East Delhi Physicians' Association®



Dear members of East Delhi Physicians Association,

Its our pleasure to introduce the first issue of e-newsletter of our association.

This contains interesting case reports & review articles that will surely enhance our clinical skills in our day to day practice in Medicine. If any of you are interested to contribute to this cause you can send us your inputs/ideas & we will accommodate them in our subsequent editions.

Let's make this effort meaningful and useful to all our members at large.

With best regards:

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News & Views

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A MAN WITH BICYTOPENIA

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A 47 yr. old man had complaints of pain in the neck and abdomen for 15 days and was on continuous painkillers (nimesulide) for last few days. He was admitted in an outside hospital and found to have subacute intestinal obstruction and was managed conservatively. He developed malena, had hemoglobin- 7.5 g%, platelet count 96,000 and was suspected to have NSAID induced GI bleed. Subsequently patient developed fever with widal 1:160 titre and was started on antibiotics for the same. Patient's Hb kept on falling (upto 5.3 g %) and was given total 8 units of blood transfusion. Bone Marrow (outside) revealed Amegakaryocytic thrombocytopenia. Patient was referred to AIIMS as a case of bicytopenia with occasional epistaxis for 10 days and paleness of body. On examination patient did not have any external bleeding spots, lymphadenopathy or hepato-splenomegaly. He had hemorrhoids. On investigation he had Hb- 8.4 g%, TLC- 8100, platelet count 15,000. Peripheral smear showed significant polychromasia, occasional schistocytes, Differential count-N 50, L 13, M 2, E 1, Myelocytes 16%, metamyelo 18%, 34 nRBCS/100 WBCs, reticulocyte count 7.5%. Differential diagnoses of Evan's syndrome or ITP with anemia (secondary to blood loss) were kept. Serum LDH was 597 U/l, Coomb's test (direct and indirect) were negative, stool for OB negative (2 days). LFT revealed S. bilirubin- 2.4/1.9 mg/dl , SGOT/PT-117/140, ALP- 2565 IU/L, GGT-125, Protein/Alb-6.0/3.0, PT-18.2 /12 seconds. Viral markers were negative. CT chest and abdomen done revealed pleural thickening. Bone marrow aspiration was tried twice but could not be aspirated. BM Biopsy imprint smear showed very few cells and extensive areas of necrosis in two separate biopsies. UGI endoscopy done in v/o malena which revealed a deep excavating ulcer (Lesser curve and posterior gastric wall), had raised margin and surrounding mucosa looked infiltrated. Biopsy of the lesion showed foci of infiltration by signet ring cells. So the final diagnosis was Signet ring cell adenocarcinoma with extensive bone marrow necrosis and patient was referred to Surgical Oncology.

Discussion

Bone marrow necrosis (BMN) is defined as necrosis of myeloid tissue and medullary stroma in large areas of the hematopoietic bone marrow. BMN was described for the first time in 1942, in a patient with sickle cell disease who died of cerebral infarction. It's characterized by a disruption of normal BM architecture with a considerable loss of fat spaces. Aplastic anemia with loss of myeloid tissue and no destruction of the reticular structure. There is no destruction of the spicular architecture as is seen in aseptic necrosis.

Prevalence observed by Dunn et al. was 0.4 % among 10,856 aspirates. Two other studies estimated the prevalence to be 0.5- 1% in cancer patients. Causes include malignancies in 90% of all cases (hematological malignancies- 60% including ALL 18% and AML 13%, solid organ tumors 30%), non malignant causes include infections (pneumonia, TB, viral), drugs (sulfasalazine, interferons, chemotherapeutic drugs) and sickle cell disease.

Patient can present with anemia (91 %), thrombocytopenia (78%), bone pain, fever, leukoerythroblastic picture, high ALP and LDH. Bone marrow aspiration is unsuccessful and

multiple aspirations from various sites are necessary. Aspirate can be serosanguineous, watery, dark red or even clear fluid and can smear very unevenly. Bone marrow scanning can be done with Technetium 99m sulfur colloid and Indium chloride or MRI guided aspiration or biopsy can be done.

Immune complex mediated damage is present. Mechanical obstruction in sickle cell disease, DIC-fibrin plugs, metastatic carcinoma (aggregates of carcinomatous cells) , leukemia can lead to damage. Tissue hypoxemia after failure of the microcirculation and endothelial injury causes vascular obstruction in BM. There is release of toxins, cytokines, or vasoactive substances from damaged cells. TNF has been implicated in the pathogenesis.

Prognosis greatly depends on underlying disorder. BMN in childhood ALL does not compromise CR and survival. BMN in a patient with a solid tumor seems to be a sign of generalized disease (metastasis) and predicts a short survival. In conclusion, an underlying malignancy should be strongly searched in patients with bone marrow necrosis.

The 75th Annual Meeting of the American Diabetes Association (ADA) was held at the Boston Convention and Exhibition Center in MA (June 5-9, 2015). Endocrinologists, diabetes educators, research scientists and many different health care professionals from around the world gathered to learn about significant advances in the prevention, diagnosis and treatment of people with diabetes.

This year's meeting featured thousands different educational opportunities and presentations, including symposiums, posters and abstracts. As usual, key leaders in the field of diabetes were on hand to deliver information and resources critical to diabetes care.

The wealth of information shared was presented in eight areas, which included acute and chronic complications, behaviorial medicine, epidemiology/genetics, immunology, obesity and islet biology.

Important topics from this meeting:

1. Comparative Durability of Second-Line Glucose-Lowering Therapy in Type 2 Diabetes
2. Dapagliflozin Did Not Raise Cardiovascular Risk in Elderly Diabetic Patients Over a 4-Year Period
3. Expanding the Role of Clinical Diabetes Educators Intensifies Diabetes Management
4. First Cardiovascular Outcome Trial of a GLP-1 Agonist Finds No Cardiac Risk or Benefit. (Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial)
5. Integrating Diabetes Education into Primary Care Is Feasible and Beneficial
6. Primary Endpoint Met for Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

ACUTE TYPE-B AORTIC DISSECTION

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A 58 year old male, a known hypertensive and a chronic smoker, presented in emergency with the complaints of sudden onset severe chest pain radiating to back and legs for last 3hrs. On examination, the patient was conscious and oriented. His pulse was 90/min; BP – 170/100 mm Hg. On local examination, both lower limb pulses were absent with no signs of visceral malperfusion. CT peripheral angiogram revealed aortic dissection (De-Bakey III b) with aneurysmal dilatation of descending thoracic aorta. Entry point of dissection was 2 cm distal to origin of left SCA with significantly reduced true lumen flow to visceral arteries and legs.

Patient was taken up for emergency endovascular repair of aortic dissection under general anesthesia and spinal drainage catheter for CSF drainage (to prevent spinal cord ischemia and spinal paraplegia). Right CFA in groin was exposed. The true lumen was identified and stent-graft device (Valiant Captiva 34-34mm x 200mm) was introduced over super stiff wire. Marking pigtail catheter was introduced through left CFA, check angiogram taken and confirming the position of the stent graft; stent-graft was deployed till celiac artery origin followed with proximal extension by another stent-graft (Valiant Captiva 34-34mm x 200mm) from just distal to the left subclavian artery origin. Final aortogram showed good exclusion of the false lumen and enlargement of true lumen caliber with good distal flows to legs.

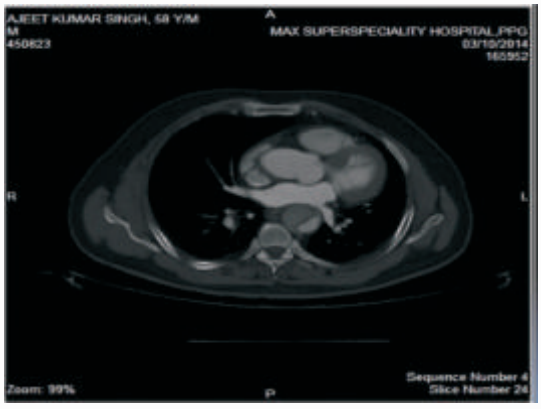

Fig: CT- Angiogram: Markedly compressed true lumen of descending thoracic aorta

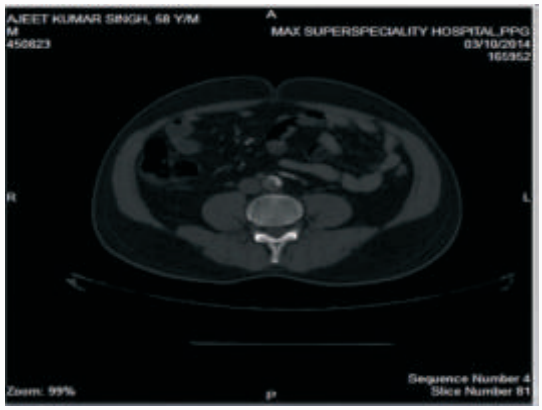

Fig: CT- Angiogram: Markedly compressed true lumen of infra renal aorta

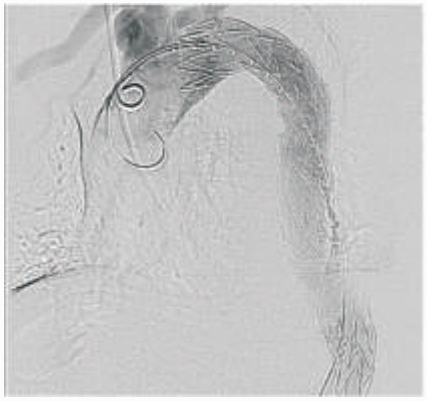

Fig: Final aortogram shows good opacification of the true lumen and left CCA with no flow into false lumen

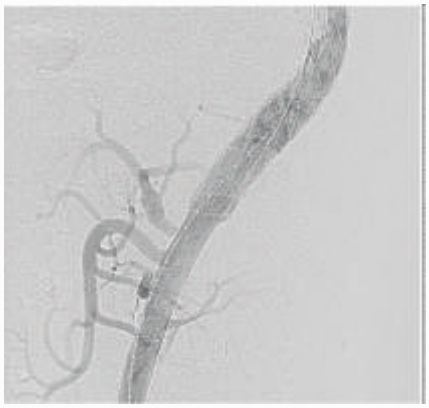

Fig: Final aortogram shows good opacification of the true lumen

Chronic type-B Aortic Dissection

A 74 year old female, a known hypertensive, presented in the OPD with complaints of sudden onset pain in chest and back 3 months back. She visited some hospital elsewhere where she was managed conservatively. CT aortogram revealed aortic dissection (De-Bakey III b) with intimal flap starting just distal to the origin of left subclavian artery till bilateral iliac arteries. Proximal most descending aorta show focal aneurysmal dilatation (maximum diameter - 5.4 cm). The patient was taken up for the hybrid procedure (Surgical bypass with thoracic aortic endovascular repair- TEVAR).

Under GA, left carotid-subclavian bypass was done initially (to preserve vertebral artery and intercostals arteries flow to prevent spinal paraplegia). Right CFA in groin was exposed. The true lumen was identified and the stent-graft device (Zenith TX2 38-34mm x 202mm) was introduced over super stiff wire. Marking pigtail catheter was introduced through left CFA, check angiogram taken and after confirming the position of the stent graft; the device was deployed starting from just distal to Left CCA covering the origin of left subclavian artery. This was followed by deployment of the extension limb (Zenith TX2 34-30 x 194 mm) till celiac artery origin. Final aortogram showed good exclusion of the false lumen.

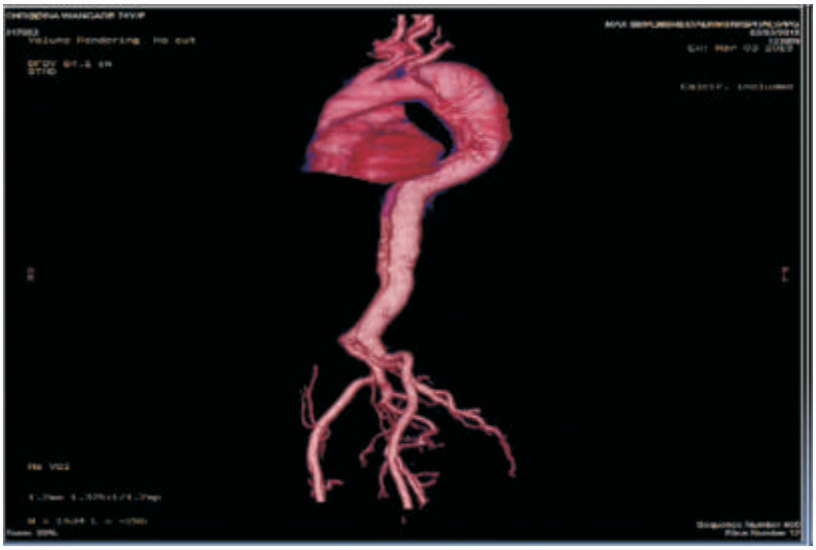

Fig: CT-peripheral angiography (3D recon): Type B Aortic dissection starting just distal to the origin of left subclavian artery

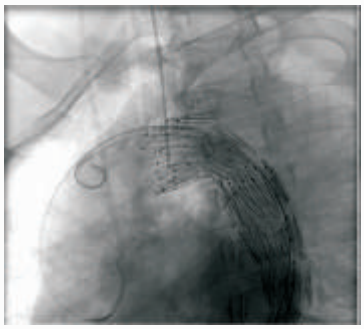

Fig: TEVAR: Good opacification of the true lumen with exclusion of the false lumen

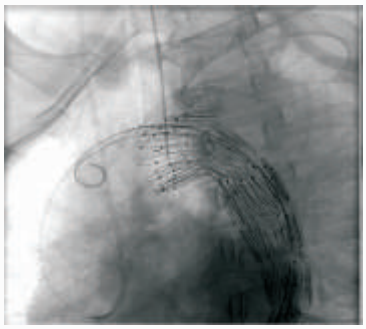

Fig: TEVAR: Good opacification of the true lumen with opacification of the left carotid- subclavian bypass graft

Review of Literature

Aortic dissection is characterised by separation of the layers of the aortic wall due to extraluminal blood that has entered the aortic wall through an intimal tear and passes longitudinally along the tunica media separating the intima from the adventitia; thus creation of "false lumen". An acute dissection of the aorta is one which presents within 14 days of the onset of the disease process. The associated mortality rate is about 1%–3% per hour with 20%–30% of deaths occurring in the first 24 hours and roughly 80% in 2 weeks. Unfortunately diagnosis is not uncommonly delayed or missed with lethal consequences.

The most commonly used classification system is that of DeBakey, which divides the dissections into 3 types: I – involving the ascending aorta and a variable amount of descending or thoraco-abdominal aorta; II – dissection limited to the ascending aorta; and III – dissection of the descending aorta either without (IIIa) or with (IIIb) involvement of the abdominal aorta.

Several risk factors associated with aortic dissections are high blood pressure (hypertension), male sex, age> 60 years, genetic disorders affecting the blood vessel wall (Marfan's syndrome, Ehlers-Danlos syndrome), atherosclerosis, aortic coarctation. bicuspid aortic valve and trauma.

It requires high index of suspicion to diagnose aortic dissection based on a patient's history and physical examination. Patients typically present with severe, sharp or 'tearing' back pain (in dissection distal to the left subclavian artery) or anterior chest pain (in ascending aortic dissection). However, as the dissection can affect any of the arteries arising from the aorta, other presentations include stroke, a pulseless limb or abdominal organ dysfunction such as renal failure or intestinal ischemia.

Once the diagnosis is suspected, the initial management is to initiate full monitoring including heart rate, blood pressure, urine output and central venous pressure. The systolic blood pressure should be reduced to around 100– 120 mmHg to prevent further dissection and â-blockade should be instituted. The diagnosis needs to be confirmed by means of a CT aortogram and trans-oesophageal echocardiography. This provides an assessment of the risk of impending rupture and allows a decision to be made with regards the urgency and type of operation necessary. Options include open replacement of the aorta with reimplantation of arteries with or without aortic valve replacement depending upon the location and extent of the dissection.

For DeBakey type I and II dissections, immediate surgery is recommended. For type III acute dissection, conservative management is recommended unless dissection rapidly progresses, the aorta ruptures, or vital organs become threatened by lack of blood flow (malperfusion), In chronic type III dissection, surgery is indicated for false lumen aneurysm >4.5 cm in diameter (to prevent aortic rupture) and malperfusion syndromes. More recently, endovascular stent-grafting is being performed for type III aortic dissections; and has now almost replaced need for open surgical procedure as it has limited morbidity, mortality, minimal blood loss, shorter hospital and ICU stay and early recovery.

"The doctor of the future will give no medicine, but will educate his patients in the care of the human frame, in diet, and in the cause and prevention of disease."

-- Thomas Edison

INTERESTING CASE OF SKIN RASH

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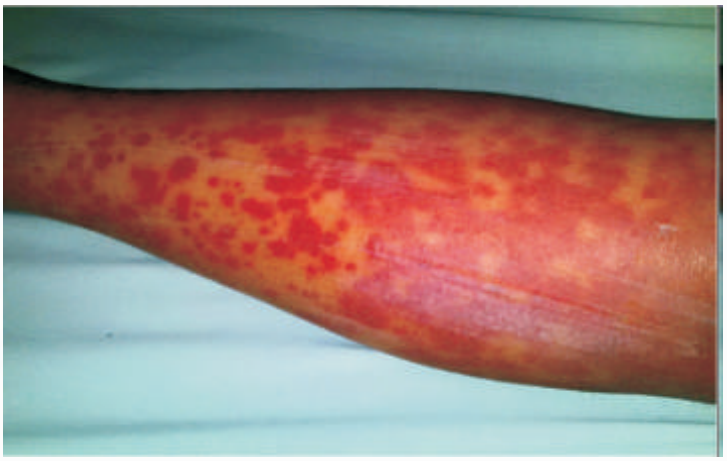
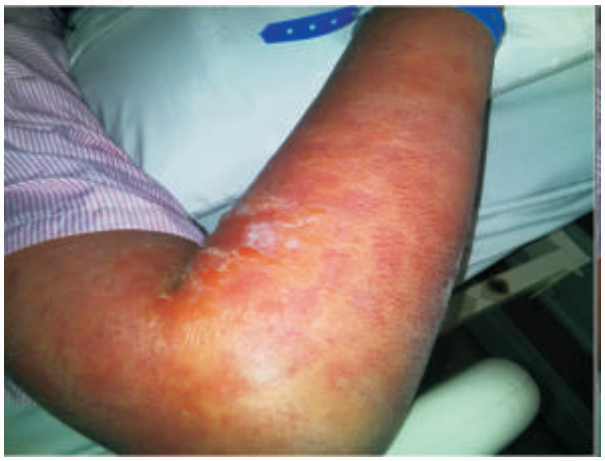
Introduction

Cutaneous adverse drug reactions (ADRs) are the most common and most reported form of adverse reactions to drugs, representing approximately 30% of all reported cases[1]. Predisposing factors are advanced age, polypharmacy, female gender, concomitant infection (particularly HIV) and genetic predisposition. Both immune-mediated and non-immune-mediated mechanisms are involved and various patterns can be seen. Acute generalized exanthematouspustulosis (AGEP) is a generalized pustular eruption that is drug-induced in more than 90% of cases[2]. Few case reports of infectious origin (CMV[3], Parvovirus B19) have been suspected. We report here a case of AGEP induced by a fixed drug combination of cefixime and azithromycin.

Case

31 year old female presented to the emergency department with complaints of fever on and off for 10 days, skin rashes for 1 week and loose stools and vomiting for 2-3 days. Fever started 10 days back and patient took tab cefixime and azithromycin fixed drug combination for 3 days following which fever subsided. Patient developed skin rashes 4 days after onset of fever. Rash started on the trunk and back and spread to the upper and lower limbs over a couple of days, was associated with severe itching and fever started again. Patient developed loose motions & vomiting and was hospitalized for 4 days in outside hospital and thereafter shifted to PCH. Patient had history of bilaterally symmetrical polyarthritis for past 2-3 months, was RA factor positive and was taking sulfasalazine and hydroxychloroquine for past 1 month. There was no other significant past history/family history or any history of drug allergies. She was a non smoker with no history of alcohol use. No recent travel history.





On physical examination she was mildly dehydrated with facial puffiness and vital signs were stable. A complete skin examination revealed extensive sheets of erythema all over the body with small pustular lesions, superficial vesiculation and exfoliation (more on the back) with no mucosal involvement. Other systemic examination was unremarkable except decreased air entry in right side of chest.

Laboratory investigations revealed leukocytosis (TLC- 37,630 with polymorphs 42% and eosinophils 28%), procalcitonin- 8.2 ng/ml, albumin 2.2, GGT-268, SGPT-156, SGOT-140. Inciting drugs were stopped and patient was initially started on Inj Imipenam and Teicoplanin as TLC counts increased upto 65,800. Patient had to be given steroids 10 days after initial appearance of rash (dexamethasone 8 mg BD for 2days and rapid tapering over a week) as she developed new skin lesions , following which skin lesions and TLC count improved. Skin biopsy revealed spongiosis of lining squamous epithelium with few corneal pustules, dermis shows mild to moderate mixed inflammation comprising of neutrophils, lymphocyes and occasional eosinophils. Lesions completely disappeared within 2-3 weeks of stoppage of drug. Thus a diagnosis of AGEP was made.

Discussion

Acute generalized exanthematouspustulosis(AGEP) is characterized by a fever (>38˚ Celsius) and a cutaneous eruption with non-follicular pustules on an edematous erythematous background. Onset of symptoms is abrupt within 2days to 2-3 weeks of drug exposure. Scarletiniform eruptions start from intertriginous areas, or face then spread to trunk and lower limbs with multiple small pinhead sized, (5mm) non – follicular sterile pustules. Mucous membrane involvement is usually mild (20%) limited to oral mucosa. After 2 weeks generalized desquamation occurs after pustules subside. Neutrophilic Leukocytosis predominates with eosinophilia in 30 % cases. Mild liver and kidney function derangements can be seen[2].

Upto 90% of cases can be attributed to drug reactions[2]. Most common offending drugs are antibiotics (beta lactams, macrolides,sulphonamides), antifungals (itraconazole,terbinafine), anticonvulsants(carbamazepine, phenytoin) and others. In our case patient gave history of taking sulfasalazine and hydroxychloroquine for past 1 month so the possibility of DRESS syndrome was entertained but the typical skin lesions and skin biopsy favoured AGEP.

Skin biopsy reveals subcorneal or intraepidermal pustules, papillary oedema with perivascular infiltrate of neutrophils and some eosinophils. Chief differential diagnosis includes pustular psoriasis.

Withdrawal of the offending drug and other supportive treatment is sufficient in most cases. Topical steroids and systemic steroids can be given[5]. In severe cases (eg.overlap with TEN) infliximab[4] and etanercept have been used. In our case steroids had to be given as the patient developed some fresh lesions after 10 days of withdrawal of offending drug.

The identification of responsible drug can sometimes present a major challenge in cases receiving multiple drugs. Differentiating from other drug induced eruptions (DRESS, SJS/TEN) is important for treatment and prognostication[6].

Clinical sign's	DRESS	SJS/TEN	AGEP
Onset of eruption	2-6 wks	1-3wks	48 hrs
Infiltrated papules	+++	-	++
Pustules	+	-	**+++**
Blisters	+	**+++**	+
Mucous membranes	+++	+++	Rarely
Other organ involvement	+++	+++	**+**
Histological pattern of the skin	Lymphocytic infiltrate	Epidermal necrolysis	**Subcorneal pustules with neutrophilic infiltrate**
LAB FINDING-			
Neutrophils	Normal or increase	Decrease	**+++**
Eosinophils	**+++**	Normal	+

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"A vigorous five-mile walk will do more good for an unhappy but otherwise healthy adult than all the medicine and psychology in the world."

- Paul Dudley White

THYROID STORM

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Introduction

Thyrotoxic Crisis or Thyroid storm is a life threatening, emergency hyper metabolic state induced by excessive release of thyroid hormones in patients suffering from Thyrotoxicosis. Hall mark of the disease is the presence of life threatening arrhythmias ranging from sinus tachycardia to atrial flutter and fibrillation to ventricular tachycardia**.** Tachycardia disproportionate to the fever should give rise to high index of suspicion in making the correct diagnosis.

Apart from Anti thyroid drugs, number of agents ranging from Glucocorticoids to Beta blockers have been used to control heart rate in this clinical situation. However, associated Hypotension may prevent the use of Beta blockers, making the clinical situation worse. Presenting a case where in Ivabradine was used successfully to control the heart rate in the setting of Thyrotoxic crisis associated with hypotension and shock.

Case Report

- 42 yr. Diabetic Obese Female presented to OPD with complaints of weakness, difficulty in breathing for last two days which has increased in severity for last twelve hours.
- On examination, she had a feeble pulse with heart rate was 135 beats per minute, BP 70 mmHg Systolic, extemeties were cold and moist because of sweating, However the oxygen saturation (SpO2) was 98% on room air, Chest showed Normal vesicular breathing on auscultation. Quick systemic examination was unremarkable.
- She further gave history of off and low grade fever for last seven days, and she had been passing little urine over last 2 days which had further reduced to few drops since last night. Urgent capillary blood sugar was found to be 202mg%. ECG showed marked sinus tachycardia. Xray chest was normal.
- In the given clinical situation a provisional diagnosis of Septicemia with Shock was entertained. Patient was admitted and started on intravenous fluids, broad spectrum antibiotics and supportive treatment. After about 1 litre of Ringer Lactate/ Normal Saline had been infused patient became better, systolic BP came up to 90 mmHg. But heart rate remained high varying from 135-148 bpm. Emergency Lab reports available by now showed: Hb 11.2gm%, TLC 10080 cells/cm, DLC N62, LL27 M10, HCT 33.7%, Blood Urea 60mg%, Serum Creatinine 2.9 mg% Serum Electrolytes Normal, LFT Normal,SpO2 98% - 100 % on room air.
- As patient was still maintaining Systolic BP of 90 mmHg despite adequate hydration, heart rate persistently at 140-145 bpm, urine output still poor, patient was started on Inj Dopamine 1 amp in 50 mL of 5% Dextrose @ 1-2mL/Hr gradually built upto 5mL/Hr. BP started rising to 110 mmHg systolic but patient started complaining of ghabrahat (palpitations) Tachycardia increased to 160 bpm and patient was not tolerating Dopamine.

Tachycardia out of proportion to existing clinical picture,normal TLC, DLC, SpO2 98% on room air with a clear chest led us to review the diagnosis and history was revisited. Patient came up with the history of vague joint pains involving small joints of hands for which she had been visiting a quack, the possibility of chronic corticosteroid usage with abrupt stoppage was thought of and a probability of Addisons Crisis was entertained.

- In view of the possible Addison's Crisis patient was given 100 mg of hydrocortisone I V. Initial response was encouraging, tachycardia settled to 140 bpm from 160 bpm, BP started increasing and hence IV hydrocortisone was continued. There was sustained increase in blood pressure, urine output improved but sinus tachycardia continued to persist disproportionate to the clinical picture.
- Tachycardia which was hitherto being perceived as protective phenomenon was thought to be causative factor and it was decided to decrease the heart rate with a view to improve the cardiac output. Use of Beta blockers to decrease heart rate was a ruled out in view of impending risk of further lowering the blood pressure hence patient was started Tab. Ivabradine 5 mg. Within one hour patient started responding wonderfully, heart rate started coming down,BP started going up. In about 8 hrs heart rate came down to 102 bpm, BP became 116/80 mmHg, urine output increased 100ml/hr. Hence dopamine was tapered within 8 hours.
- By the time more lab reports were available, T3 523ng/dl,T4 21.3 ugm/dl, TSH <0.01miU, Anti – TPO 275.90 U/mL (Normal 0-60 U/mL), Patient was re-examined: she had mild Diffuse Goitre for which a radioisotope thyroid scan was done which showed both lobes of thyroid diffusely enlarged and hence final diagnosis of Grave's Disease with Thyroid Storm was made and patient was started on anti thyroid medication Methimazole.

Discussion:

- **Ivabradine** is a novel medication used for the symptomatic management of stable angina pectoris. Ivabradine acts by reducing the heart rate via specific inhibition of the funny channel, a mechanism different from that of beta blockers. Unlike Beta Blockers Ivabradine is a cardiotonic agent. Ivabradine was approved by the European Medicines Agency in 2005 and by the United States Food and Drug Administration in 2015.
- Apart from angina, it is also being used off-label in the treatment of inappropriate sinus tachycardia. Some reports are available in literature where Ivabradine has been used forreducing the heart rate in patients with sepsis or septic shock, along with supportive care like fluids, vasopressors, broad spectrum antibiotics.
- However this is possibly the first case wherein Ivabradine has been used successfully in a case of thyrotoxicosis associated with Thyroid storm to decrease heart rate in a setting of hypotension associated with disproportionate sinus tachycardia.

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HYPOSKILLIA

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Hyposkillia -deficiency of clinical skills. By definition, those afflicted are ill-equipped to render good patient care. "Hyposkilliacs" – physicians who cannot take adequate medical history, cannot perform a reliable physical examination, cannot critically assess the information they gather, cannot manage a sound treatment plan, have little reasoning power and communicate poorly. Moreover they rarely spend enough time to know their patients thoroughly . These individuals, however do become proficient at a number of things. They learn order all kinds of tests and procedure—but don't always know when to do and how to interpret them. they using so many sophisticated test and procedures, they inevitably and unwittingly acquire a laboratory –oriented rather than a clinical approach. also learn to play the number game.

The helping hand and healing touch of a physician replaced with vigorous and rigorous application of new technology in the field of medicine have altered the relationship between doctor and pat good patient care. ient; specialized physicians know more and more about less and less; doctors treat diseases rather than people; medical schools teach the science but ignore the art of medicine, medical technology has outpaced moral understanding; and hospitals have become cold, impersonal mazes. A three thousand year tradition, which bonded doctor and patient in a special affinity of trust, is being traded for a new type of relationship. Healing is replaced with treating, caring is supplanted by managing, and the art of listening is taken over by technological procedure. Doctors no longer minister to distinctive person but concern themselves with fragmented, malfunctioning biologic parts. The distressed human being is frequently absent from the transaction.

The time has come to abandon disease as the focus of medical care. The changed spectrum of health, the complex interplay of biological and no biological factors, the aging population, and the interindividual variability in health priorities render medical care that is centered on the diagnosis and treatment of individual disease at the best out of date and at worst harmful. A primary focus on disease may inadvertently lead to under treatment, overtreatment, or mistreatment. The numerous strategies that have evolved to address the limitations of disease model, although laudable, are offered only to a select subset of persons and often further fragment care. Clinical decision making for all patients should be predicated on the attainment of the individual goals and the identification and treatment of all modifiable biological and nonbiological factors, rather than solely on the diagnosis, treatment, or prevention of individual diseases. Medical care must evolve to meet the health care needs of patients in the 21st century.

The introduction of increasingly sophisticated technology is certainly one reason. Compared with the sharp images provided by ultrasonography, magnetic resonance imaging, computerized tomography, endoscopy and angiography, a patinet's history is flabby, confused, subjective and seemingly irrelevant. Furthermore, it takes a good deal of time to elicit a full history. According to some doctors, technology has become a sufficient substitute for talking with patient.

The decline in respect for doctors is also accelerated by the extraordinary hubris instilled in medical students. They are taught a reductionist medical model in which human beings are presented as complex biochemical factories. A sick person is merely a repository of malfunctioning organs or deranged regulatory systems that respond to some technical fix. Within this construct, the doctor, as exacting scientist, uses sophisticated instruments and advanced methods to engage in exciting act of discovery. Society also places a much higher premium on technology than the listening or counseling. Time spent in an operating room or performing an invasive procedure is rewarded tenfold more than conversation with patients or family. Current medical practice focuses on the acute, emergency medicine and is largely indifferent to preventing disease and promoting health. Since preventive medicine, though recognized as the most cost-effective approach to illness, is time intensive, it is completely neglected. Diligent prevention invariably plays second fiddle to heroic cures. Antole Broyard thus lements "I wouldn't demand a lot of my doctor's time. I just wish he would brood on my situation for perhaps five minutes, that he would give me his whole mind just once, be bonded with me for a brief space, survey my soul as well as my flesh to get at my illness, for each man is ill in his own way…. Just as he orders blood tests and bone scans of my body, I'd like my doctor to scan me, to grope for my spirit as well as my prostate. Without some such recognition, I am nothing but my illness" Healing is best accomplished when art and science are conjoined, when body as spirit are probed together. More than half century ago, Boston physician Francis Peobody counseled that the secret of care of the patient is caring for the patient.

Twenty five hundred years ago, Hippocrates counseled, "For where there is love for man, there is also love of the art. For some patients, though conscious that their position is perilous, recover their health simply through their contentment with the physician." In sixteenth century, Paracelsus, the great German physician of his era, included among the basic qualifications of a physician "intuition which is necessary to understand the patient, his body, his disease. He must have the feel and touch which make it possible for him to be in sympathetic communication with the patient's spirit." One kind word on the bed side can cure many ills. "Patient doing well do not interfere," wrote Sir William Osler, a great clinician of the last century. "God give me deliverance from treating suffering human beings as a cse, not letting the well alone, and making my interventions worse than his disease," was the daily prayer of Hutchinson.

A double-blind computerised, prospective study was undertaken in London to study the role of listening to the patient and reading the referral letter from the family doctor vis-à-vis examining the patient physically and investigating the patient with all the gadgets in the diagnosis of medical out-patients. The study showed that 80 per cent of the accurate final diagnosis and one hundred per cent of the future management strategies could be arrived at, at the end of listening to the patient and reading the referral letter. This could only be refined 4% more by the physical examinations and only 8 per cent by all the investigations Lord Platt, had written in 1949 that "if one were to listen to the patient long enough, the patient would give away his/her diagnosis."

The Basis of Clinical Diagnosis

The cornerstones of good clinical diagnosis are a good history, a thorough clinical examination and relevant investigations interpreted in the light of knowledge and experience. Diagnostic talent has to be assiduously cultivated. A good clinical examination is both an art and a

science. The art lies in eliciting physical findings; the science rests in their proper interpretation. The art and science of medicine must be present in equal measure for maximum patient benefit. The art of medicine is subtle and mixed intrinsically with its science. First and foremost it lies in a good history – an art which can never ever be perfectly mastered by even the most accomplished physician. It lies in the ability to spot and appreciate the significance of one more subtle physical signs that no gadget or machine could possibly recognize. Above all, it consists of looking at a sick patient holistically, and in assessing not just the body, but the mind, emotions, the true self. The art of medicine is the art of healing, not just treating, not even just curing. Yet it is only when art and science joins hands that healing is best accomplished. The aim of examination and, if needed, investigation is to clarify the situation further.

In some cases the diagnosis is not at all obvious and there may even be difficulty in thinking of an illness which could explain the clinical features. Techniques which may help in these circumstances include:

1. Listing the possible causes of the pivotal findings. This discipline is sometimes useful in thinking of diseases which could otherwise be overlooked. A junior doctor who is studying in examinations is more likely to find this useful than a senior doctor whose memory of lists will have faded.

2. Considering the possible organs in which disease could cause the main complaint. This requires only an elementary knowledge of anatomy. If the patient has a pain in the right upper quadrant of the abdomen it could be due to disease in gall bladder, liver, kidney or colon. If this seems unlikely, other anatomical structures may also need to be considered, such as the nearby pleura, peritoneum or pancreas.

3. Thinking of the pathophysiological mechanisms by which a particular symptom could arise. A sudden blackout could be due to a fall in cerebral perfusion for which there are several possible causes, e.g. a faint, dysarrhythmia, or obstruction of the vertebro-basilar circulation. Alternatively, it could be due to a sudden overwhelming electrical discharge in the brain, i.e. a fit. Hypoglycaemia may also be considered, but is much less likely when the loss of consciousness is sudden.

4. Scanning a list of disease processes in the hope of unearthing something which could explain the symptoms. This will include considering congenital , metabolic, neoplastic, infective, iatrogenic, degenerative, vasculitic, nutritional deficiencies and allergic causes.

At present, scientific medicine, even in a narrower sense, lacks precise solutions to most chronic ailments such as arthritis, heart disease, neuro degenenerative disorders, autoimmune disease, and the most cancers. While the scientific pace is quickening, we have a long way to go before these major disorders are fully understood. In the absence of cure, these diseases require management, usually over a lifetime. The only the available medical approach is to assuage symptoms, to slow and where possible halt a downhill course, to help the patient maintain a positive outlook, and to prevent the disease from taking charge of his or her life. These goals can be achieved only when patient expectations are narrowly focused on the attainable. To gain clarity in coping with a chronic problem the doctor should be able to able to answer the following six questions:

1. Are the symptoms from a precisely understood medical entity for which a definitive cure exists?
2. If the disease is not curable, can symptoms nonetheless be ameliorated?
3. If a disease is life threatening, what is the approximate life expectancy?
4. If not life threatening, is the disease likely to plateau or progress? If so, over what time frame?
5. Are there attendant complications and how are these to be mitigated, or better still, prevented? If that is the possibility, what is the quality of life?
6. Will a change in one's lifestyle make a substantial difference in outcome in relation to well-being and survival?

It should never be forgotten that the diagnosis is made primarily for patient's benefit and not the doctor's, when no benefit can be seen in pursuing a diagnosis further the process should be abandoned. The decisive factor is the physician's breadth of clinical experience. If a patient's problem remains unsolved after many months, it is worth seeking a physician who has more experience with that particular diagnostic problem.

Medicine is the science of uncertainty and art of probabilities. The practice of medicine is far from straightforward: there are difficult choices to be made and risks to take. We associate science with consistency and certainty, the complex technology with modern society relies so heavily. Clinicians cannot afford to avoid uncertainty or pass it off as inherent aspect of the art of medicine. It was Bertrand Russel who said, "there is nothing more tiring than uncertainty and nothing more futile". Our aim must be to make the best decisions but with the understanding that despite this, sometimes there will be undesirable outcomes. When the correct decision is unclear it is as well to remember "First do not harm" common things occur commonly". Medical treatment is more effective when standard pharmacological intervention is combined with the management of emotional distress. Sick people need physician who can understand their disease, treat their medical problems and accompany them through their illness. It is not enough for physicians to mean well; the physician must know enough to do well. The efficiency and the effectiveness of medical interaction will be enhanced if the physician converse with concern and creates an expression to leave an everlasting impression. Without knowledge, empathy and the highest ethical standards, no one can be truly good physician. A physician steeped in the art knows the value of kindness, sympathy and caring in the healing of a patient. The art of medicine remains all-pervasive even when its science fails or has reached its utmost limits. When all the marvels of science are of no avail to unfortunately ward of the fatal end, it is well to remember the time honored Hippocrates aphorism "cure rarely, comfort mostly and console always".

People don't get along
Because they fear each other
People fear each other
Because they don't know each other
They don't know each other
Because they have not
Communicated with each other (10)

-Martin Luther King

ACUTE KIDNEY INJURY: FREQUENT ASKED QUESTIONS???

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How do you define Acute Kidney Injury?

AKI is generally characterized by an abrupt deterioration in kidney function that disrupts metabolic, electrolyte and fluid homeostasis over a period of hours to days. It is defined as any of the following:

a) Increase in Serum Creatinine by 0.3 mg/dL or more within 48 hours.

b) Increase in Serum Creatinine to 1.5 times the baseline, which is known or presumed to have occurred within prior 7 days.

c) Urine volume less than 0.5 ml/kg/h for atleast 6 hours.

What is the incidence of Acute Kidney Injury, worldwide and Indian perspective?

Acute kidney injury (AKI) is a common and serious problem affecting millions and causing death and disability for many. The incidence of AKI is rapidly increasing, particularly among patients admitted with acute illness in the Intensive Care Unit. AKI affects approximately, 35% of ICU patients, and around 50% of these are due to sepsis. AKI has an overall mortality rate of 45%, mortality rate of sepsis-induced AKI is much higher, at over 70%. There is a paucity of data in India regarding the true incidence and prevalence of AKI. In a study from North India, Kohli *et al*.(2007), reported the incidence of hospital-acquired AKI was 2.1/1000 admissions and the incidence of community-acquired AKI (CAAKI) was 6.6/1000 admissions. Similarly in recent study by Kaul *et al*.(2012) from North India, the prevalence of sepsis-induced CAAKI was 13.9% and overall mortality rate among patients with CAAKI was 26.2% but sepsis-induced CAAKI had the highest mortality.

What are the clinical implications of AKI ?

Patients with AKI present with the signs and symptoms related to the underlying cause and later on may develop complications such as fluid overlaod, dyselectrolytemia and uremia.AKI is associated with increased mortality in critically ill patients, increased risk of development of chronic kidney disease (CKD) and accelerated progression of already existing CKD to end stage renal disease (ESRD).

Who all are at risk for Acute Kidney Injury:

Exposures and susceptibilities for nonspecific acute kidney injury

CAUSES OF ACUTE KIDNEY INJURY

Exposures	Susceptibilities
Sepsis	Dehydration and volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	Chronic Kidney Disease
Cardiac surgery (especially with cardiopulmonary bypass)	Chronic disease (heart, lung, liver)
Major noncardiac surgery	Diabetes
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

What is the etiopathogenesis of AKI?

On the basis of etiology, AKI is classified into pre-renal, intrinsic and post-renal AKI.The pre-renal type includes all the causes related to volume depletion, post-renal type includes all the causes related to acute urinary retention and intrinsic AKI is caused by sepsis, ischemia or nephrotoxins. Intrinsic AKI may also be a manifestation of acute glomerulonephritis.

How do you stage patients with AKI?

AKI is staged according to rate of rise of serum creatinine and decrease in urine output.

STAGING OF ACUTE KIDNEY INJURY

Stage	Serum creatinine	Urine output
1	1.5 – 1.9 times baseline OR e”0.3 mg/dl(e”26.5µmol/l) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for e”12 hours
3	3.0 times baseline OR Increase in serum creatinine to e”4.0 mg/dl(e”353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients<18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for e”24 hours OR Anuria for e”12 hours

How do you investigate AKI ?

Ratio of Blood urea nitrogen to creatinine(BUN/Creatinine), Fractional excretion of sodium(FeNa), urine osmolality and analysis of urinary sediment are key investgations to differentiate different etiological types of AKI. Kidney function tests (KFT) and ultrasonography(to look for kidney size, echogenicity and cortico-medullary differentiation) are helpful to differentiate AKI from CKD.

What are the general principles of management of AKI?

a) Optimization of hemodynamics

b) Avoidance of nephrotoxic agents

c) Dose adjustment of all medications as per estimated glomerular filtration rate(e-GFR)

d) Correction of fluid and electrolyte abnormalities

e) Treating the underlying cause

f) Dialysis whenever indicated

Recommended readings:

- John A Kellum and Norbert Lameire et al. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements 2012;2(1).
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"We have not lost faith, but we have transferred it from God to the medical profession."

- George Bernard Shaw

AMBULATORY BLOOD PRESURE MONITORING

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Ambulatory Blood Pressure Monitoring is a non-invasive technique by which multiple indirect blood pressure recordings can be obtained automatically over a period of 24 hours -day and night at regular intervals (usually 30 min). Apart from BP it also measures other parameters such as pulse, mean arterial pressure (MAP), pulse pressure (PP), Hyperbaric Index (HI), morning surge, dipping patterns and double product.

The introduction of technology in the form of ambulatory automated blood pressure monitors has allowed multiple, standardized measurements to be made away from clinical environment, and has addressed many of the errors associated with conventional sphygmomanometry. ABPM is safe and can be done in young, elderly and pregnant patients also.

NICE updated guidelines recommend that people who are found to have BP of 140/90 mm Hg or higher during a clinic visit should be offered ABPM.

Why Abpm is Preferred over Conventional Methods

- ABPM provides a profile of BP away from the medical environment, thereby allowing identification of individuals with white coat hypertension. Usually such patients show higher BP when recorded in the clinic, which is actually normal.
- ABPM records BP and other parameters which act as a predictors of CVD, LVH, stroke, ISH in comparison to clinical visits or home measurements of BP which are confined to SBPand DBP measurements only.
- ABPM also demonstrates the efficacy of anti hypertensive medication over a 24 hour period and helps in optimizing the dosage, duration, frequency and type of anti-hypertensive medication.

Indications

❖ **White – Coat Hypertension** (WCH):also called isolated office or clinic hypertension,is defined as the occurrence of BP values higher than normal when measured in the medical environment, but within the normal range during daily life, usually defined as average daytime ambulatory BP (ABP) or home BP values (<135 mm Hg systolic &<85 mm Hg diastolic). It is common, being present in about a quarter of people who appear to have hypertension with conventional methods. CBPM in such cases is misleading and leads to inappropriate diagnosis and treatment planning. Lifelong treatment may be prescribed unnecessarily and if antihypertensive medication is given to people whose 24 hour pressures are normal they may be made unwell by adverse effects of medication. People with WCH are at greater risk of developing true hypertension and glucose intolerance. They need regular check- ups and repeat ABPM every 1-2 years.

1. **White Coat Effect** is a phenomenon found in hypertension patients whereby CBPM is usually higher than the average daytime ABPM. Patients diagnosed with severe hypertension by CBPM may have only moderate or mild hypertension.
2. **Masked Hypertion (MH)** is defined as a normal BP in the clinic or office (<140/90 mm Hg), but an elevated BP out of the clinic (AMBP or home BP >135/85 mm Hg) this phenomenon is usually suspected in subjects with a family history of hypertension,diabetic patients,patients with multiple risk for CVD, smokers.persons

with sedentary / unhealthy lifestyle,renal disease and proteinuria,daytime hyperactivity and in people with transient hypertension.

Individuals with MH have been shown to have a greater than normal prevalence of organ damage, particularly with an increased prevalence of metabolic risk factors, left ventricular mass index, carotid intima-media thickness and impaired large artery dispensability compared with patients with a timely normal BP level in & out of the clinic or office.

3. **Nocturnal Hypertension :** Recent studies have indicated that dip in the nocturnal BP is of great significance. If the nocturnal BP is more than the daytime BP or is equivalent to that, then such patients are at higher risk of developing CVD. Such patients are categorized as non-dippers. It could also be associated with secondary hypertension. In hypertensive patients, the absence of a nocturnal BP dipping has been associated with the development of target organ damage, viz,LVH, microalbuminuria and occurrence of cerebrovascular and cardio vascular events.

   The non-dipper BP pattern is frequent in obstructive sleep apnea, so that undiagnosed sleep disordered breathing might play a role in the genesis of the altered BP pattern of some non-dipper hypertensive patients. Sleep apnea and arterial hypertension are frequently associated conditions.

   Diabetic patients exhibit significantly greater non-dipping patterns than patients without diabetes. Elevated asleep SBP mean is the major basis for the diagnosis of hypertension and / or suboptimal BP control among patients with diabetes, thus, among uncontrolled hypertensive patients with diabetes, >89% might potentially exhibit nocturnal hypertension. Accordingly, ABPM is the gold standard for the proper diagnosis of hypertension and assessment of CVD risk in patients with diabetes.

4. **Secondary Hypertension :** A high prevalence of nocturnal hypertension and/or non-dipping has been reported, among other conditions, in patients with orthostatic autonomic failure, shy-Dragger syndrome, vascular dementia, Alzheimer type dementia, cerebral atrophy, phaeochromocytoma, autonomic neuropathy, cerebrovascular disease, ischemic arterial disease after carotid endarterectomy, neurogenic hypertension, fatal familial insomnia, catecholamine producing tumors, Cushing's syndrome, exogenous glucocorticoid administration mineralocorticoid excess syndromes, Addison's disease, asthma, Pseudohypoparathyroidism, salt sensitive essential hypertension, essential hypertension with liver, renal and cardiac transplantation, CHF and recombinant human erythropoietin therapy.

   Various prescription medication such as pain relievers, antidepressants and drugs used after organ transplants – can cause or aggravate BP In some patients birth controls pills, decongestants and certain herbal supplements including ginseng, licorice and ephedra may have the same effect. Many illegal drugs such as cocaine and methamphetamine, also increase blood pressure.

   Secondary hypertension is more common in children than adults. AMBP readings may be useful in differentiating primary from secondary hypertension as adolescents with secondary hypertension have been shown to manifest greater nocturnal SBP loads and greater daytime and nocturnal DBP loads than children with primary hypertension. These patterns were highly specific for differentiating between essential and secondary hypertension.

5. **Hypertension in Elderly :** There is progressive increase with aging in the prevalence of non-dipping and nocturnal hypertension after 40 years of age. Also, isolalated SBP is one of the most common phenomenon seen in elderly patients . Different studies have revealed that SBP measured conventionally in the elderly may average 20 mm Hg higher than daytime ABPM, leading to inevitable overestimation of ISH and subsequent over treatment of the subject. Elderly subjects, at a threshold age even < 60 yrs. should be evaluated by ABPM to corroborate the diagnosis of hypertension, ensure proper evaluation of CVD risk associated with alterations in the 24 hour BP pattern and establish the most appropriate chronotherapeutic scheme to increase CVD event free interval.

6. **Hypertension in Pregnancy :** The measurement of BP in pregnancy is fundamental to diagnosing and managing hypertension…. ABPM is a better predictor than conventional BP measurement for the development of pre-eclampsia and fetal growth restriction. Studies of ABPM have shown that sleep hypertension is common in women with gestational hypertension or pre- eclampsia. The best role for ABPM is to determine whether women have essential HT or white coat HT. It has been observed that pregnant female suffering from white coat HT tends to have more C-section and low birth weight babies than normotensive patients.

   ABPM during gestation, starting preferably at the time of the first obstetric check-up following positive confirmation of pregnancy, provides sensitive endpoints for use in early risk assessment and guide for establishing prophylactic or therapeutic intervention and should thus be regarded as the required standard for the diagnosis of hypertension in pregnancy. ABPM has been suggested as logical approach to overcome the low sensitizing and specifying of clinical BP measurements in pregnancy.

   In normotensive pregnancies, BP steady decreases up to middle of gestation and then increases up to the day of delivery. In contrast, women who develop gestational HT or pre-eclampsia show stable BP during the first half of pregnancy and a continuous linear BP increase thereafter until delivery.

ABPM	Ist Trimester < 14 weeks	IInd Trimester 14-27 weeks	IIIrd Trimester > 27 weeks
Awake Mean			
SBP	115	115	118
DBP	70	69	72
Asleep mean			
SBP	99	98	104
DBP	58	56	60

7. **Resistant Hypertension :** A patient should be categorized as resistant to treatment if the ABPM determined awake and/or sleep SBP or DBP means are greater than the stipulated reference diagnostic thresholds when ingesting ³3 anti-hypertensive of different classes [Ideally including a diuretic unless contraindicated] with at least one of them ingested as a full daily dose at bedtime.

   A bedtime hypertensive medication regimen, in conjunction with proper patient evaluation by ABPM to corroborate the diagnosis of true resistant hypertension, should be the preferred therapeutic approach for patients with resistant hypertension.

Role of ABPM in Treatment Planning

- ABPM plays a major role in guiding the drug treatment. Multiple recordings of SBP and DBP help to decide whether anti-hypertensive therapy is required or not, Excessive or under treatment can be avoided.
- On the basis of ABPM, risk factors can be identified such as CVD, CKD, LVH, Stroke, microalbuminuria. Treatment planning on the basis of such factors is more effective.
- Different ABPM studies have shown that patients taking amlodipine-perindropril show more decrease in nighttime SBP than patients on atenolol-thiazide.
- NH can be managed properly with ABPM. CBPM is misleading in such cases.
- Effect of ongoing medication can also be evaluated.
- Bed time treatment can be planned more efficiently on the basis of ABPM as compared to CBPM.

Assessing Abpm Report

1. **Pulse Pressure :** It is the difference between SBP andDBP. Normal range is 40 to 50 mm Hg. Higher value indicates isolated systolic hypertension which is mostly found in elderly patients. Lower value suspect isolated diastolic hypertension. A significant relationship has been seen between pulse pressure and CV morbid events. 24 hour pulse pressure is considered as the single independent predictor of fatal cardiac events.

   Pulse Pressure as a blood pressure parameter is an important mortality predictor and among hemodialysis patients, PP appears to be a stronger independent predictor of morbidity and mortality than other BP parameters. Elevated SBP and reduced DBP lead to increased pulse pressure and the increased demand placed on the heart by elevations in PP lead to – LVH, CHF, Ventricular arrhythmias, MI, decreased left ventricular ejection fraction, aortic root dilation, CBV events, QT abnormalities and higher incidence of sudden cardiac death.

   Lower DBP has further effect of reducing coronary perfusion pressure, leading to ischemia. For every 10 mm Hg increase in pulse pressure, there was 12% increased hazard of death.

2. **Mean Arterial Pressure :** MAP is derived from patient's systolic and diastolic blood pressure. It is often used as a surrogate indicator of blood flow and believed to be a better indicator of tissue perfusion than SBP as it accounts for the fact that two-third of Cardiac Cycle is spent in diastole. MAP also tends to remain unchanged in the arterial system from ascending aorta to peripheral arteries.

   MAP = DAP+[SBP-DBP)/3]

   Normal Range = 70 to 110 mm Hg

   - ❖ MAP greater than 60 mm Hg is enough to sustain the organs of the average person.Awake MAP less than 70 is a predictor of stroke events independently.If the fall is significantly below this number for an appreciable time, the end organ will not get enough blood flow and will become ischemic.

3. **BP Variability** independently contributes to target organ damage, cardiovascular events, and mortality not only in hypertensive patients but also in subjects with diabetes mellitus and CKD. Therefore, amelioration of BPV has been suggested as an additional target of the treatment of cardio vascular diseases. ABPM provides an insight into the features of 24 hour BPV which cannot be assessed with either clinic or home BP

measurements. Thus, allowing homogeneous distribution of anti-hypertensives over 24 hour and further reducing the adverse effect on end target organs by reducing the magnitude of BP variations.

4. **Diurnal Blood Pressure :** BP usually follows a circadian pattern with values peaking during the day time and then falling after midnight. ABPM allows knowing BP absolute values and gives information about circadian BP rhythm.

   On the basis of fall in nocturnal SBP, Patient's are categorized as –

Dippers	=	10-20% [which is considered as normal)
Non-Dipping	=	0-10%
Extreme Dipper	=	>20%
Reverse Dippers	=	<0%

   a) **Non-Dipping Pattern –** Patients exhibiting non-dipping patterns have high prevalence for CV events, LVH, Left Ventricular mass index. In treated hypertensive patients, non-dipping pattern also indicates early LV dysfunction and adverse cardiac remodeling. High incidence of microalbuminuria and CKD is also seen. Normotensive individuals with a non-dipper BP profile represent a clear paradox, because they neither have normal BP nor low CVD risk.

   b) **Reverse Dipping –** Reverse dipping is more apparent with patients of renal dysfunction and with proteinuria. The proportion of reverse dippers was higher among those who had a CV event. Reverse dippers have the worst cardiovascular prognosis, both for stroke and cardiac events.

Higher Nighttime BP Associated Worse Outcome

- Nocturnal autonomic dysfunction.
- Disturbed baroreflex sensitivity
- Sleep apnea
- Abnormal Na handling
- Nocturnal volume overload

   c) **Extreme Dipping –** In extreme dipping nocturnal blood pressure is significantly low as compared to diurnal blood pressure.Incidence of non-fatal ischemic stroke and silent myocardial ischemia is particularly high in extreme dippers complicated with atherosclerotic arterial stenosis. Extreme-dipping status of nocturnal BP is closely associated with excessive morning surge and orthostatic hypertension.

5. **Hyperbaric Impact (HBI) :** The HBI is defined as the total area during the entire 24-hour period of any given subjects BP being above a time-varying threshold defined by a tolerance interval calculated as a function of patient sex and CVD risk.A HBI > 15 mm Hg x hour indicates suspected hypertension that will require repeated subject evaluation by ABPM to confirm/refute the diagnosis of hypertension.HBI> 50 mm Hg x hour indicates hypertensionHBI > 15 mm Hg x hour [In Pregnant Patients) is an independent indicator of hypertension.

6. **Morning Surge :** Normal morning BP surge is a physiological phenomenon but an exaggerated morning BP surge is a CVD risk. Exaggerated morning surge in BP constitutes a risk for stroke independent of 24 hour BP. Morning BP surge increases cardiac after load and arterial stiffness, contributing to the progression of LVH leading to end organ damage.

In hypertensive patients, the rising surge has been significantly correlated with LV mass index and A/E ratio, which represents diastolic function, also show Prolonged QTC duration. Hypertensive patients with morning BP surge had higher levels of carotid-intima media thickness and urinary catecholamine excretion.Silent cerebral infarcts (SCIS) are the strongest markers of clinical stroke, are more frequently detected by brain MRI in the exaggerated morning BP surge patients than in normal patients. More than 20% surge in the morning in the SBP increases the stroke risk by 22%.

Follow-up with ABPM

The following Protocol is recommended for the periodic evaluation and follow-up of patients by ABPM.

- For hypertensive Patients – Patients whose prescriptions are modified either by addition of new drugs or dose, duration has been changed in such cases ABPM must be repeated within the ensuing 3 months.
- For hypertensive patients whose BP is established to be properly controlled according to ABPM reference threshold and whose therapeutic regimen, therefore, necessitates no modification, ABPM should be repeated every 6 months [complicated patients] to every 12 months [Uncomplicated Patients].
- For Uncomplicated person with either normotension, white coat hypertension or masked hypertension and unaffected by compelling clinical conditions associated with increased CVD risk – including diabetes, CKD & Past CVD events – ABPM should be repeated within 2 yrs., the time interval should be reduced to 1 yr for complicated normotensive subjects.

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SOFOSBUVIR: A NEW ERA IN THE MANAGEMENT OF CHRONIC HCV INFECTION

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Hepatitis C, caused by various genotypes of the Hepatitis C virus (HCV), currently infects more than 170 million people around the world. Chronic hepatitis C virus (HCV) infection is a cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. For the past two decades, interferon-based therapy has been the mainstay of HCV treatment, but success has been limited by poor tolerability and suboptimal sustained virological response (SVR) rates, even when combined with ribavirin. Boceprevir and telaprevir were the first direct-acting antiviral (DAA) drugs to be approved for the treatment of HCV in 2011, and resulted in improved SVR rates from approximately 40–44% to 68–75% in treatment-naïve patients with genotype 1 HCV.

However, because of rapid emergence of viral resistance with protease inhibitor monotherapy, these agents are only effective when used as triple therapy in conjunction with peginterferon and ribavirin. Consequently the use of these NS3/4 protease inhibitors adds to the adverse event profile of peginterferon plus ribavirin, particularly in patients with cirrhosis where cytopaenias and other serious adverse events represent a significant safety concern.

What Is Sofosbuvir?

Sofosbuvir is a new drug candidate for hepatitis C treatment, with the chemical name L-Alanine, N-[[P(S),2'R]-2'-deoxy- 2'-fluoro-2'-methyl-P-phenyl-5'-uridylyl]-, 1-methylethyl ester and a molecular formula of C22H29FN3O9P. Previously known as PS-7977 or GS-7977, it has shown promising results in numerous in vitro studies against all the genotypes of HCV. It is a nucleotide analog that is a highly potent inhibitor of the NS5B polymerase in HCV. This drug has shown high efficacy in combination with several other drugs with and without PEG-INF, against HCV. Sofosbuvir is of special interest among the directly acting antiviral drugs under development, due to its high potency, low side effects, oral administration, and high barrier to resistance.

Pharmacology of sofosbuvir

Sofosbuvir is a prodrug of 2'-deoxy-2'-fluoro- 2'-C-methyluridine monophosphate that is converted within hepatocytes to its active uridine triphosphate form, causing chain termination during replication of the viral genome. In vitro, the active triphosphate inhibits recombinant NS5B polymerases from HCV genotypes 1-4 with similar half maximum inhibitory concentration values for each genotype, indicating broad activity across HCV genotypes.

Sofosbuvir is primarily eliminated from the body via the kidney as GS-331007 (formerly called PSI-6206), an inactive nucleoside metabolite. In a study of hepatic impairment, HCV-infected subjects with moderate hepatic impairment were administered sofosbuvir 400 mg QD for 7 days; sofosbuvir was generally well tolerated and resulted in similar systemic exposure to GS-331007 as noncirrhotic subjects. Significant declines in HCV RNA were

observed in all subjects over 7 days of dosing. Therefore, dose modifications are not required in hepatic impairment. There is no clinically significant interaction of sofosbuvir with food, or with co-administration of cyclosporine or tacrolimus.

When and in whom to initiate HCV therapy

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure, and as such, is expected to benefit nearly all chronically infected persons. Evidence clearly supports treatment in all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. Urgent initiation of treatment is recommended for some patients, such as those with advanced fibrosis or compensated cirrhosis.

Goal of treatment

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable in large prospective studies in more than 99% of patients followed up for 5 years or more. Patients in whom an SVR is achieved have HCV antibodies, but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial liver histology improvement. Assessment of viral response, including documentation of SVR, requires use of US Food and Drug Administration (FDA)-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of 25 IU/mL or lower.

Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase (ie, alanine aminotransferase [ALT], aspartate aminotransferase[AST]) levels and a reduction in the rate of progression of liver fibrosis. Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons, SVR is associated with a more than 70% reduction in the risk of liver cancer (hepatocellular carcinoma) and a 90% reduction in the risk of liver-related mortality and liver transplantation. Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients. HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful antiviral therapy for HCV infection. These reductions in disease severity contribute to dramatic reductions in all-cause mortality.Patients achieving SVR have substantially improved quality of life, which includes physical, emotional, and social health. Because of the myriad benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving an SVR, preferably early in the course of their chronic HCV infection before the development of severe liver disease and other complications.

Current treatment guidelines for the management of chronic HCV infection

Patients without cirrhosis

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a Genotype 1b	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV 12 wk without RBV	No	12 wk without RBV	12 wk without RBV
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Patients with compensated cirrhosis (CTP A)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a Genotype 1b	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV 12 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

Currently apart from sofosbuvir, none of the other DAAs are available in India, so we shall discuss only regimens available in India.

Treatment of HCV genotype 1 infection

Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN-á, daily weight based ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively), and daily sofosbuvir (400 mg) for 12 weeks.

This combination has been evaluated in the NEUTRINO Phase III trial in treatment-naïve patients. The overall SVR rate was 89% (259/291), 92% (207/225) for subtype 1a and 82% (54/66) for subtype 1b. Patients with cirrhosis had a lower SVR rate than non-cirrhotic patients (80% vs. 92%, respectively). Patients who failed on this regimen did not select HCV variants resistant to sofosbuvir.

Preliminary results from two large-scale US real-life studies are available. In HCVTARGET 2.0, the overall SVR4 rate with the triple combination of PegIFN-a, ribavirin and sofosbuvir was 85% (140/164; 55% were treatment-naïve and 45% treatment-experienced patients). SVR4 was achieved in 90% (114/ 127) of non-cirrhotic patients but 70% (26/37) of cirrhotic patients.

In the TRIO real-life study, which included 58% of treatment-naïve and 42% of treatment-experienced patients, SVR12 was achieved in 81% (112/138) of treatment-naïve non-cirrhotic patients and 81% (25/31) of treatment-naïve cirrhotic patients, and in 77% (30/39) of treatment-experienced patients without cirrhosis and 62% (53/85) of treatment-experienced patients with cirrhosis (intent-to-treat) receiving PegIFN-a, ribavirin and sofosbuvir.

The combination of sofosbuvir and ribavirin should not be used in patients infected with HCV genotype 1. None of the other accepted regimens are available in India.

Treatment of HCV genotype 2 infection

The best first-line treatment option for patients infected with HCV genotype 2 is the IFN-free combination of sofosbuvir and ribavirin.

Patients infected with HCV genotype 2 must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively), and daily sofosbuvir (400 mg) for 12 weeks. Therapy should be prolonged to 16 or 20 weeks in patients with cirrhosis, especially if they are treatment experienced.

Cirrhotic and/or treatment-experienced patients can be treated with weekly PegIFN-á, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks.

Cirrhotic and/or treatment-experienced patients can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks.

Treatment of HCV genotype 3 infection

Patients infected with HCV genotype 3 can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively), and daily sofosbuvir (400 mg) for 24 weeks.

This therapy is suboptimal in treatment-experienced cirrhotic patients and in patients who failed to achieve an SVR after sofosbuvir plus ribavirin treatment, who should be offered an alternative treatment option

Patients infected with HCV genotype 3 can be treated with a combination of weekly PegIFN-á, daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks.

This combination is a valuable option in patients who failed to achieve an SVR after sofosbuvir plus ribavirin treatment.

Patients infected with HCV genotype 3 without cirrhosis can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks.

Treatment of HCV genotype 4 infection

Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN- á, daily weight based ribavirin (1000 or 1200 mg in patients <75 kg or >75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks.

Patients infected with HCV genotype 4 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily for 12 weeks. Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin.

Patients with compensated cirrhosis, including treatment-naive and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or >75 kg, respectively). Patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin.

Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) 12 weeks. Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively) is recommended in patients with cirrhosis.

Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks. Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively) is recommended in patients with cirrhosis.

Treatment of HCV genotype 5 or 6 infection

Patients infected with HCV genotype 5 or 6 can be treated with a combination of weekly PegIFN-á, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or e"75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks.

Patients infected with HCV genotype 5 or 6 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered

once daily. Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin.

Patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or e”75 kg, respectively).

Monitoring of treatment efficacy

In order to monitor treatment efficacy, HCV RNA level measurements should be performed at specific time points. A real-time PCR-based assay with a lower limit of detection of 15 IU/ml should be used to monitor HCV RNA levels during and after therapy.

In patients treated with the triple combination of PegIFN-á, ribavirin and sofosbuvir for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12 (end of treatment), and 12 or 24 weeks after the end of therapy.

In patients treated with an IFN-free regimen, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment in patients treated 12 or 24 weeks, respectively), and 12 or 24 weeks after the end of therapy.

Adverse effects of Sofosbuvir

Sofosbuvir has shown a good safety profile in clinical trials; a small decrease in the Hb levels (0.54 mg/dl) and reduction in the cumulative events in comparison to interferoncontaining regimens is seen. Common adverse events observed include: Headache, insomnia, fatigue, nausea, dizziness, pruritis, upper respiratory tract infections, rash, back pain, grade 1 anemia, and grade 4 lymphopenia. No neutropenia, thrombocytopenia, or any serious adverse events are associated with sofosbuvir treatment. In the monotherapy treatment groups, nausea and fatigue seemed to be the only adverse events possibly correlated to sofosbuvir. An overall improved tolerability was seen with sofosbuvir compared to the interferonbased regimens.

ECG QUIZ

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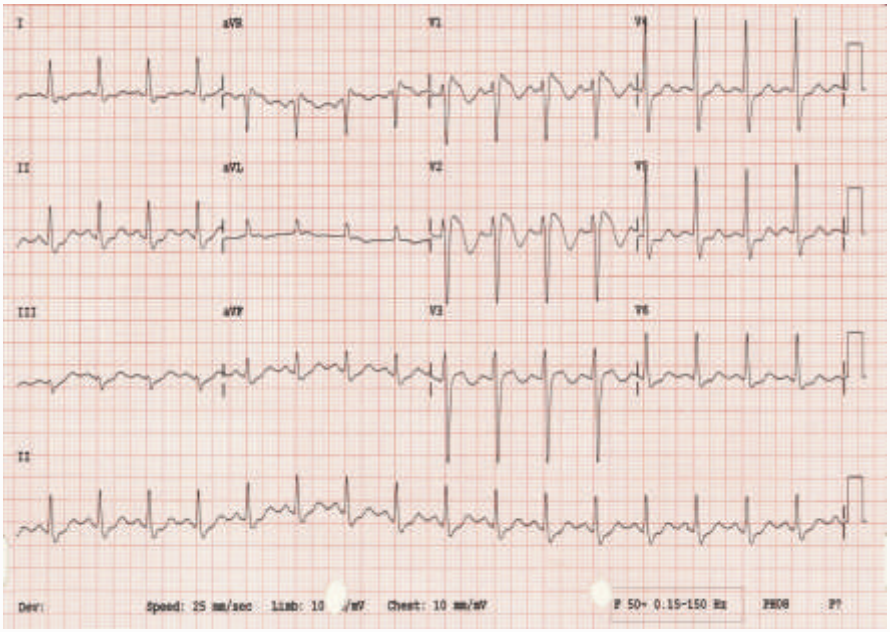
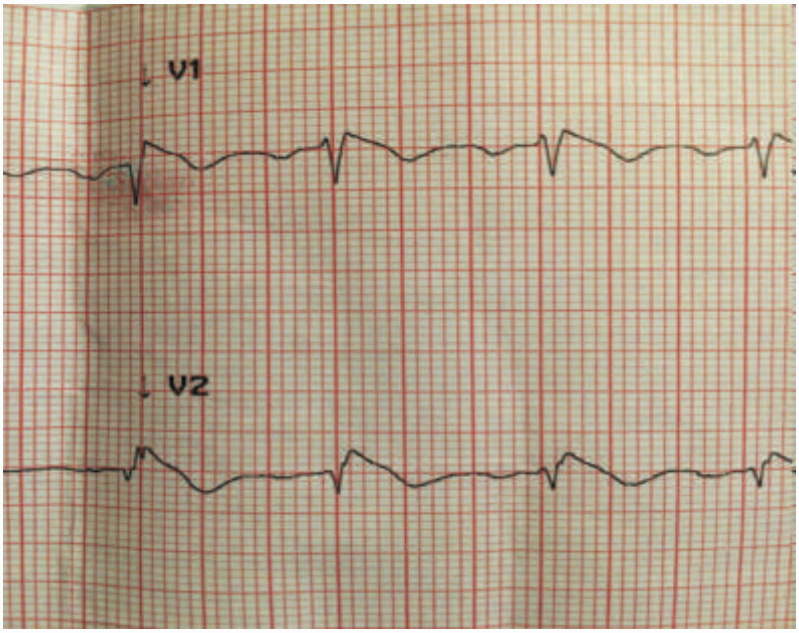
- 39 year male presented with h/o syncope
- Family h/o sudden death at young age
- Patient also gives h/o of fever 2 days





Diagnosis ???

Interpretation of ECG

RBBB or incomplete RBBB in V1-V3 with convex ST elevation

Diagnosis

- Typical example of Brugada Syndrome

Criteria for brugada Type 1 Morphology:

1. R'-wave at least 2 mm in V1 or V2
2. But no distinct R'-wave because the ST segment takes off at an angle from the peak
3. The ST segment is convex upward ("coved"). [They use terminology of "concave downward"]
4. The peak at the high takeoff does not correspond with the J-point. It is BEFORE the J-point, as measured in other leads (such as lead II across the bottom).
5. Gradual downsloping of ST segment such that at 40 ms after the takeoff, the decrease in amplitude is less than 4 mm (in this example, it is less than 1 mm). In normal RBBB, the decrease in amplitude is much greater).
6 ST is followed by a symmetrically negative T-wave
7. "The duration of QRS is longer than in RBBB," and "there is a mismatch between V1 and V6." This criterion is perplexing and not well explained.
8. The downsloping should be such that the Corrado index is greater than 1.0 (see example above).

This is the ratio: [ST elevation at the J-point] divided by [ST elevation at 80 ms after the J-point].

Brugada Syndrome

- Autosomal dominant genetic mutation of sodium channels
- Causes syncope, v-fib, self terminating VT, and sudden cardiac death
- Can be intermittent on EKG
- May precipitated after fever
- Most common in middle-aged males
- Can be induced in EP lab
- Need ICD

'Laughter is the best medicine, unless you're diabetic then insulin comes pretty high in the list "

- Jasper Carrott