DIAGNOSIS AND MANAGEMENT OF DIURETIC RESISTANCE

Jules B. Puschett, M.D.
Diuretic Resistance

A clinical circumstance in which patients do not respond to a combination of salt restriction and even large doses of diuretics.
A 53-year old white male with a history of dilated cardiomyopathy and chronic congestive heart failure is seen in the emergency room because of shortness of breath. His cardiomyopathy is thought to be due to ethanol abuse. He has been taking furosemide 120 mg bid, lisinopril 40 mg daily, K-Dur-20 bid, and digoxin .25 mg daily. On a recent echocardiogram, his ejection fraction was 17% and evidence of left ventricular hypertrophy was present. He admits to recent dietary indiscretion related to the ingestion of fast food. Physical exam reveals a middle-aged white male in moderate respiratory distress. Blood pressure is 100/60. Respirations are 36 per minute. There is jugular venous distention. There are bilateral crepitant rales in the lower half of the lung fields posteriorly, an S3 gallop sound, tachycardia at 120/min, and 1+ peripheral edema. Chest x-ray reveals cardiomegaly and pulmonary edema.
**Laboratory Studies**

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ECG shows T wave inversion in the lateral precordial leads.
The patient is treated with $O_2$ by face mask, 120 mg of furosemide IV q 12 h and a 2 gram sodium diet. The following morning he is improved symptomatically but is still dyspneic at rest. His S3 gallop is not as prominent but is still present and his rales are now limited to the lower third of his lung fields. Blood pressure is 105/65. BUN and creatinine are now 34 and 1.4 mg/dl, respectively. Electrolytes are: sodium 135, potassium 3.8, chloride 98 and total CO$_2$ 26 mEq/L. Urine output is about 1200 cc for the first 18 hours.

Would you make an adjustment in diuretic administration? If so, what would you do?
A 47 year old African-American male is seen in the outpatient department for his regular appointment. He is complaining of progressively increasing edema. He has been an insulin dependent diabetic for 22 years and has a history of hypertension and proteinuria. His medications include: enalapril 20 mg daily, furosemide 80 mg p.o. bid, insulin 30 units of NPH in the morning and 10 units in the evening, simvastatin 20 mg at bedtime. He is on an 1,800 calorie ADA, low-fat diet, with no added salt.

Physical examination reveals a blood pressure of 140/90 and a pulse of 87. Positive findings include a normal chest, cardiac and abdominal exam. There is 3+ pitting edema of the feet, ankles, and lower legs bilaterally. Neurologically, hypoesthesia is noted to mid-calf, but the exam is otherwise negative. The prostate is not enlarged and is non-tender. There are no rectal masses.
CASE STUDY #2 -B

**Most Recent Laboratory Studies**

**Hematology**
Hemoglobin 11.5 gm/dl, Hematocrit 35%, WBC 8,700, Platelets 370,000

**Chemistries**
BUN 26 mg/dl, Creatinine 1.6 mg/dl, Sodium 138, Potassium 4.2, Chloride 101, total CO₂ 22mEq/L, Blood Sugar (fasting) 112 mg/dl, Cholesterol 222 mg/dl, Serum Albumin 2.7 gm/dl, Total Protein 5.9 gm/dl.

Twenty-four hour urine studies reveal a creatinine clearance of 62 ml/min corrected for body surface area and a protein excretion of 11.3 gm. Hemoglobin A1C is 7.9.

In this patient with increasing edema despite diuretic therapy, what steps would you take?
Diuretic Resistance

- Physiological basis for diuretic action
- Causes and mechanisms of diuretic resistance
- Therapeutic strategies
Diuretic Resistance

- **Physiological basis for diuretic action**
- Causes and mechanisms of diuretic resistance
- Therapeutic strategies
Requirements for Diuretic Effectiveness

1. Glomerular filtration
2. Delivery of the diuretic to its site of action within the kidney
3. Delivery of sodium to the nephron segment at which the diuretic acts
4. Responsiveness of the tubular site to the diuretic
5. Absence of major reabsorption of rejected sodium ions at nephron sites proximal to that of diuretic action
Relationship between drug excretion rate (abscissa) and sodium excretion (ordinate) for four loop of Henle diuretics. From: Brater DC, *Drugs* 41(Suppl.3):14-22, 1991.
Diuretic Resistance

- Physiological basis for diuretic action
- **Causes and mechanisms of diuretic resistance**
- Therapeutic strategies
Causes of Apparent Diuretic Resistance

I Compliance problems
   A Failure of patient to comply with drug administration regimen
   B Failure to adhere to low-sodium intake

II Administration of diuretic at infrequent intervals, allowing “rebound” to occur
Mean values for the pattern of renal sodium excretion ($U_{NaV}$) during twice daily oral administration (08.00 and 20.00 hr) of placebo (P) compared with furosemide (F).

Causes of True Diuretic Resistance - I

I Failure of diuretic to reach tubular site of action in sufficient concentration.

A Reduced or delayed bioavailability

1 Decreased and/or delayed gastrointestinal absorption

a Congestive heart failure

b Anasarca
Schematic illustration of the altered pharmacodynamics of response to loop diuretics observed in patients with congestive heart failure (CHF). Also shown is the diminished overall response that occurs as a result. \( FE_{Na^+} \) = fractional excretion of sodium.

Causes of True Diuretic Resistance - II

A Reduced bioavailability (continued)

2 Reduced secretion of diuretic into tubular lumen
   a Reduced glomerular filtration rate
      I Acute or chronic renal failure
      II Circulatory compromise or “inadequate arterial filling.”
         (a) Congestive heart failure
         (b) Advanced liver disease
   b Elderly
   c Transplantation (furosemide nonresponders: reduced plasma and renal clearance)
Causes of True Diuretic Resistance - III

A  Reduced bioavailability (continued)

3  Reduced availability of diuretic within tubular lumen

a  Nephrotic syndrome (protein binding of drug)
Causes of True Diuretic Resistance - IV

B  Interference by other drugs with diuretic effects
   1  NSAID’s (mechanism of ↓d natriuresis unknown):
   2  Captopril (furosemide, but not hydrochlorothiazide)
   3  Cimetidine (inhibits tubular secretion of amiloride)
   4  Other antihypertensives

C  Tubular adaptation to chronic diuretic administration

II Failure of diuretic regimen to blockade transport at (a) major sites (s) of sodium reabsorption
Diuretic Resistance

• Physiological basis for diuretic action
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Diuretic Resistance
Therapeutic Measures - I

1. Enforce dietary sodium restriction
2. If large doses of oral drug have been ineffective, switch to intravenous administration
3. Depending on the clinical circumstance, begin with 40 - 80 mg. of i.v. furosemide, or its equivalent (1- 2 mg. of bumetanide; 50 - 100 mg of ethacrynic acid; or 20 - 40 mg. of torasemide)
Table 1. Sodium restricted diets.

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<tr>
<th>Sodium content</th>
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<tr>
<td>4 g 175 mEq</td>
<td>No added salt; suitable for outpatients</td>
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<tr>
<td>2 g 87 mEq</td>
<td>Mild restriction; suitable for outpatients; excludes obviously salty foods</td>
</tr>
<tr>
<td>1 g 43 mEq</td>
<td>Moderate restriction; rarely achievable by outpatients</td>
</tr>
<tr>
<td>500 mg 22 mEq</td>
<td>Severe restriction</td>
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<tr>
<td>250 mg 11 mEq</td>
<td>Rigid restriction; Unpalatable</td>
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Diuretic Resistance
Therapeutic Measures - II

4. Increment the dose if no response in 3-4 hours; then increase again (top dose is usually 200 mg. (? 240 mg) of furosemide or its equivalent).

5. Add second agent: e.g., give 5-20 mg. metolazone orally; then ONE HOUR LATER, give, e.g., 80-120 mg. furosemide or 40-60 mg. torasemide intravenously. Metolazone and torasemide are long-lasting, need only be given once daily.

6. Consider intravenous infusion of furosemide or bumetamide vs. bolus injection. Torasemide effect is prolonged; infusion not necessary.

7. A site 4 agent may be added.
Urinary potassium excretion ($U_{K,V}$) is plotted against that of sodium ($U_{Na,V}$) when steady-state ethacrynic acid diuresis (middle symbol in each curve) was superimposed upon maximal water diuresis (symbols on left) following which metolazone was administered (symbols on right) ($n = 4$). Each data point is the mean of 2 to 3 consecutive clearance periods.
CASE STUDY #1 - A

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**Mechanisms and Therapeutic Strategies**

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<td>Renal Failure</td>
<td>Decreased renal blood flow; decreased diuretic tubular secretion → reduced diuretic in the tubular lumen</td>
<td>Increment dosage</td>
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<td></td>
<td>Sequential nephron blockade.</td>
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<tr>
<td>Nephrotic Syndrome</td>
<td>Binding of diuretic to luminal protein. (Mechanisms as above in patients with renal failure)</td>
<td>Increase dosage.</td>
</tr>
<tr>
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<td></td>
<td>Increase dosing frequency (? i.v. infusion).</td>
</tr>
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## Diuretic Resistance
### Mechanisms and Therapeutic Strategies II

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<td>Cirrhosis</td>
<td>Unknown (Pharmacokinetics normal; pharmacodynamics must therefore be altered, but cause is unknown: perhaps increased proximal reabsorption along with enhanced distal transport related to secondary hyperaldosteronism); ? decreased drug absorption</td>
<td>Sequential nephron blockade.</td>
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<tr>
<td>Congestive Heart Failure</td>
<td>Intravenous dosing: pharmacodynamic abnormalities, mechanism unclear. Oral dosing: altered time course of absorption (delayed and prolonged)</td>
<td>Increment dose. Increase frequency of dose. Sequential nephron blockade.</td>
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