Hypertension and the Renal Transplant Patient

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Prevalence of Hypertension

- 45.4% of adults greater than 18 years of age in the US have HTN according to the ACC/AHA (American College of Cardiology/ American Heart Association)
- Rates of HTN in the US are higher in males, those with obesity, older adults, those living in rural areas, AA adults and those with CKD
- Global prevalence of HTN is about the same as HTN in the United States
- Renal transplant recipients rates of HTN range from 50-80% in adults and 47-82% in pediatric recipients

Who Publishes Guidelines for Hypertension

1. American College of Cardiology (ACC)/American Heart Association (AHA)
2. European Society of Hypertension (ESH)/International Society of Hypertension (ISH)
3. National Institute for Health and Care Excellence (NICE)
4. Joint National Committee 8 (JNC 8)
5. Kidney Disease Outcomes Quality Initiative (KDIGO)

American College of Cardiology (ACC)/American Heart Association (AHA) Definition of HTN

Normal blood pressure: SBP <120 mmHg and DBP <80 mmHg

Elevated blood pressure: SBP of 120 to 129 mmHg and DBP of <80 mmHg

Hypertension:

- Stage 1: Systolic 130 to 139 mmHg or diastolic 80 to 89 mmHg
- Stage 2: Systolic at least 140 mmHg or diastolic at least 90 mmHg

***always use higher value to determine stage

European Society of Hypertension (ESH)/International Society of Hypertension (ISH) and National Institute for Health and Care Excellence (NICE) Definition of HTN

Definition of hypertension according to office, ambulatory, and home BP levels per guideline statements

SBP/DBP	Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-hour ABPM
ACC/AHA Guidelines 2017[1]	≥130/80	≥130/80	≥130/80	≥110/65	≥125/75
ESC/ESH Guidelines 2018[2]	≥140/90	≥135/85	≥135/85	≥120/70	≥130/80

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HBPM: home blood pressure monitoring; ABPM: ambulatory blood pressure monitoring; ACC/AHA: American College of Cardiology/American Heart Association; ESC/ESH: European Society of Cardiology/European Society of Hypertension.

Data from:

1. *Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018; 71:e127.*
2. *Williams B, Giuseppe M, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018; 39:3021.*

Joint National Committee 8 Definition of Hypertension

- Most of us are familiar with JNC 8 guidelines
- Seems to be 1 of the most referenced/used in the clinical practice of renal transplantation
- Has specifications for patients with kidney disease, DM, and accommodates for age
- Recommends safer usages of ACEi and ARBs

JNC 8 Guidelines: What's New

- Compared with previous JNC guidelines; JNC 8 allows for higher BPs goals and advocates less use of multiple classes antihypertensive meds
- Patients ≥ 60 yo without kidney disease or DM: goal BP is now less than 150/90mmHg
- Patients 18-59yo with no major comorbidities and in pts 60 years or older who HAVE diabetes, CKD or both DM and CKD BP goal is less than 140/90mmHG
- 1st line treatment now limited to 4 classes of medications
- Thiazide-type diuretics
- Calcium channel blockers
- ACEi
- ARBs

JNC 8 Guidelines: What's New

- 2nd and 3rd line therapy is now just higher doses or combinations of the 1st line drugs : ACEi, ARBs, CCBs, thiazide-type diuretics
- Several meds designated as later-line /alternative
- A1/ß blockers (carvedilol/Coreg), vasodilating B-Blockers (nebivolol/Bystolic), central A2/-adrenergic antagonist (clonidine), direct vasodilators (hydralazine), loop diuretics (furosemide), aldosterone antagonist (spironolactone) and peripherally acting adrenergic antagonist (reserpine)

Special Populations with JNC 8 Guidelines

- Initial therapy: African decent NO CKD: use CCBs and thiazides instead of ACEi
- CKD regardless of ethnic background: use ACEi and ARBs either as 1st line therapy or in addition to 1st line therapy
- 75 years or older with impaired kidney function: use CCBs and thiazide-type diuretics instead of ACEi/ARBs due to risk of hyperkalemia, increasing sCR further

***ACEi and ARBs should not be used in the same patient at the same time

Other Guideline Recommendation

Table 2 **Target Blood pressure guideline for kidney transplant recipients.**

Medical Society/Guideline	Recommended BP target
ACC/AHA[65]	< 130/80 mm Hg
JNC 8 (2014)[66]	Not defined
Kidney disease outcomes quality initiative (KDOQI)[67]	-Goal of 125/75 mm Hg for transplant recipients with proteinuria. -Goal of 130/85 in the absence of proteinuria
Kidney disease: Improving Global outcomes (KDIGO)[68]	< 130/80
European Best Practice Guidelines for Renal Transplantation 2002[19]	Target BP ≤ 125/75 mm Hg in proteinuria patients
Canadian Society of Nephrology[69]	Patients with significant proteinuria; Target Blood pressure is < 130/80 mm Hg
British Renal Association[70]	< 130/80 mm Hg

A reasonable target blood pressure is < 140/90 mmHg for transplant recipients who do not develop proteinuria. (Are you sure about the recommended first line agents?)

HTN Post Renal Transplant

- HTN is noted in about 85% of renal transplant
- The following risk factors lend a higher incidence of posttransplant HTN:
  - Pretransplant HTN
  - Increased BMI
  - Male Sex
  - Presence of native kidney
  - Delayed or chronic allograft dysfunction
  - Cyclo, FK and/or glucocorticoid therapy
  - Recurrence of primary disease in transplanted allograft
  - Acute Rejection

Contributing Factors to HTN in Renal Transplant Recipients

Kidney-Related Causes

- Allograft Dysfunction
  - Delayed Graft Function
  - Acute Rejection
  - Chronic Allograft Injury
- Immunosuppressive Agents
  - Steroids
  - Calcineurin Inhibitors

Contributing Factors to HTN in Renal Transplant Recipients

- Donor Characteristic
  - Poor allograft quality (Extended Criteria donor)
  - Pre existing donor HTN
  - Genietic variant: : APOL1
  - Disparity between donor and recipient size
- Renal Artery Stenosis
- Ischemic Nephropathy

Nonkidney-related Causes

Primary Aldosteronism

Obstructive Sleep Apnea

Allograft Dysfunction

- **Delayed Graft Function:** The need for dialysis the 1st few weeks posttransplant can lead to volume overload and acute increase in BP

  Treatment: Remove excess fluid with dialysis or diuretics

- **Acute Rejection:** HTN primarily due to Na++ retention, increased activity of renin angiotensin system and allograft dysfunction. Worsened by the use of high dose steroids used for treatment

  Treatment: Reversal of rejection

- **Chronic Allograft Injury**: Due to chronic AMR or interstitial fibrosis/tubular atrophy (IFTA), microangiopathy, or recurrent glomerular disease

  Treatment: Treat like HTN in patient with CKD

Immunosuppressive Agents

- **Glucocorticoids:** Exacerbates HTN when high doses are used (early post transplant)

  Treatment: Weaning down to maintenance dose

- **Calcineurin Inhibitors:** Play some role in almost all pts with HTN. BP usually lower with FK than Cyclo. Combo of FK and mTOR usually the worst for HTN
  - Cyclo: increases both systemic and renal vascular resistance
  - FK: causes HTN by activation of renal Na++chloride cotransporter.

  Treatment: Adjustments in IS

Renal Artery Stenosis

- Usually occurs 3m to 1y posttransplant
- Most commonly occurs at renal artery anastomosis, donor renal artery, or feeding native artery
- Clinical features
  - Worsening HTN
  - HypoK
  - Decreased kidney functioning in the setting of ACEi/ARBs
  - Episodes of flash pulmonary edema
  - Abdominal bruit
  - **Treatment:** Reversal of stenosis with medical therapy or revascularization

Donor Characteristic

- There is suggestive evidence that the transplanted kidney may have prohypertensive or antihypertensive properties
- Multiple studies in transplantation show inherited tendency to HTN is found primary in the kidney (APOL1)
- Larger studies found a “HTN kidney” transplanted into a normotensive recipient had a greater chance of a HTN response that other donor combinations

Outpatient BP Monitor
Fresh Transplant

- Posttransplant HTN should be treated to protect against cardiovascular disease and HTN injury to the transplant
- Posttransplant HTN has been linked with decreased long term graft survival
- Posttransplant HTN immediate postop can be tricky within the first few weeks. HTN in the first few weeks posttransplant can be due to
  - Pain and/or anxiety
  - Volume overload/graft dysfunction
- Graft dysfunction could be due to rejection, ischemia, CNI toxicity
- Delicate balance between maintaining organ perfusion (prevent thrombus) and Proper BP control

Outpatient BP Monitoring
Fresh Transplant

- Immediate posttransplant period avoid hypotension to maintain adequate allograft profusion and prevent graft thrombus. How “high” BPs are permitted vary among centers (140-160/90s)
- Patients that were being treated for HTN before transplant usually resume their meds after transplant with the exception of ACEi/ARBs (usually holds for first 3-6 months) ACEi/ARBS
  - Increase sCR concentration
  - Hyperkalemia
  - Prevent recovery from anemia

Long-Term Post Transplant Management of HTN

- These are usually patients 3 to 6 months and beyond
- Usually centers target BPs per guidelines: Most often JNC 8
- Most centers ask patients to monitor at home. Centers usually do not rely on clinical BPs only since most often they are higher (BPs afford a large degree of interindividual variability)
- IS: CNIs are generally reduced to lowest possible dose to prevent rejection in response to HTN. Maintenance of pred usually not discontinued

New Onset HTN Posttransplant

- CCBs: dihydropyridine CCBs have been shown to reduce graft loss and minimize CNI induced vasocontraction
  - Amlodopine
  - Felodopine
  - Nifedipine
    - AVOID nondihydropyridine CCBs since they are potent CYP3A/4 inhibitors and use with CNIs (FK and Cyclo) or with mTOR inhibitors (sirolimus/everolimus) will lead to increased levels
      - Diltiazem
      - Verapamil

Additional Options Uncontrolled HTN

- No contraindication in any class of meds in kidney transplant recipients
- Second line therapy guided by the patients comorbidities

Measuring BP Pearls

- Most importantly: make sure your clinical partner know how to take a manual pressure and how to determine the proper cuff size
- Marked differences between clinical BPs and home BPs
- 3 consecutive reading (average readings)
- Remember circadian variations: peak in am, trough in sleep (no dipping trough in HTN patients puts them at greater risk for cardiovascular events)
- NIH suggest season BP variations of higher in winter and lower in summer
- Automated vs manual BP
- Transplant patient (dialysis access): Ankle pressures are usually higher, some wrist monitor vary up to 20mmHG versus manual pressure

Measuring BP Pearls

- Targetbp.org by the AHA/AMA has great info on how pt's should appropriately measure BPs at home
- OTC/Herbals interfere with IS med and with some HTN meds (biggest offenders are cough and cold meds)
- Don't forget lifestyle management

Measuring BP Pearls

Best proven nonpharmacologic interventions for prevention and treatment of hypertension*

	Nonpharmacologic intervention	Dose	Approximate impact on SBP		
			Hypertension	Normotension	Reference
Weight loss	Weight/body fat	▪ Best goal is ideal body weight, but aim for at least a 1 kg reduction in body weight for most adults who are overweight. Expect about 1 mmHg for every 1 kg reduction in body weight.	-5 mmHg	-3 mmHg	[1]
Healthy diet	DASH dietary pattern	▪ Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	-11 mmHg	-3 mmHg	[2,3]
Reduced intake of dietary sodium	Dietary sodium	▪ Optimal goal is <1500 mg/day, but aim for at least a 1000 mg/day reduction in most adults.	-5 to -6 mmHg	-2 to -3 mmHg	[4,5]
Enhanced intake of dietary potassium	Dietary potassium	▪ Aim for 3500 to 5000 mg/day, preferably by consumption of a diet rich in potassium.	-4 mmHg	-2 mmHg	[6]
Physical activity	Aerobic	▪ 90 to 150 minutes/week. ▪ 65 to 75% heart rate reserve.	-5 to -8 mmHg	-2 to -4 mmHg	[7,8]
	Dynamic resistance	▪ 90 to 150 minutes/week. ▪ 50 to 80% of maximum 1 repetition weight. ▪ 6 exercises, 3 sets/exercise, 10 repetitions/set.	-4 mmHg	-2 mmHg	[7]
	Isometric resistance	▪ 4 × 2 minutes (hand grip), 1 minute rest between exercises, 30 to 40% maximum voluntary contraction, 3 sessions/week. ▪ 8 to 10 weeks.	-5 mmHg	-4 mmHg	[9,10]
Moderation in alcohol intake	Alcohol consumption	▪ In individuals who drink alcohol, reduce alcohol to:¶ • Men: ≤2 drinks daily. • Women: ≤1 drink daily.	-4 mmHg	-3 mmHg	[11-13]

SBP: systolic blood pressure; DASH: Dietary Approaches to Stop Hypertension.

* Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.

¶ In the United States, one "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).[14]

Proper Blood Pressure Measurement

Checklist for accurate measurement of blood pressure

Key steps for proper BP measurements	Specific instructions
Step 1: Properly prepare the patient	1. Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 minutes. 2. The patient should avoid caffeine, exercise, and smoking for at least 30 minutes before measurement. 3. Ensure patient has emptied their bladder. 4. Neither the patient nor the observer should talk during the rest period or during the measurement. 5. Remove all clothing covering the location of cuff placement. 6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.
Step 2: Use proper technique for BP measurements	1. Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically.* 2. Support the patient's arm (eg, resting on a desk). 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used. 5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.
Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. 2. Separate repeated measurements by 1 to 2 minutes. 3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20 to 30 mmHg above this level for an auscultatory determination of the BP level. 4. For auscultatory readings, deflate the cuff pressure 2 mmHg per second, and listen for Korotkoff sounds.
Step 4: Properly document accurate BP readings	1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number. 2. Note the time of most recent BP medication taken before measurements.
Step 5: Average the readings	1. Use an average of ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.
Step 6: Provide BP readings to patient	1. Provide patients the SBP/DBP readings both verbally and in writing.

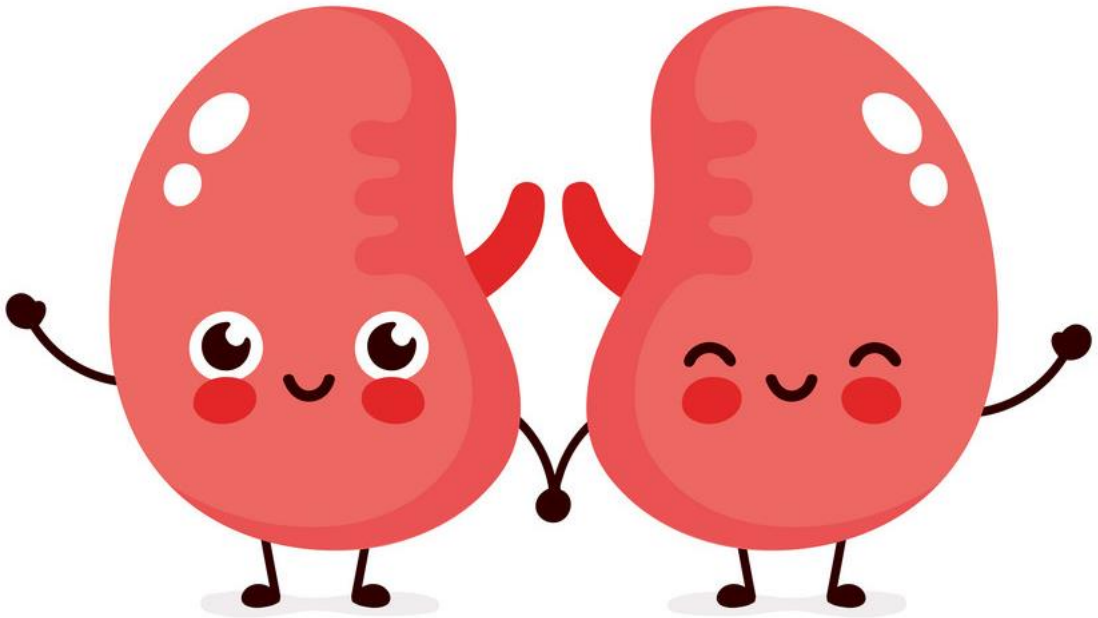
BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

* Devices should be checked at least twice yearly against a mercury sphygmomanometer for accuracy.

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
• Adagrasib • Atazanavir • Ceritinib • Clarithromycin • Cobicistat and cobicistat-containing coformulations • Darunavir • Idelalisib • Indinavir • Itraconazole • Ketoconazole • Levoketoconazole • Lonafarnib • Lopinavir • Mifepristone* • Nefazodone • Nelfinavir • Nirmatrelvir-ritonavir • Ombitasvir-paritaprevir-ritonavir • Ombitasvir-paritaprevir-ritonavir plus dasabuvir • Posaconazole • Ritonavir and ritonavir-containing coformulations • Saquinavir • Tucatinib • Voriconazole	• Amiodarone¶ • Aprepitant • Berotralstat • Cimetidine¶ • Conivaptan • Crizotinib • Cyclosporine¶ • Diltiazem • Duvelisib • Dronedarone • Erythromycin • Fedratinib • Fluconazole • Fosamprenavir • Fosaprepitant¶ • Fosnetupitant-palonosetron • Grapefruit juice • Imatinib • Isavuconazole (isavuconazonium sulfate) • Lefamulin • Letermovir • Netupitant • Nilotinib • Ribociclib • Schisandra • Verapamil	• Apalutamide • Carbamazepine • Enzalutamide • Fosphenytoin • Lumacaftor • Lumacaftor-ivacaftor • Mitotane • Phenobarbital • Phenytoin • Primidone • Rifampin (rifampicin)	• Bexarotene • Bosentan • Cenobamate • Dabrafenib • Dexamethasone◊ • Dipyrone • Efavirenz • Elagolix, estradiol, and norethindrone therapy pack◊ • Eslicarbazepine • Etravirine • Lorlatinib • Mitapivat • Modafinil • Nafcillin • Pexidartinib • Rifabutin • Rifapentine • Sotorasib • St. John's wort

Questions?



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