Hypertensive Urgency (Severe Asymptomatic Hypertension)

- Relatively asymptomatic patient with a blood pressure in the "severe" range (ie, ≥180/≥120 mmHg), often a mild headache, but no signs or symptoms of acute end-organ damage. This entity of Severe Asymptomatic Hypertension is often called Hypertensive Urgency.

- The most important aspect of the initial assessment of the patient with severely elevated blood pressure is to exclude acute, ongoing, target-organ damage, which would indicate a diagnosis of Hypertensive Emergency rather than Severe Asymptomatic Hypertension.
Hypertensive Urgency

- How quickly should the blood pressure be reduced?
- What is the blood pressure target during this period of time?
- How should this goal be achieved?
Hypertensive Urgency: Rapidity of BP Lowering

- In adults with severe asymptomatic hypertension, the goal of management is to reduce the blood pressure to ≤160/≤100 mmHg. However, the mean arterial pressure should not be lowered by more than 25 to 30 percent over the first several hours.

- Patients judged to be at high risk for imminent cardiovascular events due to severe hypertension, including those with known aortic or intracranial aneurysms, should have their blood pressure lowered over a period of HOURS.

- Patients with severe asymptomatic hypertension who do not require rapid lowering of their blood pressure (see above) should have their blood pressure lowered over a period of DAYS.
Hypertensive Urgency: Choice of Agents for more RAPID BP Lowering

- Oral clonidine (but not intended as long-term therapy) at a dose of 0.2 mg
- Oral captopril (if the patient is not volume depleted) at a dose of 6.25 or 12.5 mg
- Oral furosemide (if the patient is volume overloaded) at a dose of 20 mg (or higher if the renal function is not normal)
**WARNING!!!**

- **sublingual nifedipine is contraindicated** in this setting and should **not** be used. Cerebral or myocardial ischemia or infarction can be induced by aggressive antihypertensive therapy if the blood pressure falls below the range at which tissue perfusion can be maintained by autoregulation. This has been most often described with sublingual nifedipine, which may produce an unpredictable and uncontrolled blood pressure reduction as well as severe ischemic complications. This was a major reason why the use of nifedipine capsules for hypertension is not approved by the United States Food and Drug Administration and why most hospitals' intensive care units and emergency departments restrict the use of this medication.
Hypertensive Urgency: Choice of Agents when BP lowering can occur over DAYS

- Previously treated hypertension:
  - Reinstitution of prior medications (especially those associated with rebound hypertension, eg, central alpha-2-agonists, high-dose beta blockers) in nonadherent patients.
  - Increase the dose of existing antihypertensive medications, or add another agent.
  - Addition of a diuretic, and reinforcement of dietary sodium restriction, in patients who have worsening hypertension due to high sodium intake.

- Untreated hypertension:
  - There are no data supporting the use of a particular agent in patients whose blood pressure should be reduced over a period of several days
  - Most patients with a blood pressure ≥20/10 mmHg above goal will require two or more chronic antihypertensive agents to achieve the goal blood pressure
The patient with severe asymptomatic hypertension is usually managed in the emergency department since exclusion of acute end-organ damage requires laboratory testing and the patient may require administration of medications and several hours of observation. However, the patient can often be safely managed in the clinician's office if the evaluation and management can be carried out in that setting.

Patients at high risk for acute cardiovascular events (e.g., longstanding diabetes, known coronary artery disease or prior stroke) should probably be admitted.

Ideally, the patient should be observed for a few hours to ascertain that the blood pressure is stable or improving, that they indeed remain asymptomatic, and that they have received referral to an appropriate source of long-term medical care. If this occurs, the patient can be sent home with close follow-up over the subsequent days directed toward evaluation for symptoms related to hypertension or hypotension and adjustment of medications to achieve the initial blood pressure goal of ≤160/100 mmHg.

In reliable patients who can monitor their blood pressure at home, close phone follow-up may substitute for direct clinician visits.
Hypertensive Emergency

- Patients with significantly elevated blood pressure that have signs or symptoms of acute, ongoing target-organ damage have a Hypertensive Emergency. Hypertensive emergencies can develop in patients with or without preexisting chronic hypertension. Often, the diastolic pressure is ≥120 mmHg, but there is no specific threshold.
Hypertensive Emergency

EVALUATION AND DIAGNOSIS — The history and physical examination in patients presenting with a severely elevated blood pressure should determine whether or not any of the following are present:

- Acute head injury or trauma
- Generalized neurologic symptoms, such as agitation, delirium, stupor, seizures, or visual disturbances
- Focal neurologic symptoms that could be due to an ischemic or hemorrhagic stroke
- Flame hemorrhages, exudates (cotton-wool spots), or papilledema when direct fundoscopy is performed, as these are consistent with grade III or IV hypertensive retinopathy and can be associated with hypertensive encephalopathy
- Nausea and vomiting, which may be a sign of increased intracranial pressure
- Chest discomfort, which may be due to myocardial ischemia or aortic dissection
- Acute, severe back pain, which might be due to aortic dissection
- Dyspnea, which may be due to pulmonary edema
- Pregnancy, as such patients with severe hypertension could have preeclampsia or develop Eclampsia
- Use of drugs that can produce a hyperadrenergic state, such as cocaine, amphetamine(s), phencyclidine, or monoamine oxidase inhibitors, or recent discontinuation of clonidine or other sympatholytic agents
Hypertensive Emergency: Fundoscopy

Images showing various fundoscopic findings in hypertensive emergency:

- Retinal hemorrhage
- Cotton wool patch
- Optic disc swelling
- Hard exudate

These findings are critical in diagnosing and managing hypertensive emergencies.
Hypertensive Emergency

- In addition, the following tests may be performed to evaluate the presence of target-organ damage:
  - Electrocardiography
  - Conventional chest radiography
  - Urinalysis
  - Serum electrolytes and serum creatinine, Hgb and PLT count
  - Cardiac enzymes (if an acute coronary syndrome is suspected)
  - Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain (if head injury, neurologic symptoms, hypertensive retinopathy, nausea, or vomiting are present)
  - Contrast-enhanced CT or MRI of the chest or transesophageal echocardiography (if aortic dissection is suspected)
Hypertensive Emergency

- It is generally unwise to lower the blood pressure too quickly or too much, as ischemic damage can occur in vascular beds that have grown accustomed to the higher level of blood pressure (i.e., autoregulation). For most hypertensive emergencies, mean arterial pressure should be reduced gradually by about 10 to 20 percent in the first hour and by a further 5 to 15 percent over the next 23 hours.

- The major exceptions to gradual blood pressure lowering over the first day are:
  - The acute phase of an ischemic stroke – The blood pressure is usually **not** lowered unless it is ≥185/110 mmHg in patients who are candidates for reperfusion therapy or ≥220/120 mmHg in patients who are not candidates for reperfusion therapy.
  - Acute aortic dissection – The systolic blood pressure is **rapidly** lowered to a target of 100 to 120 mmHg (to be attained in 20 minutes)
Hypertensive Emergency

- AUTOREGULATION of CEREBROVASCULAR RESISTANCE

- Cerebral blood flow — Following a significant increase in ICP, brain injury can result from brainstem compression and/or a reduction in cerebral blood flow (CBF). CBF is a function of the pressure drop across the cerebral circulation divided by the cerebrovascular resistance, as predicted by Ohm's law.

- \[ \text{CBF} = \frac{(\text{CAP} - \text{JVP})}{\text{CVR}} \]

- where \( \text{CAP} \) is carotid arterial pressure, \( \text{JVP} \) is jugular venous pressure, and \( \text{CVR} \) is cerebrovascular resistance.

- Cerebral perfusion pressure (CPP) is a clinical surrogate for the adequacy of cerebral perfusion. CPP is defined as mean arterial pressure (MAP) minus ICP.

- \[ \text{CPP} = \text{MAP} - \text{ICP} \]

- Autoregulation — CBF is normally maintained at a relatively constant level by cerebrovascular autoregulation of CVR over a wide range of CPP (50 to 100 mmHg). However, autoregulation of CVR can become dysfunctional in certain pathologic states, most notably stroke or trauma. In this setting, the brain becomes exquisitely sensitive to even minor changes in CPP.

- Another important consideration is that the set-point of autoregulation is also changed in patients with chronic hypertension. With mild to moderate elevations in blood pressure, the initial response is arterial and arteriolar vasoconstriction. This autoregulatory process both maintains tissue perfusion at a relatively constant level and prevents the increase in pressure from being transmitted to the smaller, more distal vessels. As a result, acute reductions in blood pressure, even if the final value remains within the normal range, can produce ischemic symptoms in patients with chronic hypertension.
Hypertensive Emergencies

- Neurologic emergencies
- Cardiac emergencies
- Vascular emergencies
- Renal emergencies
- Sympathetic overactivity resulting in hypertensive emergencies
Hypertensive Emergency: Neurologic

- Ischemic stroke – Patients with acute ischemic stroke-in-evolution are most often not given antihypertensive drugs unless they are candidates for TPA and their initial blood pressure is $\geq 185/110$ mmHg or if their initial blood pressure is $\geq 220/120$, even if they are not candidates for reperfusion therapy.
Hypertensive Emergency: Neurologic

- Hemorrhagic stroke – Management of blood pressure in patients with spontaneous intracerebral hemorrhage and subarachnoid hemorrhage is complicated by competing risks (e.g., reducing cerebral perfusion) and benefits (e.g., reducing further bleeding). An international trial involving 2839 subjects with onset of symptoms less than six hours prior to presentation and a baseline blood pressure of 150 to 200 mmHg found that lowering blood pressure (within one hour) to <140 mmHg was safe and produced nonsignificant benefits on death and major disability. United States guidelines indicate that blood pressure-lowering therapy should be given in this setting if there are no contraindications.
Hypertensive Emergency: Neurologic

- **Head trauma** – Head trauma with increased intracranial pressure can produce severe elevations in blood pressure. Hypertension is usually treated in this setting only if the cerebral perfusion pressure (mean arterial pressure minus intracranial pressure) is >120 mmHg and the intracranial pressure is >20 mmHg.
Hypertensive Emergency: Cardiac

- **Acute heart failure** – Patients with acute left ventricular dysfunction and pulmonary edema should usually receive loop diuretics. An easily titratable vasodilator (eg, sodium nitroprusside, nitroglycerin) is often added to reduce afterload. Drugs that increase cardiac work (eg, hydralazine) or acutely decrease cardiac contractility (eg, labetalol or other beta blocker) should be avoided. The goal of these therapies is amelioration of heart failure and improvement in pulmonary edema, which can often be achieved with a 10 to 15 percent reduction in blood pressure.

- **Acute coronary syndrome** – Severe hypertension associated with an acute coronary syndrome (including acute myocardial infarction) is appropriately treated with intravenous nitroglycerin, nicardipine, or esmolol to reduce the underlying coronary ischemia and/or increased myocardial oxygen consumption and to improve prognosis.
Vascular emergencies — Vascular emergencies include acute aortic dissection and severe hypertension in patients who have recently undergone vascular surgery.

● **Acute aortic dissection** – Patients with acute aortic dissection are treated to rapidly reduce the blood pressure to a goal systolic of 100 to 120 mmHg within about 20 minutes of diagnosis, although this target is not based upon clinical trial evidence. An intravenous beta blocker is given first (usually esmolol, but labetalol, propranolol, and metoprolol can also be used) to reduce the heart rate below 60 beats per minute and the shear stress on the aortic wall. In addition, a vasodilator (often nitroprusside or clevidipine) is typically required to quickly achieve the goal blood pressure.

● **Severe hypertension in patients with recent vascular surgery** – Severe elevations of blood pressure can threaten suture lines and, therefore, such patients are often treated with rapidly acting intravenous antihypertensive agents in an intensive care unit setting. Although this is common practice, no controlled studies have proven the benefit of this intervention.
Hypertensive Emergency: Renal

- **Renal emergencies** — Severe hypertension may occasionally cause acute injury to the kidneys (acute hypertensive nephrosclerosis, formerly called "malignant nephrosclerosis"). This condition is characterized by hematuria (usually microscopic hematuria, which is found in approximately 75 percent of patients with hypertensive emergencies) and an elevated serum creatinine. It is important to determine whether or not these findings are recent since they may predate the severe blood pressure elevation in some patients.

- When renal injury occurs as a result of severe hypertension, the common pathologic findings include fibrinoid necrosis of small arterioles and "onion skinning" of small renal arteries. The histologic changes are indistinguishable from other forms of the hemolytic-uremic syndrome; however, a kidney biopsy is seldom performed in such patients. The renal vascular disease leads to glomerular ischemia and activation of the renin-angiotensin system, possibly resulting in exacerbation of the hypertension.

- Antihypertensive therapy often leads to worsening kidney function, sometimes requiring dialysis, although this reduction in kidney function may be reversed with long-term blood pressure control. By contrast, fenoldopam is associated with a temporary improvement in renal function and is therefore a useful antihypertensive agent in patients with renal hypertensive emergencies.
Hypertensive Emergency with TMA

- Reversible microangiopathic hemolytic anemia and thrombocytopenia have been seen in patients with malignant hypertension. On occasion, the patient with malignant hypertension may present with microangiopathic hemolysis, renal insufficiency, and thrombocytopenia. The presumed mechanism is the associated endothelial/vascular injury, which, in turn, leads to fibrin strand formation, shearing of RBCs, and the trapping and removal of platelets. Very rapid control of the hypertension is critical; with good control the survival rate at 5 years is 75 percent.

- There appears to be a correlation between plasma renin levels, renal dysfunction, and microangiopathic findings, thereby pointing to the possible role of renin accelerated vascular damage in the pathophysiology of this complication.

- In one study of 97 patients with malignant hypertension, 27 percent had microangiopathic hemolytic anemia. The group with MAHA was clinically more severe, with higher creatinine levels, higher systolic BP, and a greater need for dialysis (58 versus 3 percent).
Hypertensive Emergency with TMA

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows), other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large platelet in the center (dashed arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).
Hypertensive Emergency: Renal

- **SCLERODERMA RENAL CRISIS**

  - SRC is an early complication of SSc that almost invariably occurs within the first five years after the onset of the disease.
  - **●** Acute onset of renal failure, usually in the absence of previous evidence of significant kidney disease.
  - **●** Abrupt onset of moderate to marked hypertension, often accompanied by manifestations of malignant hypertension such as hypertensive retinopathy.
  - SRC is a thrombotic microangiopathy similar to malignant nephrosclerosis and TTP/HUS.
  - The optimal antihypertensive agent is an ACE inhibitor. The most experience has been with captopril, which is our preferred ACE inhibitor.
  - **Captopril** has the advantages of rapid onset (peak effect at 60 to 90 minutes) and short duration of action, which permit rapid dose titration. Intravenous enalaprilat is not routinely used since it has a long duration of action (up to 36 hours). However, a single dose may be given in patients who have impaired mental status, followed by oral captopril therapy through a nasogastric tube.
  - The principal goal of initial captopril therapy is to return the patient to his or her previous baseline blood pressure within 72 hours. Since the hypertension is usually acute in SRC, rapid blood pressure reduction to baseline does not usually carry the risks seen with rapid blood pressure lowering in patients with longstanding hypertension.
  - **All** patients are treated with captopril, which is continued even if the serum creatinine initially continues to rise.
Hypertensive Emergency: Sympathetic Overactivity

- Withdrawal of short-acting antihypertensive agents (especially clonidine, propranolol, or other beta blockers) can be associated with severe hypertension and may mimic the signs and symptoms of pheochromocytoma. Typically, reinstitution of the recently discontinued drug will lower the blood pressure. Oral clonidine will begin to lower blood pressure within an hour; however, some beta blockers take much longer to lower the blood pressure and, therefore, short-acting intravenous medications are often required while waiting for the reinstituted beta blocker to achieve an effect.

- Pheochromocytoma can also produce severe hypertension and acute target-organ damage.

- Cocaine, Methamphetamines

- Unless a beta blocker was recently withdrawn, administration of a beta blocker alone is contraindicated in these settings since inhibition of beta receptor-induced vasodilation can result in unopposed alpha-adrenergic vasoconstriction and a further rise in blood pressure.
Hypertensive Emergency: Meds

- **Nitrates** — Nitrovasodilators such as nitroprusside and nitroglycerin provide nitric oxide that induces vasodilatation of both arterioles and veins

- **Nitroprusside** — when administered by intravenous infusion, begins to act within one minute or less, and once discontinued, its effects disappear within 10 minutes or less. Frequent monitoring is required since this drug can produce a sudden and drastic drop in blood pressure.
  - The recommended starting dose of nitroprusside is 0.25 to 0.5 mcg/kg per minute. This can be increased as necessary to a maximum dose of 8 to 10 mcg/kg per minute, although use of these higher doses should generally be avoided or limited to a maximum duration of 10 minutes.
  - Nitroprusside is metabolized to cyanide, possibly leading to the development of cyanide (or, rarely, thiocyanate) toxicity that may be fatal. This problem, which can manifest in as little as four hours, presents with altered mental status and lactic acidosis. Risk factors for nitroprusside-induced cyanide poisoning include a prolonged treatment period (>24 to 48 hours), underlying renal impairment, and the use of doses that exceed the capacity of the body to detoxify cyanide (ie, more than 2 mcg/kg per minute). The risk of toxicity can be minimized by using the lowest possible dose, avoiding prolonged use (ie, no more than two or three days), and by careful patient monitoring (with special attention to unexplained acidemia or decreasing serum bicarbonate concentrations).
  - Nitroprusside can result in dose-related declines in coronary, renal, and cerebral perfusion.

- **Nitroglycerin** should not be given to pregnant women, patients. In addition, nitroprusside should be avoided, if possible, in patients with impaired renal function.

- **Nitroglycerin** — Nitroglycerin is also administered by intravenous infusion and is similar in action and pharmacokinetics to nitroprusside except that it produces relatively greater venodilation than arteriolar dilation. It has less antihypertensive efficacy compared with other drugs used to treat hypertensive emergencies, and its effects on blood pressure are variable from person to person and, potentially, from minute to minute. However, it may be useful in patients with symptomatic coronary disease and in those with hypertension following coronary bypass.
  - The initial dose of nitroglycerin is 5 mcg/min, which can be increased as necessary to a maximum of 100 mcg/min. The onset of action is 2 to 5 minutes, while the duration of action is 5 to 10 minutes. Headache and tachycardia are the primary adverse effects. Cyanide accumulation does not occur. Methemoglobinemia has been reported in patients receiving this agent for more than 24 hours.
Hypertensive Emergency: Meds

- Calcium channel blockers

- Nicardipine — Nicardipine is a dihydropyridine calcium channel blocker (like nifedipine) that can be given as an intravenous infusion. The initial dose is 5 mg/hour and can be increased to a maximum of 15 mg/hour. Nicardipine has a better safety profile and a similar antihypertensive effect when compared with nitroprusside. The major limitations are a longer onset of action, which precludes rapid titration, and a longer serum elimination half-life (three to six hours).
Hypertensive Emergency: Meds

- Dopamine-1 agonist

- **Fenoldopam** — **Fenoldopam** is a peripheral dopamine-1 receptor agonist which, unlike other parenteral antihypertensive agents, maintains or increases renal perfusion while it lowers blood pressure. Fenoldopam may be particularly beneficial in patients with renal impairment. After starting at 0.1 mcg/kg per minute, the dose can be titrated at 15-minute intervals to 1.6 mcg/kg per minute, depending upon the blood pressure response.

- **Fenoldopam** should be used cautiously or not at all in patients with glaucoma.
Hypertensive Emergency: Meds

- **Adrenergic-blocking agents**
  
  - **Labetalol** — *Labetalol* is a combined beta-adrenergic and alpha-adrenergic blocker. Its rapid onset of action (five minutes or less) makes it a useful intravenous medication for the treatment of hypertensive emergencies. However, one trial found that labetalol has less antihypertensive efficacy as compared with nicardipine.
  
  - **Labetalol** is safe in patients with active coronary disease since it does not increase heart rate. However, labetalol should be avoided in patients with asthma, chronic obstructive lung disease, heart failure, bradycardia, or greater than first-degree heart block. In addition, labetalol should not be used without prior adequate alpha blockade in patients with hyperadrenergic states, such as pheochromocytoma or cocaine or methamphetamine overdose, since unopposed, inadequately blocked alpha-adrenergic activity can increase blood pressure if beta blockade is not complete. Labetalol can be given as a series of intravenous bolus injections or as a constant-dose infusion. The bolus dose is 20 mg initially, followed by 20 to 80 mg every 10 minutes to a total dose of 300 mg. The infusion rate is 0.5 to 2 mg/min.
  
  - **Esmolol** — *Esmolol*, a relatively cardioselective beta blocker, is rapidly metabolized by blood esterases. Its effects begin almost immediately, and it has both a short half-life (about 9 minutes) and a short total duration of action (about 30 minutes), permitting rapid titration. Esmolol is often used during anesthesia to prevent postintubation hemodynamic perturbations.
Hypertensive Emergency: Meds

- **Other agents**
  - **Hydralazine** — *Hydralazine* is a direct arteriolar vasodilator with little or no effect on the venous circulation. Thus, precautions are needed in patients with underlying coronary disease or aortic dissection, and a beta blocker should be given concurrently to minimize reflex sympathetic stimulation. The hypotensive response to hydralazine is less predictable than that seen with other parenteral agents. The use of parenteral hydralazine is primarily limited to pregnant women, although a reduction in the utero-placental blood flow has been reported in such patients.
  - **Hydralazine** can be given as an intravenous bolus. The initial dose is 10 mg, with the maximum dose being 20 mg. The fall in blood pressure can be sudden and begins within 10 to 30 minutes and lasts two to four hours.
  - **Enalaprilat** — *Enalaprilat* is the intravenously active, des-ethyl ester of the angiotensin-converting enzyme (ACE) inhibitor, *enalapril*. The hypotensive response to enalaprilat is unpredictable and depends upon the plasma volume and plasma renin activity in individual patients with a hypertensive emergency. Typically, hypovolemic patients with a high plasma renin activity are most likely to have an excessive hypotensive response. In addition, ACE inhibitors are contraindicated in pregnancy, severe renal artery stenosis with global ischemia, and severe hyperkalemia. The usual initial dose is 1.25 mg. As much as 5 mg may be given every six hours as necessary. The onset of action begins in 15 minutes, but the peak effect may not be seen for four hours. The duration of action ranges from 12 to 24 hours.
  - **Phentolamine** — *Phentolamine* is a nonselective alpha-adrenergic blocker, the use of which is limited to the treatment of severe hypertension due to increased catecholamine activity such as pheochromocytoma. *Phentolamine* is given as an intravenous bolus. The usual dose is 10 to 15 mg every 5 to 15 minutes as necessary. Patients receiving this agent who do not require intravenous therapy can be converted to oral *phenoxybenzamine*.
Hypertensive Emergency

SUMMARY AND RECOMMENDATIONS

- A **Hypertensive Emergency** is defined as severe hypertension that is associated with **acute end-organ damage**.
- Immediate but careful reduction in blood pressure is indicated in hypertensive emergencies; an excessive hypotensive response may lead to ischemic complications. A variety of parenteral and oral antihypertensive drugs are available for use in these patients.
- Parenteral drugs include **nitroprusside**, **nitroglycerin**, **nicardipine**, **fenoldopam**, **labetalol**, **esmolol**, **hydralazine**, **enalaprilat**, and **phentolamine**.
- Among patients who are severely hypertensive but asymptomatic, slower reductions in blood pressure may be provided with oral agents.