# Uncontrolled Hypertension: Similarities & Differences Across the Age Spectrum (pediatric vs adult populations)

***Development of Antihypertensive Products for Use in Pediatric Patients***

FDA, White Oak Campus

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## Financial Disclosure

The speaker for this educational activity has disclosed the following financial relationships:

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All relevant financial relationships have been mitigated.

# Overview

1. Review the importance of addressing **uncontrolled (UH)** and **treatment-resistant hypertension (TRH)**
2. Discuss the difference between UH and TRH
3. Review definitions of UH and TRH in adults and children
4. Discuss socioecological models of health and the importance of considering this model when evaluating UH in adults and children
5. Review the known etiologies of TRH in adults and children, including pathophysiology
6. Compare and contrast similarities and differences in UH and TRH across the age spectrum
7. Methods for assessing UH and TRH in adults and children

# Importance of Addressing Uncontrolled (UH) and Treatment-Resistant Hypertension (TRH)

Hypertension (uncontrolled)

* Risk multiplier: Stroke, myocardial infarction (MI), advanced stages of cardiovascular kidney metabolic (CKM) syndrome
    * 47% greater likelihood of suffering a combined outcome of death, MI, heart failure (HF), stroke, or chronic kidney disease (CKD) over the median of 3.8 years of follow-up
    * 2-fold increased risk of cardiovascular (CVD) events in patients with true TRH vs antihypertensive medication responders

*Daughtery SL, et al. Circulation. 2012. PMID 22379110. Carey RM, et al. Hypertension. 2018. PMID 30354828. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association*

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# Foundational Studies: Framingham Study

## Framingham Study Insights on the Hazards of Elevated Blood Pressure

SUMMARY OF THE ORIGINAL ARTICLE

**Epidemiologic Assessment of the Role of Blood Pressure in Stroke: The Framingham Study**

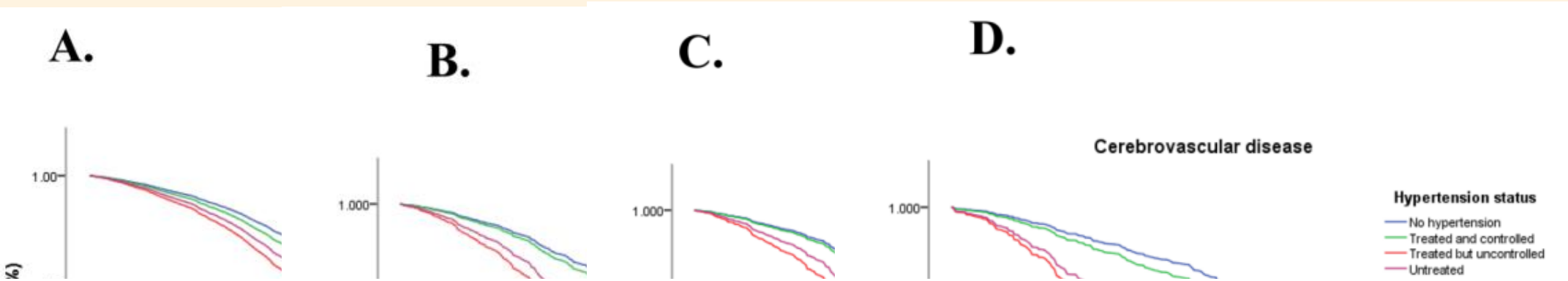
**William B. Kannel, MD, Philip A. Wolf, MD, Joel Verter, MS, and Patricia M. McNamara**

*JAMA. 1970;214(2):301-310.*

Control of hypertension whether labile or fixed, systolic or diastolic, and at any age or in either sex, appears to be central to the prevention of atherothrombotic brain infarction (ABI). Prospectively, hypertension proved to be the most common and potent precursor of ABIs. Its contribution was direct and could not be attributed to factors related both to stroke and hypertension. Asymptomatic, casual hypertension was associated with a risk of ABI about 4 times that of normotensive individuals. The probability of occurrence of an ABI was predicted no better with both blood pressure measurements or the mean arterial pressure than with systolic alone. Since there was no diminishing impact of systolic blood pressure with advancing age, the concept that systolic elevations are, even in the aged, innocuous is premature. When normotensive and hypertensive individuals were compared in each sex, women did not tolerate hypertension better than men.

See www.jama.com for full text of the original *JAMA* article.

# Foundational Studies (cont'd): NHANES




| Hypertension status | n/ N* | All-causes | | | CVD | | | Heart disease | | | Cerebrovascular diseases | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | HR (95%CI) | *p* value | n/N* | HR (95%CI) | *p* value | n/N* | HR (95%CI) | *p* value | n/N* | HR (95%CI) | *p* value |
| Normal | 1561/10300 | 1.00 (Reference) | | 357/10300 | 1.00 (Reference) | | 286/10300 | 1.00 (Reference) | | 71/10300 | 1.00 (Reference) | |
| Treated & controlled | 335/743 | 1.16 (0.95–1.42) | 0.151 | 91/743 | 1.12 (0.76–1.63) | 0.565 | 71/743 | 1.09 (0.71–1.67) | 0.693 | 20/743 | 1.24 (0.55–2.81) | 0.593 |
| Treated & uncontrolled | 635/989 | 1.62 (1.35–1.95) | <0.001 | 240/989 | 2.23 (1.66–2.99) | <0.001 | 169/989 | 2.19 (1.57–3.05) | <0.001 | 71/989 | 3.01 (1.91–4.73) | <0.001 |
| Untreated | 1019/1915 | 1.40 (1.21–1.62) | <0.001 | 339/1915 | 1.77 (1.34–2.35) | <0.001 | 245/1915 | 1.69 (1.23–2.32) | 0.002 | 94/1915 | 2.53 (1.52–4.23) | 0.001 |

*Zhou D, et al. Sci Rep. 2018. PMID: 29925884.*

# Uncontrolled HTN vs Treatment-Resistant HTN: What is the difference?

Uncontrolled Hypertension (UH)
BP ≥ goal

↓

Were secondary causes of HTN diagnosed and treated?

Were appropriate therapies prescribed?

Are prescribed therapies being taken as recommended?

Were therapeutic doses optimized, 3 or more agents, including a diuretic? (adults) (or) BP controlled on 4 optimally dosed medications

↓

All “Yes”, but BP ≥ goal=
TREATMENT- RESISTANT
HYPERTENSION (TRH)*

**Must consider the possibility of pseudo-resistance caused by white-coat effect, poor medication adherence, and suboptimal dosing. Optimal dosing: maximum and maximally tolerated dosing.*

# Categories of UH: (3)

**“White Coat” Uncontrolled HTN/ Pseudo-uncontrolled HTN**

* BP > goal based on office BP alone

**“”Masked” Uncontrolled HTN**

* BP > goal based on home BP (HBP) (oscillometric device- adults or ambulatory blood pressure monitor (ABPM)- adults and peds)

*2025 AHA/ACC Adult Hypertension Guideline. PMID 40811497*

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# Definition(s): Adults- UH

Definitions:

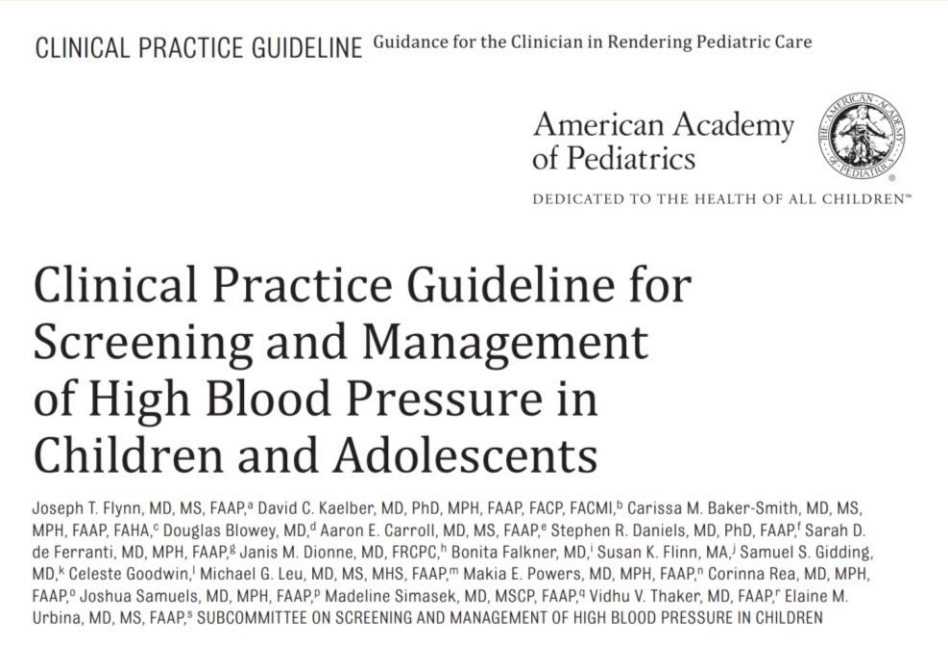
**Table 7.** Values of Systolic/Diastolic Blood Pressure for Ambulatory and Home Blood Pressure Monitoring Corresponding to Office Systolic/Diastolic Blood Pressure Levels

| Office, mm Hg | HBPM, mm Hg | Daytime ABPM, mm Hg | Nighttime ABPM, mm Hg | 24-Hour ABPM, mm Hg |
|---|---|---|---|---|
| 120/80 | 120/80 | 120/80 | 100/65 | 115/75 |
| 130/80 | 130/80 | 130/80 | 110/65 | 125/75 |
| 140/90 | 135/85 | 135/85 | 120/70 | 130/80 |
| 160/100 | 145/90 | 145/90 | 140/85 | 145/90 |

# Definition(s): Pediatrics- UH

**Definitions:**

No established definition of uncontrolled hypertension according to the 2017 AAP Clinical Practice Guideline



CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents

Joseph T. Flynn, MD, MS, FAAP,[a] David C. Kaelber, MD, PhD, MPH, FAAP, FACP, FACMI,[b] Carissa M. Baker-Smith, MD, MS, MPH, FAAP, FAHA,[c] Douglas Blowey, MD,[d] Aaron E. Carroll, MD, MS, FAAP,[e] Stephen R. Daniels, MD, PhD, FAAP,[f] Sarah D. de Ferranti, MD, MPH, FAAP,[g] Janis M. Dionne, MD, FRCPC,[h] Bonita Falkner, MD,[i] Susan K. Flinn, MA,[j] Samuel S. Gidding, MD,[k] Celeste Goodwin,[l] Michael G. Leu, MD, MS, MHS, FAAP,[m] Makia E. Powers, MD, MPH, FAAP,[n] Corinna Rea, MD, MPH, FAAP,[o] Joshua Samuels, MD, MPH, FAAP,[p] Madeline Simasek, MD, MSCP, FAAP,[q] Vidhu V. Thaker, MD, FAAP,[r] Elaine M. Urbina, MD, MS, FAAP,[s] SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN

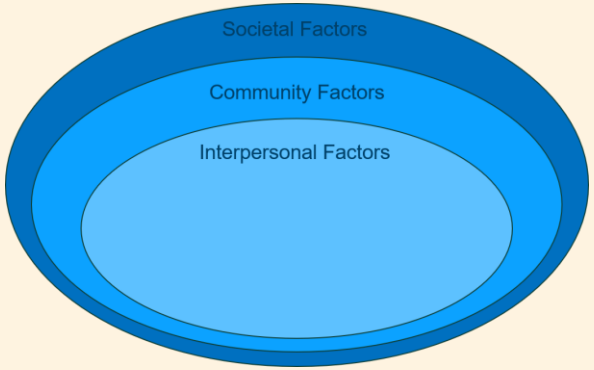
*Flynn J, Kaelber D, Baker-Smith CM> Pediatrics. 2017.. PMID 28827377.*

# Socioecological Framework & Primary HTN


*Connolly S, Zaidi A, Baker-Smith CM. Adv Kidney Dis Health. 2026. June 24: S2949-8139. PMID 42397325.*

# Prevalence and Etiologies: UC HTN, Adults

**50-80% of adults prescribed antihypertensive therapy do not take medications as prescribed.** Potential Reasons:




- Large pill burden
- Dosing complexity
- Expense
- High frequency of adverse reactions with multidrug antihypertensive regimens
- Poor patient-clinician relationship (race, older age, male)
- Clinician inertia with reduced insistence on adherence when patients are consistently nonadherent (non-judgemental clinician-patient discussion)
- Higher prevalence: race=social construct, obstructive sleep apnea (OSA), left ventricular hypertrophy (LVH), albuminuria, diabetes, CKD, higher Framingham 10-year risk score

*Carey RM, et al. Hypertension. 2018. PMID 30354828. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association*

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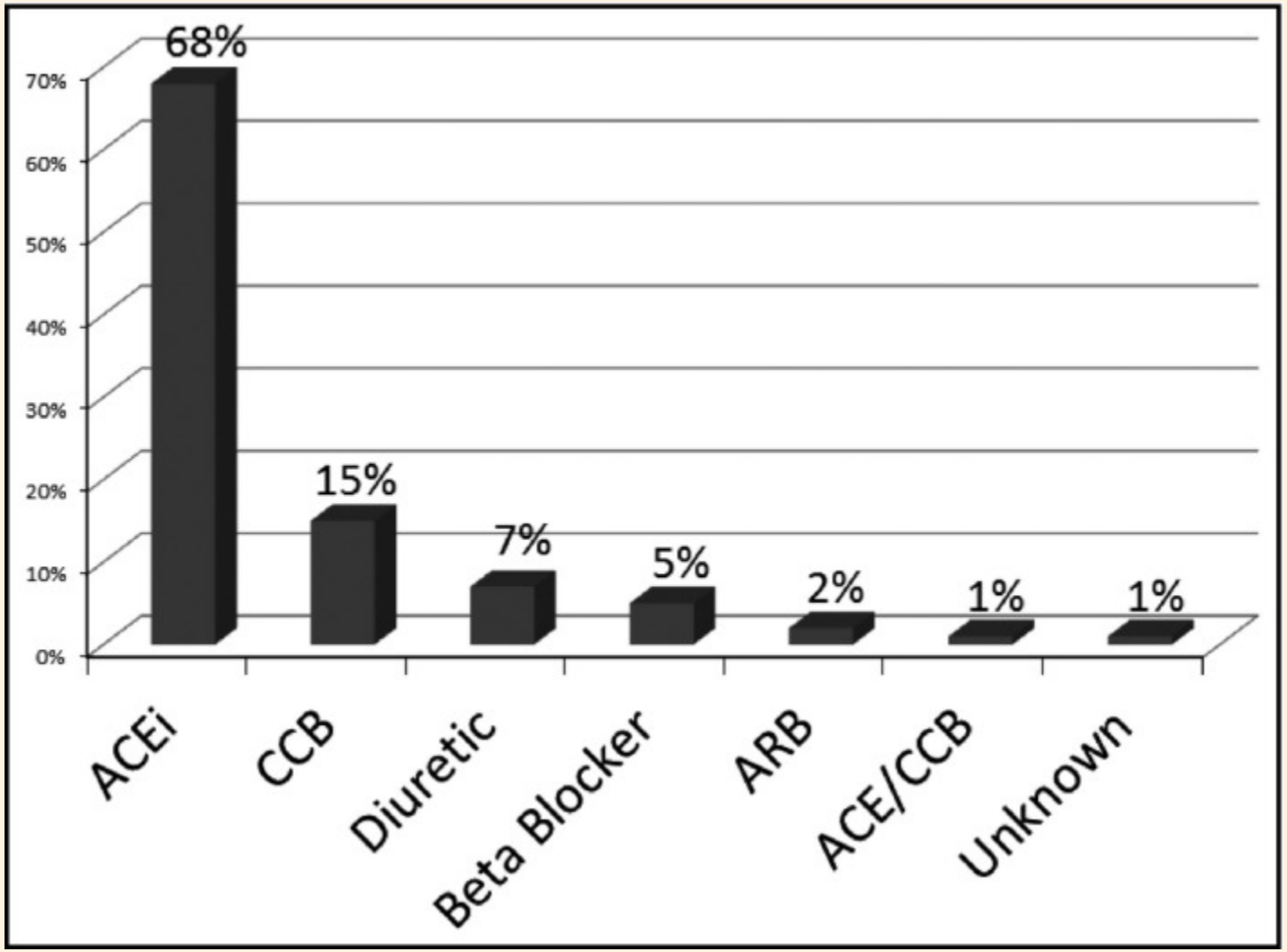
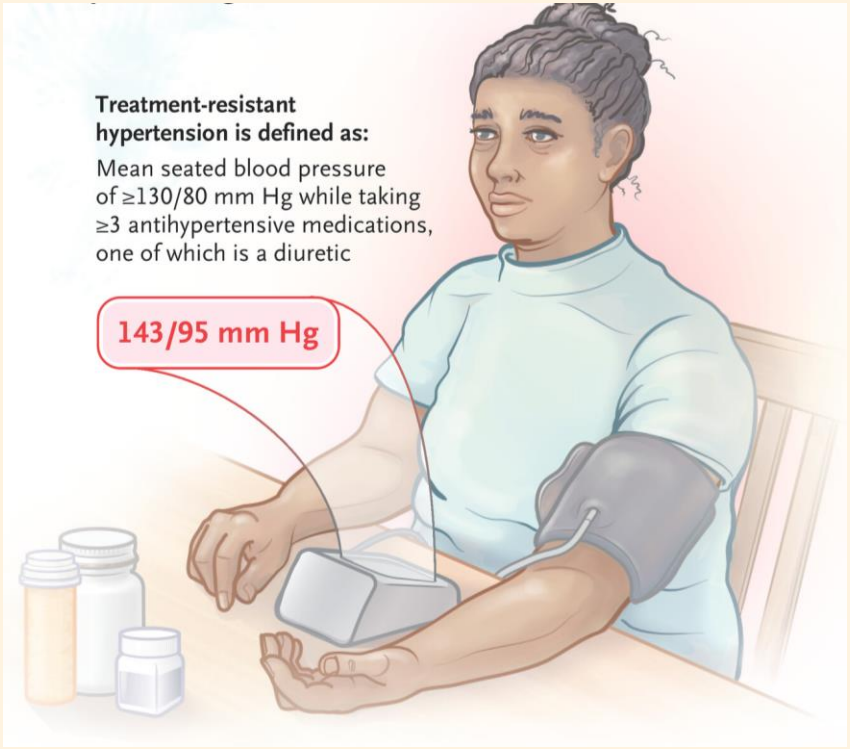
# Prevalence & Causes of UC HTN in Pediatrics




28% of children with poorly controlled blood pressure are prescribed 2+ antihypertensive medications.

*Binka E, ...Baker-Smith, CM. J Clini Hypertens. 2017. PMID 27481566.*

# TREATMENT RESISTANT HYPERTENSION (TRH)



# Definition(s): Adults- TRH

**Definitions:**

(1) Blood pressure > goal despite use of 3 antihypertensive therapies (including diuretic therapy at maximally tolerable doses); all prescribed at maximally effective doses

(2) Blood pressure = goal, requiring 4 or more antihypertensive therapies

*2025 AHA/ACC Adult Hypertension Guideline. PMID 40811497*

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# Definition: Pediatrics- TRH

**Definition less well established-** 2017 American Academy of Pediatrics (AAP) Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents

* There is currently no established pediatric-specific definition of treatment-resistant hypertension
* Consider use of the adult definition

| | |
|---|---|
| 21. Evaluate and treat children and adolescents with apparent treatment-resistant HTN in a similar manner to that recommended for adults with resistant HTN. | 7.4 |

*Flynn JT, Kaelber D, Baker-Smith CM, et al. Pediatrics. 2017. PMID 28827377*

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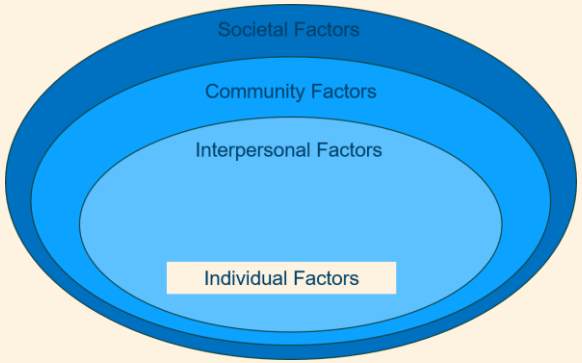
# Prevalence and Etiologies: TRH, Adults

*12 to 18% of all patients receiving antihypertensive therapy have treatment-resistant hypertension. Etiologies:

1. ET-1 elevation (potent vasoconstrictor); not targeted by conventional antihypertensive drug classes (RAS blockers, CCBs, diuretics); **OSA, obesity.** ET-1 mediates aldosterone and catecholamine release
2. Vasopressin elevation: upregulates ET-1 expression and also promotes oxidative stress (via stimulated superoxide production); **elevated total peripheral vascular resistance**.
3. **Arterial stiffness** and vascular remodeling: arterial stiffness is a result and contributor to TRH. Compromised "windkessel" cushioning within the aorta→ isolated systolic HTN. Stiffening→ remodeling of small vessels and increased peripheral vascular resistance and increased BP
4. **Obstructive sleep apnea**: sympathetic overdrive→ RAAS activation, endothelial dysfunction, and fluid retention. 2.84OR for TRH in OSA.
5. **Social factors and deprivation-influenced indices**: obesity, DM.




*Carey RM, et al. Hypertension. 2018. PMID 30354828. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association*

# Pediatric TRH- Prevalence

**Unknown prevalence of TRH in pediatrics**

* Case reports of TRH

Steps:

* confirm accurate BP measurement
* verify medication adherence
* exclude white-coat HTN (ideally with ABPM)
* screen for secondary causes
* optimize lifestyle modifications
* consider a mineralocorticoid receptor antagonist

Pediatric Nephrology (2020) 35:969–976
https://doi.org/10.1007/s00467-019-04268-w

EDUCATIONAL REVIEW

Check for updates

## Does treatment-resistant hypertension exist in children? A review of the evidence

Ian Macumber[1] · Joseph T. Flynn[2]

Received: 16 January 2019 / Revised: 20 March 2019 / Accepted: 18 April 2019 / Published online: 30 May 2019


**Abstract**
Treatment-resistant hypertension (TRH) is a well-described condition in adult patients that is associated with poor clinical outcomes. While case reports of hypertension resistant to therapy in children have been published, it is unclear if TRH truly exists in childhood. This educational review will briefly summarize recent evidence and recommendations for TRH in adults, as well as will review the literature regarding medically resistant hypertension in children and adolescents. Finally, we propose a clinical approach for evaluation hypertensive children and adolescents with apparent treatment resistance.

**Keywords** Treatment-resistant hypertension · Apparent resistant hypertension of childhood · Pediatrics · Children and adolescents

### Introduction

Treatment-resistant hypertension (TRH) in adults is defined as hypertension that is not controlled on three optimally dosed antihypertensive agents, or hypertension that is well con-

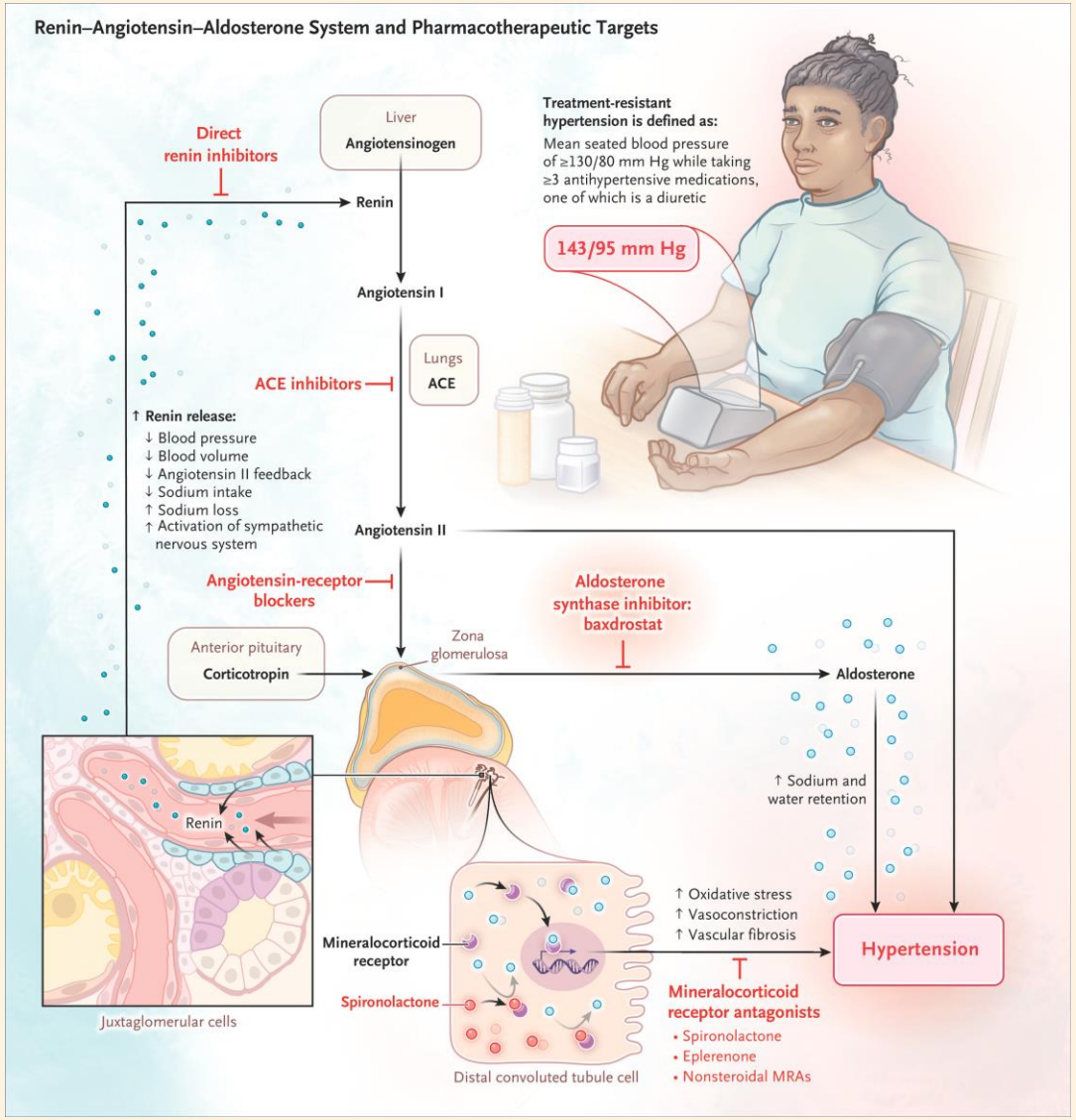
suboptimal drug dosing can lead to misclassification of patients as being treatment-resistant, which has been referred to as apparent treatment-resistant hypertension (aTRH). Many studies that have looked at the prevalence of TRH have not evaluated for these factors, making it difficult to estimate

# Pathophysiology of TRH-Adults

**Interplay of neurohormonal pathways:** inappropriate aldosterone excess (retained excess sodium and water, wasting of potassium into the urine), sympathetic overactivity, endothelin-1 and vasopressin overactivity, impaired natriuretic peptide activity, and endothelial dysfunction → volume /sodium overload, increased arterial stiffness, and kidney fibrosis

- Central mechanism is **aldosterone excess** and volume overload; aldosterone excess is renin-independent (different than the normal RAAS feedback loop); aldosterone→ sodium reabsorption in the distal nephron, vascular remodeling, endothelial dysfunction, and promotion of cardiac and perivascular fibrosis
- ***Primary aldosteronism***= most common secondary cause of TRH (5-25%)
- ***RAS resistance***: prolonged treatment with ACE inhibitor or ARB→ "aldosterone escape" or aldosterone breakthrough= aldosterone levels rebound above pre-treatment levels
- *There is a difference between TRH and refractory HTN. TRH is driven by volume overload and aldosterone excess (responds to spironolactone) vs refractory HTN (5 drugs or more, including a thiazide diuretic and mineralocorticoid receptor agonist (MRA))- due to heightened sympathetic output and normal aldosterone levels. Tx for refractory HTN is alpha-beta blockade and centrally acting sympathoinhibitors.*

# Pathophysiology of TRH, Adults (cont'd)




*Leopold JA and Ingelfinger JR. NEJM 2023. PMID 36724334.*

# "Pathophysiology" of TRH- Pediatrics

**Multifactorial:** Treatment centers on dietary sodium restriction, the elimination of substances known to increase blood pressure, and the identification of previously undiagnosed secondary HTN; thus, the pathophysiology of TRH in children is likely multifactorial

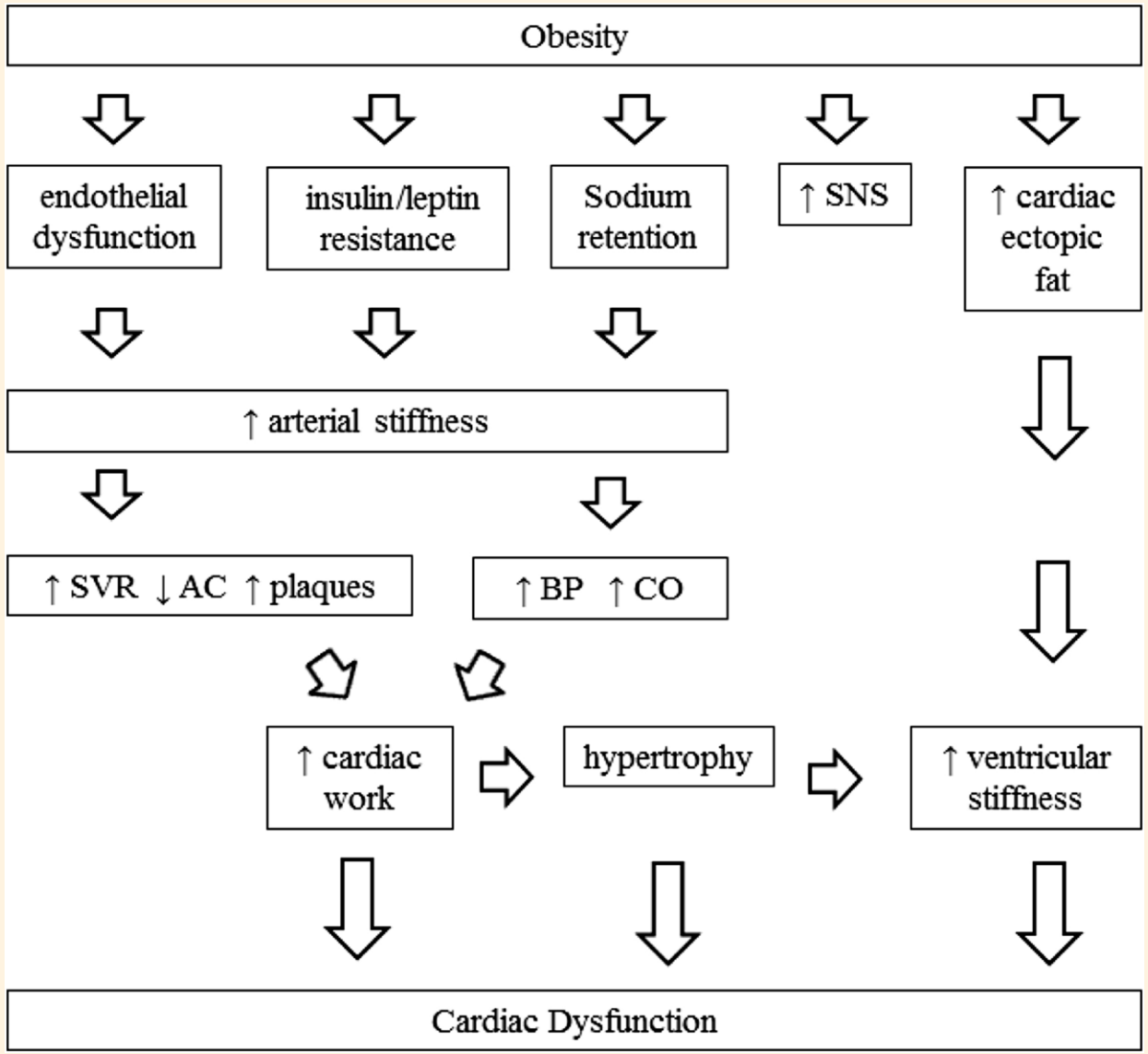
**Volume and sodium overload:** Excess dietary sodium promotes volume expansion, suppresses plasma renin activity, and diminishes the effectiveness of RAS blockers. Salt sensitivity is a particular issue in children with chronic kidney disease (impaired natriuresis → worse HTN)

**Renin-angiotensin-aldosterone system (RAS): Dysregulation** (vs inappropriate R renin-independent aldosterone excess as occurs in adults.

**Sympathetic nervous system overactivity**: Elevated plasma norepinephrine levels have been documented in children with hypertension. There can be chronically elevated sympathetic tone-obesity. Elevated insulin and leptin levels in children with obesity contribute to increased sympathetic nervous system stimulation → renal sodium retention & vasoconstriction.

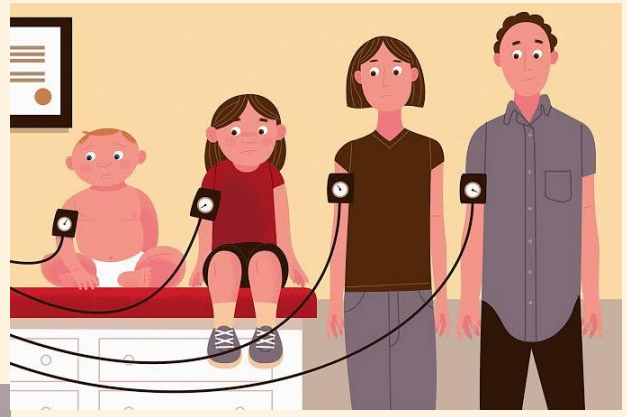
**Insulin resistance and obesity:** Obesity related HTN is the most common form of pediatric HTN. Insulin resistance → SNS activation, direct renal sodium reabsorption, & RAAS stimulation→ HTN

*Cote AT, et al. JACC 2013. PMID 23954339*

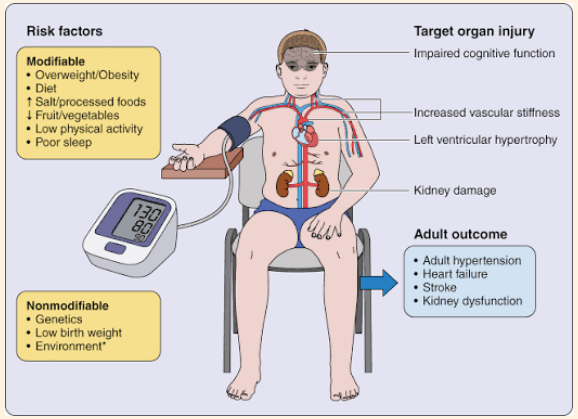



*Cote AT, et al. JACC 2013. PMID 23954339*

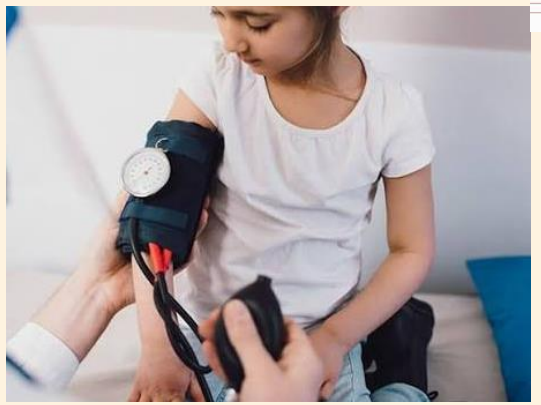
# Considering TRH in Children



Proper Interpretation




Dx'ing and Tx'ing secondary causes



Proper Measurement


Treatment Adherence

Treatment adherence includes addressing adherence to recommended lifestyle changes: dietary sodium restriction, elimination of substances known to increase blood pressure (BP), identification of previously undiagnosed secondary causes of hypertension (HTN), and optimization of current therapy and addition of additional agents as needed.

# ASSESSMENT: PEDIATRIC TRH

Consideration for potential secondary causes:

Renal parenchymal disease and renovascular disease (34-79% of secondary causes)

Coarctation of the aorta

Endocrine disorders (pheochromocytoma, hyperaldosteronism, hyperthyroidism, Cushing syndrome)

Monogenic forms (Liddle syndrome, glucocorticoid remediable aldosteronism, apparent mineralocorticoid excess)

Drug-induced hypertension (glucocorticoids, immunosuppressants, etc).

# Assessing UH and TRH

Use of out-of-office BP monitoring (adults): **Home blood pressure (adults)**

1. TRH on office BP (exclude white-coat effect = a form of pseudoresistance)
2. Perceived uncontrolled HTN (based on office BP) without TRH: If SBP ≥ 130mmHg or DBP ≥ 80mmHg but without SBP ≥ 160mmHg or DBP ≥ 100mmHg, OOBP assessment to exclude white-coat effect

prediction.[20,21] ABPM is preferred for excluding white-coat hypertension and masked hypertension among individuals not taking antihypertensive medication. However, HBPM is preferred for excluding a white-coat effect and masked uncontrolled hypertension among individuals taking antihypertensive medication as ABPM is more difficult to conduct repeatedly in clinical practice. In RCTs demonstrating a reduction in CVD events with the lowering of BP

*2025 AHA/ACC Adult Hypertension Guideline. PMID 40811497*

# Assessing TRH

Adults:

Rule out white-coat hypertension (assess out-of-office blood pressure using a home device or APBM)

Confirm antihypertensive medication adherence

Evaluate: lifestyle issues (eg, diet), drugs interfering with antihypertensive therapy effectiveness; screen for secondary causes; assess target organ damage

Pediatrics:

Rule out white-coat hypertension (assess blood pressure out of office **using ABPM- home device use is not validated**)

Confirm antihypertensive medication adherence

Evaluate: lifestyle issues (eg, diet), drugs interfering with antihypertensive therapy effectiveness; screen for secondary causes; assess target organ damage

## Table 3. Results of Cox Survival Analyses for Associations Between BP Measurements and the Secondary End Points

| BP Measurement | Hazard Ratios (95% Confidence Intervals)[a] | | | |
|---|---|---|---|---|
| | Total CHD Events (n=44) | | Stroke (n=46) | |
| | Age and Sex Adjusted | Multivariate Adjusted[b] | Age and Sex Adjusted | Multivariate Adjusted[b] |
| Systolic | | | | |
| Office | 1.04 (0.78-1.40) | 1.08 (0.80-1.46) | 1.25 (0.95-1.65) | 1.24 (0.95-1.62) |
| 24 h | 1.21 (0.89-1.63) | 1.18 (0.86-1.61) | 1.52 (1.14-2.03)[c] | 1.42 (1.05-1.92)[d] |
| Daytime | 1.16 (0.86-1.57) | 1.13 (0.83-1.54) | 1.49 (1.12-1.98)[c] | 1.39 (1.03-1.87)[d] |
| Nighttime | 1.27 (0.94-1.71) | 1.26 (0.92-1.73) | 1.44 (1.08-1.92)[d] | 1.32 (0.97-1.80) |
| Diastolic | | | | |
| Office | 0.85 (0.61-1.18) | 0.98 (0.70-1.38) | 1.00 (0.74-1.36) | 1.04 (0.77-1.41) |
| 24 h | 0.93 (0.66-1.30) | 1.00 (0.70-1.42) | 1.51 (1.08-2.10)[d] | 1.62 (1.14-2.31)[c] |
| Daytime | 0.93 (0.67-1.30) | 1.01 (0.72-1.43) | 1.52 (1.10-2.10)[d] | 1.64 (1.16-2.31)[c] |
| Nighttime | 1.01 (0.73-1.41) | 1.10 (0.78-1.55) | 1.37 (1.00-1.89) | 1.40 (1.00-1.96)[d] |
| Pulse pressure | | | | |
| Office | 1.21 (0.89-1.63) | 1.12 (0.82-1.52) | 1.38 (1.03-1.85)[d] | 1.34 (0.99-1.80) |
| 24 h | 1.38 (1.04-1.83)[d] | 1.27 (0.93-1.72) | 1.33 (1.02-1.75)[d] | 1.15 (0.86-1.55) |
| Daytime | 1.33 (0.99-1.80) | 1.21 (0.87-1.69) | 1.31 (0.99-1.73) | 1.11 (0.81-1.52) |
| Nighttime | 1.40 (1.06-1.86)[d] | 1.31 (0.96-1.81) | 1.33 (1.01-1.76)[d] | 1.16 (0.85-1.58) |
| True RH | 1.34 (0.71-2.54) | 1.46 (0.75-2.83) | 3.33 (1.49-7.49)[c] | 3.20 (1.41-7.25)[c] |

Abbreviations: BP, blood pressure; CHD, coronary heart disease; RH, resistant hypertension.

[a] Hazard ratios for continuous variables were standardized by calculating them for 1-SD increments.

[b] Adjusted for sex, age, body mass index, diabetes mellitus, current smoking, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine level ($\log_{10}$ transformed), and number of antihypertensive drugs in use. Ambulatory BPs were further adjusted for their respective office BPs.

[c] $P<.01$.

[d] $P<.05$.

# Unknowns- Knowledge Gaps

Trajectories of BP: Can HTN treatment in pediatrics reduce the likelihood of TRH in adulthood (e.g., HTN requiring renal denervation)?

Pseudo-resistant HTN: Is there a CVD-related benefit to treating pseudo-resistant HTN in adults? (adults treated for HTN with white coat effect/high in office BP?

Are there comorbidities that possibly ‘ advance’ the pathophysiology of TRH in pediatrics toward causes of TRH in adults (e.g., conditions that accelerate aldosterone excess?)

Is TRH in children primarily driven by excess aldosterone as in adults or by heightened sympathetic output as occurs in cases of refractory hypertension in adults (normal aldosterone levels)?

# Conclusions:

Uncontrolled hypertension (UH) and treatment-resistant hypertension (TRH) are associated with a significantly greater risk for cardiovascular disease (CVD) and are thus critical targets for improving cardiovascular health (CVH) and for lowering long-term CVD risk across the lifespan.

Socioecological models of health are significant contributors to UH and TRH. These risks should not be ignored.

Definitions of UH and TRH are less well-defined in pediatrics, and adult definitions are currently frequently applied to the pediatric population.

The pathophysiology of TRH/UH when not related to social factors, may differ in adults vs children with greater likelihood of increased aldosterone levels in adults and increased activation of the sympathetic nervous system in pediatrics- however, data is limited.

Diagnosis of TRH (or UH) should include the measurement of out-of-office BP: home BP (adults) or ABPM (peds or adults).

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