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Hypertension Curriculum Review

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Clinical Features and Management of Selected Hypertensive Emergencies

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A hypertensive emergency, defined as an elevated blood pressure with evidence of acute target organ damage, can manifest in many forms, including neurological, cardiac, renal, and obstetric. After diagnosis, effective parenteral antihypertensive therapy (typically, nitroprusside starting at 0.5 μg/kg/min, but some physicians prefer fenoldopam or nicardipine) should be given in the hospital. In general, blood pressure should be reduced about 10% during the first hour and another 15% gradually over 2–3 more hours. The exception is aortic dissection, for which treatment includes a β blocker, and the target is systolic blood pressure <120 mm Hg after 20 minutes. Oral antihypertensive therapy can usually be instituted after 6–12 hours of parenteral therapy. Consideration should be given to secondary causes of hypertension after transfer from the intensive care unit. Because of advances in antihypertensive therapy and management, "malignant hypertension" should be malignant no longer.
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Although great strides have been made in the treatment of hypertension since the First Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in 1977, occasionally patients still present to emergency departments (and occasionally to physicians' offices) with hypertensive crises. This term includes both hypertensive emergencies and hypertensive urgencies (Table I). Fortunately, we now have excellent medications available for both the acute, in-hospital treatment of hypertensive emergencies, as well as outpatient management of chronic hypertension. These improvements have led to a major decrease in the 1-year mortality rate after a hypertensive emergency from 80% (in 1928) to 50% (in 1955) to only 10% (in 1989). In 1928, the prognosis after a hypertensive emergency was so poor that the term "malignant hypertension" was coined to emphasize that the average patient's longevity was about the same as a person diagnosed with cancer. Because of modern therapy, this term is now used only by hospital administrators and diagnosis-related group coders. Today, an affected patient's prognosis depends more on the level of cardiac, renal, and cerebral function at presentation, and the chosen treatment, and not on how high the blood pressure (BP) was initially.

During the initial evaluation of a person with a severely elevated BP, the most important thing is to assess whether there is ongoing acute target organ damage. If so, it is a hypertensive emergency, and the BP should be carefully lowered within minutes. If not, the patient has a hypertensive urgency, and more time can be taken to lower the BP; the most important aspect of the treatment of this diagnosis is assuring adequate follow-up (usually within hours to days) to an appropriate source of care for chronic hypertension.

Acute target organ damage due to hypertension can manifest in one or more of several organ systems (Table I). Typically, acute neurological signs and symptoms, acute cardiac ischemia and/or pulmonary edema, aortic dissection, acute renal failure, gross hematuria or epistaxis, catecholamine excess states, and eclampsia/preeclampsia are the most common.

NEUROLOGICAL EMERGENCIES

In the patient with very high BP and neurological findings (including altered mental status), a thorough examination of the optic fundi by direct ophthalmoscopy can be very helpful in making a proper diagnosis (Table II). Patients with papilledema or new hemorrhages or exudates have hypertensive emergencies, and often manifest some degree of hypertensive encephalopathy as well. A thorough initial neurological examination is also essential, as it should document the extent and severity of focal neurological defects that may be due to an acute stroke, which would change the target BP to be achieved.

Neurological emergencies are the most difficult to distinguish from one another (Table II). Hypertensive encephalopathy is typically a diagnosis of exclusion, since hemorrhagic and thrombotic strokes are usually diagnosed by demonstrating focal neurological deficits and a corroborating computed axial tomographic or magnetic resonance imaging scan of the head. Subarachnoid hemorrhage is diagnosed after lumbar puncture. Hypertension associated with head trauma (Cushing's reflex) usually has a typical history and corroborating physical findings to assist in the diagnosis. The management of each of these conditions is somewhat different. Sodium nitroprusside is still the drug typically chosen for encephalopathy, and can be used in other conditions, but recent data using nimodipine for subarachnoid hemorrhage have shown both antihypertensive and anti-ischemic effects, and improved long-term outcomes. The goal BP during treatment also depends on the presenting diagnosis, and is lower for encephalopathy than for acute stroke in evolution (Table III). The BP goal when treating hypertension associated with head trauma is controversial and not well-studied.

Whether hypertension observed during a "stroke-in-evolution" should be treated at all, and what target BP should be achieved, are very controversial issues. Many older stroke neurologists believe that any pharmacological lowering of BP will threaten the "watershed" areas of the brain that are not yet underperfused due to the stroke, and will worsen the final neurological deficit. "Evidence-based medicine" agrees with this opinion, in that there are no data showing that lowering of BP is beneficial during the first few hours after stroke onset; many feel it would be unethical to undertake such a study. Some younger neurologists believe that BP should not be allowed to soar (perhaps over 180/110 mm Hg) after the first few hours of hospitalization. Both groups might agree that if BP lowering is to be attempted, a short-acting, IV administered drug should be given, and the patient examined frequently. If neurological symptoms worsen or progress, IV drugs like nitroprusside, nicardipine, or fenoldopam can be quickly discontinued, and the BP will return toward its previous level.

CARDIAC EMERGENCIES

There are three major types of hypertensive emergencies that directly involve the heart and great vessels: acute myocardial ischemia/infarction, pulmonary edema, and aortic dissection. Patients with very elevated BPs should have an electrocardiogram to identify cardiac ischemia, auscultation of the lungs and other maneuvers to detect signs of heart failure, and, if appropriate to the patient's presentation, at least a chest x-ray to assess the pulmonary vasculature and diameter of the aorta. Controversy exists as to whether patients presenting with acute aortic dissection should have time-consuming radiological tests, or whether an echocardiogram or other simple, noninvasive test is sufficient to make the diagnosis before recommending surgery. Most authorities agree that quickly controlling the systolic BP to <120 mm Hg, using both a β blocker and a vasodilator, is more important than the technique used to identify the dissection.

Patients who present with hypertensive emergencies involving cardiac ischemia/infarction or pulmonary edema are typically given either nitroglycerin or nitroprusside, although a combination of drugs is often used in these settings. IV nicardipine is useful in managing patients with cardiac ischemia; several similar, but orally administered, dihydropyridine calcium antagonists have received US Food and Drug Administration (FDA)-approved indications for the treatment of angina pectoris. As with all vasodilators, IV nicardipine causes reflex tachycardia and increases cardiac oxygen demand, but this has not been a major problem when treating hypertension after cardiac surgery. Although nicardipine has not been studied sufficiently in acute myocardial ischemia, there are strong theoretical grounds for its use, along with efforts to preserve the myocardium and open the obstructed coronary artery (by thrombolysis, angioplasty, and/or surgery). Acute administration of an angiotensin-converting enzyme inhibitor improves outcomes after pulmonary edema. Typical treatment includes an IV diuretic (typically furosemide), an IV angiotensin-converting enzyme inhibitor (typically enalaprilat), and then nitroprusside (if the BP has not yet been controlled with the previous two interventions). The target BP for hypertensive emergencies involving cardiac ischemia/infarction, or pulmonary edema is that which improves cardiac

perfusion; typically only a 10%–15% reduction in BP is sufficient to see a dramatic improvement in symptoms.

Patients with hypertensive emergencies involving aortic dissection are managed in a somewhat different fashion. Upon diagnosis, an IV β blocker is given along with the antihypertensive agent (classically, nitroprusside), and the goal BP is much lower, and should be achieved more quickly, than in other hypertensive emergencies; typically, 120 mm Hg systolic BP is recommended to be achieved within 20 minutes. Usually, pharmacological therapy is only a temporary prelude to definitive surgical therapy, which should be planned with dispatch. Depending on the location and extent of the dissection and the status of the patient, long-term medical therapy can be more appropriate than surgery.

VASCULAR EMERGENCIES

Two other less common situations that call for rapid lowering of BP are patients whose BP threatens recently-placed suture lines, and patients who have severe epistaxis unresponsive to the usual anterior and posterior nasal packing. Vascular surgeons are typically unhappy when their otherwise technically excellent results are threatened by elevated shear stress from severely elevated BP. This is well-treated by an IV administered vasodilator; many surgeons prefer fenoldopam because of its salutary renal effects. Patients with brisk blood loss from the nasal cavity are often frightened by the amount and rate of bleeding, which can exacerbate hypertension; an IV administered vasodilator and perhaps a low-dose, short-acting anxiolytic agent can be very helpful in controlling these stimuli.

HYPERTENSIVE EMERGENCIES WITH HEMATURIA AND/OR RENAL IMPAIRMENT

Many patients who present with hypertensive emergencies have microscopic hematuria or acutely worsened renal function; gross hematuria is less common, but should trigger urologic evaluation after BP reduction has been achieved. A urinalysis and measurement of serum creatinine should be performed initially in the assessment of all patients with very high BP. Access to medical records is important to establish whether the current level of serum creatinine is higher than historical levels.

During treatment for hypertensive emergencies, many patients with acute-on-chronic renal impairment display a temporary worsening of renal function, even when BP is lowered correctly. This is, in fact, the reason "essential hypertension" was originally named, since it was thought in the late 1800s that it was essential that the BP be elevated to maintain proper perfusion of the kidneys. The need for acute dialysis is sometimes precipitated by BP reduction in the setting of a hypertensive emergency, but many patients are able to escape dialysis if BP is well-controlled during long-term follow-up.

Optimal drug therapy for hypertensive emergencies with renal signs or symptoms is controversial. Although nitroprusside is the drug with the longest track record, many physicians are impressed with the dopamine-1 agonist, fenoldopam mesylate, which not only avoids potential cyanide and thiocyanate toxicity seen with prolonged infusions or high doses of nitroprusside,

Table I. Common Hypertensive Emergencies and Urgencies*

Hypertensive emergency
Severe elevation in blood pressure accompanied by acute target organ damage, which must be reduced within minutes, usually with parenteral drug therapy
Neurologic emergencies
Hypertensive encephalopathy
Acute ischemic stroke
Intracranial hemorrhage
Cerebral embolism/thrombotic stroke
Subarachnoid hemorrhage
Acute head trauma/injury
Cardiac emergencies
Cardiac ischemia/infarction due to coronary artery disease
Acute left ventricular failure/pulmonary edema
Vascular emergencies
Aortic dissection
Recent vascular surgery
Epistaxis unresponsive to anterior/posterior packing
Catecholamine excess state emergencies
Pheochromocytoma
Drug-related
Tyramine-containing foods in a patients on monoamine oxidase inhibitors
Withdrawal of centrally-acting α_2-agonists (clonidine, methyldopa, guanabenz, guanfacine, etc.)
Phencyclidine, cocaine, or other sympathomimetic agonist
Pregnancy-related emergency
Eclampsia
Hypertensive urgency
Severe elevations in blood pressure, with no acute target organ damage, which must be reduced within hours, usually with oral medications in the outpatient setting
Perioperative hypertension
Hypertension after organ transplantation
Hypertension associated with severe burns

*Very high blood pressure (≥180/110 mm Hg) without acute target organ damage is *never* an emergency and does not require parenteral drug therapy. Adapted with permission from *Crit Care Clin.* 2001;17:435–451.

Table II. Similarities and Differences in Neurological Hypertensive Emergencies

	Acute Cerebral Infarction	Subarachnoid Hemorrhage	Intraparenchymal Hemorrhage	Hypertensive Encephalopathy
History				
Duration of symptoms	Acute	Acute	Acute	Subacute
Headache	Variable	Severe	Variable	Severe
History of hypertension	Common, but variable	Common, but variable	Common, but variable	Nearly universal
Physical examination				
Retinopathy	Variable: 0–IV	Variable: 0–IV	Variable: 0–IV	Variable: II–IV (usually III or IV)
Focal neurologic deficits	Characteristic of location of infarction	Variable	Characteristic of location of hemorrhage	Unusual; varies with BP level
Laboratory findings				
Lumbar puncture	Usually normal, except opening pressure	Xanthochromic or frankly bloody	Xanthochromic or frankly bloody	Usually normal, except opening pressure
CAT scan	Can show area of infarct	Usually normal	Often shows area of hemorrhage	Usually normal

BP=blood pressure; CAT=computed axial tomography. Adapted with permission from *Curr Hypertens Rep*. 2003;5:486–492.

Table III. Initial Drugs and Blood Pressure Targets Recommended for Specific Types of Hypertensive Emergencies

Type of Crisis	Drug of Choice	Blood Pressure Target
Neurologic		
Hypertensive encephalopathy	Nitroprusside*	25% reduction in mean arterial pressure over 2–3 h
Intracranial hemorrhage or acute stroke in evolution	Nitroprusside* (controversial)	0%–25% reduction in mean arterial pressure over 6–12 h (controversial)
Acute head injury/trauma	Nitroprusside*	0%–25% reduction in mean arterial pressure over 2–3 h (controversial)
Subarachnoid hemorrhage	Nimodipine	Up to 25% reduction in mean arterial pressure in previously hypertensive patients, 130–160 mm Hg systolic in normotensive patients
Cardiac		
Ischemia/infarction	Nitroglycerin or nicardipine	Reduction in ischemia
Heart failure	Nitroprusside* or nitroglycerin	Improvement in failure (typically 10%–15% decrease in blood pressure)
Aortic dissection	β blocker + nitroprusside*	120 mm Hg systolic in 30 min (if possible)
Renal		
Hematuria or acute renal impairment	Fenoldopam	0%–25% reduction in mean arterial pressure over 1–12 h
Catecholamine excess states		
Pheochromocytoma	Phentolamine	To control paroxysms
Ingestion of cocaine or other sympathomimetic	Phentolamine	0%–25% reduction in mean arterial pressure over 2–3 h
Drug withdrawal	Drug withdrawn	Typically only one dose necessary
Pregnancy-related		
Eclampsia	$MgSO_4$, methyldopa, hydralazine	Typically <90 mm Hg diastolic, but often lower

*Some physicians prefer an IV infusion of either fenoldopam or nicardipine, neither of which has potentially toxic metabolites, over nitroprusside. Recent studies have also shown improvements in renal function during therapy with the former, as compared with nitroprusside. Adapted with permission from *Curr Hypertens Rep*. 2003;5:486–492.

but also has some acute beneficial effects in the kidney. Several controlled clinical trials have shown that, as compared with nitroprusside, fenoldopam infusion improves natriuresis, diuresis, and creatinine clearance, at least while the drug is infused. Since renal failure due to hypertensive emergency is rare, sufficient patients have not been enrolled in clinical studies to show a statistically significant difference in the risk of dialysis.

The recommended strategy for lowering of BP during treatment of a hypertensive emergency due to renal signs or symptoms is usually a 10%–20% reduction in mean arterial pressure during the first hour or two, and then a further 10%–15% during the next 6–12 hours. It is seldom necessary (or recommended) to lower the BP to "normal," as this increases the risk of acute renal failure.

HYPERTENSIVE EMERGENCIES DUE TO CATECHOLAMINE EXCESS STATES

True hypertensive emergencies due to an excess of catecholamines are rare, but can usually be attributed to one of three common presentations: pheochromocytoma, monoamine oxidase inhibitor crisis, and intoxication with cocaine or other drugs of abuse. Patients with pheochromocytoma often present with typical symptoms (headache, hyperhydrosis, and severe hypertension); frequently there are clues to this diagnosis on physical examination of the skin (e.g., café-au-lait spots, neurofibromas, port wine stains, etc.). Most patients who take monoamine oxidase inhibitors have been warned about drugs and foods that can precipitate hypertensive emergencies, but sometimes there are dietary indiscretions, and sometimes food labels do not list all potentially harmful ingredients. A thorough medication history often provides the only clue that a hypertensive emergency may be attributable to a monoamine oxidase inhibitor or a drug of abuse.

Treatment of hypertensive emergencies due to catecholamine excess states usually begins with an IV α blocker (phentolamine), and the β blocker is added thereafter only if necessary. Patients with severe burns can be well-treated with a β blocker (alone). Many patients with very elevated BPs due to sudden withdrawal of their antihypertensive agents (e.g., clonidine) are easily managed by reinstituting such therapy; typically, only one dose is necessary before improvement in BP occurs. These strategies are typically successful within minutes-to-hours in lowering BP; if there is no response, other diagnostic and treatment alternatives should be investigated.

HYPERTENSIVE EMERGENCIES DURING PREGNANCY

Hypertensive emergencies during pregnancy are defined somewhat differently than for nongravid patients. Because BP usually declines during pregnancy, hypertensive emergencies and preeclampsia are typically found at much lower levels of BP than in nonpregnant patients. Because of the risk of eclampsia and the large risks to both mother and fetus, obstetricians are usually much more vigilant about an elevated BP than other physicians. Many of the usual drugs used for hypertension are contraindicated in pregnancy. Nitroprusside is metabolized to cyanide, which is especially toxic to the fetus. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are contraindicated in the second and third trimesters of pregnancy because of nephrotoxic and other adverse effects in the fetus. Magnesium sulfate, methyldopa, and hydralazine are the drugs of choice, with oral nifedipine or β blockers being drugs of second choice in the United States. Although nifedipine has been implicated in precipitating at least one emergency Cesarean delivery, several clinical studies have been published demonstrating the efficacy of oral nifedipine for acute lowering of BP during pregnancy and preeclampsia. IV fenoldopam is currently being studied in pregnancy, but does not yet have FDA approval for this indication. No matter which drug is chosen, delivery of the infant will often improve hypertension in pregnancy, and is often hastened by the obstetrician under these conditions.

DRUG THERAPY OF HYPERTENSIVE EMERGENCIES

There are multiple therapeutic options for drug treatment of hypertensive emergencies; the best specific therapy depends somewhat on the type of hypertensive emergency and the particular patient. Sodium nitroprusside is the drug with the longest track record, and is probably the cheapest drug to purchase. In many hospitals, however, standard operating procedures dictate that nitroprusside can only be used in an intensive care unit, with an arterial line in place. When the special circumstances of such monitoring are included in cost calculations, other drugs without such requirements often have the advantage. Thus, mini-bolus doses of labetalol or even IV infusion of fenoldopam may be cheaper overall, as these drugs can be administered with the patient outside the intensive care unit, with only a BP cuff to monitor the results.

In the last several years, the FDA has expressed interest and concern about the risk of toxicity with high doses or prolonged infusions of nitroprusside, and has issued a "black-box warning" for the drug. Nitroprusside is also light sensitive, and IV lines and bags containing the drug must be protected, usually with aluminum foil. These issues have led to the development and marketing of competitors for nitroprusside, although none is offered to most hospitals at a similar price.

The most likely competitor for nitroprusside in the treatment of most hypertensive emergencies is

fenoldopam. This dopamine-1 agonist was developed as a vasodilator with specific actions in the renal, splanchnic, and coronary circulation (which have descending concentrations of dopamine-1 receptors, but more than other vascular beds). Unfortunately, it has variable oral bioavailability, and therefore its use was restricted to IV administration, where its 7–9 minute serum half-life is reasonable, and the lack of toxic metabolites may be an advantage. Unlike dopamine itself, fenoldopam has little activity at dopamine-2, β-, or α-adrenergic receptors, and therefore can be increased in dose from 0.1 μg/kg/min initially, until sufficient vasodilation (and BP reduction) occurs. In clinical studies in hypertensive emergencies, it showed specific benefits in renally-impaired patients, with short-term increases in natriuresis, diuresis, and endogenous creatinine clearance, all of which were very similar to those seen in more carefully-controlled studies in patients with lesser degrees of hypertension. Fenoldopam was approved by the FDA in September, 1998 for the inpatient short-term (48 hour) management of severe hypertension when rapid, but quickly reversible, emergency reduction of BP is clinically indicated, including malignant hypertension with deteriorating end-organ function. The side effects of fenoldopam include headache, dizziness, and flushing (typical of any vasodilator); reflex tachycardia, excessive hypotension, and brisk diuresis have also been seen.

A second alternative to nitroprusside, IV nicardipine, was approved by the FDA in 1991, and is somewhat longer acting than either nitroprusside or fenoldopam. It is most widely used for acute treatment of hypertension in patients with coronary disease and after cardiac surgery, where its coronary arterial dilating properties are helpful. Its profile of symptomatic side effects is typical of vasodilators and not much different from fenoldopam.

There are a number of new agents for hypertensive emergency in use in Europe that may eventually become available in the United States. These include: urapidil (an α blocker which also interferes with both central and peripheral uptake of serotonin) and IV felodipine or lacidipine (two dihydropyridine calcium antagonists).

After the BP has been controlled for a suitable period of time (typically 12–24 hours) to allow autoregulation to be reestablished, the parenteral antihypertensive agent should be gradually withdrawn in favor of oral medications. Typically, a short-acting calcium antagonist is given orally, and the IV administered medication down-titrated over an hour or two before moving the patient to the general medical floor. During the next day or so of hospitalization, appropriate diagnostic studies should be launched to investigate a possible secondary cause of hypertension. A 24-hour urine collection (begun when the patient had a very elevated BP) that contains levels of catecholamine metabolites within the reference ranges is strong evidence against a pheochromocytoma. Probably the most important aspect of the treatment of a hypertensive emergency is to assure adherence to antihypertensive therapy during long-term follow-up.

CONCLUSIONS

Patients presenting with a hypertensive emergency should be quickly diagnosed and promptly started on effective parenteral therapy (typically, nitroprusside 0.5 μg/kg/min) in the hospital. BP should be reduced about 10% during the first hour and another 15% gradually over 2–3 more hours. Oral antihypertensive therapy (often with an immediate-release calcium antagonist) can be instituted after 6–12 hours of parenteral therapy. Consideration should be given to secondary causes of hypertension after transfer out of the intensive care unit. Because of advances in antihypertensive therapy and management, "malignant hypertension" should be malignant no longer.

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