Tackling Stroke One Module At A Time

Blood Pressure Management in Acute Stroke

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JNC-8 Recommendations

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- Treat HTN persons aged 60 years or older to a BP goal of <150/90 – Strong evidence
- Treat HTN persons 30 through 59 years of age to a diastolic goal of less than 90mmHg – Strong evidence
- Insufficient evidence in HTN persons <60 years for a systolic goal
- Insufficient evidence in HTN persons <30 years for a diastolic goal
  - Goal of <140/90 recommended for these groups
  - Use same goal for CKD with/without DM

Disclosures

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- Speakers Bureaus:
  - Chiesi (Cardene)
  - Genentech (Activase)

Hyperacute BP Management

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- Precise, rapid control is necessary.
  - Too low may be deleterious to perfusion
  - Too high may increase risk of hemorrhage in ischemic stroke, or hemorrhagic expansion in intraparenchymal hemorrhage
- Drug choices:
  - Nitropaste – commonly used, but better venous than arterial action
  - Bolus drugs – may work, but may be a “shot in the dark”
  - Intravenous drips – appropriate next step; simple vs. complex agents

Overview

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- Hypertension is the most common condition seen in primary care and all to prevalent in acute care
- Failure to achieve control of BP is common among hypertensive patients
- Hypertension is the single most important modifiable risk factor for a number of diseases: Stroke, heart, and kidney disease

ASA Guidelines for Acute Ischemic Stroke BP Management

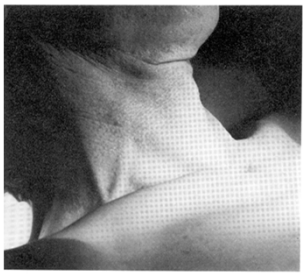
If *treating* with Activase tPA:

BP Level (mm Hg)	**Treatment**
Pre-Treatment SBP >185 or DBP > 110	Labetalol 10-20 mg over 1-2 minutes, or Nicardipine infusion started at 5mg/hr and titrated upward to max of 15 mg/hr
During & After t-PA SBP >180 DBP >105	Same as above

If *not treating* with tPA, BP may be left untreated up to:
SBP 220 mm Hg & DBP 120 mm Hg

Myocardial Dysfunction May Determine Need for BP Lowering

- Consider tolerance of left ventricular afterload!



ASA Acute ICH BP Guidelines

- Aggressive reduction of BP should occur rapidly in patients with acute ICH
- Goal should be < 140/90 mm Hg
- Drug treatment recommendations:
  - Continuous infusions to reduce variability
  - Nicardipine infusion initiated at 5 mg/hr and rapidly titrated upward to a maximum of 15 mg/hr

Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) Trial

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Quereshi AI, et al. *Critical Care Medicine* (2009)

- 3 groups:
  - 170-200 mm Hg (n=18); 1 neurologic deterioration; 0 SAE; 3 deaths.
  - 140-170 mm Hg (n=20); 2 neurologic deteriorations; SAE = 1; 2 deaths.
  - 110-140 mm Hg (n=22); 4 neurologic deteriorations; SAE = 3; 5 deaths.
- Blood pressure reduction to low systolic BPs is safe.
- Small effect noted on hematoma expansion.

Arterial Pressure Monitoring

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- Things to consider:
  - Cuff size – too small a cuff, too high a pressure and vice a versa
  - NIBPs are generally very accurate at measurement of MAP, but there is less agreement between NIBP and arterial line for systolic and diastolic pressure
  - When in doubt, verify

*INTE*nsive blood pressure *R*eduction in *A*cute *C*erebral *H*aemorrhage *T*rial - II

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Anderson, CS et al. NEJM 2013

- Aggressive reduction of BP (<140/90) in patients with ICH vs. standard of care (180/105)
- No significant reduction in hematoma volume, however non-significant trend (p=0.06) towards improved 90 day outcome in patients undergoing aggressive BP reduction
- Aggressive BP lowering was “safe”

Ideal Characteristics of Acute Antihypertensive Agents

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- Rapid onset of action
- Predictable dose response
- Titratable to desired blood pressure
- Minimal dose adjustments
- Minimal adverse effects
- No need for arterial line or ICU admission
- Ability to safely start oral agents and wean without labile BP response

Labetalol

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- Adrenergic receptor blocking agent with both selective alpha$_1$ and nonselective beta receptor blockade at a ratio of 1:7 (alpha$_1$: beta)
- Use in acute stroke traced to NINDS tPA trial; selected because it "works quickly (onset 5-15 min.), and not too well." (Expert opinion, NINDS Trialists).
- Give as 10 mg IV bolus over 1-2 minutes; may repeat or double the dose every 5 to 15 minutes up to a total of 150 mg
- Contraindicated in patients with a history of asthma due to beta$_2$ effects, and in patients with CHF, heart blocks and/or sinus bradycardia due to beta$_1$ effects

Nicardipine Administration

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- Not compatible with Ringers lactate or sodium bicarbonate
- Generic requires special infusion bags to prevent absorption of active drug
- Cardene® premix 2 year shelf life
- 0.1 mg/mL (20 mg / 200 mL) or 0.2 mg/mL (40 mg / 200 mL)
- Drip initiated at 5 mg/hr (50 mL/hr single strength)
- Maximum infusion rate should not exceed 15 mg/hr (150 mL/hr single strength)

Enalaprilat

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- Angiotensin converting enzyme inhibitor effecting the renin-angiotensin-aldosterone system
- Less effective in patients with low-renin hypertension (primarily Black population)
- Dose=1.25 mg delivered as 1 mL bolus over 5 min q6hr. Onset of action ~15 minutes; peak 2-4 hours
- Subsequent doses may have more pronounced peak effects than the initial dose
- May contribute to angioedema response (more common in Black population)
- Do not use in pregnancy (oligohydramnios; fetal craniofacial and skull deformities) or impaired renal function

Cleviprex™ (clevidipine butyrate) Injectable Emulsion

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- Similar IV dihydropyridine calcium channel-blocking antihypertensive to nicardipine
- Similar ultra-short half life with rapid onset and offset; titratable
- Lipid emulsion; supplied in premixed, ready-to-use vials
- Contraindicated in patients with severe aortic stenosis
- Additional contraindications due to formula: Allergies to soybeans, soy products, eggs, or egg products; defective lipid metabolism such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia.

1. Cleviprex Prescribing Information; August 1, 2008;
2. Nordlander M, et al. *Cardiovasc Drug Rev*. 2004;22:227-250;

Nicardipine

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- IV calcium channel blocker (dihydropyridine class) for short term BP control
- Selective arteriolar vasodilation; more selective for vascular smooth muscle than cardiac muscle (minimal negative inotropic & chronotropic effects)
- Ultra-short half life; rapid onset and offset
- Can be aggressively titrated to rapidly decrease BP
- Maintains or increases cardiac output through afterload reduction and coronary artery vasodilation
- Few dosage adjustments needed; no arterial line necessary; can be given in Step Down Unit
- Contraindicated in severe aortic stenosis

Non–Weight-Based Dosing Regimen

(clevidipine = 0.5 mg per 1 mL)

Initiate Cleviprex™ (clevidipine butyrate) IV infusion at 1-2 mg/h

Double the dose every 90 sec initially,
then as BP approaches goal, increase dose by less than double and lengthen time between dose adjustments to every 5-10 min

~1- to 2-mg/h increase will generally produce an additional 2- to 4-mmHg decrease in SBP

Monitor BP and heart rate continuously during infusion, and then until vital signs are stable

- **Desired therapeutic dose is 4-6 mg/hour; most patients were treated with maximum doses < 16 mg/hour (limited experience with doses as high as 32 mg/hour.**
- **Lipid load restriction = no more than 1000 mL/24 hours (~21 mg/hr).**

Sodium Nitroprusside (Nipride)

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- Potent, direct arterial and venous vasodilator
- Rapid/immediate onset of action at low intravenous infusion doses
- Must calculate µg/kg/min
- Requires arterial line insertion with q15 minute blood pressure monitoring in the ICU
- Potential for thiocynanate poisoning with doses approaching 10 µg/kg/min or prolonged use
- Needs its own line to avoid labile BP response related to infusion of secondary fluids

Oral Antihypertensive Agents & Alternatives

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- Choices:
  - ACE-I or angiotensin receptor blockers (ARB)
  - Thiazide diuretics
  - Calcium channel blockers
  - Adrenergic receptor blockers
  - Clonidine
  - Spironolactone
  - Minoxidil
- Carotid body stimulators

Sodium Nitroprusside (Nipride)

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- Infusion mixed as Nipride 50mg in 250 cc D5W; can double concentrate if necessary to restrict infusion volume
- Weigh patient prior to starting infusion to determine proper µg/kg/min dosage
- Infusion usually started at 0.1-0.5 µg/kg/min and titrated to effect
- Use caution when administering oral agents concurrently while trying to wean infusion

JNC-8 Guidelines

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- "In the general non-Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor(ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)"

Hydralazine

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- Precise mechanism of action is not fully understood
  - Direct relaxation of vascular smooth muscle associated with altered cellular calcium metabolism
  - Preferentially dilates arterioles with minimal venous effects
- Increases renin activity in plasma, presumably as a result of increased renal juxtaglomerular cell renin secretion in response to reflex sympathetic discharge
  - Increased angiotensin II, aldosterone secretion, sodium reabsorption
- Average maximal decrease in blood pressure usually occurs 10 - 80 minutes after administration
- May exacerbate angina in patients with CAD
- Duration of effect may make it an inappropriate choice

ACE Inhibitors & ARBs: What's the difference?

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- ACE inhibitors block the conversion of angiotensin I to angiotensin II; also inhibit degradation of bradykinin (thought to be associated with "cough" in ACE-I users)
  - Results in increased circulating renin levels
- ARBs block the vasoconstriction and aldosterone-secreting effects of angiotensin II by blocking its binding to AT_1 receptors
  - Results in increased circulating renin and angiotensin II levels

ACE & ARB

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- Pro's:
  - Prevents activation of angiotensin II receptors in the brain that promote systemic hypertension and potent intracranial arterial constriction
  - Blocks aldosterone release
  - Beneficial myocardial remodeling and renal perfusion effects
- Con's:
  - Avoid in pregnancy
  - Angioedema
  - Cough (ACE-I)
- NOTE: Moderate quality of evidence to support use as add-on therapy in CKD to improve renal outcomes

Calcium Channel Blockers

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- Pro's:
  - Originally, the ALLHAT trial showed the benefits of CCB and diuretic therapy use for blood pressure control in Black population (ABCD)*
- Con's:
  - Consider classification selected and effect on myocardial contractility (avoid negative inotropes); dihydropyridines best (i.e. amlodipine)
  - Nimodipine (high dose) has been shown to be detrimental in acute ischemic stroke and should be avoided
    - BI < 60 (OR=10.2; 95%)
    - Death (OR=4.3)
- Recommendation: Consider dihydropyridine class agent (e.g. amlodipine) as initial, or combined CCB/HCT initial therapy in Black patients.

*Panel on Hypertension; Scientific Sessions 2004; AHA.
**Rahman M et al. Annals of Internal Medicine. 2006;144(3):172-180.

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- "In the general Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic and/or CCB. (For general black population: Moderate Recommendation –Grade B; for Black patients with diabetes: Weak Recommendation – Grade C)"

Adrenergic Receptor (Beta) Blockers

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- Pro's:
  - Relatively inexpensive
  - Excellent choice for patients with precursor rhythms for atrial fibrillation (e.g. frequent PACs), or history of CAD/MI
- Con's:
  - Abrupt discontinuation DANGEROUS
  - Side effects (depression, impotence) may cause non-compliance
  - Selectivity of agent must be considered
- Recommendation: Consider use if beneficial due to cardiac history or as additive agent prn.

Thiazide Diuretics

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- Pro's:
  - Very inexpensive, easily available
- Con's:
  - In acute management, may predispose to dehydration, especially in patients with risk factors (i.e. tube feeding)
  - Dehydration may increase blood viscosity and precipitate decreased blood flow through residual stenoses in acute ischemic stroke; maintain euvolemia
- Recommendation: Probably better in outpatient management or as a secondary treatment arm in acutely ill patients (especially ischemic stroke)

Clonidine

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- Alpha adrenergic receptor blocker
- Bradycardia and AV block may occur when given in combination with calcium channel blockers
- Abrupt withdrawal of clonidine in patients concurrently receiving beta blockers may result in life threatening rebound hypertension
- May be beneficial in reducing spasticity during recovery phase

Spironolactone

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- Aldosterone antagonist
  - Blocks actions in distal nephron
  - Causes retention of potassium and increased excretion of sodium
  - Beneficial effects in heart failure and acne
- Delayed onset of effect to ~ 48 hours
- Used commonly as add-on therapy with a thiazide or loop diuretic to counteract potassium wasting

Summary

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- Hypertension is the single most important and most common risk factor for two leading causes of death
- Use of 1 agent across all patients is unlikely to produce adequate blood pressure control; individualize! Patients with hypertension ALMOST ALWAYS require at least 2+ medications to achieve optimal control
- Patients and clinicians MUST work as partners to achieve blood pressure control

Minoxidil

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- Should be considered when other drug classifications have failed to control blood pressure
  - When adding Minoxidil to an existing "potent" blood pressure medication regime, go slow!
    - Start 5 mg
    - Titrate dose upward to effect achieved
    - Target dose = 10-40 mg; Max dose = 100 mg
  - Usually given with beta-blockers to prevent rebound tachycardia
  - Add a loop diuretic to prevent fluid volume retention & CHF
  - Monitor for pericardial effusion that may progress to cardiac tamponade

Carotid Sinus Stimulator

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- Rheos system for treatment of blood pressure in patients that are refractory to medicinal management alone
  - Activates baroreflex and reduces sympathetic tone: Decreases heart rate; dilates vasculature
  - "Brain's cardiovascular center is tricked into believing BP is actually higher than it is"
- Direct stimulation
  - Pacing electrodes are implanted close to the carotid sinuses; connected to a pulse generator implanted in the chest