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Day to day clinical practice and current management of emergency hypertension in various clinical conditions.

KEYWORDS: Hypertensive emergencies, pathophysiology, pharmacology.

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ABSTRACT *Severe elevation of blood pressure >180/120 mmHg in presence of acute organ damage leads to hypertensive emergency and patients should have their BP lowered immediately but not to normal level. The most common clinical presentations of hypertensive emergencies are cerebral infarction, pulmonary edema , hypertensive encephalopathy and congestive heart failure .Other clinical presentations associated with hypertensive emergencies include intracranial hemorrhage, aortic dissection, and eclampsia, as well as acute myocardial infarction. Early screening, evaluation and proper management of hypertensive emergencies can prevent morbidity and mortality at the mass level.*

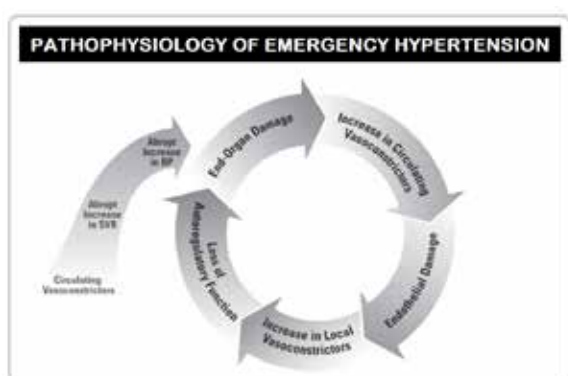
1. Introduction-

Around 1 billion people are suffering from systemic high blood pressure (BP) across the worldwide where as emergency hypertension is found in upto 2.5 to 3.5 % of patients with systemic hypertension. Globally cardiovascular disease accounts for approximately 17 million deaths annually, nearly one third of the total . Of these, complications of hypertension account for 9.4 million deaths worldwide every year . Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke. Asymptomatic nature, previously undiagnosed, irregular or irresponsible treatment or rural unethical practice in developing countries results in hypertensive emergencies and increased morbidity and mortality. Early screening, evaluation and proper management of hypertensive emergencies can prevent morbidity and mortality at the mass level. Severe elevation of BP >180/120 mmHg in presence of acute organ damage leads to hypertensive emergency and patients should have their BP lowered immediately but not to normal level.

2. Pathogenesis and management approach.

The pathogenesis of hypertensionis multifactorial; increase in mechanical stress and vascular wall damage could increase vascular permeability along with pressure. There is cell proliferation and activation of the coagulation cascade. The endothelial cell surface lining of the vascular compartment is damaged leading to endothelial cell dysfunction, which further promotes vasoconstriction and platelet aggregation. Activation of the renin-angiotensin-aldosterone system is responsible for raised blood pressure . Angiotensin II is a very potent vasoconstricting substance but in addition it also increases the elaboration of cytokines such as interleukin-6 and NF-kappaB, which is a pro-inflammatory factor. There is white blood cell adhesion, as well as proliferation of vascular smooth muscle cells. NADPH, which generates reactive oxygen species, is also increased. There is a reduction of nitric oxide, which is a protective substance, that leads to vasodilation and inhibition of platelet aggregation, and again, this leads to this inflammatory factor. So this is not a simple situation. There is not a single drug that attacks all of these potential targets within the cascade of hypertensive emergency. Oxidative stress then leads to a reduction in nitric oxide, which is a protective substance, and an increase in reactive oxygen species. Endothelial dysfunction is thought to be the final common pathway. There is a reduction in vasodilation and an increase in vascular adhesion molecules, the activation of coagulation, and platelet aggregation.

Figure-1 Pathophysiology of Emergency Hypertension.



The history and the physical examination determine the nature, severity, and management of the hypertensive event. The history should focus on the presence of end-organ dysfunction, the circumstances surrounding the hypertension, and any identifiable etiology. The most common clinical presentations of hypertensive emergencies are cerebral infarction (24.5%), pulmonary edema (22.5%), hypertensive encephalopathy(16.3%), and congestive heart failure (12%). Other include intracranial hemorrhage, aortic dissection, eclampsia and acute myocardial infarction. In pregnant patients, acute hypertensive crisis usually results from severe preeclampsia and can lead to maternal stroke, cardiopulmonary decompensation, fetal decompensation caused by reduced uterine perfusion, abruption, and stillbirth.

The duration and severity of the patient's preexisting hypertension should be evaluated along with the patient's medication history. Details of antihypertensive drug therapy and compliance, intake of over-the-counter preparations such as sympathomimetic agents, and use of illicit drugs

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such as cocaine are important elements of the medication history. In addition, it is important to elicit information about the presence of previous end-organ dysfunction, particularly renal and cerebrovascular disease, and any others (eg, thyroid disease, Cushing disease, systemic lupus).

Patients may complain of specific symptoms that suggest end-organ dysfunction may be present. Chest pain may indicate myocardial ischemia or infarction, back pain may denote aortic dissection and dyspnea may suggest pulmonary edema or congestive heart failure. The presence of neurologic symptoms may include seizures, visual disturbances, and altered level of consciousness and may be indicative of hypertensive encephalopathy.

The physical examination should assess whether end-organ dysfunction is present. BP should not only be measured in both the supine position and the standing position (assess volume depletion), but it should also be measured in both arms (a significant difference may suggest aortic dissection).The presence of new retinal hemorrhages, exudates, or papilledema suggests a hypertensive emergency. Evaluattion for heart failure may be indicated by raised jugular venous pressure, crackles on auscultation, and peripheral edema. Central nervous system findings may include changes in the patient's level of consciousness and visual fields, and the presence of focal neurologic signs. Abdominal masses or bruits may be noted.

Investigations-Obtain electrolyte levels, as well as measurements of blood urea nitrogen and creatinine levels to evaluate for renal impairment. Hematuria or proteinuria and microscopic urinalysis to detect red blood cells or RBC casts should also be performed. A complete blood cell and peripheral blood smear should be obtained to exclude microangiopathic anemia, and a toxicology screen, pregnancy test, and endocrine testing may be obtained, as needed. If there is clinical evidence of pulmonary edema or the patient has chest pain, ECG ,chest radiography and 2D Echocardiography are indicated. Patients with neurological signs should be evaluated with a head CT scan and/or MRI Imaging.

Treatment approach must be aggressive in the emergency department in presence of emergency medical officer and/or cardiac physician. After quick evaluation of severe hypertension with organ damage, we should start medicine either sublingually or intravenously. The indication of different pharmacological agents are depend on target organ damage with concerned pathophysiology of various clinical conditions. Parenteral intravenous drugs are ideally used in emergency hypertension which are capable to achieve target BP , not to normal level. Current pharmacological approach is beneficial to physicians for their daily routine practice , we can see table-1.

Table-1 Pharmacological Management of Emergency Hypertension

	Drug	Onset of action	Dose	Mechanism	Indication	Adverse effects
a	Enalaprilat	15 min	0.625–2.5 mg every 6 hr IV	Angiotensin converting enzyme	Acute left ventricular failure	Acute renal failure in patients with bilateral renal artery stenosis Prolonged half-life
b	Esmolol	1- 2 min	500 µg/kg bolus IV or 50– 100 µg/kg/min by infusion.	Short acting beta-1 selective blocker	Acute aortic dissection Perioperative conditions	Hypotension, nausea Asthma First-degree atrioventricular block Heart failure
c	Clonidine	15 min	0.1 mg oral	Centrally acting alfa adrenergic agonist	hypertensive crises, particularly in hypertensive urgencies renal impairment may benefit from a lower initial dose. Patients should be carefully monitored	dry mouth and drowsiness
d	Furosemide	15 min	0.5-1 mg/kg (or 40 mg) IV over 1-2 minutes; may be increased to 80 mg if there is no adequate response within 1 hour;not to exceed 160-200 mg/dose	Loop diuretic	Acute pulmonary edema ,raised intracranial pressure	Hyperuricemia , Hypokalemi, Anaphylaxis Anemia,Anorexia Diarrhea,Dizziness
e	Hydralazine	5-20 min	5–20 mg IV bolus or 10–40 mg IM; repeat every 4–6 hr	Direct relaxation of vascular smooth muscle cells	Eclampsia	Tachycardia, flushing, headache Sodium and water retention Increased intracranial pressure Aggravation of angina
f	Labetalol	2- 5 min	20–80 mg IV bolus every 10 min; 0.5– 2.0 mg/min IV infusion	Competitive blocker of alfa-1 and beta adrenergic receptors	Most hypertensive emergencies, except acute left ventricular failure Should be avoided in patients with asthma	Bronchoconstriction Heart block Vomiting, scalp tingling Heart failure exacerbation
g	Nicardipine	1- 2 min	5–15 mg/hr IV infusion 1	Calcium channel blocker	Most hypertensive emergencies except acute heart failure Should be used cautiously in patients with myocardial ischemia	Tachycardia, headache, flushing Local phlebitis Aggravation of angina

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h	Nitroglycerine	3- 5 min	5–100 µg/min IV	Potent venodilator, reduce preload coronary vasodilator, at higher doses acts as arteriolar dilator.	Myocardial ischemia , heart failure	Headache, tachycardia, flushing Methemoglobinemia Requires special delivery system due to drug binding to tubing
i	Phentolamine	15 min	5–15 mg IV bolus	Nonselective alfa-adrenergic blocker	Catecholamine excess	Tachycardia, flushing, headache
j	Sodium nitropruside	2- 5 min	0.25–10 µg/kg/min IV	Arterial and venous dilator acts via release of nitric oxide	Most hypertensive emergencies Should be used cautiously in patients with high intracranial pressure or azotemia	Nausea, vomiting, Thiocyanate and cyanide intoxication, Increased intracranial pressure Methemoglobinemia Delivery sets must be light resistant
k	Fenoldopam	1-5 min	0.1–0.3 µg/kg/min IV	selective dopamine agonist acting upon the dopamine DA_1 receptor, causing both vasodilation and natriuresis.	Most hypertensive emergencies Should be used cautiously in patients with myocardial ischemia	Headache, flushing, tachycardia Local phlebitis Mild tolerance after prolonged infusion May reduce serum potassium .ECG changes: nonspecific T-wave changes/ventricular extra systoles

3. Current management of emergency hypertension in various clinical conditions.

3.1 Acute pulmonary edema

The treatment strategy in hypertensive emergency with acute pulmonary edema is to decrease preload and afterload and to lower the blood pressure thereby "unloading" the failing heart. Immediately treatment should start with sublingual nitroglycerin, intravenous (iv) loop diuretic; furosemide and iv morphine with sitting posture. This is accomplished by using vasodilators eg nitroprusside or nitroglycerin. Concomitant use of loop diuretic may be indicated for optimal results in cases of volume overload in the setting of acute left ventricular failure. Intravenous nitroglycerin is preferred in the case of heart disease or when arterial pressure (AP) is not too high (arbitrarily a systolic pressure of less than 180 mmHg may serve as criterion). The Angiotensin-converting enzyme inhibitors are effective vasodilators, iv enalapril is effective in rapidly lowering AP in hypertensive emergencies with chronic heart failure. Use of noninvasive mechanical ventilation has proven to be one of the most important measures to resolve the symptoms. For bearers of mitral stenosis with a good ventricular function, an iv beta-blocker may be used to reduce heart rate and decrease LVEDP (Left ventricular end diastolic pressure).

3.2 Acute aortic dissection

Aortic dissection occurs when a false lumen is created in the wall of the aorta. Ascending aortic dissections require immediate evaluation by a cardiothoracic surgeon for an emergency surgical procedure. Type B dissections are usually managed medically in collaboration with a surgeon. The goal of therapy is to prevent progression of the dissection. The arterial pressure should be maintained as low as possible without compromising end-organ perfusion. This is typically done with a combination of iv sodium nitroprusside and a β-blocker, eg, esmolol; however, labetalol can also be used as a single agent. Beta-blockers are used to blunt the reflex tachycardia associated with the treatment of aortic dissection with sodium nitroprusside. Beta-blockers also limit the force and velocity of contraction, which, if left unchecked, can lead to propagation of the dissection. Calcium channel blockers are considered second-line interventions. The theory behind this management strategy is that reducing the force of left ventricular contractions, thus dilating the vessels, will enhance laminar flow and lessen stress on the aortic wall. Turbulent flow is increased by using a vasodilator alone. The target pressure should be lower and tolerated by the patient. Systolic levels of 100 to 120 mm Hg are ideal.

3.3 Acute coronary syndrome (ACS)

Initial pressure control is done with sublingual nitrate followed by iv morphine if pain does not abate. Then nitroglycerin is given continuously at a titration speed to reduce AP by 30%. A very abrupt reduction must be avoided as it may reduce coronary perfusion. The goal of antihypertensive therapy in acute Myocardial Infarction is to decrease cardiac work by decreasing after load and increasing coronary perfusion pressures. After bedsided 2D Echo assessment with fair LV function , a beta-blocker must be administered until the heart rate is reduced. The current AHA/ACC guidelines suggest that oral b-blockers can be given any time within the first 24 hours of presentation. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be used for patients with hypertension and left ventricular dysfunction or pulmonary congestion within 24 hours.

3.4 Hypertensive encephalopathy

Hypertensive encephalopathy occurs mainly in patients with chronic uncontrolled or malignant hypertension . With sudden elevation of AP, the upper threshold of the self-regulatory capacity of the cerebral blood flow may be surpassed with consequent hyper cerebral perfusion leading to an endothelial dysfunction, rupture of the hematoencephalic barrier, cerebral edema and micro hemorrhages. Hypertensive encephalopathy is clinically characterized by acute or subacute symptoms such as headache, lethargy, confusion, vision disorders, vomiting and seizures. A CT scan of the brain will always be required to exclude other neurological affections, mainly stroke. The goal of therapy is to initially decrease the BP by not more than 20-25% of the mean arterial pressure. The basis of this goal is that hypoperfusion occurs at the lower end of the cerebral perfusion autoregulation curve, which approximates about 25% of the baseline mean arterial pressure. On the other hand, hyperperfusion occurs at the upper limit of the autoregulatory curve, which is the basis for cerebral dam-

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age. The recommended agent of choice is nitroprusside iv, followed by labetalol iv infusion.

3.5 Malignant hypertension

Malignant hypertension represent as an neuroretinopathy and acute or subacute renal failure. Clinical features like asthenia, malaise, weight loss and cardiovascular or neurological symptoms are usually found. If not properly managed, one year mortality is of approximately 80-90% reported. Previously inexistent proteinuria to overt acute renal failure and retinopathy manifests itself by papilledema at the eye. Treatment is with iv sodium nitroprussiate until a 20% decrease of systemic blood pressure in 2 hours, followed by gradual pressure control in 2 or 3 days with oral medication.

3.6 Acute Stroke

Based on the guideline from the Stroke Council for the American Heart Association for acute ischemic strokes, if the patient is not eligible for thrombolysis , treatment starts only with blood pressures > 220/120 mmHg. With patients who are eligible for thrombolysis then treatment is initiated when the BP is > 185/110. Treatment is with nicardipine, sodium nitroprusside, or labetalol may be used to reduce AP by 10% to 20% in 24 hours. Arterial pressure, usually, drops spontaneously to the levels prior to ischemic stroke in 4 days, without any antihypertensive treatment. In subarachnoid hemorrhage, the same procedures suggested for hemorrhagic stroke are pertinent, however nimodipine must be the first choice of treatment, as it reduces risk of cerebral infraction associated to vasospasm. For any stroke condition, the neurological worsening associated to a decrease of BP must be treated by reducing or even interrupting nitroprussiate administration.

3.7 Preeclampsia/Eclampsia

Preeclampsia is the combination of hypertension and proteinuria in a pregnant woman after the 20th weeks' gestation. Preeclampsia becomes eclampsia when the patient has a seizure. Hypertension management is unique in pregnancy, in that many common drugs are contraindicated because of the potential toxic effects on the fetus. The elevated BP seen in eclampsia/preeclampsia can be quickly and safely lowered to "normal levels" at no increased risk for inducing cerebral or cardiac ischemia. Control of the BP is important to help prevent cerebral vascular complications; however, evidence for the prevention of the progression of preeclampsia into eclampsia is not clear. The classic agent used is hydralazine, although labetalol has recently gained favor. Labetalol had similar efficacy and fewer side effects. Magnesium sulfate is added to the regimen for seizure prophylaxis and has been shown to lower the progression of preeclampsia to eclampsia in randomized trials.

3.8 Hypertensive emergencies caused by excess of cathecolamines

The goal of therapy is BP control without exacerbation of the condition. Several agents are recommended, including phentolamine, nitroprusside, and labetalol. Pure β-blockers are contraindicated, since they may exacerbate the condition due to unopposed alpha activity. True hypertensive emergencies caused by excess of cathecolamines are rare.

The main causes are **pheochromocytoma**, users of MAO inhibitors that ingest food containing tyramine, cocaine or amphetamine users or sudden interruption of antihypertensives such as clonidine and beta-blockers (easily manipulated by restarting treatment). Occasionally pheochromocytomas present with the typical triad of headache, sudoresis (Profuse sweating) and severe hypertension.

In the setting of **cocaine-induced catecholamine excess,** benzodiazepines have been shown to decrease the centrally mediated and peripheral sympathomimetic outflow that contribute to the symptoms of cocaine, such as elevated BP, chest pain, and agitation. Benzodiazepines help to lower the systemic arterial pressure, lower the heart rate, and decrease psychomotor hyperactivity. Benzodiazepines treat both the central and peripheral manifestations of cocaine intoxication, with few side effects.

3.9 Perioperative hypertension

Nitroprusside, nitroglycerin, and esmolol are preferred. Target the perioperative BP to within 20% of the patient's baseline pressure, except if there is the potential for life-threatening arterial bleeding. Perioperative beta blockers are the first choice in patients undergoing vascular procedures or in patients with an intermediate or high risk of cardiac complications.

In the way of summary of current management of emergency hypertension in various clinical conditions with line of drug treatment, we can approach immediately in the emergency department with the help of the table-2 and also we can paste it on the wall of emergency room which may helpful for emergency medical officers in daily practice.

Table-2 Line of treatment of emergency hypertension in various clinical conditions.

Clinical conditions	Drug of choice	Other treatment
Acute pulmonary edema	Nitroglycerine iv	Frusemide iv, Enalaprilat iv
Acute stroke	Nimodepine s/l , Labetalol iv	Nicardipine sl,Sodium nitropruside iv
Hypertensive encephalopathy	Sodium nitropruside iv, Labetalol iv	Nicardipine sl , Enalaprilat iv
Malignant hypertension	Clonidine oral , Labetalol iv	Prazopress , Nicardipine sl
Preeclampsia (pregnancy)	Labetalol iv	Hydralazine iv , Nicardipine sl
Eclampsia (pregnancy)	Magnesium sulphate iv	Labetalol iv
Pheochromocytoma crisis	Phentolamine iv	Labetalol iv
Sympathetic excess syndrome	Clonidine oral	Labetalol iv
Sympathetic excess with cocaine	Benzodiazepine iv, Phentolamine iv	Clonidine , Avoid beta blocker
Acute aortic dissection	Labetalol iv, Nitroprusside iv	Avoid direct vasodilators
Acute coronary syndrome	Nitroglycerine iv	Esmolol iv but avoid in heart failure
Perioperative hypertension	Esmolol iv	Nitroglycerine iv

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4. Conclusion

Hypertensive emergency consists of a syndrome where significant elevation of the systemic arterial pressure leads to acute target-organ damage, threatening life. It requires immediate treatment and assessment whether or not target-organ dysfunction is present; if it is, this differentiates emergency from urgency. Symptoms reflect target-organ damage, including primarily the brain, the heart, the eyes, and the kidneys, as well as the rest of the vasculature. Energetic measures must be taken for immediate treatment, initially with intravenous administration of drugs to reduce arterial pressure in emergency and orally in Urgency. And lastly, ischemic stroke is a special situation where BP should not be rapidly reduced nor should it be lowered too far.

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