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SYMPOSIUM SESSION

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PLENARY LECTURE

PL-1

SURGICAL ROLE FOR STROKE PATIENTS

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No Abstract

PL-2

WHAT WE DO KNOW ABOUT NEUROSCIENCE? NEUROSCIENCE IN THE UNDERSTANDING FOR THE FUTURE LIFE

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Neuroscience is a science that continues to develop parallel with the development of new diseases. Life that starts from the period of growth to degeneration, both in pathology and physiology is inseparable from the growth range of nerve tissue along with its accompanying hormones. The quality of this growth is inseparable from the quality of stimulus or inhibition of cognition and motor. Stimulus in the form of light, known as circadian rhythm, plays a major role in regulating autonomic nerve activity, the immune system in this case the corticotropin release hormone (CRH), the growth hormone (GH) that regulates neurohormonal secretion and inhibition in the hypothalamus.

Purba et al's research, Arch Gen Psychiatry; 1996; 53: 137-143, in major sufferers of depression, finding the number of arginine-producing Vasopressin (AVP) seurons in the paraventricularis nucleus (PVN) in the hypothalamus increases 56% of the number of neurons of healthy people. AVP has the potential to stimulate CRH. This increase in the number of neurons is considered a feedback reaction to the pathology of this depression. The same thing is synergistically found that behavior can improve executive function and preferably, through self-control, in the form of regulating desires, resisting temptation. Other synergistic reactions from various studies indicate a feedback reaction where better executive functions enable people to lead a healthier lifestyle. This is concluded in "Two-way Relations between Executive Function and Healthy Behavior" or "A Bidirectional Relationship between Executive Function and Health Behaviors." One other study published by researchers at the University of Aberdeen, University of Stirling and University College Dublin, used data of 4,555 adults through the English Longitudinal Study of Aging. This researcher analyzed the relationship between physical activity and executive function with variables of age, sex, education, wealth and disease. This study proves that the relationship between physical activity and executive function is a synergistic relationship. In the future, research on the role of neuroscience in life must be further deepened because Neuroscience belongs to a doctor regardless of his expertise. This is very important in the prevention of both the role of pharmaceutical drugs and more specific psychotherapy so as to avoid negative therapeutic effects.

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PL-3

RIGHTS AND OBLIGATIONS OF DOCTORS LIFE

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PL-4

THE ROLE OF GENERAL PRACTITIONERS AS THE IMPLEMENTEROFPRIMARY SERVICES IN THE JKN ERA: CHALLENGES AND EXPECTATIONS

Badan Penyelenggara Jaminan Sosial Kesehatan (BPJS)

SYMPOSIUM SESSIOM

MEDICOLEGAL

SS-1

PROTECTING YOURSELF FROM LAWSUIT THREATS IN MEDICAL PRACTICE

Herkutanto
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No Abstract

SS-2

DOCTOR'S ETHICS IN PROMOTION AND ADVERTISEMENT

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No Abstract

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PEDIATRIC

SS-3

STUNTING

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No Abstract

SS-4

PEDIATRIC NUTRITION CARE

Melanie Widjaja
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No Abstract

SS-5

MANAGEMENT OF SEIZURE IN CHILDREN

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Seizure is a horrible incident, to both parents and children, which happens up to 10% of children. It is clinically manifested as self limiting stereotypical movements due to abnormal neurons electrical activity. Febrile seizure is the most common seizure happened to children ages 6 – 60 months when body temperature is above 38^{o}C which not caused by intracranial process including electrolyte or metabolic problems. Febrile seizure categorized as simple and complex based on it's clinical manifestation, duration, and other neurological problems. Further evaluation is not done regularly. Neuroimaging and electroencephalogram done when focal seizure is found, while lumbar puncture done when seizure, fever, meningeal signs are found, vaccination status is not clear, or pretreated with antibiotics. Acute febrile seizure can be treated similarly like other acute seizure based on the treatment algorithm. Maintenance in febrile seizure is given for 1 year in patient with complex febrile seizure. Antipyretic such as paracetamol and ibuprofen is also recommended.
Nonfebrile seizure, such as epilepsy is defined by *International League Against Epilepsy* (ILAE) in 2005 by clinically as at least two unprovoked (reflex) seizures occuring in >24 h apart, one unprovoked seizure and a probability to general recurrent risk (at least 60%) after two unprovoked seizure, occuring over next 10 years, and diagnosis of an epilepsy syndrome.Diagnosis of epilepsy estabished based on history taking and physical examination especially in neurologic examination searching for repeated seizures, focal or generalized followed by normal or disturbed development. Antiepileptic drugs for epilepsy given for 2 years based on types of seizure. Status epilepticus (SE) is continuous seizure or repeated seizure without gaining back conciousness between seizure for 30 minutes. Treatment for status epilepticus, following the algorithm of treatment, need intravenous antiepileptic drugs, and Intensive Care Unit to solve the refracter SE. Beside antiepileptic drugs, important

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management for seizure should includes securing airway, breathing, and circulation, also proper education for both parents to optimize holistic management.

SS-6

POST-RESUSCITATION/PRE-REFERRAL NEONATES STABILIZATION: BASIC BABY GROWTH AND DEVELOPMENT OPTIMIZATION PRINCIPAL

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No Abstract

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OBSTETRICAN & GYNECOLOGIST LECTURE

SS-7
EARLY DETECTION IN GYNECOLOGY MALIGNANCY

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No Abstract

SS-8
WHAT'S NEW ON PRE-ECLAMPSIA ?

Patrick Bayu
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No Abstract

SS-9
A WELL-PLANNED PREGNANCY TO REDUCE MATERNAL MORTALITY RATE (MMR)?

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No Abstract

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INTERNAL MEDICINE

SS - 10

ANTIHYPERTENSIVE DRUG STRATEGIES FOR PATIENT WITH CHRONIC KIDNEY DISEASE

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Hypertension occurs in around 80-85% in Chronic Kidney Disease (CKD)patients and progressed accordingly with worsening kidney function. The lower the Glomerular filtration rate, the higher the frequency of hypertension. Factors effecting the occurrence of hypertension are sodium retention, increased activity of renin angiotensin aldosterone system, increased sympathetic activity, Secondary hyperthyroidism which increases intracellular calcium that will increase blood pressure, administration of erythropoietin and disturbance of Nitric oxide function. Strategies of antihypertensive drugs in patient with CKD is differentiated with the presence of Proteinuria. If there is proteinuria, the first drug of choice will be angiotensin converting enzyme inhibitor (ACEI or ARB). Possible side effect from this drug group are hyperkalemia and worsening of kidney failure for 1-2 weeks. If this occurred, it would be recommended to stop this type antihypertensive drug but if there are no complications these drugs should be continued. If Edema occurred in proteinuria patients, loop-diuretic could be addeFPUREd that will also increase antihypertension and reduce proteinuria due to the trigger of anti-proteinuria effect from ACEI and ARB. If the hypertension remains uncontrolled, non-dihydropyridinesantihypertensive such as diltiazem or verapamil should be administered. For patients without proteinuria, other classes of anti-hypertensive drugs such as dihydropyridines (amlodipine) or alpha-2-adrenergic agonist class (clonidine). If resistant hypertension is present, mineral corticoid receptor antagonist such as Spironolactone or eplerenone should be added. Be cautious for side effects which may cause Hyperkalemia or reduced kidney functions, and it is ought to stop this medication.

SS-11

ANEMIA THERAPY IN CHRONIC KIDNEY DISEASE

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Anemia in Chronic Kidney Disease (CKD) has been observed since 170 years ago by Richard bright who've observed patient with CKD became pale : "after a time, the healthy colour of the contenance fades." Sir Robert Christison in 1839 said :"by far the most remarkable character of the blood in the advantage stage of the Bright's Disease is a gradual and rapid reduction of its colouring" and "no other natural disease came as close to hemorrhage for impoverishing the red particles of the blood." Around the year 1950 it was discovered that erythropoietin and kidney as the main producer of erythropoiesis. 5 years after erythropoietin gene cloning was done, in the late 1980 a recombinant human EPO (rHuEPO) was found. After rHuEPO, the response mechanism of cells toward hypoxia known as hypoxia inducible factor 1

(HIF-1) was discovered. Two proteinsHIF-α dan HIF-β. HIF-α is produced continuously, at reduced oxygen level, it will be hydroxilized by HF-prolyl hydroxylases. This Enzyme function as an oxygen sensor as it needs oxygen asa a co-substrate. After hydroxylization, HIF-αis recognized by von Hippel-Lindau protein and destroyed. HIF-β is not sensitive towards hypoxia so when hypoxia occurred, HIF-α increases and will translocate to the core and form a heterodimer with HIF-β, erythropoietin so the production of erythropoietin increases.

Anemia is often caused by erythropoietin deficiency, iron deficiency, blood loss, life-shortened erytrosit, inflammation, infection, blood abnormalities, Hyperparathyroidism, hemolysis, and malnutrition. Anemia in CKD increases mortality, increases hospitalization, worsening of cardiac function, reduce cognitive skills, and reduce patient's quality of life. Even though epidemiologically anemia was discovered in CKD St. I, unfortunately evaluation of anemia only begins in CKD St. 3. Pathologically anemia CKD will only occur in patient with CKD St. 3. Five percent of USA and UK suffered CKD St. 3 – 5 and 15% of it suffered anemia according to the WHO criteria.

Diagnosis of Anemia in iron deficiency is measured by percentage of hypochromic red cells (>6%; only if the measurement is possible under 6 hours), reticulocyte hemoglobin content (<29pg), or reticulocyte haemoglobin equivalent (RetHe) <27,2 pg (Sensitivty 93,3%, specificity 83,2%). Ferritin and transferrin saturation should not be use as a sole monitor for iron deficiency. In normal population ferritin <30 ng/ml or TSAT <15% is enough to diagnose iron deficiency but is not accurate in patient with CKD. TSAT <21% sensitivity 81% for iron IV response prediction but only with 63% specificity. One problem in diagnosis of iron deficiency in HD patient, Ferritin 100 -200 ng/ml with low sensitivity 41-48% with specificity of 75 – 100% and Sat Transferrin 20 – 21% with sensitivity of 81 – 88% and specificity 63%.

- HD patient: Iron deficiency in ferritin < 300 ng/ ml or TSAT < 20%.
- CKD non-dialisis patient: iron deficiency in ferritin < 100 ng/m or TSAT < 15%.
- In CKD patient ,Possible iron deficiency even with ferritin and TSAT normal or high

Reticulocyte Hb content (CHr) is a test which uses a short-age reticulocyte, it only last for 24 hours, Hb/iron can indicate the latest iron status with limited uses. Hypochromic red blood cells percentage can also be used but needs immediate process likewise CHr or RetHe. ESA therapy begins from Hb < 10 g/dl and should be supervised with KGH. The Hb target for CKD-HD, CKD-PD, CKD non-D are 10 – 12 g/dk. Hb level should not be >13 g/dl and at 12> g/dl increases mortality rate due to cardiovascular disease. erythropoietin is a highly glycosylated molecule consisting of 165 amino acid and is mainly produced in the kidney cortex and a little in the liver. ESA therapy is the main anemia CKD therapy, For example Epoetin Alpha which is similar with erythropoietin native (Epotrex, Epodion, Hemapo, Eprex, Renogen), Darbepoetin alfa with a difference of 5 amino acid from epoetin alpha with an addition of carbohydrate causing a longer half-life 2-3x (Aranesp), Methoxy polyethylene glycolepoetin beta, with the longest half-life (approx. 130 hours) (Recormon, CERA : Mircera), Epoetin delta, omega.

Issuing of ESA to Hb <10 g/dl and others causes of anemia are already removed, there is no more absolute iron deficiency anemia that is ST <20% and FS <100 ng/mL (PGK nonD and PGK PD), <200 ng/ml (PGK HD), there is no severe infection, attention to hypertension (180/110) and hyper-coagulation with dosage of Epoetin α and β: 2000-5000 IU 2x/weeks or 80-120 u/kg/mg Subcutaneous, CERA 0,6 ug/kg or

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50-75 ug every 2 weeks. Hb increases 0,5-1,5 g/dl in 4 weeks, monitor Hb / 4 weeks, if target of response is reach, maintain the dosage until the target is achieved, increase the dosage 25% if the target of response is not reached yet, if increase of Hb >1.5 g/dL in 4 weeks or Hb 12-13 g/dL decrease the dosage 25%, if more than 13 g/dL discontinued ESA, if Hb level is naturally high, mortality is not increased in HD patient. Monitoring the iron status and give iron supplement, administering of Erythropoietin continued if the patient is hospitalized, if Hb <10,5 or >11,5 adjust the dosage, if Hb is more than 12 (except >13g/dL) the dosage is decreased but not stopped.

Iron Target:

- 100-500 ng/L pasien HD,
- 100-500 ng/mL non-HD
- <6% hypochromic red cells (HRC)/TSAT >20%

Erythropoiesis id effective if the amount of erythropoietin and iron are enough, iron deficiency occur if ≥50% patients that does not undergo dialysis and is higher in patients that undergo dialysis, PGK patients lose iron as much as 1-3 g/years on HD, chronic bleeding caused by dysfunction of thrombocyte due to uremia, frequent phlebotomy, blood that is left in the HD machine, infection/inflammation, high hepcidin reduce iron absorption. The disturbance of Iron absorption, excessive oral iron is not better than placebo, except phosphatase binder ferric citrate. Iron supplementation is important because PGK patient prone to deficiency. There is many PGK patient that also suffer from functional iron deficiency, where iron cannot be used for erythropoiesis (reticuloendothelial cell iron blockade). The indication for blood transfusion is if Hb <7 g/dL or Hb <8 g/dL with cardiovascular disturbance with the target of Hb 7-9 g/dL. Candidate for kidney transplant need to avoid blood transfusion and if needed by leukocyte filter.

SS-12

GOUT AND CHRONIC KIDNEY DISEASE

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Chronic Kidney Disease(CKD) and nephrolithiasis are commonly found amongst patient with gout. Futhermore, it is difficult to ascertain if hyperuricemia preceded CKD or whether the reverse is true. Most studies documented that high uric acid level can induce glomerular hypertension and renal disease as note by the development of arteriolosclerosis, glomerular injury and tubulointerstisial fibrosis. Lowering plasma uric acid concentration may slow the progression of renal disease.

The managemet of gout follows the same four principles regardless the presence of CKD : manage hyperuricemia, terminate acute attacks, prevent complication resulting from deposition of monosodium urate, and optimise dietary and lifestyle factor. A mayor challange in treating patients with gout is to avoid theraupetic interactions with common comorbidities including hypertension, coronary artery disease expecially CKD.

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SS-13

ARRHYTHMIA IN CHRONIC KIDNEY DISEASE

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No Abstract

SS-14

CHRONIC KIDNEY DYSFUNCTION IN DECOMPENSATED HEART FAILURE: WHAT IS THE CURRENT EVIDENCE?

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Acute or chronic cardiac dysfunction may induce acute or chronic decreased kidney function or the other way around and increase mortality. The term Cardiorenal syndrome indicate the involvement of these two important organs. The management of chronic kidney disease or dysfunction in heart failure can be very challenging. Recent studies had tried to use many new therapeutic strategies to improve clinical outcomes and decrease mortality. Diuretic resistance is still a serious problem and needs more effective treatment options. Better understanding of the physiological mechanism of disease will encourage better therapeutic approach. However, ongoing studies raise new hope in guiding better management of this challenging disease.

SS-15

DIABETES MELLITUS IN CHRONIC KIDNEY DISEASE PATIENTS: WHICH MEDICINE MUST BE CHOSEN?

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No Abstract

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CARDIOLOGY

SS-16

BASIC SKILL AND KNOWLEDGE FOR HEART FAILURE

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No Abstract

SS-17

UPDATED HEART FAILURE PHARMACOLOGICAL THERAPY

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No Abstract

SS-18

INTERVENTION FOR HEART FAILURE:TECHNOLOGIES & DEVICES

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In the recent years, drugs have undergone rapid development along with therapeutic devices for heart failure therapy. This is due to the large expenses demanded by hospital admission compared to outpatient care, such that measures are taken to reduce the need of hospital admission in heart failure.
Approximately half of heart failure patients die within 5 years after diagnosis. This provokes a rapid development in drugs and therapeutic devices in heart failure.
For three decades, developments of drugs have been attempted for heart failure therapy. Despite an improving prognosis in the morbidity and mortality of heart failure, both factors remain significant. For the last decade, therapeutic devices have been developed in hopes of decreasing the rate of morbidity and mortality.
Interventional therapeutic devices are meant to improve the patient's quality of life and decrease the number of hospital admissions owing to heart failure.

Monitoring of Pulmonary Pressure in Prevention of Hospital Admission Due To Heart Failure
The CardioMemsHF System® is a system that monitors the pressure within the pulmonary artery that has passed the qualifications through FDA(Food Drug Administration) in 2014. It is capable of detecting fluid retention in case of worsening congestive heart failure, and alert the clinician before the patient's condition worsens and requires admission. This provides clinicians with the opportunity to manage heart failure proactively, not reactively. Should there be a rise in pressure, pharmacologic therapy can be adjusted according to ensuing condition, such that the risk for admission is reduced.
Following the success of earlier studies, The Champion study observed heart failure patients with a preserved ejection fraction(HFpEF) and those with a reduced ejection

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fraction(HFrEF), as well as patients with various co-morbid factors, such as chronic kidney failure. Ensuing studies also yield well results, showing how treatment of heart failure based on pulmonary artery pressure may improve quality of life and frequency of admission.
The decline in admission frequency each year reaches 33%, whilst in patients with HFpEF, the frequency of hospital admissions decrease up to 50%.

Intra-atrial Shunt Devices (IASD)
A therapeutic device for heart failure following a new concept. That is, IASD, when applied subcutaneously with a trans-catheter, lowers the left atrial pressure by making a tiny hole-like passage (shunt) between left and right atria. Data regarding the use of this device has not been numerous, but has yielded positive and safe results.
HFpEF presents itself with it's complex pathophysiology which proves a great hurdle in treatment. There is an elevation in left atrial pressure, especially during exercise. This causes pulmonary venous hypertension, which in turn causes lung ingestion and shortness of breath. IASD is designed to lower these pressures. Corvia Medical's IASD System® has completed the initial study consisting of 64 heart failure patients. A one-year data from the REDUCE LAP-HF study in 2016 showed an improvement in functional NYHA(New York Heart Association) class, in scoring of quality of life, and in 6-minute walk with well safety scores.

Permanent Pacemaker for Heart Failure
It is suspected that there is an imbalance between sympathetic and parasympathetic stimulation, in which there is an increase in sympathetic stimulation and a decrease in parasympathetic tone, which worsens the prognosis of congestive heart failure and results in disruption of the functions of other organs aside from the heart. Neurostimulation is the therapy of choice for such conditions.
Several therapeutic strategies have been researched pertaining to the alterations within the imbalanced autonomy as a novel therapy for congestive heart failure. This therapy involves the stimulation of vagal tone, spinal cord, baroreflex activation therapy, and kidney denervation therapy. However, study results have not proven satisfactory.
CRT(Cardiac Resynchronization Therapy) is the therapy of choice that has been proven for some heart failure patients. CRT is a type of pacemaker that sends small electrical signals to both ventricles to achieve synchronized contraction. This will improve the heart's ability to pump blood and oxygen to the whole body.
The indication for CRT use is a heart failure patient with a NYHA functional class III or IV that remain symptomatic despite optimal pharmacologic therapy, with an LVEF ≤35% along with a prolonged QRS duration.

Mitral Valve Clip and Left Ventricle Partition for Heart Failure
Another form of intervention is the mitral valve clip and left ventricle partition to reduce left ventricular volume(less invasive ventricular enhancement=LIVE). The reduced left ventricular volume will ease the heart when pumping blood and can rid the areas of infarction that do not contract efficiently.
A device that strengthens ventricular contraction less invasively and hybrid is the Revivent TC®. The advantage of this strategy is: minimally invasive, does not require halting of the cardiac rhythm(on beating heart), eliminate scar tissue without ventriculotomy/sternotomy, without a heart bypass machine, without an aortic cross clamp, without the risk of ischemicarrest.

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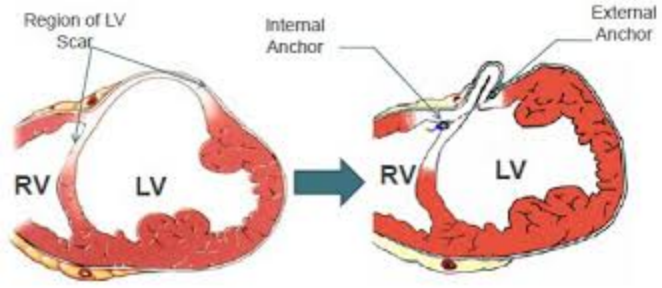
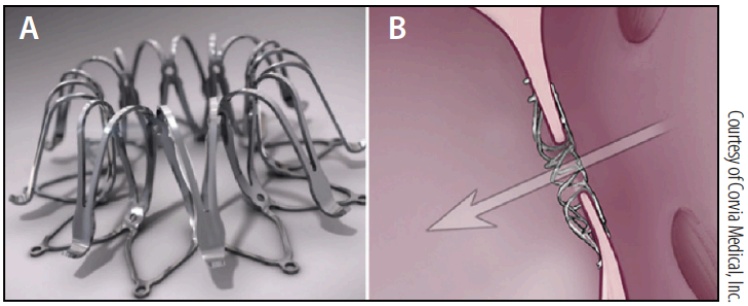
MitraClip® is the therapy of choice for heart failure patients with moderate-to-severe or severe mitral regurgitation secondary due to left ventricular dysfunction, in which symptoms persist despite optimal treatment according to the algorithm. Trans-catheter mitral reparation reduces the frequency of hospital admission due to heart failure, reduces the number of mortality, improve quality of life and functional capacity.

The therapy of choice for heart failure aside from the drugs developed within the last decade, includes CRT, Mitraclip®, neuromodulators, Revivent®and IASD.

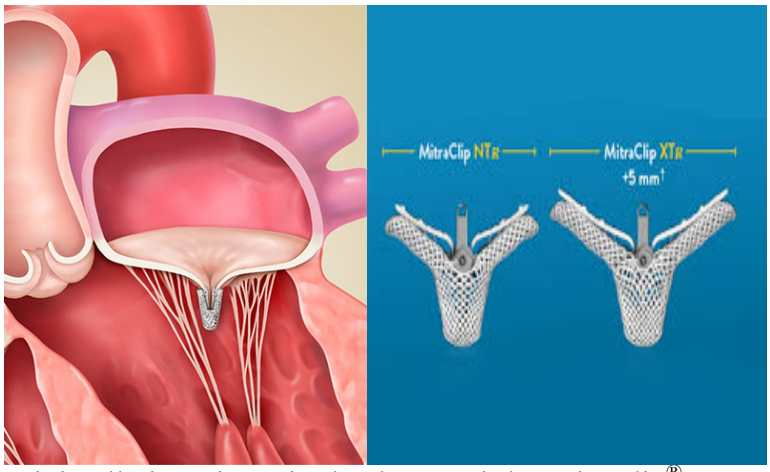
It is also important to consider the heart failure patient's perspective concerning the usage of technology to preserve oneself, as well as an adequate understanding regarding the access to technology, can help increase the effectiveness of interventional therapy in the treatment of heart failure. The aim is to improve the patient's consent, prognosis and reduce medical cost.



Less invasive ventricular enhancement (LIVE) by Revivent TC® System



Transcatheter Intra-atrial Shunt Device (IASD)



Minimally invasive mitral valve repair by Mitraclip®

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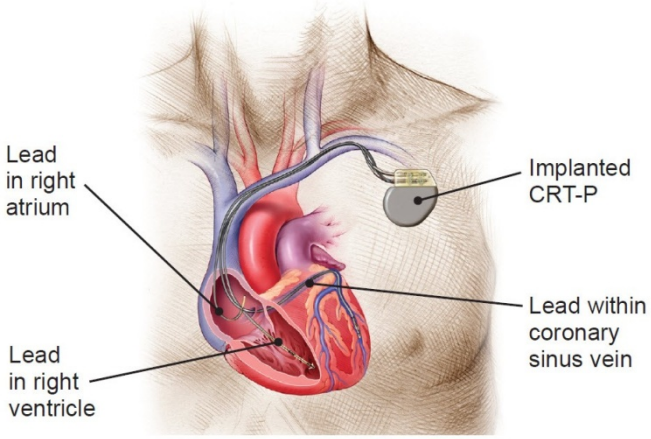

Cardiac Resynchronization Device (CRT)

SS-19

Improving QOL and Outcomes of Heart Failure patients: The Roles ofHeart Failure Clinic

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No Abstract

SS-20

CASE DISCUSSION CARDIOLOGY LECTURE

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No Abstract

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NEUROEMERGENCY

SS-21

NEUROEMERGENCY CASES, DID I MISS THE DIAGNOSIS?

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No Abstract

SS-22

SEIZURE, EPILEPSY, STATUS EPILEPTICUS : MANAGEMENT IN DAILY PRACTICE

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No Abstract

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SURGERY

SS-23

A COMPREHENSIVE WOUND MANAGEMENT IN DIABETIC FOOT

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For many physicians, wound is a significant part of daily practice. Whether it is intentional eg. a surgical wound, or unintentional such as the diabetic wound, we will always face many types of wound. Not all wound are the same. Diabetic ulcers had been the most challenging problem to the physician, the patient, and the health care system. Not only chronic, diabetic ulcers also time consuming, high morbidity, high recurrency, prone for amputation and great risk for septic condition which is life threatening.

We recognize this challenge as universal and a great concern for physician. Therefore, we decide to introduce about the importancy of wound management, and discuss some significant information regarding various wound types and their respective management. Moreover, we expect to gain understading about preventing and reducing the morbidity of diabetic ulcer.

At the end of the discussion, participants should be able to regain understanding of the TIME concept, learn new techniques and apply the proper dressing that would escalate the recovery in diabetic foot wound management.

Diabetic ulcers are the most common cause of non traumatic foot and leg amputation. The incidence rate of developing foot ulcers is 25% of all diabetic patients; leading to 8-22% ipsilateral reamputation, 26-44% contralateral, and 13-40% mortality at 1 year. The diabetic foot ulcer is mainly neuropathic in origin, with secondary pathogenesis being a blunted leukocyte response to bacteria and local ischemia due to vascular disease. These wounds usually occur on weight-bearing areas of the foot.

There are many classifications of the diabetic ulcer, but the main purpose is to clarly identify and prevent the progress. The Wagners classification will provide easy and simple assessment that understood worldwide. Depth, extent (size), location, general appearance, odor, and notation of exudates are all essential components of wound evaluation and need to be recorded at baseline

This will lead to frequently asked question about traditional vs modern dressing. The modern dressing is costly, but good for maintain the moisture balance which can promote angiogenesis and any other growth factors, manage exudate and prevent infection. Altogether, patient should be informed about how to prevent the recurrency of the wound and maintain the systemic balance of blood sugar. This is a challenging issue to decrease the level of morbidity and amputation in diabetic ulcer patients. The earlier the diagnosis is made, the better the prognosis.

After identification, the choice of ideal dressing should be made to maintain the moisture balance of the wound. There are 3 simple steps that should be mastered in diabetic ulcer management which are :

(1) Recognition and correction of underlying cause
(2) Wound care with proper dressing
(3) Prevention of recurrence

By understanding the pathophysiology, we can sharply diagnose by Wagner classification, control the systemic underlying cause, then choose the proper modern dressing to make the recovery faster.

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SS-24

ULTRA LONG ACTING INSULIN FOR TYPE 2 DIABETES WITH BETTER GLUCOSE CONTROL AND SAFETY PROFILE

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Diabetes is a global pandemic. Poor glycemic control and the hypoglycemic event is a major issue in diabetes management. Missing basal insulin administration is the problem in patient compliance that leads to poor glycemic control. Insulin degludec is a new ultra long-acting basal insulin. It has a unique pharmacokinetic pharmacodynamics profile due to its deposition of multi hexamers insulin chain in subcutaneous tissue.
This review discusses the efficacy in reducing HbA1C, achieving glycemic control and its safety profile regarding hypoglycemic adverse effect.
Keyword*: basal insulin, insulin degludec, glycemic control, hypoglycemic*

Diabetes is a global pandemic. It is estimated 10 million Indonesian suffered diabetes and its related complication.[1] Diabetes is contributing at least 6-year cumulative lifetime reduction and when it accompanies with cardiovascular complication the reduction is more than 15 years.
Poor glycemic control is a dramatic problem in diabetic management despite developing new medication and implementing guideline. In Indonesia, only less than half patient received the targeted HbA1C less than 7%.[2] The best HbA1C reduction is achieved by using insulin. Despite its powerful glucose control, it has a fatal hypoglycemic effect resulted from the fluctuation of blood glucose control in 24 hours. This left us in search of potential basal insulin with excellent blood glucose control, less hypoglycemic effect and less variability. At the moment, there are determir and glargine. They are the long-acting basal insulin with 12-hourhalf-life. These basal insulin required a strict tight scheduled basal injection with lessflexibility of time administration A recent study showed that ~50% of patients with type 2 diabetes had intentionally missed a basal insulin injection, with 22% reporting that they had missed a dose in the previous 30 days (mean of three doses) and 24% reporting that they had mistimed an injection by >2 h (mean of 4.2 occasions) in the last month.[3]Many of patient fail to fulfill the requirement resulting miss the HbA1C target. This is the unmet needs in diabetic management.[4]
The dark side of insulin treatment is the danger of hypoglycemia. Hypoglycemia is the commonest side effect of insulin treatment for diabetes and is the single greatest barrier to achieving and maintaining good glycaemic control. Severe hypoglycemia (requiring assistance for recovery) is associated with significant morbidity and mortality. It causes stress and anxiety and may influence self-management and glycaemic control.It is also common during sleep (nocturnal hypoglycemia). Neurological manifestations include coma, convulsions, transient hemiparesis and stroke, while reduced consciousness and cognitive dysfunction may cause accidents and injuries. Cardiac events may be precipitated such as arrhythmias, myocardial ischaemia, and cardiac failure. Hypoglycemia can affect all aspects of life, including employment, driving, recreational activities involving exercise, and travel, and measures should be taken in all of these situations to avoid this potentially dangerous side-effect of insulin therapy.[5]

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To answer this unmet need, the discovery of new potential basal insulin is needed. Degludec is the new basal insulin with a potential 25 hours half-life, and action lasts up to 42 hours. It creates a new class of ultra long basal insulin. The new synthesis of analog insulin is formed by replacing threonine in 30 positions with B-chain (Des-B30, "De") and attachment, via a glutamic linker ("glu"), of a 16-carbon fatty diacid (hexadecanoic diacid, "dec") to lysin in the position 29 in the B-chain. Therefore, the new insulin called "degludec". The structure was added zinc and resorcinol to form hexamers. The presence of zinc and phenol creates dihexamers. After decludec injection into subcutaneous tissue, dihexamers will form into linear multihexamers chain, which will precipitate in the tissue. This multi hexamers chain serves as a depot of insulin. The acylation of lysine B29 participates in the protraction mechanism, permitting albumin binding in the bloodstream. Slow dispersion of zinc ions from the subcutaneous depot allows a predictable gradual dissociation into insulin monomer, which exactly behaves like human insulin regarding insulin receptor binding and activation and the subsequent metabolic effects. Following the injection, insulin concentration is gradually increased and reach its maximum plasmatic concentration (Cmax) after 10-12 hr and terminal half-life (1/2) of 17-15 hr, which is twice as that glargine and determir. The degludec concentration in the bloodstream was steadily achieved after 2-3 days with once-daily dose. There is no further accumulation because at this point the daily injection dose matching the daily eliminated amount when the repeated dose is given in the adequate interval.[6]

This ultra long basal insulin action allowed us to achieve the targeted goal with a flexibility fashion and safety profile. Therefore, the efficacy needs to be evaluated and compare it to the current basal insulin available in the market in term reducing HbA1C and measure its adverse hypoglycemic effect.

Non-inferiority glucose control and hypoglycemic effect

First of all, BEGIN: ONCE LONG study by Zinman,[7] et al in 2012, try to answer the inferiority blood glucose control outcome in comparison with previous long-acting basal insulin, glargine 100. The result showed that degludec control blood glucose similar to Glargine in term of achieving HbA1C 7% and has 36% lower nocturnal hypoglycemic adverse reaction. BEGIN: BB study by Hollander[8], was designed to investigate the longer-term safety and efficacy of insulin degludec compared with insulin glargine in the same population. The overall rate of hypoglycemia was 24% lower ($p = 0.011$) and the rate of nocturnal hypoglycemia was 31% lower ($p = 0.016$) with insulin degludec in the extension trial set, while both groups of patients achieved similar glycaemic control.

Asian patients with type 2 diabetes tend to be characterized more by impaired insulin secretion than increased insulin resistance. [9] BEGIN ONCE ASIA is a multinational, 26-week, open-label, treat-to-target trial with Asian type 2 DM patient. The result confirmed that degludec is non-inferior to glargine in reducing HbA1C and 38 % reduction in nocturnal hypoglycemic rate ratio. In order to investigate the consistency of the results across different definitions of hypoglycemia, a post-hoc, patient-level meta-analysis included six randomized, controlled, 26- or 52-week phase 3a trials in insulin-naïve participants with Type 2 diabetes mellitus was done. The risk of nocturnal hypoglycemia was significantly lower with degludec vs. glargine for all hypoglycemia definitions and trial periods. The nocturnal hypoglycemia rates were lower with insulin degludec vs. insulin glargine across all definitions, timescales, and trial periods.[10] A meta-analysis of 7 phase 3a trials revealed that degludec 10% more success in achieving FBG < 5 mmol/L without nocturnal hypoglycemia as it compares to glargine.

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Flexibility of administration

The next series of BEGIN study tried to assess the flexibility of degludec administration within 8-40 hours. This study called BEGIN: FLEX BOT. This study evaluated 3 different groups: first, the 8-40 hours flexible administration, the second group is after meal administration, third is the same time each day administration. The primary outcome of this study is the evaluatenon-inferiority of reducing HbA1C. The result showed the flexible admiration group is not inferior in reducing HbA1C. No difference in overall and nocturnal hypoglycemic was found in both groups.[11]

Switching therapy to degludec

A randomized control trial was conducted to evaluate the efficacy in switching basal insulin to degludec from glargine or neutral protamine Hagedorn. In term of HbA1C reduction, degludec has similar potential as it compares to glargine. The nocturnal hypoglycemic was significantly 25% lower in degludec. SWITCH 2 studies is a crossover study between insulin degludec 100 and insulin glargine 100 revealed that degludec reduce 42 % of the nocturnal hypoglycemic event and 45 % of severe hypoglycemia. Switching therapy to degludec is obtained by using 1:1 dose of previous glargin dosage. If the premixed insulin was used, switch the basal dose component to degludec.[12]

The other issue in diabetes management is preventing the major adverse cardiac event (MACE). DEVOTE study, a double-blind, treat-to-target, event-driven cardiovascular outcomes trial involving 7637 type 2 diabetes patients was done in comparison with insulin glargine. The result showed that insulin degludec has 9% lower MACE hazard ratio.At 24 months, the mean HbA1C level was 7.5±1.2% in each group, whereas the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128±56 vs. 136±57 mg per deciliter).[13] The safety profile was assessed in this study. The number of patients who would need to be treated with degludec rather than glargine to avert 1 severe hypoglycemic event is 40.[10] Patients with type 2 diabetes at high risk for cardiovascular events, degludec was non-inferior to glargine in terms of the incidence of cardiovascular events.[13]

The last but not least is to evaluate the efficacy and safety profile in a real world setting. CONFIRM study compared the real-world effectiveness of degludec and glargine U300 in insulin-naïve patients with T2D. This retrospective, non-interventional comparative effectiveness study used electronic health records of U.S.-based patients from Explorys, with propensity-score matching to balance baseline characteristics between cohorts. At follow-up reduction, HbA1C was significantly lower with degludec (−1.5%) vs. glargine U300 (−1.2%). Rates of hypoglycemia were significantly lower with degludec vs. glargine U300, similarly, the proportion of patients experiencing hypoglycemia was significantly lower with degludec.[14]Lastly, EU-TREAT, a multicenter retrospective study, evaluated switching treatment from other basal insulin to degludec. HbA1c decreased by −2.2 (−2.6; −2.0)mmol/mol at 6 months vs baseline. Rate ratio of overall (0.79 [0.69; 0.89]), non-severe nocturnal (0.54 [0.42; 0.69]) and severe (0.15 [0.09; 0.24]) hypoglycaemia was significantly lower in the 6-month post-switch period vs the pre-switch period. Total daily insulin dose decreased by −4.88 [−5.52; −4.24] U (−11%) at 6 months vs baseline.[15]

Dosage

Most randomized controlled trials on degludec report a similar dose requirement of degludec, as compared to other basal analogs. Several studies reveal a slightly lesser dose requirement of degludec (14-20%). The recommendations consider a dose

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reduction of 20-30%if a twice-daily basal regime is converted to once daily analog. This feature encourages the switch from other basal insulins to insulin degludec.[14]

Conclusion

Insulin degludec is a new ultra long acting basal insulin. It should be used daily administration with flexible schedule injection. It is not inferior in reducing HbA1C compared to insulin glargine. However, it has more safety profile in terms of severe hypoglycemix, confirmed hypoglycemic and nocturnal hypoglycemic rate ratio. This insulin degludec provides a better glucose control and less hypoglycemic event.

SS-25

PATHWAY TO EXCELLENCE: PRENOTOFICATION, HYPERACUTE, ACUTE AND POST ACUTE

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No Abstract

SS – 26

THE ROLE OF RAPID INSULIN ANALOGUE IN DIABETES MANAGEMENT FOCUSED ON GLULISINE CLINICAL EVIDENCE

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Pathophysiology of hyperglycemia consist of fasting hyperglycemia that is affected by level of basal insulin and liver response to insulin, as well as post prandial hyperglycemia that is affected by the release of early insulin to the liver, muscle, adipocyte, as well as glucagon suppression. Effort to normalize HbA_{1c} have to decrease the level of fasting blood glucose and prandial. Insulin is divided into basal insulin that control blood fasting blood glucose and between meals and insulin prandial/bolus that control blood glucose level after meals. Control of blood glucose cannot be done only by giving basal insulin because in one year a majority has not reached the target. When patients are diagnosed, 50% undergo complications, 50% loss of function of cell β while two out of three patients do not reach the target HbA_{1c}. IDF recommendation about the management of the glucose levels after food consumption states that post prandial hyperglycemia causes oxidative stress, inflammation, and dysfunction of endothelium that will increase the risks of retinopathy, decrease of coronary blood flow, increase of cancer risks and decrease of cognitive function. Now insulin is still the most effective anti-hyperglycemic drug. Many forms of insulin include basal insulin, pre-mixed insulin, and fast acting insulin. They have their own portions in the regulation of blood glucose level. The target of HBA_{1C} for patient of DM type 2 is below 7%, fasting blood glucose level is below 110 mg/dl, and level of blood glucose 2 hours after food consumption is below 180mg/dL. Basal Insulin is one of the choices to begin therapy by controlling fasting blood glucose level, continued by prandial insulin such as glulisine to control blood glucose level comprehensively after fasting blood glucose is controlled.

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SS-27

MANAGEMENT OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS

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Cancer is recognized as an independent and major risk factor for venous thromboembolism (VTE). Venous thromboembolism (VTE) occurs in 10-20% of patient with cancer and is associated with significant mortality and morbidity in cancer patients. It is also the second leading cause of death in cancers patients. Occurrence of VTE has been proven to increase the likelihood of death in cancer patients by two- to six fold.[1,2]

The pathophysiology of thrombosis associated to cancer is complex and not fully understood yet. Patients with cancer have a pro-thrombotic state as the result from the synergic activity of several factors involved. Stasis of blood causes by bed rest or by the tumor compression; vascular injury caused by infiltration of cancer cells, drugs, or therapeutic devices and blood hypercoagulability is due to the release cancer cell pro-coagulant factors which activate platelet and clotting cascade. The key roles are played by tissue factors, inflammatory cytokines and platelets.[3]

VTE risk factors can be grouped in three general categories: patient-related factors, cancer-related factors and treatment-related factors. Predictive models have been established to assess the probability of developing VTE according to risk factors. Khorana score has been validated to estimate the risk of VTE in ambulatory cancer patients receiving chemotherapy comprises five predictive variables, cancer site, platelet count, hemoglobin level (or the use of erythropoiesis-stimulating agents), leucocyte count, and body mass index. Other predictive PROTECHT score adds platinum and gemcitabine based chemotherapy to those variables in Khorana score. The Ay score adds D-dimer soluble p-selectin ass additional risk factors for VTE in ambulatory cancer patients.[4,5]

The current standard of cancer recommended by international guidelines is the use of low-molecular-weight heparin (LMWH) for 6 months for the management of cancer-associated thrombosis (CAT). The evidence form randomized controlled trials showed that LMWH significantly reduced the risk of recurrent VTE compared with vitamin K antagonists and Unfractionated heparin (UFH). Overall the recurrence rate was not negligible, and it reached 6.7% to 16.9% with LMWH and 11% to 38% with UFH. Major bleeding was also evaluated up to 10 months of follow-u, and both treatments were associated with high rates of bleeding. In cancer patients with VTE, early maintenance treatment (10 days to 3 months) and long term treatment (beyond 3 months) with LMWH showed better outcomes in terms of VTE recurrence without majoring the risk of bleeding.[4,6]

But, patients with CAT have a high risk of VTE recurrence of up to 20% despite on anticoagulation. Reasons for recurrent VTE might include non-compliance, temporary cessation of therapy due to bleeding of for procedures, inadequate dosing, cancer progression, and the presence of heparin-induced thrombocytopenia. Management strategies for recurrent VTE include switching to LMWH if an oral anticoagulant is used, dose escalation of LMWH or in last option consider insertion of vena cava filter to prevent pulmonary embolism.[1]

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VTE is preventable disease when thromboprophylaxis is appropriately used. As recommended by International Clinical practice guideline ACCP, cancer patients undergoing surgery or hospitalization for acute medical illness or with reduced mobility should benefit from thromboprophylaxis, in the absence of bleeding or other contraindications to anticoagulants. Thromboprophylaxis in cancer outpatients receiving systemic therapies is still under debate, except for pancreatic ambulatory cancer patients where prophylaxis confers a sustained reduction in VTE. In near future, strategies were developed to improve prophylaxis in cancer patients and to find the best appropriate anticoagulant regimen for individualized cancer patient.[7]

Primary central nervous system (CNS) tumors incidence has been increasing over the last 30 years, especially in elderly persons. Metastatic disease to the CNS occur ten times more often than primary brain tumors, which estimated 20% to 40% of patients with systemic cancer will develop brain metastases. Brain tumors have risk to develop thrombosis but they can be complicated by hemorrhagic transformation or tumor infiltration of spinal cord with potential intra-spinal bleeding. Conclusion from few studies that concerned VTE in brain tumors is that brain tumor is not contraindication to anticoagulation. As to prophylaxis in medical patients, benefits and risks have to be weighed individually using predictive scores such as the Khorana model to indicate treatment. While in surgical patients, prophylaxis is recommended systematically.[8,9]

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SS-28

PRACTICAL PRINCIPLES FOR IMMUNIZATIONS IN IMMUNOCOMPROMISED INDIVIDUALS: FOCUS ON QUADRIVALENT INFLUENZA VACCINES

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Immunizations, whether through active or passive methods, are without doubt the best way to prevent numerous infectious diseases, from measles to rubella to tuberculosis to hepatitis B. Epidemiological data has shown, that for the diseases that vaccine are available, the rate of prevention could be close to 80-99% and in case of Polio data shown 100% rate of protection.

Immunizations frequently associated with the pediatric and not the adult population, although numerous study has shown that adult deaths from vaccine preventable disease are 200-fold higher than children. This is an unfortunate situation, because we have numerous effective vaccines to prevent infectious disease in adults, such as Pneumococcal (PCV-13, PPSV-23), Influenza (Quadrivalent and Trivalent), Hepatitis B, Hepatitis A, Typhoid, HPV and numerous other effective vaccines.

Immunization in Immunocompromised Individuals

Immunocompromised individuals, whether primary or acquired because of HIV, autoimmune disease or chemotherapy, have a dysfunctional immune system. Disturbances in cell mediated and antibody mediated immunity makes them vulnerable to numerous infections, ranging from viral, bacterial and parasitical infections. Numerous interventions, from cytokine therapy, granulocyte transfusions, adoptive T cell transfers and antibody infusions are available to increase the protection from infectious agents. Nevertheless, the most cost effective and efficient methods are by means of targeted immunizations against common pathogens.

Vaccinations are safe and efficacious in immunocompromised individuals, but several rules are must be followed. First do not administer live attenuated vaccines, that could become active infections in individuals with supressed immune function. In conjunction with this, do not give vaccination in highly immunosupressed individuals, as the antibody production will become negligible. Below is an adapted table from Adult Immunization Task Force of Indonesian Society of Internal Medicine, that described the recommend vaccination for immunocompromised adults.

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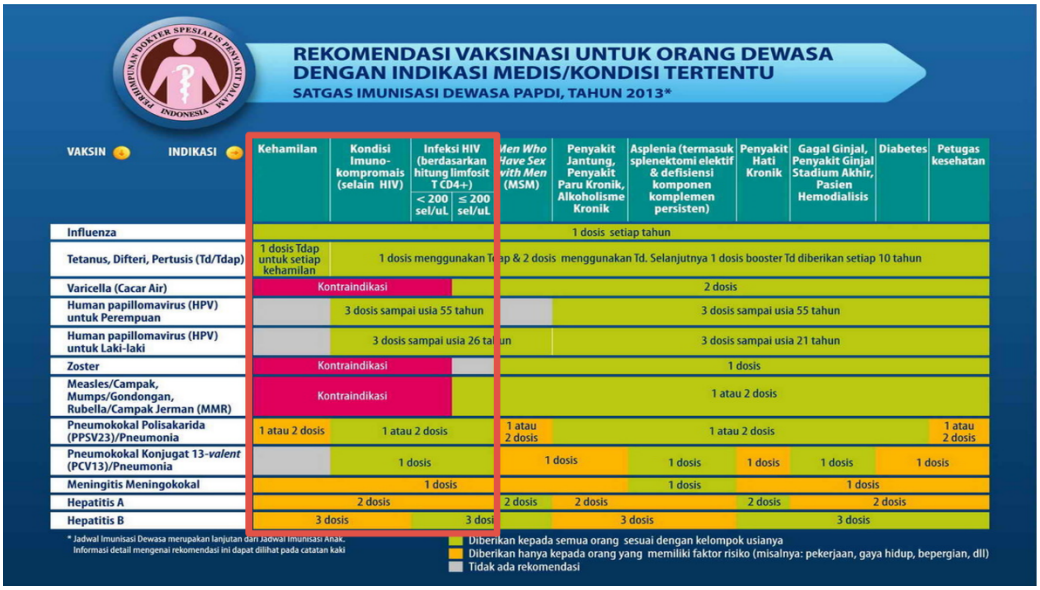

Image 1. Recommended Vaccination Schedules according to the Adult Immunization Task Force of Indonesian Society of Internal Medicine.

Influenza vaccine is one of the most important and safe vaccination to be given to immunocompromised individuals. Metanalysis published in 2006 in BMC Infectious Disease has shown that influenza vaccinations has been proven to be safe and effective in HIV-infected individuals. Recent 2014 guidelines from the Infectious Disease Society of America (IDSA) recommended annual influenza vaccinations for immunocompromised patients aged >= 6 months (strong, moderate). Recent development in Quadrivalent Influenza Vaccine, with 2 A and 2 B strain of inactivated influenza virus has given better coverage and efficacy in preventing infections.

SS-29

10 YEARSOF DPP4 INHIBITION: UNDERSTANDING NEW SCIENCEAND CLINICAL TREATMENT FOR PATIENTS WITH T2DM

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No Abstract

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LUNCH SYMPOSSIUM

SS-30

MANAGEMENT OF HYPERTENSIVE PATIENT WITH CCB IN DAILY PRACTICE

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No Abstract

SS-31

DIABETIC KIDNEY DISEASE

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No Abstract

SS-32

NEW COMBINATION OF DIURETIC AND CALCIUM CHANNEL BLOCKER IN HYPERTENSIVE ELDERLY

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Hypertension is a major medical issue. Hypertensive prevalent increases with age. Hypertension in elderly is a unique circumstance due to response to therapy and target blood pressure. The recent guideline aims a threshold of 140-159 as threshold treatment and target systolic blood pressure (SBP) 130-139 mmHg in elderly population. The combination antihypertensive is recommended to be used. Indapamide is potential diuretic in reducing SBP. Amlodipine serve as the best agent to control BP variability. This review discusses the potential BP control and safety profile of indapamide/amlodipine combination.
Keyword*:* *hypertension, elderly, indapamide, amlodipine, SBP reduction*

Hypertension is a major medical problem in our world today. It is estimated that 1 in 4 person above 50 years old has hypertension.[1] As the people get older the hypertension risk goes bigger. Management of hypertension has a challenging issue in last decades. Only less than a half patient achieve the blood pressure goal.[1] The risk of complication is increased in uncontrolled hypertensive patient. Mortality and morbidity related to hypertension disease has been a toll of its consequences.[2] SPRINT study provides us a new hallmark in treating hypertensive patient. It revealed that the lower SBP target associated with reducing mortality and morbidity.[3]
Increasing number of older people has its own health problem. Hypertension is the most prevalent problem in this population. More than a half of them have hypertension. Hypertension in elderly is complex spectrum of health issue. The management can be perplexity in determining the threshold and the outcome. In the other hand this population is at risk to poli-pharmacy related adverse reaction. The

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other issue is economic issue in treating the burden of care related to hypertension in this specific population. The treatment is clearly demonstrated to be beneficial in this population. However, the treatment should be tailored to each individual.[4]This review explored the potential of new set antihypertensive fixed combination with indapamide and amlodipine in treating hypertensive elderly. The method is to review evidence from current studies on hypertension especially in elderly population.

Hypertension in elderly

In 2018, according to ESH/ESC guideline, hypertension in elderly is defined as systolic blood pressure (SBP) over 140 mm Hg and diastolic blood pressure (DBP) over 90 mm Hg. The threshold treatment in elderly is divided into 2 age groups. For those 65-80 years old, the threshold is SBP 140-159 mmHg. Meanwhile in those above 80 years old, the threshold is SBP above 160 mmHg. The target SBP is 130-139 mmHg. It is recommended to start with two drugs combination antihypertensive. The exceptions are frail elderly and those at low risk and with grade 1 hypertension (SBP <150 mmHg). [5]

Pathophysiology

Both systolic bloodpressure and diastolic blood pressure is increasing with age. SBP rise progressively until 80 years old, whereas DBP increase until 60 then to be steady or slightly decrease.[6] The mechanism is not clearly understood. The major effect is the aging process of cardiovascular system. Aortic and large-artery wall thickness increase large vessel elasticity decrease with age. The reduction of vessel elasticity results in an increase in peripheral vascular resistance. Baroreceptor sensitivity is modified with age. Changes in the balance between beta-adrenergic vasodilation and beta-adrenergic vasoconstriction are in favor of vasoconstriction that increases peripheral vascular resistance and BP. Sodium retention due to increased intake and decreased excretion could also contribute to hypertension. A fall in plasma renin with increasing age has been demonstrated. However the renin-angiotensin system is not consider as a major mechanism.[2]

Numerous of medication has been developed in the last four decades. Several classes have been discovered since the breakthrough of diuretic drugs in 1950. Beta-blocker came in late sixties, as the calcium antagonist drug were developed and the emergence of ACE inhibitor and ARB in 2000. At the moment, we have at least five different classes. Despite of all the development of these drugs, the management of hypertension hasn't been satisfied enough.

It may take more that one class of antihypertensive drug to controllable the blood pressure. The combination of two or three drugs has been evaluated and studied lately. Several combinations such as ACE-inhibitor and diuretic, CCB and ACE-i, as well CCB and ARB have been used widely. The result revealed a promising controllable blood pressure in hypertensive patient. Reducing the number of pill to be consumed by patient through making it fixed combination drug is a breakthrough strategy in gaining better patient compliance. The new set of fixed combination consists of diuretic and CCB is a new player in controlling blood pressure. It starts showing significant benefit and lower risk of adverse outcome.

Elderly is a unique population. This elderly patient come with multiple diseases and loss of functional capacity. Most of them are relatively difficult to treat problem due to their complexity of the diseases. Several of them suffer from poli-pharmacy despite

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achieving the treatment goal. Hypertensive elderly need to be treated effectively and gain their realistic goal of treatment. The goal is to lower the mortality and morbidity as well slowing the progression of deteriorating organ function and maintain their quality of life at the fullest.

Indapamide

Indapamide is a unique diuretic medication for treating hypertension. It is a benzamide-sulfonamide-indole. Its molecule contains both a polar sulfamoyl cholobenzamide moiety and a lipid-soluble methylindoline moiety. It differs from thiazide, thus it doesn't have thiazide ring and contain only one sulfonamide group. It is a yellowish crystalline (tetragonal) powder. It is the first indoline, a new class of antihypertensive. The peak concentration is achieved within two hours. It has 14 hours half-life, and it eliminated predominantly by kidneys (73%) and gastrointestinal (23%). It may interact directly with the subunits of delayed rectifier potassium channels, thereby blocking both slow and rapid K+ current through the channels. Through the homeostasis mechanism in balancing total ion concentration (Ca++, Na+), it reduces vascular hyperactivity and peripheral and arterial vascular resistance, possibly by inhibiting trans-membrane ionic influx, probably calcium ions, and stimulating prostaglandin E2 synthesis, thereby causing vasodilatation. The diuretic effect is resulted by inhibiting reabsorption of sodium and chloride, primarily as a result of action on the cortical diluting segment of the renal distal tubule, thereby promoting urinary excretion of water and electrolytes.[7]

Indapamide has been intensively studied in broad population, especially in older adult. It has been a choice in treating hypertension in elderly. Among all other diuretic, indapamide serves the safest profile, since it has less metabolic consequences, such as electrolytes imbalance and blood glucose disturbance. It doesn't harm like loop diuretic in elderly that is so detrimental because of the increased risk of falling related to volume depletion and electrolyte imbalance.

HYVET trial is the largest study of hypertensive elderly. It include 3845 patient from Europe, Australia, Asia and North Africa who were 80 years old and has a sustain systolic blood pressure of 160 mmHg or more. This trial used indapamide or perindopril to achieve the target BP of 150/80 mm Hg. The primary endpoint was fatal or fatal stroke. The results provide us evidence that antihypertensive treatment with indapamide, with or without perindopril, in elderly is beneficial. The treatment was associated with 30% reduction of fatal and non-fatal stroke. Baquet, et al[8] reported a meta-analytical study on the efficacy of antihypertensive drugs reveal that indapamide appeared to be the most effective rock for producing significant reductions in SPB within 8-12 weeks.Roush, et al[9] evaluated ahead to head comparison of hydrochlorothiazide with indapamide. It is reported that indapamide has 54% more potent in reducing BP without resulting excess in metabolic disturbances. Indapamide has at potential BP control over 24 hours. This particular potential was proved by the through to peak ratio at 89%.[10] The 24-hour control is maintain at 1 year, it is confirmed the long-term efficacy of indapamide SR 1.5 mg. Amlodipine serves as the best antihypertensive agent in controlling BP variability, and it was followed by indapamide based on X-CELLENT ABPM study.[11]Indapamide in this study was associated with reduction HR variability at night. Amlodipine or indapamide sustained release SR treatment was associated with a significant reduction in BPV, and the mechanism of those reductions was possibly

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attributable to lowering BP or ameliorating the autonomic nervous system regulation or both. The combination of the 2 agents might help to optimize such properties.[11]In SYST-EURO trial, blood pressure variability is a risk factor for stroke.

Two drugs combination

Levi, et al, evaluated CCB and diuretic combination efficacy. Among all antihypertensive treatment, the combination of CCBs with diuretics is the most effective treatments in lowering BPV.[12]Evidence from the individual-therapy trials and available combination-therapy trials suggest that in patients who require more than one anti-hypertensive therapy, combination of CCBs and thiazide-like diuretics should be the initial strategy.[13]

Indapamide and amlodipine

The single pill combination indapamide SR/amlodipine is evaluated its efficacy and acceptability in EFFICIENT trial, a phase 4 study in 2014. This study included hypertensive patient that is uncontrolled with CCB or grade 2 and 3 hypertension. The results were mean SBP decrease 28.5 mmHg and DBP 15.6 mmHg. Blood pressure control was achieved in 85% patients. Only 2% reported side effect of this single pill combination.[14]

In 2015, NESTOR study evaluated the efficacy of indapamideSR/amlodipine in hypertensive type 2 diabetes patients with microalbuminuria. This study compare indapamide SR/amlodipine and enalapril/amlodipine. The post hoc analysis after 52 weeks revealed that indapamide SR/amlodipine decrease 26 mm Hg and enalapril/amlodipine 21 mm Hg, thus it has 5 mmHg mean SBP lowering.[15] Treatment with indapamide SR/amlodipine was well tolerated. The rate of pedal edema was similar with enalapril combination. There is a slight change in potassium level and hyperuricemia in indapamide group, but there is no difference in fasting glucose, lipids, hyponatremia and creatinine clearance in both groups.[15]Sub-analysis for elderly patient, above 65 years was revealed that mean systolic BP reduction was greater with indapamide SR/amlodipine 6.2 mmHg. Indapamide SR/amlodipine was also associated with greater BP response. Indapamide SR/amlodipine is more effective than enalapril/amlodipine for lowering systolic BP in elderly patient.[16]Dominiczak, in 2016, performed a randomized controlled trial assessing the systolic blood pressure (BP)-lowering efficacy and tolerability of the single-pill combinations (SPC) of indapamide sustained release (SR)/amlodipine vs valsartan/amlodipine over 3 months. At week 12, indapamide SR/amlodipine was as effective as valsartan/amlodipine at reducing office systolic BP.Amongst patients with BP uncontrolled on ABPM at baseline (BP >130/80 mmHg), indapamide SR/amlodipine was significantly more effective at week 12 at reducing office systolic BP vs valsartan/amlodipine. The adverse effect was found similar in both groups.[17]

Conclusion

Hypertensive older patient has a clear benefit in BP control management. It has shown to lower the stroke risk. The new target was established to achieve SBP below 140 mmHg and it is recommended to use combination therapy. Indapamide is potent antihypertensive especially in elderly. Amlodipine is the best antihypertensive in reducing blood pressure variability. Indapamide SR/amlodipine combination has superior BP control and reducing BP variability, effective lowering BP variation with a safety profile.

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SS-33

TIPS & TRICK HOW TO OPTIMIZED ANTENATAL CARE (ANC)

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No Abstract

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SS-34

THE CELLULAR AND MOLECULAR CHANGES OFTHE LIVER AND PANCREAS IN TYPE 2 DIABETIC RAT WITH HEPATOCELLULAR CARCINOMA

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Background:A number of clinical trial studies have identified that Type 2 Diabetes mellitus is regarded as a new risk factor for liver cancer through lipogenesis, however the cellular and molecular changes of the liver and pancreas have not been explored thoroughly.
The aim of this study is to explore the cellularand molecular changes of the liver and pancreasin diabetic type 2 rat induced hepatoma (HCC).
Material and method: Twenty of maleWistarrat, 7 weeks old with 250 gram body weight were used and divided evenly into 2 groups. All rats which given high fat diet (HFD) daily for 4 weeks then injectedStreptozotocin(STZ)i.p. twice at one week interval with a dose of 45mg/kg BW. Hyperglycemia rats with fasting blood glucose (FBG) ≥ 250mg/dl divided into control and treated groups; the control was injected with sterile saline and the treated group was injected with Diethylnitrosamine (DEN) once a week, thenthey weresacrificed at 7 and 14 weeks afterwards. The liver and pancreas were moved from the body to be prepared for histology specimen and western blotting samples. The fixed liver sections werestainedwith H&E forcounting the number of neoplastic prominent nucleoli hepatocytes and observing the changes architecture of hepatic parenchyma. The fresh tissue of the liver and muscles were keep in the buffer for measuring the level of protein Sterol Regulatory Element-binding Proteins 1c(SREBP1c).
Result: The section of pancreas demonstrated significantly ($p<0.05$) decrease number and volume of Langerhans islet in hyperglycemia rats. The section of liver parenchyma of HCC rats showed abundant hepatic nodules and significantly ($p < 0.05$) higher number of prominent nucleoli. The level of SREBP protein wassignificantly increased.
Conclusion: The progression of liver carcinogenesis in T2D rats demonstrated cellular and molecular changesshown by increasing volume of Langerhans islet, number of pre-neoplastic hepatocytes and enhancingexpressionof SREBP1c level.

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THE EFICACY OF METFORMIN TO SUPPRESS THE EXPRESSION OF SREBP-1c AND HEPATOCYTES TRANSFORMATION IN TYPE 2 DIABETES TOWARDS LIVER CARCER

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Background: Metformin, a first line therapy for the treatment of type II diabetes(T2D) has been reported to reduce a risk of carcinogenesisina number of in vivo studies. Although metformin demonstratedas anti-cancer properties, however the effect of metformin on preventing carcinogenesis in the liver has not yet been studied clearly.
The aim of this study is to explore the efficacy of metformin in the supression of transformation hepatocytes and expression of Sterol Regulatory-Element-Binding-Protein-1c (SREBP1c) as a factor in liver lipogenesis.
Material and method:Fourty (n=40) male Wistar rats were induced hyperglycemia, then divided into 4 groups as follows, the first and second group were injected with sterile saline and diethylnitrosamine (DEN) 70mg/kgBW once a week, respectively. The third and fourth groups of T2D injected with DEN were given metformin 125 mg/kg BWor 250 mg/kg BW mixed in drinking waterdaily.The blood taken from the rat tail was measured for fasting blood glucose (FBG) every week. All groups of rats were sacrificed at7 and 14 weeks afterfirst injection of DEN. The paraffin fixed liver sections stained with H&E were observed for general examination of liver parenchyma and number neoplastic hepatocytes,whereas their fresh liver and muscle tissues were prepared to evaluate the protein level of SREBP1c with Western Blot.
Result: the liver sections demonstrated fatty degeneration with abundant number of prominent nucleolihepatocytes, as one characteristic of transformation hepatocytes.The administration of metformin either in the dose of 125 mg/kg BW or 250 mg/kg BWdecreasedthe level of FBG, the number of prominent nucleoliand the expression of protein SREBP1c,significantly ($p<0.05$).
Conclusion:Metformin may prevent the type 2 diabetes toward liver carcinogenesis through declining the neoplastic hepatocytes and suppressing the expression of protein SREBP 1c.
Key words: *Type 2 diabetes, neoplastic hepatocytes, SREBP1c, liver carcinogenesis*

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No Abstract