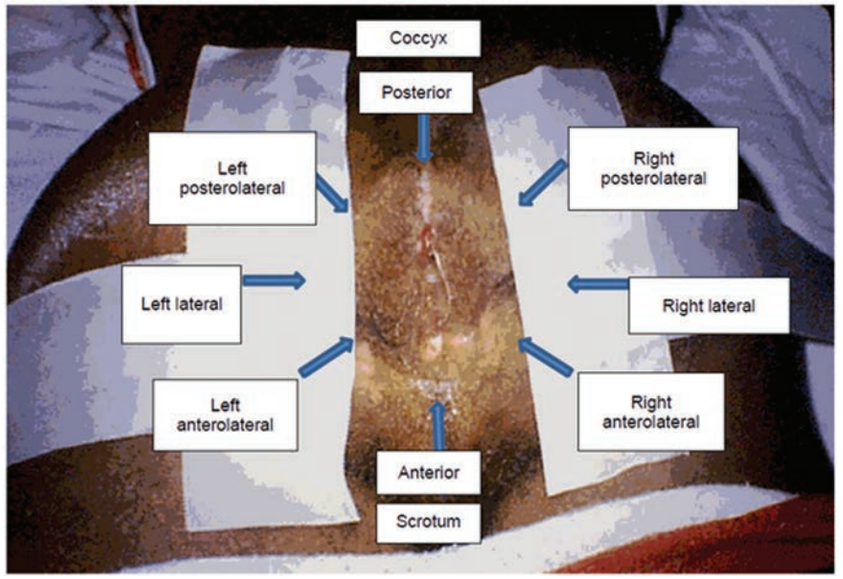
Examination

Digital rectal examination

This is best describe based upon anatomic directions according to the picture below.

It is also best to talk to the patient during the exam and let them know what you are doing and what to expect.

Figure (1). Anatomical description of perianal region



Perineal region should be inspected first.
Do you see thickening of the skin? Erythema? Drainage from the skin? Drainage from the anus? Is the drainage clear? Pus? Blood? Is there swelling or asymmetry? Is there tissue prolapsing out of the anal canal? Is there redundant tissue around the anus? Is there a mass or extra skin?

After inspection, you can palpate the area. Start where the skin looks normal about 2-3 cm away from the anal verge, circumferentially. If this is unremarkable, then you can gently palpate right at the anal verge. Do you feel induration? Is there tenderness? Is the patient tender in the posterior midline? Anterior midline? Left lateral? Right lateral?

If there is an indurated area press on it to detect any drainage come out from the anal canal.

You can also try to spread the anal verge open with gentle traction; this may give you some idea of the strength of the anal sphincter muscles. You can instruct Valsalva maneuver as this helps to efface some of the anus. This can be especially helpful if a patient is tender in the anterior or posterior midline.

If there is an anal fissure and there is tenderness at that location, the examination needs to be stopped. If the patient does not have a fissure, then digital rectal examination can be continued.

Again, asking the patient to bear down while inserting your finger helps them to relax their sphincter. During the rectum exam, you should be able to feel the prostate or cervix anteriorly. You can also feel a shelf on the sides at the top of the anal canal, which is the insertion of the levator ani muscles. Posteriorly, you should be able to feel the coccyx. Be sure to pay attention for any masses or laxity in sphincter tone. You should also have the patient contract their sphincter muscle and squeeze as if holding in a bowel movement. This will give you a general idea of the strength of the external sphincter muscle and their underlying continence.

It is after this, depending on the working diagnosis, patient's presentation, and the equipment available in the office, a physician may perform proctoscopy, or even flexible sigmoidoscopy.

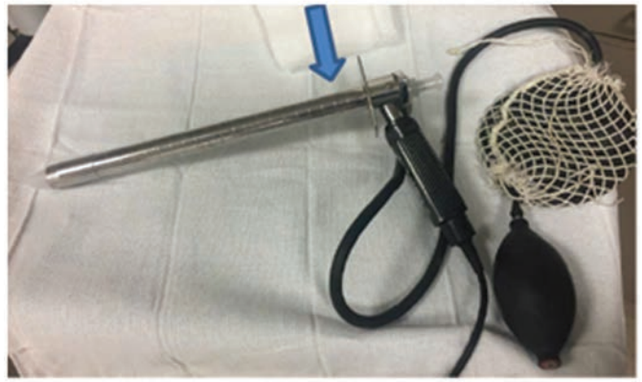
Diagnostic Studies

PROCTOSCOPY: A proctoscope is approximately 7 cm long. It comes in various sizes and shapes. This does not require bowel prep, nor does it require sedation, as this can be easily done in the office for most patients. If a patient has significant pain on exam, and a cause for the pain cannot be determined in the office, then an exam with sedation can be done in the endoscopy room or in the operating room, if needed. The proctoscope allows one to see the whole anal canal and, depending on patient habitus and type of scope used, it can also allow one to see the distal rectum for 2-4 cm above the dentate

line. It is helpful to evaluate internal hemorrhoids, the extent of a small anal cancer or anal condyloma within the anal canal, as well as to look for internal fistula openings. The patient can be placed in a kneeling position on a table, or in the lateral decubitus position. The examiner also uses a lamp to shine within the scope, though most commonly used proctoscopes now have a small light built into the handle.

SIGMOIDOSCOPY: A rigid sigmoidoscope is 25 cm long. As the average rectum is 15 cm long, it is obvious that with full insertion, the lower part of the sigmoid can be seen. This does not require a bowel prep, but for best evaluation, a patient will perform one or two enemas prior to the procedure to allow the rectum to be free from stool. This also does not require sedation if the patient does not have severe pain or anxiety, and can be routinely done in the office. Patients may be positioned in the knee-chest position but more frequently, they are either positioned in a lateral decubitus position or on a procto table. This is frequently performed to evaluate malignancies that may be extending more proximal than what can be seen by a proctoscope. This is the standard technique used to measure the distal edge of a higher tumor from the anal verge, as is done for rectal cancers, to determine the location in the rectum. Since the entire rectum can be visualized, this is an ideal scope to evaluate for proctitis and to perform biopsies of any lesions in the rectum.

Figure (2). Rigid Sigmoidoscope



FLEXIBLE SIGMOIDOSCOPY: This is a 60 cm long flexible endoscope. Therefore, it is quite easy to reach the splenic flexure and even the transverse colon using this technique. This can be done in the office in unprepped patients for similar reasons as the rigid sigmoidoscope, though it is often difficult to get beyond the sigmoid colon in the office due to the tortuosity of the colon and cause discomfort to the patient. This can also be performed with sedation and a small prep of enemas and oral laxatives. If performed in an Endoscopy lab, sedation is often used which makes examining the descending and transverse colon more comfortable for the patient. In combination with a stool test for occult blood, a flexible sigmoidoscopy can be used for colorectal cancer screening since more cancers affect the left colon than the right. It is also frequently used for younger

patients without significant family history to assess them for rectal bleeding that does not have other concerning signs, such as anemia.

Figure (3). Flexible Sigmoidoscope

Patients can be positioned on the procto table or lateral decubitus position in the office and in the Endoscopy lab, the patients are placed in the lateral decubiti position. Biopsies can be performed through the scope along with tattoo and injections for locating the lesion, and bleeding control, when needed. While polypectomy snares can technically be introduced through the scopes, unless the patient is fully bowel prepped, snare polypectomy with electrocautery is avoided due to combustible gas that may be present in an unprepped patient.

COLONOSCOPY: The colonoscope is like the flexible sigmoidoscope but longer, about 165-180 cm long depending on brand and model. This scope can reach to the cecum and even intubate into the terminal ileum. This is the scope that is used for screening for colon cancer, and for surveillance. The patients must be fully bowel prepped and, therefore, biopsies of larger masses and snare polypectomy can be performed. This is performed in the endoscopy room with IV sedation as scoping the transverse and ascending colon can be uncomfortable. Patients are positioned in the lateral decubitus position.

MANAGEMENT

Anal Fissure: Mainstay of acute treatment is analgesia and anal sphincter muscle relaxants, e.g. topical GTN 0.2% ointment, diltiazem 2% ointment. Local anesthetics are helpful early in treatment.

Thrombosed External Hemorrhoid: Most patients who present urgently benefit from surgical excision which can be performed at out-patient department or emergency room under LA. Excision gives more rapid symptom resolution, a lower incidence of recurrence and a longer remission interval.

Prolapsed Hemorrhoids: Prompt surgical treatment is essential. While waiting for surgery, the following measures may help to reduce the pain and symptoms.

- Warm sitz baths
- Topical ointments or creams containing corticosteroids, LA, antiseptics or decongestants
- Medical treatment with micronized purified flavonoids e.g. Daflon
- Topical GTN has been reported effective in strangulated internal hemorrhoids by decreasing internal sphincter tone

Perianal Abscess: Perianal abscesses almost always require surgical drainage, even if they have spontaneously discharged. Drainage leads to an open cavity that typically takes 3-4 weeks to heal. Patients with diabetes, immunosuppressive, evidence of systemic sepsis or substantial local cellulitis require urgent drainage.

Anal Cancer: Proper staging is essential in management of anal cancer. In early cases, local surgery is the best to preserve defecation function but in locally advanced cases, abdomino-perineal resection is performed. Neo-adjuvant chemoradiation can reduce the rate of APR.

Conclusion

Some anorectal disorders may present as an emergency. A detailed history taking and a careful physical examination, including digital rectal examination and proctoscopy, is essential for correct diagnosis and plan of treatment. Clinicians should maintain a high index of suspicion for anorectal sepsis and anorectal neoplasms. If in doubt, the attending physicians should not hesitate to consult an expert e.g. colorectal surgeon about the diagnosis, proper management and appropriate follow-up.

References

1) Anorectal emergencies, Lohsiriwat V, Division of Colon and Rectal Surgery, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, *World J Gastroenterol* 2016 July 14; **22 (26)**: 5867-5878.

2) ACS/ASE Medical Student Core Curriculum Perianal Problems

Updates in the Clinical Care of HIV; TB and HIV Prevention - ART

Myanmar Society of HIV Medicine

Diagnosis

Confirmation of HIV Status

As per the Myanmar National Guidelines for Clinical Management of HIV/AIDS, the confirmation of the diagnosis is arrived if all 3 rapid tests (WHO pre-qualified tests - namely Determine, Unigold and Statpak) are positive. ELISA is alternatively used in some setting (eg. NHL) as the first test.

Note: ELISA is NOT a confirmation test. It is a screening test. There is no single confirmation test apart from Western Blot, which is rarely used in routine clinical setting.

When tests for HIV diagnosis are sent to laboratories in the private sector, the tests named above might not always be used. Care should be taken that a highly sensitive screening test is always followed by a confirmatory test, which needs to have 100% specificity. As with all clinical conditions - the attending clinician needs to interpret the lab results with a view of the clinical background. E.g in a person with a history of injecting drug use, presenting with oral thrush and a large herpes zoster scar, the serological lab results will be a confirmation of a diagnosis highly suspected in the clinical setting.

On the other hand in an apparently healthy person, with no history of risk behaviours - a positive screening test should be interpreted with caution. Repeated testing, with confirmatory tests should be carefully done.

As HIV testing is being offered to more and more people now, this needs to be considered carefully. In the hospital setting, where clinicians are caring for people who are already symptomatic, the chance of false positive cases will be rare. But in the public health setting, where tests are offered to people with no symptoms, the chance of false positive tests might be a challenge.

Verification/Retest before ART

It is advised to repeat HIV tests (e.g. all 3 tests, mentioned earlier), for verification before life long treatment initiation. WHO stated that only after verification should someone be put on ART (Antiretroviral Therapy). Thus a patient might have to undergo 6 tests altogether before starting ART.

Early Infant Diagnosis

All infants born to or who have been breast-fed by a mother who is having HIV are called HIV-exposed infants. It is essential for HIV diagnosis be done at 4 - 6 weeks of age. A negative HIV test result is valid only when the baby is not breast-fed. Unlike adults, HIV

virological tests (either HIV DNA on Dried Blood Sample; or HIV RNA on DBS or plasma) are used. Antibody tests for HIV are difficult to interpret in infants. If a DNA or RNA test result is positive, ART can be started immediately, but a second sample must be collected and sent to the laboratory.

In settings where virological tests are not available, serological tests can be used when the child is 9 months old and is not breast feeding. In this scenario, a negative result can exclude HIV infection. For the child with a positive antibody test result who is well and healthy, the diagnosis needs to be rechecked and confirmed when the child is 18 months or older. The same protocol as in adults needs to be followed.

For all children breast-fed, by an HIV positive mother, HIV testing should be done 3 months after stopping breast feeding.

Principle of starting ART

There have been few needs to update - advice on ART initiation since 2016. Anti-retroviral Therapy can be started in anyone with HIV infection who has the diagnos is confirmed and verified and counseled. The current strategy is “test and treat”, regardless of CD4 count and WHO staging. From a practical point, blood tests like CD4, CBC, HBsAg, HCV antibody, Serology test for syphilis, liver and renal function, Chest X-ray are optional but desirable in an asymptomatic patient. For those who are ill or symptomatic, more investigations may be necessary.

For ill patients, major opportunistic infections must be diagnosed and treated before starting ART. Tuberculosis is the commonest OI (Opportunistic Infection). ART should be started two weeks after anti-TB treatment has been started. The second leading cause of death among OIs is cryptococcal meningitis in which case ART should be started 4-6 weeks from the introduction of antifungal therapy. For other major OIs (cerebral toxoplasmosis, pneumocystis pneumonia, penicilliosis etc), ART can be started two weeks after specific therapy.

Prevention of TB

In highly TB endemic countries like Myanmar, most if not all PLHIV are considered to be already infected with TB. Presence of at least one of four symptoms (fever, cough, loss of weight and night sweats) indicates the possibility of the patient has active TB. It should be investigated accordingly (Sputum microscopy, Gene X'pert, urinary LAM antigen in those with CD4 < 100, USG of abdomen can help identify tuberculous lymph nodes and CXR). All others who are asymptomatic are assumed to have latent TB infection (LTBI) which predisposes them 21 times to the risk of developing active TB. Besides ART, treatment of LTBI further reduces the risk of developing TB. There are a number of different treatment regimens for LTBI (6-month INH, 9-month INH, weekly Rifapentine and INH for 12 doses etc). 6-month INH (called Isoniazid Preventive Therapy, IPT) is currently practiced in Myanmar. It can be given regardless of ART, CD4 count, prior anit-TB or pregnancy.

Prevention of other OI

CPT (Cotrimoxazole Preventive Therapy)

Septrin (Co-trimoxazole) 960 mg OD protects against the following 5 infections - (cerebral toxoplasmosis, pneumocystis pneumonia, malaria, recurrent respiratory tract infections and frequent gastroenteritis). It is given to those with CD4 less than 350 cells/ cmm. In case of major Cotrimoxazle allergy, Dapsone 100 mg OD can be given.

Choosing ART

There are now 3 ART regimens to choose for an adult PLHIV, all including a TDF/3TC backbone: TDF/3TC/EFV600, TDF/3TC/EFV400 and TDF/3TC/DTG. The last combination is preferred by WHO. TDF is better avoided if e-GFR is less than 50 ml/min. In those patients, ABC/3TC/DTG can be used.

Studies in Africa have shown the association of neural tube defect and Dolutegravir (DTG) if DTG is exposed during early pregnancy (first 8 weeks of gestation). The relative risk is 3 times but the absolute risk is low. WHO stated that the overall benefit outweighs the risk and DTG can be given to women of childbearing age - if informed consent is obtained. If the patient does not wish to take the small risk, EFV can be used. After first trimester and especially for late pregnancies, DTG became the preferred drug due to its high genetic barrier and rapid viral suppression. DTG should be taken 2 hours before or 6 hours after vitamins and antacids containing bivalent cations, which reduce its absorption. It is also important to increase the DTG dose to 50 mg BD when anti-TB drugs containing rifampicin are being prescribed at the same time.

Up to early 2019, EFV400 has not been approved to be used in pregnancy if given together with Rifampicin. More recent WHO guidelines state that EFV400 can safely be used in this situation.

Monitoring

Monitoring of Treatment response:

The goal of treatment is sustained maximal HIV viral suppression (a viral load which is below the detectable limit in the assay used, usually < 40 copies/ul). Viral load monitoring should be done two times in the first year (at 6 month and 12 month) then yearly. CD4 is also a measure of treatment success. For those whose CD4 rises above 400 cells/cmm (> lower limit of normal value) and viral load undetectable for one year, routine CD4 monitoring can be stopped.

Treatment failure is defined as persistently high viral loads (2 tests done 3 months apart) over 1000 copies/ml despite good adherence. First line ART (TDF/3TC or ABC/3TC based regimens) are changed to second line ART (AZT/3TC. If the 3rd drug is EFV, it can be changed to DTG or LPV/r , and if the 3rd drug is DTG, it can be changed to LPV/r).

Monitoring of drug related toxicities:

If patient is on a TDF based regimen, serum creatinine is checked every 3 months for the first year and every 6 months thereafter. If AZT is used, Hb is checked every 3 months for the first year and every 6 months thereafter.

Prevention of HIV infection in those who have substantial risk by Pre-Exposure prophylaxis (PrEP)

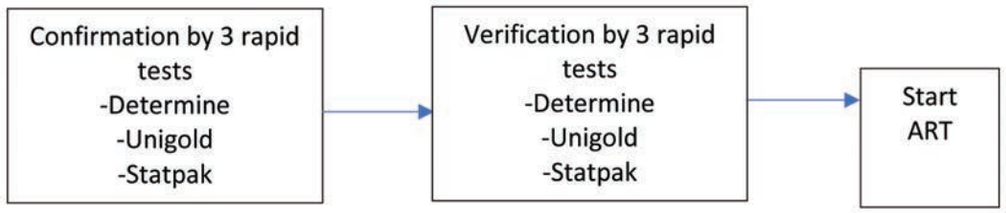
For HIV negative men who have unsafe or unprotected sex with men (MSM), female sex workers (FSW) and for anyone who has a partner or partners with high-risk behavior/untreated HIV infection and are not using condoms consistently - PrEP can help to prevent HIV transmission. It is important to note that it is not a substitute for condoms. PrEP is a combination of two ARV drugs (TDF/3TC or TDF/FTC) taken daily. PrEP will be effective 7 days after starting taking it in heterosexual risk settings. This is known as daily PrEP. Daily PrEP can be stopped 7 days after the last exposure, if no further risk exposures are anticipated.

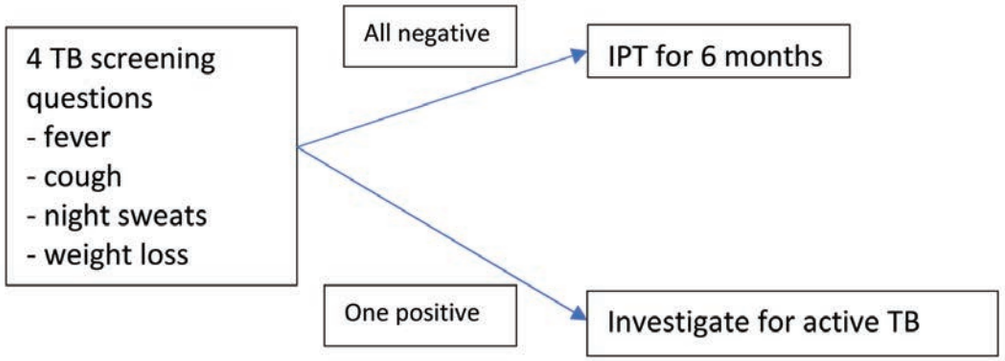
MSM with infrequent high risk exposure have another option called “event-driven PrEP”. Two tablets of TDF/3TC combination is to be taken 2 to 24 hours before expected sex. The second dose of one tablet is to be taken 24 hour after the first dose and the third dose of one tablet is to be taken 48 hours from the first dose (2-1-1). Exposure Driven-PrEP cannot be used for heterosexual men and women, and those with HBV infection. MSM may swap between daily PrEP and Event Driven-PrEP, depending on the frequency of the risk behaviours. Creatinine and HIV status must be checked every 3 month.

Post-exposure prophylaxis (PEP)

PEP is to be taken as soon as possible, and no later than 72 hours, after significant exposure either in an occupational setting or a non-occupational setting. (percutaneous, non-intact skin or mucous membrane exposure, and sexual exposure with a source person who is HIV positive or whose HIV status is unknown). Exposure with an HIV negative person is not eligible for PEP. Currently, TDF/3TC/DTG regimen is the most commonly used PEP regimen with lowest side effects and best completion rate. It is to be taken OD for 28 days.

Algorithms for ART and IPT initiation





First line ART for adults, adolescents, including women of child bearing age and pregnant mothers

1st line →	If VL > 1000 for 2 times →	2nd line	Comment
TDF/3TC/DTG	Preferred by WHO	AZT/3TC + LPV/r	
TDF/3TC/EFV400	Alternative 1st line	AZT/3TC + DTG or LPV/r	DTG preferred
TDF/3TC/EFV600	Alternative 1st line	AZT/3TC + DTG or LPV/r	DTG preferred
ABC/3TC/DTG	When e-GFR < 50	AZT/3TC + LPV/r	

Monitoring

Baseline		Follow-up		
Essential	Desirable	Tm success	Drug toxicities	Frequency
HIV diagnosis	CBC	CD4	Hb for AZT	Every 3 month, then every 6 month
	HBV, HCV, STS		Creatinine for TDF	Every 3 month, then every 6 month
	Creatinine			
	ALT	Viral load	ALT	Symptom directed
	CXR		Total bilirubin	Symptom directed
	Pregnancy test			

Management and care of people living with HIV is a lifelong matter. The quality of care and follow-up definitely impacts not only the lifespan but also the health span of them. ART initiation and management of OI is only the beginning of a long journey. Managing co-infections like STIs, HBV and HCV, co-morbidities such as HIV related neoplasms and metabolic conditions, and treatment related complications as in the forms of renal, liver and hematological manifestations will also need to be attended.

The psychological, social and reproductive needs of the PLHIV need even more careful discussion.

General Principles of Writing a Scientific Article for Publication

Preventive and Social Medicine Society

Introduction

Researchers, scientists and faculty members from academic institutions need to know general principles of writing scientific articles to disseminate new knowledge and findings of their research work in periodicals especially scientific journals published either locally or internationally. Therefore this article is provided as follow. Firstly it is necessary to know the term 'science'. It is defined as the intellectual and practical activity encompassing the *systematic* study of the structure and behaviour of the physical and natural world through observation and experiment. Scientific (adj.) means 'based on or characterized by the methods and principles of science; *systematic*; methodical'.

The general principles

The principles of writing a scientific article for publication include two parts. **Part (I)** How to prepare a manuscript for (international) journals and **Part (II)** related information - (1) Choosing the right journal, (2) Use and abuse of citations, (3) Ethics in research and publication, and (4) Response to editors' and reviewers' comments.

1. Part (I) How to prepare a manuscript for (international) journals

This is first step for writing a scientific article. General structure of a research article includes title, abstract, keywords, main text (IMRD) (ie. introduction, methods, results and discussion), conclusion, acknowledgement, references and supplementary data or supporting materials. In this IMRD, **I**ntroduction stands for what you/others did, why you did it, **M**ethods for how you did it, **R**esults for what you found, and **D**iscussion for what it all means.

Length of the manuscript are: Title should be informative and not too long; Abstract should has one paragraph (< 250 or 350 words); Introduction 1.5-2 pages; Methods 2-3 pages; Results 6-8 pages; Discussion 4-6 pages; Conclusion 1 paragraph; Figures 6-8 (one per page); Tables 1-3 (one per page) and References 20-50 papers (2-4 pages). Additional requirements in submission of manuscript also includes (i) List of abbreviations, (ii) Declaration, (iii) Ethics approval and consent to participate, (iv) Consent for publication, (v) Availability of data and materials, (vi) Competing interests, (vii) Funding, (viii) Authors' contributions, (ix) Authors' information and (x) Endnotes.

When you organize your manuscript, the first thing to consider is the order of sections which is very different from the order of items on your prepared manuscript. Steps to organizing your manuscript are as follow:

(1) Prepare the **Figures** and **Tables**

(2) Write the **Methods**
(3) Write up the **Results**
(4) Write the **Discussion**
(5) Write a clear **Conclusion**
(6) Write a compelling **Introduction**
(7) Write the **Abstract**
(8) Compose a concise and descriptive **Title**
(9) Select **Keywords** for indexing
(10) Write the **Acknowledgements**
(11) Write the **References**

You also need to consult the 'Publisher's Guides for Authors'.

Step 1. Prepare the figures and tables

Remember that 'a figure is worth a thousand words'. Your data are the driving force of the paper, so your illustrations are critical. Generally, Tables show actual results and Figures comparisons of results. Whatever your choice is, no illustrations should duplicate the information described elsewhere in the manuscript. Another important factor is that Figure and Table legends must be self-explanatory. When presenting your tables and figures, you must mind to avoid crowded plots using only three or four data sets per figure and well-selected scales; to think about appropriate axis label size; to include clear symbols and data sets that are easy to distinguish; and never to include long boring tables (e.g., chemical compositions of emulsion systems or lists of species and abundances). You can include them as supplementary material. If you use Photographs, each must have a scale marker, or scale bar, of professional quality in one corner.

Step 2. Write the Methods

'How the problem was studied?' If your paper is proposing a new method, you need to include detailed information so a knowledgeable reader can reproduce the experiment. All chemicals must be identified. Do not use proprietary, unidentifiable compounds. For examples: For chemicals, use conventions of the **International Union of Pure and Applied Chemistry** and the official recommendations of the **IUPAC - IUB Combined Commission on Biochemical Nomenclature**. For species, use accepted taxonomical nomenclature **(WoRMS: World Register of Marine Species, ERMS: European Register of Marine Species)**, and write them always in italics, and For units of measurement, use **International System of Units (SI)**.

Step 3. Write up the Results

'What have you found?' Only representative results should be presented. The results should be essential for discussion. For statistical rules, you need to indicate the statistical tests used with all relevant parameters: e.g., mean and SD: 44% (±3); median and

interquartile range: 7 years (4.5 to 9.5 years). Mean and SD are for normally distributed data and median and interquartile range for skewed data. For numbers, use two significant decimal digits unless more precision is necessary (eg. 2.08, not 2.07856444). Never use percentages for very small samples (e.g., 'one out of two' should not be replaced by 50%). For the data, decide on a logical order as presented in the methods section. Do not include references.

Step 4. Write the Discussion

Here you must respond to what the results mean. Probably it is the easiest section to write, but the hardest section to get right. This is because it is the most important section of your article. Here you get the chance to sell your data. Take into account that a huge numbers of manuscripts are rejected because the Discussion is weak. Do not reiterate the results in discussion. Mind the following points.

(i) Avoid statements that go beyond what the results can support.
(ii) Avoid unspecific expressions (eg. 'higher temperature', 'at a lower rate', 'highly significant'. Quantitative descriptions are always preferred (eg. 35°C, 0.5%, $p < 0.001$, respectively).
(iii) Avoid sudden introduction of new terms or ideas (you must present everything in the introduction; these will be confronted with your results)
(iv) Speculations on possible interpretations are allowed, but these should be rooted in fact, rather than imagination.
(v) Revision of Results and Discussion is not just paper work.

Step 5. Write a clear Conclusion

How the work advances the field from the present state of knowledge. In some journals, it's a separate section; in others, it's the last paragraph of the Discussion section. Without a clear conclusion section, reviewers and readers will find it difficult to judge your work and whether it merits publication in the journal. A common error in this section is repeating the abstract, or just listing experimental results. Trivial statements of your results are unacceptable in this section.

Step 6. Write a compelling Introduction

This is your opportunity to convince readers that you clearly know why your work is useful. A good introduction should answer the following questions:

(i) What is the problem to be solved?
(ii) Are there any existing solutions?
(iii) Which is the best?
(iv) What is its main limitation?
(v) What do you hope to achieve?

Hypothesis and objectives must be clearly remarked at the end of the introduction. Expressions such as ‘novel’, ‘first time’, ‘first ever’, and ‘paradigm-changing’ are not preferred. Use them sparingly.

Step 7. Write the Abstract

Tells what you did and what the important findings in your research are. It is the advertisement of your article. Avoid jargon, uncommon abbreviations and references. Provides a short perspective and purpose of your paper. Gives key results but minimizes experimental details. Write a short description of the interpretation/conclusion in the last sentence. Also check the 'Guide for authors' of the journal, but normally they have < 250 words. Again, Two whats are essential. **What has been done?** and **What are the main findings?** Some journals recommend the outline of Background, Methods, Results and Conclusion to be included in Abstract.

Step 8. Compose a concise and descriptive title

Title must be self-explanatory. It is your first opportunity to attract the reader's attention. First readers are the Editors and the Referees. Readers are also the potential authors who will cite your article, so the first impression is powerful. Keep it informative and concise (ie. clear, descriptive and not too long)

Example

Original title: Preliminary observations on the effect of salinity on benthic community distribution within an estuarine system, in the North Sea

Revised title: Effect of salinity on benthic distribution within the Scheldt estuary (North Sea)

Comments: Long title distracts readers. Remove all redundancies such as ‘studies on’, ‘the nature of’, etc. Never use expressions such as ‘preliminary’. Be precise.

Step 9. Select keywords for indexing

Keywords are used for indexing your paper. They are the label of your manuscript. Avoid words with a broad meaning and words already included in the title. Also check ‘the Guide for Authors’ and look at the number of keywords admitted.

Step 10. Write the Acknowledgements

Thank people who have contributed to the manuscript but not to the extent where that would justify authorship. (eg. Technical help and assistance with writing and proofreading). Thank your funding agency or the agency giving you a grant or fellowship. Include the Grant number or Reference.

Step 11. Write up the References

Avoid excessive self-citations and excessive citations of publications from the same region. Minimize personal communications. Do not include unpublished observations, manuscripts submitted but not yet accepted for publication, publications that are not peer reviewed, grey literature, or articles not published in English. You can use any software, such as **EndNote** or **Mendeley**, Use appropriate Referencing style (eg. Harvard or Vancouver). Finally, check the spelling of author names, year of publications, usages of "et al.", punctuation, and whether all references are included.

2. PART (II) Related information

Next step after preparing your manuscript is Choosing the right journal.

2.1. Choosing the right journal

Select a peer-reviewed journal focusing the right target audience. It will affect you career advancement and you probably get professional reputation and funding opportunities. There are several criteria to select the journal for manuscript submission.

Question 1: Is there a match between the subject of your article and the journal's aim and scope? (This point is the most common reason to reject if not matched)

For examples, *Histopathology* journal is good for surgical and diagnostic histo-pathologists, and *The Journal of Pathology* good for pathophysiological and pathogenetic mechanisms of human diseases. If your paper is a case study, go to Journal which publishes case reports.

Question 2: What is the readership and target audience?

Consider multidisciplinary journal, specialty journal, and how popular the journal is among your peers.

Question 3: Is the journal highly visible?

Once your paper is published, it should be easy to find by other researchers. Journal visibility plays an important role in this regard. Consider the journal is included in electronic databases, indexed in ISI’s Web of Science, in popular subject-specific databases in your field, and available online/circulating in print.

Question 4: What is the CV value of publication?

Also look at Editorial board members, Journal sponsorship, the journal's impact factor. Talk to senior, established colleagues for their advices. Think of which journals they regularly read, which journals they feel have a high standard of articles.

Question 5: What is the journal's turnaround time?

It is time interval between submission of manuscript usually electronically and sending of editorial decision. It depends on peer review period. Consider how many issues the journal publishes in a year, monthly Journal or published once a year. Also look at dates of submission and acceptance. While you choose a journal for publication, you should ensure the following:

(i) Does the subject of your article match the journal's subject focus?
(ii) Does the journal accept the article type you intend to submit?
(iii) Is the journal read by your target audience?
(iv) Is the journal included in bibliographic and subject-specific databases?
(v) Does the journal have an online edition?
(vi) Is the journal's impact factor in line with your requirements?
(vii) Is the journal regarded as a prestigious one in its field by colleagues and peers?
(viii) What is the turnaround time for articles submitted to the journal?
(ix) How many times a year is the journal published?
(x) What are the publication charges?
(xi) Is the length and structure of your manuscript acceptable to the journal?

Once you have taken a preliminary decision on the journal, Read 'the Instructions to Authors' to discover article format, word count, citation styles, photograph specifications, publication costs, etc. This will help you make a final decision to submit your manuscript to that Journal.

2.2. Use and misuse of citations

Types of citations are:

(i) Referential citation: a work or part of a work is cited for what it contributes to the field
(ii) Critical citation: a work or part of a work is cited because it is believed to mislead the field

Functions of citations are:

(i) Verification function: to check for accuracy
(ii) Acknowledgement function: to make credit for its contribution
(iii) Documentation function: for object of the research Deviations from ideal citation practice are:
  (i) Selective citation through need for conciseness: That is citation from 'discovery' article and review article
  (ii) Selective citation in support of a viewpoint: Found even in numerous high quality studies
  (iii) Selective citation to enhance reputation: Self-citation or the citation of colleagues with a view to enhancing one's own or the colleague's reputation (reputation citation) is clearly unacceptable

  (iv) Selective citation for convenience: It is easy to get (convenience citation)
  (v) Selective citation by country of origin: Refers to one's own country of origin. It is found even in US and UK.
  (vi) Citing inaccessible sources: Citing conference papers or their abstracts, submitted articles, in-house papers, or unpublished reports (the so-called gray literature). In website, problems occur over time as websites move or become inaccessible.
  (vii) Citing unevaluated sources: Citing to book chapters, letters, conference presentations, abstracts, opinion pieces, and other material that has not been peer reviewed.
  (viii) Citing without reading
  (ix) Overuse of citations: A long list of citations to support a single statement when fewer would be sufficient
  (x) Coercive citation

Following principles can be applied:

(i) Support all nonobvious, substantive claims by citation or direct evidence.
(ii) Do not support statements of the obvious by citation.
(iii) If there is an authoritative review on a well-supported statement, this may be used in place of original articles.
(iv) When citing original articles, cite the discovery article together with a small number of other articles that illustrate the generality of the phenomenon.
(v) Resist the propensity to do the following:
  (a) Prefer citations from your own country of origin unless the finding in question is country specific;
  (b) Prefer citations from yourself and colleagues;
  (c) Limit citations to those that support a contention, when in fact there are others that conflict with it;
  (d) Cite output that is readily retrievable if there are more appropriate references; and
  (e) Provide an unnecessarily large number of citations for a single statement.
(vi) Avoid citing inaccessible sources wherever possible.
(vii) When using citations in support of substantive statements, either use references that have been through some kind of peer-review process or provide an appropriate caveat.

2.3. Ethics in Research and Publication Authorship

An 'author' is generally considered to be an individual who has made a significant intellectual contribution to the study.

Three basic criteria are:

(i) Substantial contribution to the study conception and design, data acquisition, analysis, and interpretation
(ii) Drafting or revising the article for intellectual content
(iii) Approval of the final version

The following are some general guidelines:

(i) The order of authorship should be 'a joint decision of the co-authors'.
(ii) Individuals who are involved in a study but don't satisfy the journal's criteria for authorship, should be listed as 'contributors' or 'acknowledged individuals'. Examples include: assisting the research by providing advice, providing research space, departmental oversight, and obtaining financial support.
(iii) For large, multi-center trials, the list of clinicians and centers is typically published, along with a statement of the individual contributions made. Some groups list authors alphabetically, sometimes with a note to explain that all authors made equal contributions to the study and the publication.

Three types of authorship are considered unacceptable:

(i) 'Ghost authors', who contribute substantially but are not acknowledged (often paid by commercial sponsors)
(ii) 'Guest authors', who make no discernible contributions, but are listed to help increase the chances of publication
(iii) 'Gift authors', whose contribution is based solely on a tenuous affiliation with a study.

Conflict of interest

Transparency and objectivity are essential in scientific research and the peer review process. The most obvious conflicts of interest are financial relationships such as:
Direct - employment, stock ownership, grants, patents, and
indirect - honoraria, consultancies to sponsoring organizations, mutual fund ownership, paid expert testimony.

Undeclared financial conflicts may seriously undermine the credibility of the journal, the authors, and the science itself. (eg. an investigator who owns stock in a pharmaceutical company that is commissioning the research)

Conflicts can also exist as a result of personal relationships, academic competition, and intellectual passion. eg. a researcher who has (i) a relative who works at the company whose product the researcher is evaluating, (ii) a self-serving stake in the research results (e.g. potential promotion/career advancement based on outcomes), and (iii) personal beliefs that are in direct conflict with the topic he/she is researching. The Journal can decide not to publish the manuscript on the basis of declared conflict.

Plagiarism

One of the most common types of publication misconduct is plagiarism - when one author deliberately uses another's work without permission, credit, or acknowledgment.

Plagiarism takes different forms, from literal copying to paraphrasing some else's work and can include data, words and phrases, ideas and concepts.

Plagiarism has varying different levels of severity, such as (i) how much of someone's work was taken–a few lines, paragraphs, pages, the full article, (ii) what copied-results, methods, or introduction section. When it comes to your work, always remember that crediting the work of others is a critical part of the process. You should always place your work in the context of the advancement of the field, and acknowledge the findings of others on which you have built your research.

Simultaneous submission

Authors have an obligation to make sure their paper is based on original (never before published) research. Intentionally submitting or re-submitting work for duplicate publication is considered a breach of publishing ethics. Simultaneous submission occurs when a person submits a paper to different publications at the same time, which can result in more than one journal publishing that particular paper. Duplicate/multiple publication occurs when two or more papers, without full cross-reference, share essentially the same hypotheses, data, discussion points, and/or conclusions. This can occur in varying degrees in the form of literal duplication, partial but substantial duplication, or even duplication by paraphrasing.

Research fraud

Research fraud is publishing data or conclusions that were not generated by experiments or observations, but by invention or data manipulation. There are two kinds in research and scientific publishing: (i) Fabrication: making up research data and results, and recording or reporting them, (ii) Falsification: manipulating research materials, images, data, equipment, or processes. It includes changing or omitting data or results in such a way that the research is not accurately represented. It might falsify data to make it fit with the desired end result of a study. To help prevent fraud, most publishers have strict policies on manipulation of images and access to the reported data. Some general guidelines are suggested as follow.

For manipulation of images:

(i) Images may be manipulated for improved clarity only.
(ii) No specific feature within an image may be enhanced, obscured, moved, removed, or introduced.
(iii) Adjustments of brightness, contrast, or colour balance are usually acceptable as long as they do not obscure or eliminate any information present in the original.

For data access and retention:

(i) Authors may be asked to provide the raw data in connection with a paper for editorial review. All data for a specific paper should be retained for a reasonable time after publication. There should be named custodian for the data.

(ii) Studies undertaken in human beings, e.g. clinical trials have specific guidelines about the duration of data retention.

Salami slicing

The 'slicing' of research that would form one meaningful paper into several different papers is called 'salami publication' or 'salami slicing'. Unlike duplicate publication, which involves reporting the exact same data in two or more publications, salami slicing involves breaking up or segmenting a large study into two or more publications. These segments are referred to as 'slices' of a study. Salami slicing can result in a distortion of the literature by leading unsuspecting readers to believe that data presented in each 'slice' is derived from a different subject sample. The following should be done.

(i) Avoid inappropriately breaking up data from a single study into two or more papers.

(ii) When submitting a paper, be transparent. Send copies of any manuscripts closely related to the manuscript under consideration. This includes any manuscripts published, recently submitted, or already accepted.

2.4. Response to Editors' and Reviewers' comments

It is a normal part of the path to publication.

(i) Get mad. Then get over it. You should expect that your submitted paper is to be modified/corrected/rejected. Editors and reviewers pointed out 'what is wrong with your paper'.

(ii) Consider what the editor's decision letter really says. It is best to just accept the decision and consider another journal. Examples of decision letters are:

Example 1. Rejection, do not resubmit.

Your paper has been examined by two expert reviewers. Unfortunately, we must decline this manuscript for publication. The reasons for this decision are indicated in the reviewers' comments.

Example 2. Declined for now, future acceptance possible.

Your paper has been examined by two expert reviewers. For the reasons explained in the comments, we cannot accept this manuscript for publication in Clinical Chemistry. We would consider a revised version that takes these criticisms into account but cannot offer assurance that submission of a revised manuscript will lead to acceptance.

Example 3. Declined for now, future acceptance very likely.

Your paper has been examined by two expert reviewers. As you will see in their comments, each reviewer finds merit in the work but makes constructive suggestions. Please consider the suggestions carefully, as the changes will produce an article that better serves you and our readers.

(iii) Wait and gather your thoughts

The Journal requests:

(a) for clarification of existing text, addition of text to fill a hole in the paper, or additional experimental details
(b) to reanalyse, re-express, or reinterpret existing data
(c) for additional experiments or further proof of concept
(d) additional data analysis
(e) you simply cannot meet.

(iv) Even if the reviewer is wrong, it does not mean you are right. So, look first at what you can do to improve the paper and satisfy the reviewer, not explain to the reviewer how he or she is wrong.

(v) Choose your battles wisely.

If your scientific paper is typical, the reviewers will ask you to make more than one modification. Explain where the reviewer may have misinterpreted the section and that you want to keep the text intact.

(vi) Do not pit one reviewer against another.

In some situations the reviewers will make diametrically opposed recommendations. Provide a logical explanation to both reviewers for why you feel that one of the suggestions would be more effective in improving the paper.

(vii) Be grateful for the reviewers' and editor's time.

Reviewers volunteer their time when they agree to evaluate a scientific paper. Be polite and thoughtful in all of your responses to the comments you received.

(viii) Restate the reviewer's or editor's comments when responding.

They will not recall the order in which the comments were written, nor will they remember the exact wording they used.

(ix) Be prepared to cut text.

A journal is expensive to produce, and the editor is responsible for balancing content and costs.

(x) Do not submit the same version to another journal.

Reviewers' comments often help improve a paper, so why not take advantage of the reviewers' advice if it can improve the paper.

Conclusion

These principles are of paramount importance and if followed, manuscripts would be accepted for publication. In addition to it, it is also required to learn 'Scientific English' to write articles grammatically.

Reference cited

Angel Borja. 11 steps to structuring a science paper editors will take seriously. https://www.elsevier.com/connect/11-steps-to-structuring-a-science-paper-editors-will-take-seriously Accessed October 2019

Universal Health Coverage (UHC)

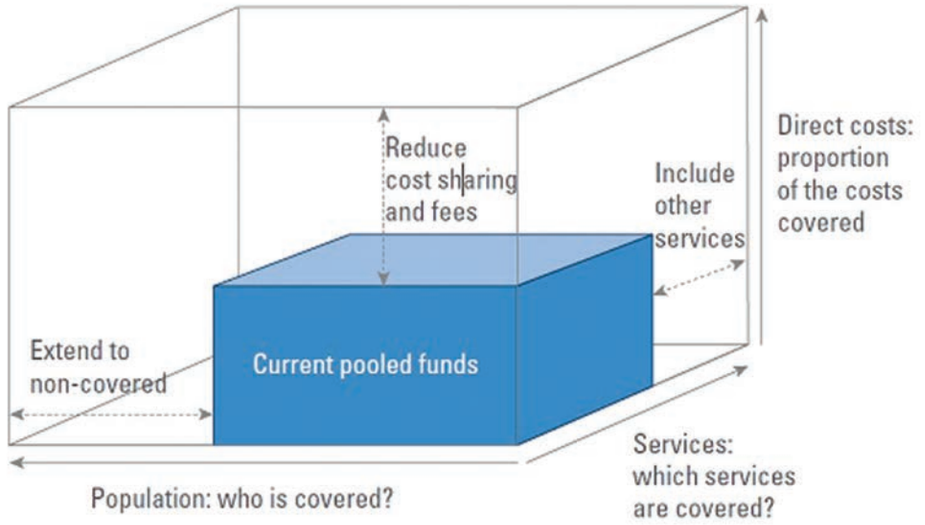
Preventive and Social Medicine Society

1. What is Universal Health Coverage?

UHC is about ***"all people having access to the health care they need without suffering financial hardship."***

UHC for a country may be defined as ***access, on equal terms, for all citizens to a specified package of the highest quality health care that country can afford without any citizens suffering financial hardship as a result.*** (Cheng, 2014)

Figure 1. The UHC Tube



Source: WHO 2010.

2. Why UHC is important?

First, health and UHC is a human right, according to Article 25 of the Universal Declaration of Human Rights (1948). Second, it can help fighting poverty in the age of escalating medical care cost. Third, it is a vital investment in human capital, which is necessary for economic growth and development. Finally, UHC is necessary because of inequality – the poor get the less from the health system than the better off.

3. How UHC can be achieved?

Option one is to make health care coverage available to the whole nation but the poor needs to be targeted by prioritizing health interventions for diseases that disproportionately affect that group. Option two is provide a larger package of

interventions to the full population but with some patient copayment, from which poor people would be exempt. It also explicitly rejects pathways that propose heavy reliance on private voluntary health insurance or "catastrophe-only" health insurance plans. (Cotlear, Nagpal, Smith, Tandon, & Cortez, 2015)

4. Some cautions in using the term "UHC"

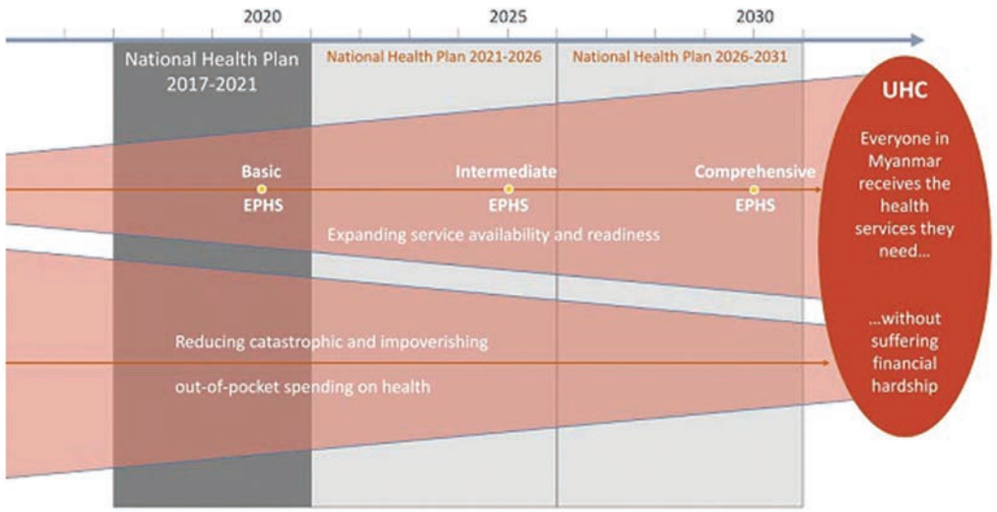
First, UHC does not mean a universally applicable package of health care services. Universal access to health care in Japan means something different from those provided in Uganda. Second, equal financial access does not necessarily mean equal physical access to health care. If there are physical barriers to health care, health insurance means nothing.

5. Sustainability of UHC

There are two kinds of sustainability in UHC: economic sustainability and political sustainability. Economic sustainability means how much a nation's GDP can be allocated to health care and political sustainability means how much the rich would be willing to pay, either with taxes or community-rated health insurance premiums, to help finance the health care needs of the poor who cannot afford to pay for that care with their own resources.

6. What does UHC mean in Myanmar?

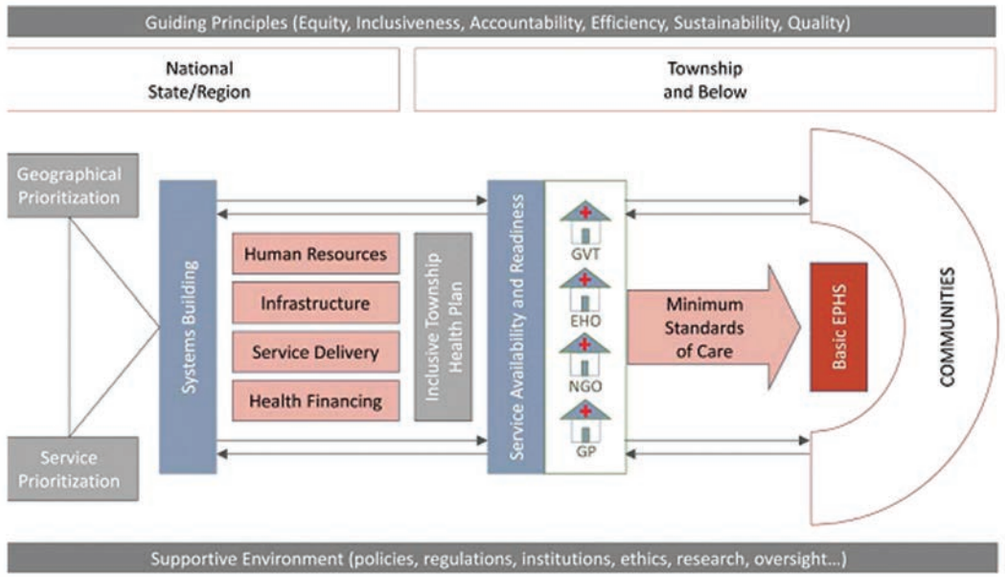
Figure 2. The National Health Plan and Universal Health Coverage Source: Myanmar National Health Plan (2017-2021)



As shown in the above figure, UNC in Myanmar means "Everyone in Myanmar receives the health services they need without suffering financial hardship. (MOHS, 2017)

Figure 3. Conceptual Framework

Source: Myanmar National Health Plan (2017-2021)



In Myanmar, on our way towards UHC, we need input not only from government providers but also from Ethic Health Organization (EHO), NGO, and GP so that we can provide essential package of health service (EPHS) to our people and upgrade our EPHS from basic package to an intermediate one and finally to a comprehensive one. At the same time, health system has been strengthened on the way to UHC.

In conclusion, UHC is "all people having access to needed health services without experiencing financial hardship". As it is a human right, it is important for everyone. Not only the establishment of UHC but also sustainability of UHC is vital and so we need to try our best to move towards UHC and find ways and means to sustain it.

References

Cheng T. (2014). Universal Health Coverage: an Overview and Lessons from Asia, 1-12.

Cotlear D., Nagpal S., Smith O., Tandon A., & Cortez R. (2015). Going Universal: How 24 developing countries are implementing Universal Health Coverage Reforms from the Bottom Up.

MOHS. (2017). Myanmar National Health Plan (2017-2021).

Safe Conduct of Local Anaesthesia

Myanmar Anaesthesiologist Society

Local anaesthetic agents can be defined as drugs which are used clinically to produce reversible loss of sensation in a circumscribed area of the body.

There are 2 classes of local anaesthetic drugs defined by the nature of the carbonyl-containing linkage group. The ester agents include cocaine, procaine, amethocaine and chloroprocaine, whilst the amides include lignocaine, prilocaine, mepivacaine and bupivacaine.

The dilute preparations are presented as percentage solutions of local anaesthetic. For example, lignocaine is available in 1% and 2% solutions for injection (with or without adrenaline). A solution expressed as 1% contains 1 g of substance in each 100 mls. The number of mg/ml can easily be calculated by multiplying the percentage strength by 10. Therefore a 1% solution of lignocaine contains 10 mg/ml of solution. A 0.25% solution of bupivacaine has 2.5 mg/ml.

Most local anaesthetics produce some degree of vasodilation, and they may be rapidly absorbed after local injection. Consequently, vasoconstrictors are frequently added, to enhance their potency and prolong their duration of action by localizing them in tissues. In addition, vasoconstrictors decrease the systemic toxicity and increase the safety margin of local anaesthetics by reducing their rate of absorption (which is mainly dependent on local blood flow). Adrenaline is the most commonly used vasoconstrictor. It is added to local anaesthetic solutions in concentrations ranging from 1 in 80,000 to 1 in 300,000, although most are usually prepared to contain a 1 in 200,000 (5 microgram/ml) concentration of adrenaline.

Adrenaline containing solutions should never be used for infiltration around end-arteries i.e. penis, ring block of fingers or other areas with a terminal vascular supply as the intense vasoconstriction may lead to severe ischaemia and necrosis.

Maximum safe dosages are often quoted for local anaesthetics with and without vasoconstrictors, but such recommendations should be treated with caution as they ignore variations caused by factors such as the site of injection, the patient's general condition and the concomitant use of a general anaesthetic.

Upper dose limits for commonly used local anaesthetic agents

Plain solution	**With adrenaline**	
Lignocaine	3 (mg/kg)	5 (mg/kg)
Bupivacaine	2 (mg/kg)	2 (mg/kg)

The addition of adrenaline reduces the peak concentration in blood, but the degree of this reduction again depends on the site of injection and the specific local anaesthetic agent.

Clinical Uses of Local Anaesthetics

1. Topical Anaesthesia
2. Infiltration Anaesthesia
3. Peripheral nerve block (Brachial block or intercostals block)
4. Central neural block (Spinal/Epidural)

Toxicity of Local Anaesthetic Agents

Local anaesthetic agents are relatively free from side effects if they are administered in an appropriate dosage and in the correct anatomical location.

Toxic side effects of local anaesthetic drugs occur when excessive blood levels occur. This is usually due to:

1. Accidental rapid intravenous injection.
2. Rapid absorption, such as from a very vascular site ie mucous membranes. Intercostal nerve blocks will give a higher blood level than subcutaneous infiltration, whereas plexus blocks are associated with the slowest rates of absorption and therefore give the lowest blood levels.
3. Absolute overdose if the dose used is excessive.

Reducing the risk of toxicity

1. Decide on the concentration of the local anaesthetic that is required for the block to be performed. Calculate the total volume of drug that is allowed.
2. Use lower doses in frail patients or at the extremes of ages.
3. Always inject the drug slowly (slower than 10ml/minute) and aspirate regularly looking for blood to indicate an accidental intravenous injection.
4. Injection of a test dose of 2-3 ml of local anaesthetic containing adrenaline will often (but not always) cause a significant tachycardia if accidental intravenous injection occurs. Most nerve blocks are more dependent on volume of drug injected than the total dose. Therefore, if more volume is needed it is better dilute the local anaesthetic with 0.9% saline than to add more local anaesthetic and increase the dose unnecessarily.
5. Add adrenaline (epinephrine) to reduce the speed of absorption. The addition of adrenaline will reduce the maximum blood concentration by about 50%. Usually adrenaline is added in a concentration of 1:200,000, with a maximum dose of 200 micrograms. (This is made up by taking an ampoule of adrenaline with a concentration of 1:1,000 = 1 mg/ml = 0.1 mg%. From this you take 0.1 ml (zero point one millilitres) and add it to each 20 ml of the local anaesthetic.)

Make sure that the patient is monitored closely by the anaesthetist or a trained nurse during the administration of the local anaesthetic and the following surgery.

Signs and Symptoms of Local Anaesthetic Toxicity

The systemic toxic effects due to local anaesthetic overdose primarily involve the central nervous and cardiovascular systems. Therefore, CNS manifestations tend to occur earlier. Brain excitatory effects occur before the depressant effects.

CNS Signs & Symptoms

Early or mild toxicity: light-headedness, dizziness, tinnitus, circumoral numbness, abnormal taste, confusion and drowsiness. Patients often will not volunteer information about these symptoms unless asked. Throughout the injection talk to the patient asking them how they feel. Any suggestion of confusion should alert you to the possibility of toxicity and you should stop any further injection.

Severe toxicity: tonic-clonic convulsion leading to progressive loss of consciousness, coma, respiratory depression, and respiratory arrest. Depending on the drug and the speed of the rise in blood level the patient may go from awake to convulsing within a very short time.

CVS Signs & Symptoms

Early or mild toxicity: tachycardia and rise in blood pressure. This will usually only occur if there is adrenaline in the local anaesthetic. If no adrenaline is added then bradycardia with hypotension will occur.

Severe toxicity: Usually about 4 - 7 times the convulsant dose needs to be injected before cardiovascular collapse occurs. Bupivacaine is considered to be more cardiotoxic than lignocaine. Severe and intractable arrhythmias can occur with accidental IV injection. The acute toxicity of local anaesthetics is due to the speed of rise of blood concentration. Therefore, a rapid injection of a small volume may cause toxicity.

Always secure intravenous access before injection of any dose that may cause toxic effects. Always have adequate resuscitation equipment and drugs available before starting to inject.

Treatment of Toxicity

1. If a patient you are attending shows any signs or symptoms of toxicity during injection of local anaesthetic stop the injection and assess the patient.
2. Treatment is based on the A B C D of Basic Life Support
3. Call for help while treating the patient

A (Airway) - Ensure an adequate airway, give oxygen in high concentration if available.
B (Breathing) - Ensure that the patient is breathing adequately. Ventilate the patient with a self inflating bag (Ambu Bag) if there is inadequate spontaneous respiration. Intubation may be required if the patient is unconscious and unable to maintain an airway.
C (Circulation) - Treat circulatory failure with intravenous fluids such as ephedrine (5-10 mg boluses) if hypotension occurs. Adrenaline may be used cautiously intravenously in boluses of 0.5 - 1 ml of 1:10,000 (1 mg in 10 ml) if ephedrine is either not available or not effective in correcting the hypotension.
Treat arrhythmias.
Start chest compressions if cardiac arrest occurs.
D (Drugs) - to stop fits such as Diazepam 0.2-0.4 mg/kg intravenously slowly over 5 minutes repeated after 10 minutes if required.
Observe the patient closely after any reaction. Treatment of local anaesthetic toxicity is likely to have a good outcome if toxicity is recognised and basic resuscitation is started early.
Monitor patients closely when using local anaesthetics.

If a reaction occurs:
Prevent hypoxia which will cause brain damage and make fits or arrhythmias more difficult to control.
Ensure that hypotension and arrhythmias are treated early.
Ensure that fits are adequately treated.
Most reactions are short-lived if the above advice is followed.

Approach to joint pain

Myanmar Rheumatology Society

Questions to be asked in patient with arthritis

1. Number of joints affected

Monoarthritis: one single joint affected
Oligoarthritis: 2-4 joints affected
Polyarthritis: > 4 joints affected

2. Acute versus chronic

Acute: onset in hours or days
Sub-acute: up to 6 weeks
Chronic: onset over weeks (more than 6 weeks) or months

3. Pattern of joint involvement (Additive versus migratory vs intermittent)

Additive: the affected joints are added progressively
Migratory: the inflammatory process flits from one joint to another
Intermittent: episodes or crises of arthritis separated by symptom-free 'intercritical' intervals

4. Distribution of joint involvement

Predominantly proximal versus predominantly distal
Proximal: arthritis mainly affects large joints - that is, proximal to the wrist or ankle
Distal: the arthritis mainly affects the small joints of the hands and feet, with or without the wrist and ankle
Large and small joints affected - there is a mixture of joint sizes

Symmetrical versus Asymmetrical
Symmetrical: affects approximately the same joint groups on each side of the body
Asymmetrical: there is no clear relationship between the joints affected on either side of the body

5. with or without inflammatory low back pain
6. with or without systemic manifestation

1. What is the number of joint involvement?
Monoarthritis
Differential diagnosis of monoarthritis (articular pain) are periarticular pain and refer pain

	Periarticular pain	Articular pain	Referred pain
Enquiry	few selective movements are painful	All joint movements are painful	Unrelated to movement
Pain on motion	Active > passive Selected m/m	Active~passive All m/m	Normal
Range of motion	Active > passive limited	Active & passive limited	Normal
Local palpation	Tenderness over affected peri-articular structure Swelling perpendicular to the joint line	Jt line Tenderness Warm Jt Jt effusion Swelling parallel to the joint line	Normal

Acute monoarthritis
Inflammatory arthritis
1. crystal arthritis (gout, pseudogout) - most common

Gout
Very rapid onset of pain and swelling - at its worst within just 6-24 hr
Very severe pain - often described as 'worst ever'
Marked tenderness - often unable to bear clothes or bed sheets touching the overlying skin
Often florid synovitis with a tense effusion, adjacent soft tissue swelling and overlying erythema (especially gout)
Episode is self-limiting, even without treatment, over a few days or a few weeks
Gout - Common joint - 1st MTPJ > any periphery joint
Provoking factors - local trauma, illness, Surgery
Sometimes associate with fever, malaise

Pseudogout
Similar pattern, over 60 years
Common joint - knee, wrist, shoulder, ankle

2. Septic arthritis
Symptoms and signs are progressive from day to day and do not plateau in the first 24 hr.
Acute or sub-acute onset of pain, swelling and sometimes erythema in a single joint

3. Reactive arthritis
History of history of preceding throat, urogenital, or gastrointestinal tract infection
can also be seen with coexistent circinate balanitis, sterile urethritis, and keratoderma blennorrhagica

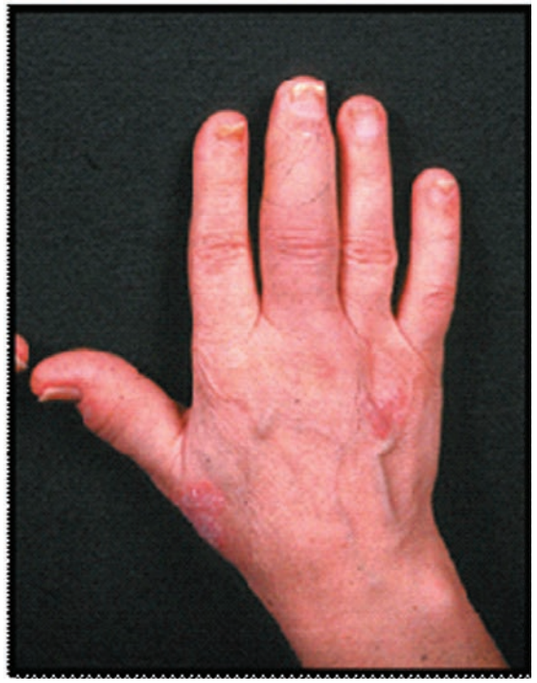
Non inflammatory
post-traumatic

Chronic monoarthritis
Inflammatory
1. Infection (TB)
2. Mono-articular presentation of oligo- or polyarthritis (juvenile idiopathic arthritis, seronegative spondylo-arthropathy)

Non-inflammatory
1. OA
2. Charcot joint
3. Tumor

Oligoarthritis
1. Reactive arthritis
2. Spondyloarthritis
- Family history of spondyloarthritis
- History of heel pain, uveitis, sacroiliitis
- usually affect large joints in the lower limb
3. Psoriatic arthritis
- History of psoriasis in the relatives
- History of heel pain, uveitis, psoriasis, dactylitis, nail pitting, onycholysis

Fig - Dactylitis



4. Enteropathic arthritis
- seen with inflammatory bowel disease

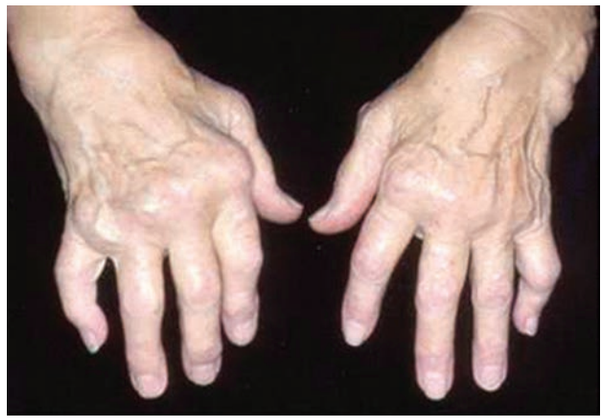
Polyarthritis
Clinical features to distinguish inflammatory to non-inflammatory joint pain

	inflammatory	**mechanical**
Pain	Activity (gentle movement) improves the symptom	More severe with use (directly related to use)
Early morning stiffness	Prolong (at least 30 min to 1 hour)	Brief (Less than 30 min)
Inactivity stiffness	Prolong	Brief
Increased warmth	+	-
effusion	+++	+/-
Coarse crepitus	-	+++

Acute polyarthritis
1. Viral arthritis (Chikungunya, Rubella, hepatitis associated, parvo virus-B19)
2. Septic (gonococal) arthritis, infective arthritis
3. Rheumatic fever

Chronic polyarthritis
Inflammatory
1. Rheumatoid arthritis
Usual age of onset is 40-60 years
May begin any time in life
May be sudden or gradual over weeks to months
Frequent fatigue, low-grade fever, anorexia, muscle / joint aches, stiffness
Extra-articular manifestations; rheumatoid nodules, Sjögren's syndrome
Joints are painful, swollen and stiff; affects joints symmetrically; primarily affects small joints, but also affects large ones

Fig - Rheumatoid arthritis affecting MCP joints of both hand

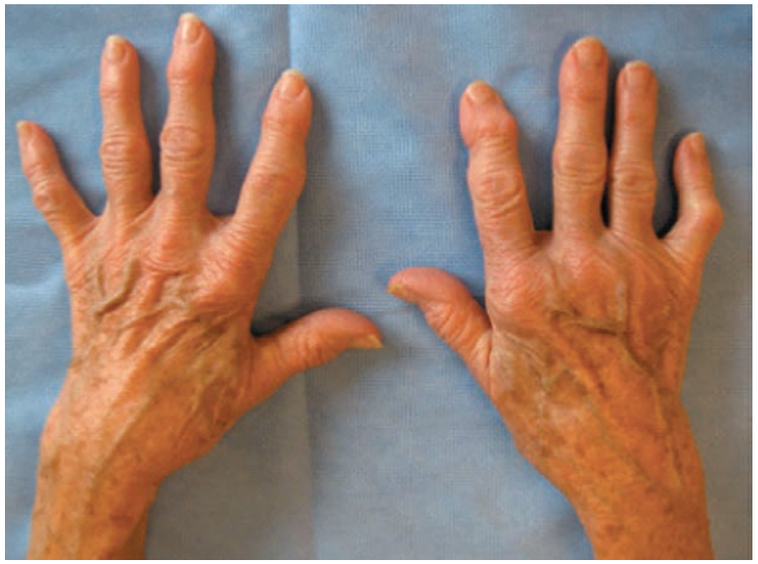


2. Psoriatic arthritis (rheumatoid form)
3. Chronic polyarticular gout
4. CPPD crystal disease (pseudo-rheumatoid)

Non inflammatory
1. Osteorthritis

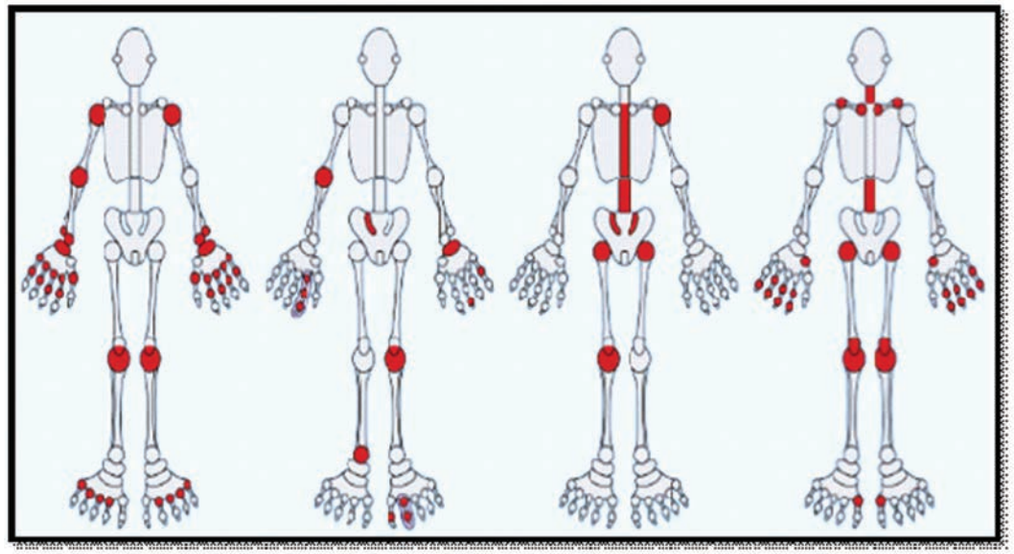
Age of onset - Most commonly occurs in individuals older than 50 years
Speed of onset - Slow; over years
Systemic symptoms - Lack of systemic symptoms
Joint symptoms - Short-lived morning stiffness; "gel phenomenon";
Joints painful without swelling or with hard, bone swelling
may affect joints symmetrically or asymmetrically; affects small joints, large weight-bearing joints such as hips and knees, and/or the spine; bony nodules in hand OA - Heberden's node (DIP joint), Bouchard's node (PIP joint)

Fig - OA hand with Heberden's node and Bouchard's node



2. What is the pattern of joint involvement?
Additive pattern - Rheumatoid arthritis
Intermittent pattern - Crystal arthritis
Migratory pattern - Rheumatic fever, Gonocccal arthritis

3. What is the distribution of joint involvement?



A. Rheumatoid arthritis **B. Psoriatic arthritis** **C. Ankylosing spondylosis** **D. Osteoarthritis**

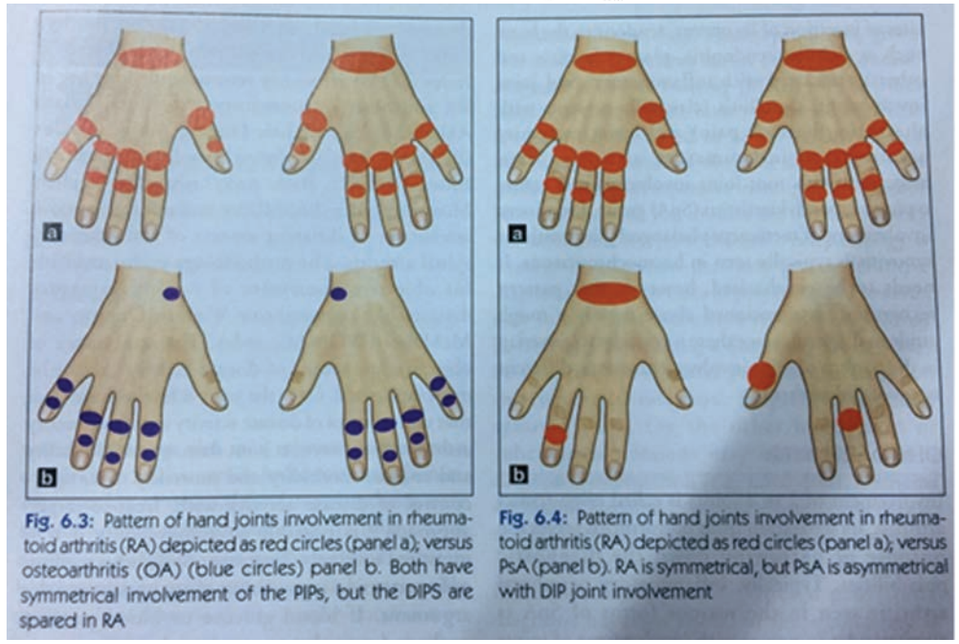


Fig. 6.3: Pattern of hand joints involvement in rheumatoid arthritis (RA) depicted as red circles (panel a); versus osteoarthritis (OA) (blue circles) panel b. Both have symmetrical involvement of the PIPs, but the DIPS are spared in RA

Fig. 6.4: Pattern of hand joints involvement in rheumatoid arthritis (RA) depicted as red circles (panel a); versus PsA (panel b). RA is symmetrical, but PsA is asymmetrical with DIP joint involvement

Hand involvement in various joint disease
4. Arthritis with inflammatory back pain - Spondyloarthritis
5. Arthritis with systemic manifestations - SLE, Still disease

References

1. EULAR online course on rheumatic diseases (module 1)
2. Manual of Rheumatology (Fifth edition)
3. Kelly Textbook of Rheumatology (Tenth edition)

Update on Anti-epileptic Drugs

Myanmar Neurological Society

An epileptic seizure is the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain. It affects more than 50 million people worldwide. The majority can have satisfactorily control of recurrent seizures.

Anti-epileptic drugs are the mainstay of epilepsy therapy. Until 1993, seven or eight major agents were available. However, newer AEDs have been approved and marketed since then. With such a large choice of AEDs, much guidance is needed in the choice of AEDs for initial therapy, later replacement mono therapy, or adjunctive therapy. Much of the neurologists pay attention to the goal of seizure remission. There must also be no side effects, but these goals are too often unmet.

I. Starting Treatment

When starting AED to a patient after one or more seizure, we need to consider chance of recurrence, negative consequences if seizure recurs and potential adverse effects of treatment.

Seizure recurrence and anti-epileptic drugs after a first unprovoked seizure

In 1982, prospective randomized trials of individuals with a first unprovoked seizure estimate the two-year recurrence risk in untreated patients to be 40 to 50 percent. Clinical variables associated with increased risk include a prior brain lesion or insult (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), and a nocturnal seizure (Level B).[1]

In randomized controlled trial by Manson and colleges in 2005, immediate and deferred anti-epileptic drug treatment for early epilepsy and single seizures are compared for time to next seizure and to 2 year remission of seizures. Immediate treatment shows increased time to next seizure (HR: 1.4 [95% CI 1.2 to 1.7]). It also reduce the time to 2 year remission of seizures. But it does not affect long-term remission in individuals with single or infrequent seizures.[3]

2015 American Academy of Neurology also state that immediate AED, as compared to delay of treatment pending a second seizure, is likely to reduce absolute risk by about 35% for a seizure recurrence within the subsequent 2 years (Level B) but it may not improve quality of life (Level C). Over a longer term (3 years), immediate AED treatment is unlikely to improve prognosis as measured by sustained seizure remission (Level B).[2]

Anti-epileptic drugs after first unprovoked seizure?

Initiation of immediate AED treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the adverse effects of AED therapy. It is also essential to consider patient preferences (AAN, 2015).[2] In 2018, a decision analysis, for anti-epileptic drugs after first unprovoked seizure, compares the expected quality adjusted life years in patients undergoing the immediate and deferred treatment. In conclusion, immediate treatment is preferable to deferred treatment in first seizure patients over a wide and clinically relevant variables, such as patient's specific co-morbidities, seizure burden and the effects of the decision on the patient's quality of life.[4,5]

A 30 year longitudinal cohort study completed in 2018, describes treatment outcomes in patients with newly diagnosed epilepsy treated with established and new anti-epileptic drugs. It assess long-term treatment outcome in newly diagnosed and treated epilepsy among 1795 patients between 1982, and 2012. If first AED failed, the second and third regimens provided an additional 11.6% and 4.4% likelihoods of seizure freedom, respectively. If not controlled with the first AED, there is 1.73 times greater odds of not responding to treatment for each subsequent regimen (OR, 1.73; 95%CI, 1.56-1.91; P < .001).[4, 5]

II. AED overview

AED can be classified into

- Standard anti-epileptic drugs (phenobarbital, phenytoin, carbamazepine, and valproic acid). They are effective but have tolerability and pharmacokinetic disadvantages.
- Second generation antiepileptic drugs (lamotrigine, topiramate, oxcarbazepine, zonisamide, and levetiracetam). They have similar efficacy and equal or better tolerability than standard drugs in focal epilepsy.
- Third generation antiepileptic drugs (lacosamide, ruifinamide, eslicarbazepine acetate, brivaracetam and perampanel). They show clear advantages in terms of selective mechanisms of action, lack of side effects on cognitive functions and lack of interactions.

III. Newer Anti-epileptic drugs

Intractable epilepsy refractory to appropriate conventional AED is an indication for the newer drugs.

Clinical utility of eslicarbazepine as current evidence

It is licensed for adjunctive treatment in adults with focal seizures. It acts by blocking the voltage-gated sodium channel. It has a half-life of 20-24 hours, therefore, it can be administered once a day. It has a low potential for drug-drug interactions. Adverse

effects were mild to moderate - commonly dizziness, somnolence, diplopia, abnormal co-ordination, blurred vision, vertigo and hyponatraemia especially in the elderly.[6]

Lacosamide add-on therapy for partial epilepsy (Review)

It was approved in 2008 as adjunctive therapy for partial-onset seizures with or without secondary generalization. It is restricted for specialist use in refractory epilepsy. It increase slow inactivation of the voltage-gated sodium channels. The drug does not interact with other AEDs. There is a risk of PR interval prolongation, and it is contraindicated in second or third degree AV block. There was a 50% responder rate in adults with refractory epilepsy.[7]

The APMA receptor as a therapeutic target in epilepsy

The most established hypothesis in epilepsy is the imbalance of excitatory and inhibitory neuronal activity. The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor has significant roles in fast excitatory neuronal transmission. Recently, the first selective AMPA receptor antagonist, perampanel, was approved as an adjunctive therapy for the treatment of partial-onset seizures. It has long half-life, justifying once-daily dosing, typically at bedtime.[8]

Tiagabine

It is an adjunctive treatment for focal seizures not controlled by other AEDs. It should be avoided in absence, myoclonic, tonic and atonic seizures due to risk of seizure exacerbation. It should not be used in patients with severely impaired liver function.

Zonisamide

It is an initial mono therapy for adults with partial-onset seizures. It is not known to be associated with clinically significant drug-drug interactions. It has a half-life of 60 hours allowing once or twice daily administration.

Brivaracetam

In January 2016, the European commission licensed brivaracetam as adjunctive therapy for adult epilepsy patients with uncontrolled partial-onset seizures. Brivaracetam may have fewer behavioral side effects than levetiracetam.

IV. Comparison between Standard and New Anti-epileptic Drugs

The largest individual randomized trial examining different anti-seizure medication as mono therapy for initial treatment of epilepsy was standard and new anti-epileptic drug trial. (SANAD)[9]

A. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an un-blinded randomized controlled trial[9]

Focusing on the results of lamotrigine and carbamazepine, this trial showed that when assessing time to treatment failure, lamotrigine was significantly better than carbamazepine.[9] For patients with partial onset seizures, lamotrigine was found to be significantly better for time to treatment failure than the current standard treatment, carbamazepine, and the newer drugs gabapentin and topiramate. For time to 12 month remission from seizures, lamotrigine was non-inferior to carbamazepine. The advantage for treatment with lamotrigine was due to its tolerability advantage over carbamazepine.[9]

B. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalized and unclassifiable epilepsy: an un-blinded randomized controlled trial[9]

It compares the longer term effects of valproate, lamotrigine and topiramate in patients with generalized onset seizures (1999-2004). For time to treatment failure, valproate was significantly better than topiramate (hazard ratio 1.57 [95% CI 1.19-2.08]), but there was no significant difference between valproate and lamotrigine (1.25 [0.94-1.68]). For Time to 12 month seizure remission, valproate was significantly better than lamotrigine overall (0.76 [0.62-0.94]), and for the IG E subgroup 0.68 (0.53-0.89) but there was no significant difference between valproate and topiramate in either group. For patients with an idiopathic generalized epilepsy, valproate was significantly better than both lamotrigine (1.55 [1.07-2.24] and topiramate (1.89 [1.32-2.70]).[9]

C. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy[10]

The study was done in newly diagnosed partial seizures with or without secondary generalization, generalized tonic - clonic seizures without clear focal origin in 12 European countries and in South Africa (2002 to 2005).

The 6 month seizure-freedom rate was almost the same for both drugs: 73.1% for levetiracetam and 72.8% for carbamazepine. Time to withdrawal was also almost identical. Fewer patients on levetiracetam (14.4%) discontinued treatment because of adverse events compared with carbamazepine CR (19.2%), although this difference did not reach statistical significance.[10]

D. Levetiracetam Vs Valproate? (SANAD II (1.8.2012-1.2.2018))[11]

Arm A: lamotrigine, levetiracetam and zonisamide in patients with untreated focal onset seizures.

Arm B: levetiracetam and valproate in patients with generalized onset seizures or seizures that are difficult to classify.

Findings from SANAD II have suggested that in patients with generalized or unclassified epilepsy levetiracetam is inferior to valproatein time to 12 month remission (LEV 24% Vs VAL 33%), 24 month remission (HR, 1.43; 95% CI, 1.06 to 1.92) and treatment failure (HR, 0.65; 95% CI, 0.50 to 0.83).[11]

E. Valproate or CBZ CR Vs Levetiracetam? (KOMET study)[12]

It is an un-blinded, randomized, study among patients aged ≥ 60 years with newly diagnosed epilepsy. It shows that time to first seizure was similar between LEV and standard AEDs (HR: 0.92, 95% CI: 0.63-1.35), LEV and VPA-ER (0.77, 0.38-1.56), and LEV and CBZ-CR (1.02, 0.64-1.63). Results of this post-hoc analysis suggest that LEV may be a suitable option for initial mono therapy for patients aged ≥ 60 years with newly diagnosed epilepsy.[12]

V. When to consider combination therapy?
Mono therapy

In comparison with combination therapy, mono therapy has better compliance, fewer side effects. It can avoid drug interactions. It may be less expensive than poly therapy.

What is the next course of action when initial mono therapy fails?

- About 50% achieve sustained seizure freedom without intolerable side-effects on the initially prescribed AED.
- If seizures persists after titration to the highest tolerated dose, the first step is to exclude noncompliance, to reassess the diagnosis, to assess appropriateness of the initial treatment, to consider other medications and illness.
- If a change in AED treatment is indicated, the conventional recommendation is to switch gradually to mono therapy with another drug. Up to 20–30% of individuals who are resistant to the initial AED achieve seizure freedom on an alternative mono therapy.
- Replacement mono therapy is favored when the first AED was not well tolerated or was totally ineffective, in elderly patients who already take other medications, in women of childbearing potential contemplating pregnancy, in patients with compliance challenges, and when financial restrictions exist. Some feel that combination therapy could be tried earlier, when the first AED seems to have been partially effective and well tolerated, and the probability of seizure freedom with mono therapy is regarded as low.[13, 14, 15]

How to combine AEDs (Principles of poly therapy)

- Drugs with synergistic action; valproate and lamotrigine (best evidence for synergism)
- Avoid AEDs with interaction
- Avoid drugs that have similar side effects

- Drugs with different mechanism of action are preferred. Anti-epileptic drugs were categorized by MOA: sodium channel blockers (SC), gamma-aminobutyric acid analogs (G), synaptic vesicle protein 2A binding (SV2), and multiple mechanisms (M). Patients were assigned a combination category based on their concomitant AED use.

When two appropriately chosen mono therapy regimens have failed, the chance of success with a third single agent is slim. Among 780 newly diagnosed epilepsies, 47% became seizure free with the first mono therapy. Another 10% responded to the second mono therapy. Only 2.3% of the cohort entered remission with the third mono therapy.[13, 14, 15]

VI. GPR 40 role and benzodiazepine resistance

Recent studies suggest that G protein–coupled receptor 40 (GPR40) is expressed in the central nervous system and is involved in the regulation of neurological function. GPR40 expression was increased in epileptic brains. GPR40 activation after status epilepticus alleviated epileptic activity, whereas GPR40 inhibition showed the opposite effect. Susceptibility to epilepsy was reduced with GPR40 activation and increased with GPR40 inhibition. Findings indicate that GPR40 modulates epileptic seizures, providing a novel anti-epileptic target.[16]

VII. Benzodiazepine resistant seizures

Benzodiazepine is the first-line treatment for status epilepticus (SE). For unknown reasons, the efficacy of benzodiazepines decreases with increasing duration of seizure activity. The anti-seizure properties are mediated by γ-aminobutyric acid type A (GABAA) receptors. The failure of GABAergic inhibition after seizure onset as the likely cause of benzodiazepine resistance during SE. Evidence supporting the role of altered GABAA receptor function as the major underlying cause of benzodiazepine resistant SE in both humans and animal models.[17]

Conclusion

The availability of new anti-epileptic drugs has broadened the spectrum of medical treatment options in epilepsy. The new agents, offer substantial choice for doctors treating patients with focal or generalized epilepsy. The newer anti-epileptic drugs are not necessarily more effective but usually better tolerated than the traditional agents, mainly because of favourable pharmacokinetic profiles and fewer interactions. Because treatment options have increased, drug therapy can now be tailored to the requirements of individual patients.

References

1. Hauser WA, Anderson VE, Loewenson RB, Mc Roberts SM. Seizure recurrence after a first unprovoked seizure. *N Engl J Med* 1982; **307**: 522-528.
2. Krumholz A, Wiebe S, Gronseth GS, Gloss DS, Sanchez AM, Kabir AA, Liferidge AT, Martello JP, Kanner AM, Shinnar S, Hopp JL. Evidence-Based Guideline: Management of an Unprovoked First Seizure in Adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society: Evidence-Based Guideline. *Epilepsy currents*. 2015 May; **15 (3)**: 144-52.
3. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D, Medical Research Council MESS Study Group. Immediate versus deferred anti-epileptic drug treatment for early epilepsy and single seizures: a randomized controlled trial. *The Lancet*. 2005 Jun 11; **365 (9476)**: 2007-13.
4. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new anti-epileptic drugs: a 30 year longitudinal cohort study. *JAMA Neurology*. 2018 Mar 1; **75 (3)**: 279-86.
5. Swaroop HS, Ananya C, Nithin K, Jayashankar CA, Babu HS, Srinivas BN. Levetiracetam: a review of its use in the treatment of epilepsy. *International Journal of Medicine and Biomedical Research*. 2013; **2 (3)**: 166-72.
6. Zaccara G, Giovannelli F, Cincotta M, Carelli A, Verrotti A. Clinical utility of eslicarbazepine: current evidence. *Drug design, development and therapy*, 2015; **9**: 781.
7. Weston J, Shukralla A, McKay AJ, Marson AG. Lacosamide add-on therapy for partial epilepsy. *Cochrane Database of Systematic Reviews*. 2015 (6).
8. Hanada T. The AMPA receptor as a therapeutic target in epilepsy: preclinical and clinical evidence. *Journal of Receptor, Ligand and Channel Research*. 2014; **7**: 39.
9. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an un-blinded randomized controlled trial. *The Lancet*. 2007 Mar 24; **369 (9566)**: 1000-15.
10. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology*. 2007 Feb 6; **68 (6)**: 402-8.
11. SANAD-II SI. A pragmatic randomized controlled trial comparing the effectiveness and cost effectiveness of levetiracetam and zonisamide versus standard treatments for epilepsy: a comparison of Standard and New Anti-epileptic Drugs (SANAD-II).

12. Pohlmann-Eden B, Marson AG, Noack-Rink M, Ramirez F, Tofighy A, Werhahn KJ, Wild I, Trinka E. Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, un-blinded KOMET study. *BMC Neurology*. 2016 Dec; **16 (1)**: 149.
13. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *New England Journal of Medicine*. 2011 Sep 8; **365 (10)**: 919-26.
14. Kwan P, Brodie MJ. Combination therapy in epilepsy. *Drugs*. 2006 Oct 1; **66 (14)**: 1817-29.
15. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. *The lancet Neurology*. 2011 May 1; **10 (5)**: 446-56.
16. Yang Y, Tian X, Xu D, Zheng F, Lu X, Zhang Y, Ma Y, Li Y, Xu X, Zhu B, Wang X. GPR40 modulates epileptic seizure and NMDA receptor function. *Science Advances*. 2018 Oct 1; **4 (10)**: eaau2357.