



Introduction:

Welcome to CUGH's bi-weekly clinical case-series, "Reasoning without Resources," by Prof. Gerald Paccione of the Albert Einstein College of Medicine. These teaching cases are based on Prof. Paccione's decades of teaching experience on the medical wards of Kisoro District Hospital in Uganda. They are designed for those practicing in low resource settings, Medicine and Family Medicine residents, and senior medical students interested in clinical global health. Each case is presented in two parts. First comes a case vignette (presenting symptoms, history, basic lab and physical exam findings) along with 6-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. Two weeks later CUGH will post detailed instructors notes for the case along with a new case vignette. For a more detailed overview to this case-series and the teaching philosophy behind it, see [Introduction to "Reasoning without Resources"](#). Comments or question may be sent to Prof. Paccione at: gpaccion@montefiore.org

Note: If you would like to be notified when a new case is posted (along with instructor notes for the previous one), send your e-mail to Katherine Unger at kunger@CUGH.org.

About the Author:

Dr. Gerald Paccione is a Professor of Clinical Medicine at the Albert Einstein College of Medicine in the Bronx, New York. His career has centered on medical education for the past 35 years – as a residency Program Director in Primary Care and Social Internal Medicine at Montefiore Hospital, and director of the Global Health Education Alliance at the school. He has served on the Boards of Directors of Doctors for Global Health, Doctors of the World USA, and the Global Health Education Consortium. Dr. Paccione spends about 3 months a year in Uganda working on the Medicine wards of Kisoro District Hospital where he draws examples for the case studies.

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CASE 53 – Body Swelling II

A 75 year old woman presents with increasing body swelling and abdominal discomfort for 1-2 months. She was previously well, the mother of 3 adult children, had no past medical history of significance, and was digging in her fields with her usual vigor 3 months ago.

Two and a half months ago she noted leg swelling bilaterally followed by abdominal swelling and discomfort, and about a month ago felt too sick to leave her house. She then developed a dry cough and some shortness of breath when walking and lying down, needing 2 pillows to feel comfortable. She never saw the color of her urine (uses a pit latrine). She had no weight loss but felt heavier and bloated. Upon direct questioning, she recalled having had a sore throat (that “lasted a month”) and fever a few months ago, but couldn’t specify when in relationship to her present illness.

She had never had her blood pressure checked before, always lived in the Kisoro district (not by a lake), never received blood transfusions, takes/took no medications or herbs, doesn’t have allergies or recent fever, rash, headache or joint pains other than in her knees at the end of a work-day, has no known liver disease or heart disease, has been widowed for 10 years and not sexually active since, and was fully active until 3 months ago.

Physical Exam: Elderly, pleasant woman sitting upright in bed in no distress

BP: 192/116... 5 minutes later, 220/120... 5 minutes later repeated again, 212/120;
HR 92; RR 20; T: 97.2 p.o. Weight 53 kilos

Skin: diffuse anasarca with pitting in legs, thighs, arms and abdomen;
“puffy” face with trace edema; no rash;

Eyes: conjunctiva: non-icteric without petechiae; mild pallor;

Fundi: no papilledema, vessels with A/V 4/5 without tortuosity or nicking; two 1mm dot hemorrhages right eye at 2 and 3 o’clock, 1 and 2 disc diameters away; 1 flame hemorrhage left eye at 11:00, 1.5 disc diameters;

Neck: no thyromegaly or nodes >1 cm; no bruits;
+JVP sitting up 10 cm above angle of Louis, with +HJR

Lungs: bibasilar crackles

Heart: PMI forceful, not prolonged (<half systole); ~2 cm in 5 ICS, 1 cm lateral to MCL; normal-loud S1, narrowly split S2; +S4; no S3 (in left lateral decubitus); no murmurs or rubs;

Abdomen: mildly distended, active bowel sounds, no bruits;
+1-2 anasarca of abdominal wall; ?shifting dullness, no fluid wave;
liver percussed ~15 cm., 6 cm below costal margin, and tender to percussion and gentle punch;
no spleen or masses; no bladder fullness or pain on percussion/palpation;

Extremities: +2 pulses bilaterally, edema to thighs, 3 mm depression lower leg over shin; joints normal;

Neurologic: mental status, cranial nerves, motor, sensory, cerebellum, gait intact; reflexes +2 diffusely

1. What is the “frame” of this patient’s presentation from history and exam (i.e. the key 3-4 clinical features the final diagnosis must be consistent with)?

- 75 year old woman, previously well without prior medical care (no prior BP readings) or history of chest pain, TIA/CVA, CHF;
- Now with severe hypertension
- 2-3 months of leg and then body swelling preceding dyspnea
- Prior symptoms of sore throat and fever (questionably) occurring within a month of swelling, with no other associated symptoms of infection, rash, joint pain, history of herb or medication use;

2. Identify 3 fundamental diagnostic questions raised by this patient’s clinical presentation that pertain to which organ is failing and which disease process is responsible. How are the answers to these questions important therapeutically?

Three broad diagnostic issues/questions are apparent from these clinical data:

- a) are the swelling and dyspnea the result of heart failure due to hypertension, or of renal failure with associated hypertension and fluid overload ?*
- b) if renal failure is present, is it due to primary renal disease (e.g. glomerulonephritis, renovascular, etc.) with associated hypertension or to hypertensive nephropathy (hypertension causing the renal failure)?*
- c) if renal failure is present, is it acute or chronic?*

The answers are important in identifying the principle targets of therapy and the choice of agents (and doses) in treating the fluid overload,

e.g.

- *lower doses of loop diuretics in this diuretic-naïve patient should work well if CHF (due to hypertension or other causes) is dominant without co-existing renal failure, (and the diuresis may quickly lower the BP if the HT was exacerbated by a surge of catecholamines from decompensated CHF);*
- *if renal disease were primary, higher doses of diuretics would be necessary and ACE inhibitors would be risky treatment if potassium couldn’t be measured;*
- *if renal disease were primary and the cause diagnosable and treatable, focused therapy (e.g. even with fluid-retaining steroids if indicated) might be the best long-term treatment of both edema and hypertension;*
- *if hypertension was the process behind either CHF or an acute or chronic renal injury, vigorous HT control would be the most important treatment goal.*

Apart from therapy, prognosis would likely be quite different between an acute renal versus a chronic renal or cardiac process: recovery is possible with many acute renal insults but not in most chronic renal or cardiac processes.

3. How does the *history and physical exam* inform these general diagnostic questions?

History:

- the patient's age of 75 without a prior cardiovascular (CV) event or earlier development of CHF suggest that the hypertension has not been very high for very long. (However, this does not mean that hypertension isn't at the root of the overall problem: after years of insidious damage to the heart or kidneys, hypertension could have entered an accelerated phase recently with the onset of renal failure).
- the months of body swelling prior to the onset of dyspnea suggests that fluid retention occurred before elevated left heart pressures, which suggests primary renal disease rather than heart disease;

Physical Exam:

- the observation of "no distress" and a relatively normal RR of 20 lowers the likelihood of the severe HT being due to a catechol response to acute cardiac decompensation.
- fundi: the arterioles were not narrowed, and nicking and tortuosity weren't seen; this strongly suggests that the hypertension has not been chronic; hemorrhages/exudates reflect the recent severity of the HT, but the vessel diameters its chronicity.
- PMI forceful, not prolonged, borderline size, modestly displaced, with no S3 audible: the S3 is an insensitive sign of CHF but the minimally displaced and borderline-size, non-prolonged PMI is more consistent with a non-dilated (not-too hypertrophied) heart relatively recently straining against increased vascular resistance than a chronically hypertrophied heart decompensating (and possibly dilating) after years of pressure overload. The exam suggests the relatively recent development of HT and dyspnea due to the fluid overload of renal failure;
- absence of abdominal or other bruits augers against reno-vascular HT. (N.B. Reno-vascular HT in an elderly woman wouldn't be likely in a region of the world with as low a prevalence of atherosclerotic risk factors as rural Uganda, and more precisely in this particular patient who probably has no other risk factors for atherosclerosis (no diabetes or smoking; lipids can't be measured in rural Africa, but hyperlipidemia is unlikely.)

4. The following lab tests and empiric trial, feasible in a district hospital, are performed and the following results are reported. What are their diagnostic implications?

- EKG: normal sinus rhythm, intervals and axis, normal P waves, normal R wave progression, no LVH by voltage, non-specific T wave flattening in I, L, V5, V6.
- U/A: s.g. 1.020; 4+ blood, 4+ protein on dipstick; microscopic: RBCs too many to count, some "dysmorphic"; scattered granular and RBC-granular casts around perimeter of coverslip.
- Hematocrit: 33
- Ultrasound: unavailable, machine "not working";
- Diuretic challenge: 200 cc output in response to 40 IV furosemide after 2 hours; then (at 2 hours), additional 80 mg furosemide led to 400 cc. more after 3 more hours;

The diagnostic implications of these test and trial results are as follows:

Tests

- EKG: the EKG would very likely reveal significant LVH if this 75 year old woman had renal or heart failure due to hypertension. Although only 15-30% of patients with LVH by echo have LVH on EKG (sensitivity of the EKG), the question we're addressing here is different: i.e. did her hypertension cause her end-organ failure (heart or kidney or both) or was it caused by it. This question can only be examined in a cohort of patients with HT who develop end organ damage, i.e. more severe disease and probably much more likely to demonstrate LVH on EKG. Although not independent of the PMI exam findings noted above, the absence

of LVH on EKG strongly support the conclusion drawn from the exam: that the hypertension is recent..

- U/A: can be an indicator of whether the kidneys are primarily or secondarily involved: a “clean” U/A without cells or sediment would suggest a hemodynamic (e.g. CHF; reno-vascular disease) over inflammatory etiology of renal failure. The U/A in this case is consistent with an inflammatory etiology of renal disease..
- Hematocrit: renal disease results in decreased erythropoietin production and thus a normocytic anemia would suggest chronic renal disease (see below).
- Ultrasound: kidney size, if bilaterally small (<9 cm), would imply chronic RD, although some forms of chronic RD have normal-size kidneys (see below); asymmetric kidneys would suggest reno-vascular disease;

Empiric trial:

- Diuretic challenge: the patient has never taken diuretics and if her renal function were normal, she should have responded with a vigorous diuresis to IV lasix. This was not a vigorous response suggesting underlying renal insufficiency - a common cause of diuretic resistance.

5. What is the likely primary organ-system diagnosis in this patient (to be called “Disease X”)?

Explain your reasoning.

The lack of LVH on EKG points away from hypertensive heart disease and diastolic CHF as the primary cause of the fluid overload and dyspnea.

The U/A reveals a very “active” sediment and significant proteinuria, both indicating glomerulonephritis.

The hematocrit of 33 is non-specific (see below)

The weak diuretic response to high doses of IV lasix over 4 hours in this diuretic-naïve patient suggests significant renal impairment and compromised GFR.

“Disease X” is renal disease.

6. a) How common is Disease X in Africa in comparison to the West? Why the difference?

b) What are the 4 most common *etiologic* causes of Disease X that lead to death in Africa?

c) What does the future portend vis-à-vis mortality from Disease X in Africa?

a) Renal disease (RD) is increasing worldwide. In the developed world, 11% have some degree of renal disease – 0.2% end-stage (GFR <15cc/min), 4.5% advanced Stage 3-4 (GFR 15-60), and 6.5% Stage 1-2 disease (GFR 60->90).

In Africa, RD is estimated to be 2-3 times more prevalent than in the West and occurs at an earlier age, but since research is sparse in Africa, population estimates are imprecise. In most hospital-based studies, 2-5% of medical admissions in Sub-Saharan African countries have either renal symptoms or significant RD (Cr>2). In rural Western Nigeria, one community-based study documented chronic RD in >20% of the adult population.

Most of the recent increase in renal disease in the West is due to the aging of the population and the inevitable toll of “man-made diseases” that increase with age, affluence and body weight – hypertension, diabetes, and atherosclerosis. Present-day Africa has 3 times the renal disease burden of the West, but for different reasons: i.e. the renal complications of infectious diseases still-rampant in Africa (but rare or eradicated in the West e.g. malaria, schistosomiasis), or lack of access to medical care (e.g. obstructive uropathy).

b) The 4 major causes of end-stage RD (ESRD) in Africa are: Chronic glomerulonephritis (25-50%), Hypertension (25-50%).... Obstructive uropathy (5-15%), Diabetes (3-20%)... Unknown (25-35%).

c) Unfortunately the future is bleak. The projected mortality of RD in Africa is a prime example of the “epidemiologic trap” of Sub-Saharan Africa: The continent is beginning to suffer from the “man-made” diseases associated with urbanization, globalization and economic growth while still mired in the rural and urban poverty that continue to breed “pestilence and famine”. Hypertension and diabetes are skyrocketing along with urbanization, Western lifestyles, decreased exercise and fast food (e.g. 80% of new cases of diabetes over the next generation will be in the developing world); and epidemic infections show few signs of abating - HIV, malaria, hepatitis, TB and schistosomiasis, all with renal complications, are out of control in most areas.

Despite its high and rising prevalence, the diagnosis and treatment of RD will continue to be financially impractical for the vast majority of those afflicted for the foreseeable future.

- 7. a) What are the principle *BEDSIDE* diagnostic classification schemes or categorizations of Disease X that carry prognostic and/or therapeutic significance?**
b) How can one differentiate among the categories by simple “bedside tests” (history, physical and basic lab)?
c) Which of the general categories of Disease X does our patient best fit?

a) Four commonly used, clinically relevant classifications of renal disease that can be assessed “at the bedside” (to varying degrees) involve timing, location, pathology and etiology:

- timing: acute vs. chronic

- location: glomerular vs. tubule-interstitial

- pathology: “nephritis” vs. “nephrosis”, reflecting the presence or absence of glomerular inflammation and useful vis-à-vis diagnosis, prognosis and therapy.

- etiology: the specific agent that caused the histo-pathologic changes in the glomeruli, tubules or both

*b) **Timing**, acute/subacute (weeks-months) vs. chronic RD can be assessed by:*

- history: evolution of the patient’s actual illness, particularly if accompanied by non-uremic symptoms/manifestations of the underlying disease process (e.g. rash, fever, arthritis, etc);

- hematocrit: Erythropoietin is produced in the renal interstitium and anemia accompanies chronic renal failure (CRF). However many patients have significant CRF without significant

anemia and, contrariwise especially in Africa, anemia is often multi-factorial and non-specific (chronic inflammation, malaria, nutrition, multiple pregnancies, etc.).

In the U.S. NHANES survey, the average Hb with a GFR >60 was 15 in men, 13.5 in women; GFR 30, 14 and 12; and GFR 15 12 and 10. At a GFR of 15 ml/min per 1.73m², only 33% of men and 67% of women were anemic (i.e. <12 Hb men, 11 women).

In patients without other obvious causes of anemia, a Hct <30-35 (weakly) suggests chronic renal failure.

- *Ultrasound: if USG is available, small kidneys (<9 cm), suggest chronic RD although diabetics or patients with amyloid infiltration with CRF can have normal-enlarged kidneys;*
- *Urinalysis: "active" sediments with hematuria and casts can be seen in both acute and chronic RD, but are more likely in acute RD. A "bland" U/A can be seen in chronic RD but also in many other forms of pre, post and parenchymal RD: vascular, myeloma/light chain disease, tubule-interstitial, drug toxicity;*
- *[Creatinine: usually unavailable in district hospitals, a changing (either worsening or improving) Cr suggests an evolving and therefore acute/subacute renal injury, while a stable Cr (especially over weeks/months) suggests chronic RD.]*

Location: glomerular (G) vs. tubule-interstitial (TI) disease

- *Blood pressure: HT suggests G > TI (the latter is often accompanied by salt-wasting and low BP).*

- *Urinalysis: until late stage disease, G maintains the ability to concentrate urine, so s.g. >1.020 suggests G, while <1.015 suggests TI.*

G is characterized by >+2 proteinuria, and if inflammatory (i.e. glomerulonephritis, GN) by hematuria, dysmorphic RBCs, and casts (see below).

TI can show trace to +2 proteinuria, WBC casts, and infrequently hematuria.

[The degree of Proteinuria in mg/day can be accurately estimated by the U/A dipstick remembering that the urine concentration (specific gravity) is inversely proportionate to the 24 hour urinary protein at any level of dipstick protein: i.e. the more concentrated the specimen, the higher the dipstick measure has to be to imply "significant" proteinuria and conversely, dilute specimens with low degrees of proteinuria by dipstick can be quite pathologic. (Am.J.Kid.Dis 2005, 45 (5), 833)

Thus, vis-à-vis "significant proteinuria" more likely to progress to CRF (>500mg/day), only 3% of those with concentrated urine, i.e. specific gravity greater than or equal to 1.030 and +1 (>30mg/dl) dipstick protein, OR specific gravity greater than or equal to 1.020 with "trace" protein, had >500 mg/day; conversely >95% of those with dilute urine, i.e. specific gravity less than or equal to 1.020 and proteinuria greater than or equal to +2 (>100mg/dl), had >500 mg proteinuria/day.

Vis-à-vis nephrotic range proteinuria >3 grams/day, none of those with +1 (>30mg/dl) OR +2 (100mg/dl) and s.g. >1.025 had >3 gm/day; and only a third of those with dilute urine, s.g. <1.015, and +2 protein had >3 gm/day; conversely, only ~half of those with +3 (300mg/dl) protein in a relatively concentrated specimen (>= 1.015) passed > 3 gm/day.]

Pathology: nephritis (glomerulonephritis, GN) vs. nephrosis (N)

The diagnostic "branch-point" in glomerular disease is "nephritis vs. nephrosis" - for which the urinalysis is key. Although both have >= +2 proteinuria, GN implies evidence of inflammation, N does not.

- *Urinalysis:*

GN is characterized by an “active” sediment:

- a) hematuria with dysmorphic RBCs (vesicular knobs attached to mis-shaped RBCs deformed as they pass through the diseased glomerular basement membrane);*
- b) RBC casts, a classic but insensitive finding which can appear either tightly packed with cells or, more commonly, with a few RBCs embedded in a granular matrix. One RBC cast essentially diagnoses GN or vasculitis, though experience and proficiency in the microscopic exam is crucial, and there’s significant variability even among nephrologists’ assessments.*
- c) WBC or epithelial casts can also be seen.*

The histo-pathologic common denominator in GN is sub-endothelial immunoglobulin deposits in contact with blood and stimulating a complement-mediated inflammatory response.

N is characterized by proteinuria with a “bland” U/A. It is often associated with sub-epithelial deposits that don’t come into contact with the circulation and thus don’t elicit inflammation.

(Clinical caveats: +2 proteinuria can be seen in TI disease; decompensated right-sided heart failure can cause glomerular-range proteinuria, and chronic glomerulonephritis (GN) can produce a falsely negative (“clean”) U/A.)

Despite the overlap between GN and N (e.g. many causes of glomerulonephritis are also causes of “nephrotic syndrome”, defined as albuminuria >3.5 grams/day with edema), the GN vs. N classifications are pragmatically useful in focusing differential diagnoses and estimating probabilities of underlying histo-pathology, etiologic agents, prognoses, and therapies.

However, ultimately the classifications of GN vs. N are (crude) urinalysis reflections of pathologic injuries which are impossible to define accurately without renal biopsy, and biopsies are not feasible in Africa for lack of resources and trained professionals. The “silver linings” in this common African scenario are:

- a) even precise histo-pathology is etiologically non-specific - many etiologic agents cause each of the diverse cellular patterns that can be seen under the microscope;*
- b) the most effective agents in the treatment of renal diseases are antibiotics active against the primary etiologic organisms (viral, bacterial or parasitic) that initially incited the pathologic immune response and, while often out of reach in rural Africa, etiologic diagnosis (and treatment) will likely be more accessible than histo-pathology in the coming years;*
- c) “idiopathic” histo-pathologic diagnoses that require cytotoxic or immune modulating drugs which are unavailable in Africa are becoming increasingly uncommon, and other idiopathic renal-only diseases can be treated with steroids (e.g. minimal change disease) which is available in Africa.*

Thus, although not ideal in many cases, armed with a GN/N classification, potentially other etiologic clues to underlying systemic disease, knowledge of local glomerular disease prevalence stratified by age, careful appraisal of the patient’s clinical evolution over time,

and in some cases, an empiric trial of steroids with careful monitoring of prescribed endpoints, histo-pathology can be often bypassed without harm to the patient.

Our patient, without signs of prior hypertension, who presents now with a 2-3 month illness at age 75 with severe hypertension, edema, and a very active sediment probably has a form of sub-acute glomerulonephritis.

8. What are *specific etiologies* of “Disease X” that are unique to Africa or much more prevalent in Africa than in the West?

- *HIV nephropathy: presents with significant proteinuria (usually nephrotic-range) but without hypertension or edema. If it’s the patient’s initial presentation of AIDS and he/she hasn’t been on ART (most patients in Africa), HIV nephropathy progresses to end-stage RD in 1-4 months, but if it develops on ART, it manifests less severe proteinuria and slower progression.*

Biopsies show a “collapsing” focal segmental glomerulosclerosis (FSGS) with advanced interstitial disease which leads to salt-losing - thus no edema or HT. Africans and American blacks are genetically prone to develop FSGS, whether “primary”/idiopathic or “secondary” to various factors such as obesity, reflux, prior renal injury (with decreased renal mass and per nephron hyper-filtration), lymphoma/cancer, etc.

Therapy includes ART (primarily), ACE-inhibition, and combination ART-steroids. Preliminary evidence suggests efficacy of steroids in combination with ART, but this is controversial.

Not surprisingly, many other causes of infection or drug-induced RD are seen commonly in HIV infected patients: membranous nephropathy (MN) from hepatitis B, membrano-proliferative (MPGN) from hepatitis C, amyloid from chronic infection, drug-induced interstitial disease or obstructive uropathy from crystals (indinavir); etc.

- *Post-streptococcal GN (PSGN), post-infectious GN, “endo-capillary proliferative GN” is the most common cause of acute GN globally. 97% of cases occur in developing countries (!) with an incidence of 10-30 per 100,000 population per year. There are 2 age peaks - children between 5-12 years, and adults older than 60 years. PSGN follows either 10-15% of cases of Group A strep pharyngitis by 1-3 weeks, or 25% of group A Strep skin infections by 3-6 weeks, occurring both sporadically and in epidemics.*

Clinically, generalized edema is seen in 2/3 and hypertension in 50-90%. Urinalysis shows proteinuria, hematuria and pyuria with RBC casts commonly (~50% of cases). The proteinuria is nephrotic range in only ~5%, but hypertensive encephalopathy and uremia requiring dialysis are additional complications of an uncommonly associated “rapidly progressive GN” with >75% of glomeruli showing crescents on biopsy.

Most importantly diagnostically, PSGN begins to resolve in children in 1-2 weeks even in severe cases and prognosis is good with complete restoration of renal function on long-term follow-up in 90-95%. Diuresis occurs within 1-2 weeks, and

creatinine is normal within a month in the vast majority. However, only partial recovery is more likely with severe disease and in adults, who are also more likely to progress or end up developing FSGS on long-term follow-up after many years.

Alternative diagnoses should be considered in the following situations when: no antecedent infection is documented, RD progresses beyond 2 weeks, increased creatinine or HT persist beyond 4-6 weeks, or microscopic hematuria persists beyond 3-6 months. The inflammatory markers resolve first; proteinuria can take years to resolve.

There is no evidence that steroids work in treating PSGN, and treatment should be aimed at diuresis and HT control.

- *Eosinophilic glomerulonephritis (KI 2007; 71:569), a form of post-infectious GN, has been reported recently from Mbarara in SW Uganda: of 41 renal biopsies (read in the UK) performed on 65 children age 2-14 years with acute GN (all had peri-orbital and leg edema and >+2 proteinuria and hematuria), 27 had endocapillary (diffuse) proliferative GN, 20 of whom had a predominantly eosinophilic glomerular infiltrate, only 1 with peripheral eosinophilia. Half showed RBC casts, all with DPGN. 91% survived, most having received penicillin; steroids were only given to those with minimal change or FSGS on biopsy, and all (8) responded.*
- *Other causes of Post-infectious (endocapillary) Proliferative GN that are (or may be) more prevalent in Africa, and that usually resolve with the infection include:*
 - *Subacute Bacterial Endocarditis: rheumatic fever is still rampant in Africa, leaving echo-documented scars on the valves of nearly 2% of school-aged children. SBE from oral flora, or ABE from Staph aureus, are commonly associated with diffuse proliferative GN.*
 - *Typhoid fever (S.Typhi)*
 - *Pneumococcal and Mycoplasma pneumonia (common infections in which renal inflammation is frequent microscopically and by urinalysis but self-limited and rarely clinically relevant.)*
 - *diverse viral infections: EBV, varicella, parvovirus, CMV, rubella, coxsackie, mumps*
 - *parasites: malaria, P.falciparum; toxoplasmosis; filariasis*
- *Hepatitis-related: B and C*

Hepatitis B (HB), endemic in Uganda, causes 3 types of renal disease particularly affecting children and the chronically infected. Overall about 65% of the Ugandan population has been infected with HBV (!) and ~10% are chronically infected (HBsAg(+)); the prevalence of hepatitis C is 3%. There's marked inter- and intra-country variation in the prevalence of hepatitis B: e.g. in the Northern part of Uganda 90% have been infected with hepatitis B and 30% are chronic carriers whereas in the Southwest, proportions are 30% and 4% respectively.

Along with these marked differences in HBV prevalence between regions come differences in the age of HBV acquisition and, with that, in the progression from acute infection to chronic infection between different age groups. Progression from acute to chronic is related to the maturity of the immune system at the time of infection.

Chronic HBV is found in 6-10% of adults with evidence of infection, 25% of children aged 1-5 years, and 70-90% of infected infants. Perinatal infection is responsible for ~20% of chronic infections in adults. About 15-25% of those with chronic HBV die prematurely of cirrhosis or HCC (in about a 2:1 ratio).

The 3 types of renal disease seen with HB infection are:

- membranous GN (MGN), presenting with the nephrotic syndrome - which usually resolves in children but progresses to renal insufficiency in adults;*
- membrano-proliferative GN (MPGN), presenting with nephritis – hypertension, hematuria, proteinuria, sometimes nephrotic syndrome, renal insufficiency developing over many months-years; occasionally associated with mixed cryoglobulinemia and hepatitis C co-infection.*
- polyarteritis nodosa: PAN can be idiopathic or secondary to HB. (In Uganda, most cases would probably be secondary.) PAN is a vasculitis of medium and small arteries that presents with fever, arthralgias, fatigue and weakness with weight loss (~70%), hypertension, and renal insufficiency – usually some proteinuria and hematuria without RBC casts or florid GN. Any organ can be involved. Particularly useful diagnostic clues are a mononeuritis multiplex of multiple peripheral nerves, asymmetric at onset, both sensory and motor – seen in ~65%; abdominal pain, often post-prandial due to ischemia ~50%; skin – livedo, ulcers, tender nodules, palpable purpura (~50%); orchitis, 20%; ENT symptoms ~10%.*

When associated with HB, PAN develops within 4 months of HB infection, quite different from MPGN and MGN which are seen patients with chronic infections.

Treatment of HB-associated renal disease is with anti-viral agents, entecavir (preferably) or lamivudine (to which resistance commonly develops) since tenofovir and adefovir are nephrotoxic. Steroids have no benefit and may be harmful in MGN and MPGN due to HB. PAN on the other hand may best be treated by a combination of steroids and anti-viral agents.

Many of these anti-viral agents may be available through HIV programs, but the resources to diagnose hepatitis B serologically are only sporadically found in rural Uganda as of 2013. If a strong suspicion exists for HB-related GN - on the basis of (even mild) elevation of LFTs if available, clinical signs of PAN, or a family history of liver disease (which may be congenital HB) - then sending the patient or his/her blood to a lab in a major city for hepatitis serology is ideal and recommended.

Hepatitis C is common in some regions of Africa and the developing world. HC usually causes MPGN with proteinuria, hematuria, and casts which progresses over many months-years to renal failure. It is often associated with a mixed cryoglobulinemia, sometimes with associated polyneuropathy and characteristic ulcers and gangrene of the feet and digits.

Treatment of HC with anti-viral agents is indicated if possible, but is not available in most areas of Africa. Steroids are not indicated.

- *Schistosomiasis: Chronic infection with *S.Mansoni* (and to some extent other species) is associated with GN in 10-15% of clinically apparent cases. Immune-complex*

deposition in the glomeruli inexorably progresses to renal failure when associated portal hypertension leads to shunting blood around the hepatic Kuffler cells, which normally clear IgA complexes, into the systemic circulation permitting Schistosoma antigen-IgA complexes to deposit in the glomeruli.

Six histo-pathologic “classes” of GN are seen in Schistosomiasis, of which Classes III and IV are the most prevalent and untreatable:

Class I - mesangial proliferative, usually a benign self-limited course with IgG complexes and transient GN;

Class II- exudative GN in association with Salmonella co-infection, deposition of IgG and complement, presenting with an acute prolonged febrile episode and diffuse GN, and fully responding to antibiotics against Salmonella and Schistosomiasis.

Class III MPGN and Class IV FSGS – the vast majority of cases, both Classes present with nephrotic syndrome, nephritis, hypertension and initially mild renal insufficiency, and both are associated with liver disease/portal hypertension and IgA deposition in glomeruli and around tubules. Three quarters progress to ESRD or have persistent renal insufficiency at 4-6 year follow-up despite therapy with steroids, cyclophosphamide and anti-schistosomal drugs, all of which are considered ineffective.

Class V: renal amyloidosis due to chronic infection, also untreatable.

Schistosomiasis infects over 200 million people, more than half of whom are symptomatic, and remains one of the most common causes of nephrotic syndrome and GN worldwide. It should be considered in endemic areas and in those with positive Schistosomal serology, particularly with associated liver disease. Unfortunately, hepatic disease, considered a prerequisite for the most common renal pathologies of Class III and IV most often causes “silent” pre-portal hypertension with preserved liver function until very late-stage disease and thus evades clinical diagnosis. So in sum, except for the rare (febrile) Class II presentations, the renal disease caused by Schistosomiasis is either self-limited (rare) or untreatable (common).

- *Quartan malaria: for decades steroid-resistant nephrotic syndrome in children leading inexorably to death within 2 years was linked to infection with P.Malariae. However the association is now disputed centering on whether the eluted glomerular immune complexes with malarial antigens are truly pathogenic or merely associated with a highly prevalent disease (P.malariae). Neither anti-malarial nor steroid therapies are of benefit.*
- *Falciparum malaria: causes acute renal failure in severe disease in adults, usually due to ATN and microvascular ischemia. However it can also cause a subacute GN, usually MPGN with hematuria, proteinuria and casts that resolves over weeks post-infection and rarely leads to renal failure or hypertension.*
- *Other “neglected” African infectious diseases, e.g. filariasis and leprosy, have been associated with post-infectious GN and MPGN...*

- *HIV-associated diseases with renal-complications:*
 - *lymphomas* are associated with nephrotic syndrome and FSGS and membranous GN
 - *TTP* is a rare association with advanced AIDS. It presents with some combination of microangiopathic hemolytic anemia (>1% schistocytes or >2 per 100x magnification), fever, thrombocytopenia, neurologic symptoms (headache, seizure, CVA, coma), and renal disease - thrombotic microangiopathy with renal insufficiency and nearly normal U/A usually, with some microscopic hematuria, mild proteinuria, and rarely GN-associated casts. Rarely MPGN is associated with TTP.
- *Amyloid nephropathy* due to either AL amyloid from monoclonal gammopathy or AA amyloid due to chronic infection is seen. Chronic infections are common in Africa given the lack of access to care and high burden of infectious disease. AA amyloid can be associated with osteomyelitis, bronchiectasis (from recurrent lung infections and asthma), schistosomiasis, tuberculosis, chronic skin infections – all of which are common and inadequately treated in Africa. Amyloid causes nephrotic syndrome with a “bland” urinalysis, and should be considered in patients with underlying chronic inflammatory diseases. Treatment of the underlying disease can ameliorate the nephropathy, and is the treatment of choice.

N.B: Interestingly, IgA nephropathy, the most common cause of GN in Asia and the West, is rare in blacks and almost never reported in biopsy series of patients with GN in Africa. Thus a paradox: Africa has a much higher prevalence of renal disease than the West, while not being affected by the most common cause of glomerular renal injury found in the West.

9. What is the most relevant differential diagnosis in our patient?

- *Post-streptococcal GN (PSGN):* PSGN is consistent with the patient’s age (second peak after 60 years), hypertension, edema, and active sediment with cellular casts, and (questionable) history of fevers and sore throat in the past months. But since PSGN improves within weeks in most patients, against the diagnosis is the long duration of clinical symptoms. However, adults have a worse prognosis with a longer course and often only a partial remission. If this patient had PSGN, she would have to fall into this less common category.
- *Post-infectious, non PSGN...* nothing diagnosable at this point, but if the history of prolonged fevers was real, infections with typhoid, EBV, CMV, toxoplasmosis, mycoplasma, etc. could have triggered an immune-complex GN. The problem with these diagnoses is lack of clinical clues (e.g. fever, lymphadenopathy, cough, etc.), the self-limited nature of most of them and the resolution of the GN post-infection which makes our patient’s course again, atypically long.
- *Hypertensive nephropathy with recent malignant HT:* for malignant hypertension to be the diagnosis, the funduscopic exam and EKG would have to be “falsely negative” (they didn’t reveal hypertensive change), and the U/A “falsely positive” for cellular casts indicating GN: Malignant HT causes fibrinoid necrosis, proteinuria and hematuria with occasional granular and cellular casts. For reasons discussed above, the HT in this

patient probably followed the RD rather than caused it, but to be sure the temporal sequence of the HT vis-à-vis the U/A abnormalities would have to be known.

- *Hepatitis B (or C) or other causes of MPGN histo-pathology such as age-related monoclonal gammopathy, still-obscure neoplasm ... or “idiopathic”.*

There are 2 other entities that are not etiologic diagnoses but rather histo-pathologic designations seen with diverse etiologies of RD. They warrant special consideration because steroids, available in Africa, are often given to treat their associated nephritic-nephrotic syndromes.

- *“RPGN”: “rapidly progressive GN” indicates crescentric necrosis of the glomerular tufts, the proportion of involvement being directly correlated with the development of renal failure over weeks to months. It reflects the extreme pathology of a number of disorders that are usually grouped into 3 categories:*

- *I: anti-glomerular basement membrane (GBM) which is likely to present with low GFRs (i.e. Cr. ~10);*

- *II: immune-complex deposition, usually secondary to a systemic disease like SLE, PSGN, mixed cryoglobulinemia (hepatitis C or B often), IgA nephropathy, etc.;*

- *III pauci-immune, ANCA-related processes like Wegeners.*

Despite proteinuria, due to the rapid development of renal insufficiency, NS is uncommon in RPGN and patients usually present with symptoms of fatigue and edema, as did our patient. (N.B. Series of more slowly progressive RPGN over months-years with NS and HTN have been reported, but most RPGN progresses over weeks-months.)

Although RPGN is non-specific and often secondary to a number of the diagnoses listed above, it warrants special mention because initial treatment of all categories is with “pulse-steroids”, available in Africa, usually followed by cyclophosphamide and plasmapheresis, unavailable in Africa. Some cases of RPGN complicating adult PSGN have seemed to respond to steroids alone (see below).

- *FSGS: “focal segmental glomerulosclerosis” is the histology found in 50% of blacks with NS in the U.S. (vs. 25% overall), in most black Africans with Schistosomiasis, and in HIV-nephropathy (“collapsing” FSGS), and is also a non-specific response to over-filtration in remaining glomeruli after significant loss of renal mass. Blacks are especially prone to develop this form of glomerular pathology in response to a variety of insults, a propensity genetically correlated recently with a specific allele. Primary FSGS can be associated with nephrotic-range proteinuria (60-75%), microscopic hematuria (30-50%), hypertension (45-65%), and chronic renal insufficiency (25-50%).*

It’s important to differentiate “primary” FSGS from FSGS “secondary” to infections since primary FSGS might respond to steroid therapy (though less so in adults) whereas secondary FSGS generally does not: Primary FSGS presents with the acute onset of NS with edema; secondary FSGS with slowly increasing proteinuria and creatinine over years, infrequent edema and non-nephrotic range proteinuria.

10-year survival of primary FSGS with NS is 30-50%, but is better (85%) without NS.

- ** *In our patient, there is no fever or other signs of vasculitis, systemic inflammatory disease or chronic infections like TB, leprosy, filariasis, etc. Hepatitis-related RD or schistosomiasis presenting for the first time at 75 years old would be unusual;*

schistosomiasis is not endemic in the Kisoro region; and the sediment is too “active” or cellular for the nephrotic pathologies of amyloid, adult minimal change disease, membranous nephropathy, or primary FSGS. IgA Nephropathy is hardly ever seen in Africa.

[N.B. Although not suspected, an HIV test was done and was negative.]

10. Which oral medications are potentially available for our patient, when should they be used, and what are the problems in using them in Africa?

Unfortunately only steroids, not cytotoxic agents such as cyclophosphamide, are available for immunosuppression in most areas of Africa.

Regardless of etiology, ACE-inhibitors should be used in proteinuric patients to slow progression, and anti-hypertensives for patients with renal hypertension. A problem with ACE-I therapy is the usually-limited ability to monitor potassium and creatinine.

The most effective therapies however are etiology specific, either removal of an offending agent or treatment of an underlying infection. Both halt immune complex formation. With NS in Africa, common medications that rarely cause NS include NSAIDs and antibiotics (ampicillin, cephalosporins and rifampin) and allergies to insect stings, etc.

Effective anti-microbial treatments for NS include ART for HIV, anti-hepatitis agents for hepatitis B and C, and antibiotics for infection-related GN or rare precipitants of minimal change disease such as syphilis, TB or mycoplasma, etc. If specific clinical diagnosis is not apparent, diagnosing or treating these infections, aside from HIV or syphilis, is usually not possible in rural district hospitals necessitating referral to regional or national centers.

So, given the universal penchant of healers to “do something”, the question often boils down to whether or not to give empiric steroids to patients with “renal disease”. (In my experience, practitioners in district hospitals in Uganda routinely give steroids once they suspect kidney disease, either nephrosis or nephritis. Is that the right thing to do?)

The following clinical observations are germane to “the steroid decision”:

- a) In children with acute onset of nephrosis without nephritis, the most common etiology (~90%) is “minimal change disease”(MCD) followed by primary FSGS. Both respond to empiric steroids, MCD over weeks, FSGS over many months.*
- b) In adults, MCD is the cause of NS in 10-15% of cases in the West. However, blacks with NS are less likely to have MCD than whites or Asians, and more likely to have FSGS on biopsy and thus the proportion of African adults with NS from MCD may be much lower. Adult MCD-NS is characterized by acute onset, usually normal Cr (although reversible acute RF can be seen), and a benign sediment without casts. Microscopic hematuria is frequently seen, and hypertension is present in nearly half. Over 70% respond to steroids, although ~70% relapse at least once and up to a third relapse repeatedly. Steroid dose is high, 1mg/kg/day, and continued for a minimum of 2 months until complete remission is achieved before tapering begins. The full course*

usually lasts ~6 months. Patients older than 40 years take longer to achieve remission but ultimately respond as well as younger patients.

- c) FSGS, if presenting like MCD with acute onset NS and edema unassociated with another disease (thus more likely to be “primary” or “idiopathic” FSGS) should ideally be treated with steroids. Secondary FSGS won’t respond to steroids and should be treated with ACE-inhibitors.

However, even in primary FSGS 5 years of steroid treatment leads to a complete response in only 20% and a partial response in only 60%. 40% don’t respond at all.

A minimum prednisone trial is 3-4 months long while assessing creatinine (not worsening) and proteinuria (improving). If efficacy is shown, treatment is continued for 8 months minimum, longer with partial responses, at 1mg/kg/day (or 2 mg/kg/qod) while assessing creatinine and proteinuria. Efficacy in this very indolent disease will only be apparent on long term follow-up (and in long-term studies) - without therapy, 30-50% are alive in 10 years, versus 80% if there’s been a complete response to steroids. If the Cr is >1.3 on presentation, only 25-30% survive 10 years.

- d) Systemic lupus erythematosus (SLE) is thought to be uncommon in black Africans despite being much more common in America in blacks than whites. How much of that difference is due to lack of access to care and under-diagnosis is controversial. In any case, SLE can present with or develop either nephritis or nephrosis usually accompanied by other manifestations of systemic inflammation, and responds to steroids.
- e) RPGN with crescents on biopsy, suggested clinically by a relatively rapid evolution of renal failure over weeks to months, is treated in the West with 3-5 days of pulse steroids followed by oral steroids, cyclophosphamide, and possibly plasmapheresis. There is no scientific evidence that steroids alone are efficacious, but scattered case reports in adults with crescentic PSGN and NS treated with pulse steroids and prednisone taper over months have suggested efficacy (e.g. ClinNephrol 2005; 63:375).
- f) PSGN or post-infectious diffuse endocapillary proliferative GN caused by other organisms does not respond to steroids (but as above, with the rare RPGN due to PSGN, pulse steroids might quell the acute inflammation and possibly preserve some renal function);
- g) IgA nephropathy (rare in Africa) usually is very indolent (progresses over many years) but if presenting with NS can be treated with a 6-month tapering course of steroids.
- h) Schistosomiasis or quartan malaria, causes of MPGN or FSGS pathology, do not respond to steroids and neither does the rare transient GN of falciparum malaria;
- i) Hepatitis B and/or C, (probably) frequent etiologies of GN in Uganda (with MPGN or membranous histo-pathologies) do worse on steroids; PAN due to hep B should be treated with steroids only in association with anti-viral agents once the diagnosis is confirmed;
- j) Membranous GN (MGN) is a common histo-pathologic finding in adult patients with NS in the West, but many more patients with MGN in Africa probably have it secondary to infections or neoplasms - for which steroids are not indicated (e.g. hepatitis).

Even in idiopathic MGN, if proteinuria is <4 gm/day, natural remission is expected without steroids; if between 4-8 gm/day, 50% remit without treatment in 3-6

- years (especially women, children and adults < 50 years old). Finally, when indicated, steroids alone are ineffective in idiopathic MGN without cyclophosphamide co-therapy.
- k) Amyloid, myeloma or monoclonal gammopathy associated nephropathies, all causes of NS in adults, don't respond to steroids.
 - l) Apart from collagen diseases such as SLE, fever with nephritis/nephrosis is usually a sign of an underlying infection complicated by renal involvement. Steroids should not be given.
 - m) Steroid therapy, particularly the long term high-dose steroid therapy required in renal disease, is fraught with serious side effects and is particularly risky in areas where side effects can't be managed or prevented. Rampant infectious disease makes chronic steroid therapy hazardous. Endemic TB in Africa makes INH prophylaxis nearly imperative, but INH isn't available in Uganda as a single drug (only in the RIPE combination pill).
 - n) Before embarking on a course of long-term, high dose steroids, a primary care infrastructure must be in place that can deliver comprehensive, continuous care with a dedicated and knowledgeable provider who has the resources to monitor renal outcomes (such as periodic creatinine and U/As) for years. Episodic care by an unfamiliar "practitioner du jour" in a rushed public clinic without diagnostic resources in rural Africa courts therapeutic failure or iatrogenic disaster.

In trying to "translate" this potpourri of histo-pathologic and etiology-specific observations into sensible clinical guidelines for empiric steroid therapy for renal disease in rural Africa - where renal biopsies, chemistries and serologic tests are unavailable, the following points seem reasonable:

- Reliable, knowledgeable follow-up is the sine-qua-non that must be in place before embarking on empiric steroid therapy in adults, which necessarily lasts 3-12 months;
- Acute onset of nephrotic syndrome over weeks, with edema and without an underlying disease or allergen evident, can be treated with a trial of 3-4 months of steroids if there are no obvious risk factors for hepatitis. This is the clinical scenario of idiopathic MCD or primary FSGS, the 2 pathologic categories that may respond to steroids. Mild-moderate HT, microscopic hematuria and a modest Cr elevation (e.g. < 1.8) are consistent with these entities and shouldn't disqualify treatment. HIV should be ruled out prior to therapy, and ideally hepatitis B (or C).
- Gradual evolution over months of NS or nephrotic-range proteinuria with weakness, fatigue and minimal edema is characteristic of secondary causes of nephrosis that won't respond to steroids. If available, an elevated Cr suggests both that the NS is "secondary" and, independently, a lower likelihood of response to steroids. ACE-inhibition and BP control (especially with diuretics), with periodic monitoring of Cr and potassium, is the safest strategy.
- Most cases of "nephritis" – hypertension, casts, significant hematuria - should not be treated with steroids for lack of efficacy when used alone in treating the most common etiologies of GN, the potential renal harm they can induce (e.g. hepatitis-induced GN), and the risk of immune-suppression they carry, particularly high in Africa.

- The only causes of glomerulonephritis (GN) for which empiric steroids should be considered are RPGN and diseases that fit the clinical picture of SLE (after infectious mimics have been considered and deemed unlikely). RPGN, a biopsy diagnosis, has to be defined clinically in regions of the world without biopsy capacity as “nephritis (with hematuria and casts) and evolution towards renal failure over weeks to months”. Diagnosing “probable RPGN” therefore necessitates multiple evaluations over weeks of urinalysis, creatinine (sent out if necessary) and clinical status. If urinalysis evidence of nephritis persists and the Cr rises 1-2 mg/dl/month, consideration should be given to pulse steroids followed by prednisone for a few months. Referral to a center with the ability to diagnose potential infectious or vasculitic etiologies, follow clinical and chemical status closely and use cytotoxic or specific anti-viral therapy when indicated is clearly ideal, but rarely possible.

11. What would be the most appropriate management strategy for our patient?

The most appropriate management strategy for our patient would be the following:

- Control the BP*
- Treat with ACE-I if possible to limit proteinuria and preserve kidney function.*
- Assess disease evolution for the possibility of RPGN, in which case steroids might be indicated.*

Given her nephritic presentation with accelerated HT and casts, our patient is unlikely to have MCD or primary FSGS, and lack of systemic inflammatory symptoms makes SLE or a vasculitic etiology unlikely as well. Steroids were unlikely to work. The big question was how fast the GN was evolving over time as a clinical indicator of possible RPGN.

A Cr and K were sent out commercially, and was 2.5, and 3.7 respectively.

Her BP was eventually controlled to ~145/90-95 on 3 medications: lasix 80 bid, captopril, and nifedipine; she diuresed 7 Kg, felt much better, and was discharged home.

A follow-up in 2 weeks revealed a Cr of 2.1, K 3.8, weight stable and BP in the same range with good medication adherence.

We decided it that she was unlikely to have RPGN but further follow-up would be needed to be sure. Steroids were withheld.

She missed the follow-up clinic visit in 3 weeks, and a community health worker was sent to her village to encourage her to return.

12. What are the realities of treating late-stage Disease X in Africa?

Late or end-stage renal disease (ESRD) is rarely treatable in Africa where governments can't afford to subsidize the costs of either dialysis or transplant (e.g. the per capita government investment in health care in Uganda is <\$10 USD /year) and the vast majority of people make 1-2 dollars/day.

As of 2008, there were only 150 dialysis units in 13 African countries (Africa comprises >80 countries), most of them serving the affluent in Nigeria, South Africa, Sudan and Mauritius. Even where there are facilities, less than 5% of those with ESRD can support dialysis therapy for >3 months.

Transplant as treatment for ESRD was possible in 5 African countries as of 2008, but <1% of Nigerians with ESRD could afford it.

13. What are the recommended screening and prevention modalities available in Africa for Disease X?

Given that end-stage disease treatment by renal replacement therapy won't be affordable in the foreseeable future, prevention of RD seems to be only option for African populations and health policy makers.

Primary prevention can be achieved by decreasing infectious disease burden overall through water and sanitation facilities, vaccination against hepatitis B, public health measures against HIV, TB, leprosy, schistosomiasis, and filariasis; etc.

Screening and effective treatment of hypertension is key, particularly in Africa, and measures to prevent the epidemic of "made-made" diseases of obesity, hyperlipidemia and type II diabetes in urban areas would be most cost-effective in view of the many problems that soon follow, including chronic renal disease.

Secondary prevention via specific screening for early stage RD in high risk groups with HT, DM, hepatitis B/C and other chronic inflammatory diseases that induce renal disease would help, but the key issue here is whether the individual or the health system can afford the recommended therapy. There are various screening programs for RD in Africa and elsewhere that are published, but have no treatment arm. The patients are told of their disease and referred to private hospitals for continuous care and medication that they can't afford. A cardinal rule of screening is the ability, before the screening begins, to close the loop and make treatment feasible. For the most part, this means an intact affordable primary care infrastructure, ACE-inhibitors for proteinuric renal disease, and management of hypertension and diabetes. Probably the most feasible screening would be with BP cuff and urinalysis.

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