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Primary care physicians often are confronted with patients presenting with either gross or microscopic hematuria. Either situation demands a clinical investigation. Gross hematuria typically calls for a referral to a urologist. In today's cost-conscious mindset, it is important to work with the urologist collaboratively toward an effective and timely work-up that avoids unnecessarily expensive or unproductive tests. Microscopic hematuria typically begins with a careful history and thoughtful investigation, most often to exclude occult neoplastic causes, and may more often involve the expertise of a nephrologist. Commonly, however, the presence of microscopic hematuria can be intermittent and the work-up unrevealing, requiring regular follow-up.

This issue highlights: definition of hematuria; epidemiology; etiology; diagnostic work-up; and common causative conditions and therapeutic implications.

—The Editor

Hematuria: Implications and Management

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Introduction

Evaluation of hematuria is a common problem in the primary practice setting. Hematuria may be distinguished between gross hematuria and microscopic hematuria. Differentiating between the two types is important in both evaluation and clinical management of either cause. Microscopic hematuria often is an incidental finding on urinalysis, whereas the patient often calls attention to manifestations of gross hematuria. In certain cases, the evaluation of the patient can yield no cause of the symptoms; however, a thorough evaluation is necessary given that the differential can extend from infection and nephrolithiasis to renal disease and malignancy.

Definition of Microscopic vs. Gross Hematuria

It is important to distinguish the difference in defining microscopic hematuria from macroscopic or gross hematuria. Microscopic hematuria is found on a urine dipstick or urinalysis often done for another purpose. The American Urological Association

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defines clinically significant microscopic hematuria as three or more red blood cells per high power field on microscopic evaluation on two of three carefully obtained specimens.[1] Note that others may advocate two or more cells as abnormal but that lowering or increasing the cutoff can result in either increasing the number of false positives or missing manifestations of significant pathology.[2] The urine sediment (or direct counting of red blood cells [RBC] per mL of uncentrifuged urine) is the gold standard for the detection of microscopic hematuria. Dipstick for heme can detect as low as 1-2 RBCs per high power field but may lead to detection of a higher number of false positives in the presence of myoglobinuria, alkaline urine with a pH greater than 9, or the presence of semen in the urine. Given the intermittent nature in which hematuria may present, some advocate for patients to have two of three specimens positive before having a formal evaluation.[3]

Therefore, if a dipstick is found to be positive, it should be confirmed with a microscopic analysis of the urine. If it is found to be negative, this virtually excludes the presence of RBC in the urine.[4] However, false-negative urinalysis has been noted in patients who ingest large amounts of vitamin C.[5]

The primary care physician may be alerted to the presence of gross hematuria based on the patient's history of brownish or red urine. The presence of as little as 1 mL of blood per liter of urine can cause this discoloration, so a thorough evaluation is necessary to help differentiate the cause. The initial step is to centrifuge the urine specimen to see if the source of discoloration is from the supernatant or urine sediment. (*See Figure 1.*)

In menstruating females, to prevent contamination of the specimen from menstrual blood, the test should be repeated after bleeding has ceased. Gross hematuria will result in detection of heme in the urinary sediment. Detection of heme in the supernatant can be caused by myoglobinuria and hemoglobinuria, which should be distinguished from gross hematuria given the different causes associated with each pathology. Separating extraglomerular causes from glomerular causes of gross hematuria is important given the different evaluation process of each cause. The presence of blood clots in the setting of gross hematuria is typically associated with extraglomerular causes affecting the lower genitourinary tract. An exception may be IgA nephropathy and Alport's disease.

In defining gross versus microscopic hematuria, it is important to note that typically neither situation causes any immediate danger to the patient, with the exception of gross hematuria caused by extraglomerular causes that may lead to obstruction of the ureter or, in trauma, can lead to massive hemorrhage. In these cases, immediate referral to a urologist is necessary. Also, in defining the symptoms the patient presents with, it is important to note the age of the patient and the time frame of the symptoms.[6] Unfortunately, even in older patients, often a source of the symptoms cannot be identified despite an extensive workup.[7]

Epidemiology

The prevalence of microscopic hematuria varies according to the age and gender of the population. The type of testing used—dipstick testing alone or combined with microscopic analysis—also affects the number of positive screening tests. Studies have reported prevalence as low as less than 1% to as high as 22%, depending on the characteristics of the populations studied.[8-9] In a large screening study of 1000 adult patients, with the screening cutoff of greater than three RBC per high power field in two of three samples, the prevalence was only 0.1%, with an increase with age older than 50 years.[2] Note that microscopic hematuria, when found, can be persistent or transient. More commonly,

Executive Summary

- Differentiating between gross and microscopic hematuria is important in both evaluation and clinical management.
- The differential diagnosis of hematuria can range from infection and nephrolithiasis to renal disease and malignancy.
- The American Urologic Association defines clinically significant microscopic hematuria as three or more red blood cells per high power field on microscopic evaluation on two of three carefully obtain specimens.
- Patients older than 40 years with hematuria are at greater risk for significant disease.
- Hematuria in young adults is more likely to be caused by renal parenchymal disease than malignancy.
- Hematuria can be the presenting symptom of cancer. Other suspicious symptoms include flank pain, fatigue, weight loss, and a palpable abdominal mass on physical examination.

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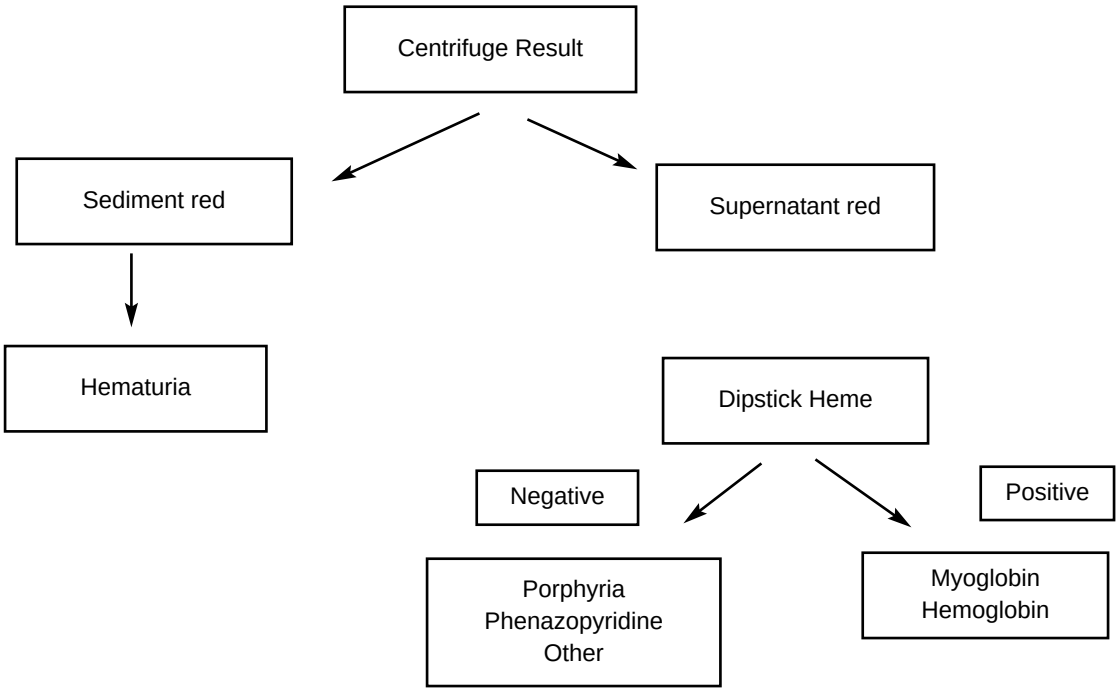
Figure 1. Approach to Gross Hematuria



transient hematuria may be precipitated by vigorous exercise, sexual intercourse, contamination, or trauma.

Screening for microscopic hematuria is controversial and has not been recommended for the general population. Although bladder cancer is the most common malignancy associated with microscopic hematuria, the decision to screen lies with the physician and consideration of risk factors for underlying disease. (*See Table 1.*)

Etiology

The cause of hematuria in the adult patient can vary in clinical significance. Causes can be secondary to benign sources, such as urinary tract infection and prostatic hyperplasia, to more severe or life-threatening causes such as bladder or renal cell malignancies. A thorough evaluation of both the upper urinary tract followed by cystoscopy can fail to identify the source of hematuria in a large number of patients. Based on several large studies, the percentage of nondiagnostic workups can range from 20-60%.[10-13] In younger patients, the likelihood of a nondiagnostic workup is higher.[14] (*See Tables 2 and 3.*)

The presence of additional abnormalities, such as proteinuria, red cell casts, or renal insufficiency, should prompt a referral to a nephrologist. These features may suggest the presence of renal parenchymal disease.

It is important to exclude benign causes such as menstruation, vigorous exercise, sexual activity, viral illness, trauma, and infection. These causes are commonly seen in a younger population presenting with hematuria. A thorough evaluation of the medication list can reveal some common medications that can cause hematuria. It should be noted that pathological gross hematuria can occur in younger individuals in a variety of conditions from bladder cancer, renal cystic diseases, and stones. (*See Table 4.*)

Patients older than 40 years with hematuria are at greater risk for significant disease. Other risk factors for significant disease that warrant a thorough workup include smoking, exposure to chemicals or dyes, analgesic abuse, and history of pelvic irradiation.[15]

Diagnostic Studies and Evaluation

As noted, a thorough history and physical examination and assessment are essential to assess a patient's risk factors before proceeding with a radiographic evaluation of the upper urinary tract, urine cytology, cystoscopy, or a referral to a nephrologist. A diagnostic algorithm for the management and diagnosis of microscopic hematuria is shown. An evaluation of genitourinary (GU) pathology is also warranted in older individuals on anticoagulation therapy, since the bleeding could originate from a malignancy. (*See Figures 2 and 3.*)

Radiographic Assessment of the Upper GU Tract. The upper urinary tract can be evaluated by the use of intravenous excretory urography, ultrasonography, and computed tomography. The goal of such imaging is to identify sources of hematuria, including renal carcinoma, urothelial carcinoma of the pelvicaliceal system and ureter, urolithiasis, renal infection, and benign conditions such as medullary sponge kidney disease, also known as papillary ectasia.

The intravenous excretory urogram (IVEU) has been the traditional initial approach for the evaluation of the upper urinary tract.[16] This study defines the anatomy of the urologic tract from the kidney to the bladder. It is a relatively inexpensive and easily

Table 1. Risk Factors

- Smoking history
- Occupational exposures chemical and dyes
  benzenes and aromatic amines
- History of gross hematuria
- Age > 40 years
- History of urologic disease
- History of irritative voiding symptoms
- History of urinary tract infections
- Analgesic abuse
- History of pelvic irradiation

Table 2. Nonglomerular Causes

- Renal and bladder malignanies
- Renal pelvis, ureteral, prostate malignanies
- Nephrolithiasis
- Pyelonephritis
- Polycystic kidney disease
- Renal trauma
- Papillary necrosis
- Sickle cell trait
- Renal TB
- Renal infarction
- Cystitis, prostatitis, and urethritis

Table 3. Glomerular Causes

- IgA nephropathy
- Thin glomerular basement membrane disease
- Postinfectious glomerulonephritis
- Membranoproliferative glomerulonephritis
- Focal glomerular sclerosis
- Alport's syndrome
- Vasculitis
- Lupus nephritis
- HUS/TTP
- Henoch Schonlein syndrome

available diagnostic tool. However, it has not proved as sensitive in detection of smaller renal tumors. One study noted that intravenous urography identified 85% of lesions greater than 3 cm but only 21-52% of smaller lesions.[17] Once a mass is detected using IVEU, further evaluation is needed using ultrasonography and computed tomography given that IVEU cannot distinguish solid masses from cystic ones.

Ultrasound is a less expensive and safer means for evaluation of microscopic hematuria because it does not expose the patient to intravenous contrast. It is limited in evaluating tumors less than 3 cm in diameter but is sensitive in detection of masses greater than 3 cm, cysts, and hydronephrosis.[17]

Computed tomography (CT) has a high sensitivity for identifying renal calculi.[18] Unenhanced CT has replaced many other imaging techniques, including ultrasound and plain radiography, as the test of choice in patients with renal colic and microscopic hematuria. Although more expensive, contrast-enhanced CT has a higher sensitivity compared to ultrasonography and intravenous urography in detection of smaller renal masses. It also can be used to characterize a mass as cystic or solid and to allow for surgical staging in the setting of a malignancy.

Although not widely used and even more expensive, MRI can be used to assess the upper urinary tract. The sensitivity of CT, however, approximates that of MRI in detection of smaller masses.[16]

Iodinated contrast should be used cautiously in patients with impaired renal function, serum creatinine over 3 mg/dL (risk for developing AKI), and contrast MRI should be avoided if possible in patients with eGFR below 35 mL/min (risk of developing nephrogenic systemic fibrosis).

Radiographic Assessment of the Lower GU Tract. Assessment of the lower urinary tract can be necessary despite finding an abnormality in the upper tract, given the possibility of two separate lesions. Assessment of the lower urinary tract includes both urine cytology and cystoscopy. The cause of asymptomatic hematuria can be unknown in up to 70% of patients even after a thorough evaluation of the upper urinary tract.[19]

Cytology and Tumor Markers. Urothelial cancer of the collecting system, ureter, or bladder is the most common malignancy detected in patients with microscopic hematuria. Cytologic evaluation of cells within the urine is an easy, noninvasive method of detecting urothelial malignancy. However, cytology is very specific, but relatively insensitive (40-76%) for the detection of bladder cancers in comparison to cystoscopy and can be less useful in detection of low-grade tumors.[20] The sensitivity is highest for high-grade lesions in the bladder and carcinoma in situ. Its primary advantage is its noninvasiveness in comparison to cystoscopy.

Positive cytology without evidence of an abnormality in the bladder should prompt an evaluation of the upper urinary tract and the prostatic urethra. If no clear lesion is found, washings of the ureters and renal pelvis can be performed.

Urine cytology specimens must be collected and stored properly to maintain a high level of diagnostic accuracy. Specimens obtained from a urinary catheter can lead to coalescing of cells in papillary groups, resulting in difficult interpretation and misdiagnosis of a low-grade TCC. Inflammation and chronic infection can cause degenerative cellular changes and atypica that can lead to misinterpretation. Care should be taken to avoid contamination with vaginal, cervical, or endometrial cells.

The role of urine flow cytometry in screening for urothelial malignancies is not clear. Flow cytometry is an automated procedure, requiring much less labor than cytology, but requires a catherized specimen. One of the drawbacks is the need for a sample with a large number of cells, making it less useful in the detection of CIS, where small populations of aneploid populations can exist.[21]

However, thus far, it appears that both cytology and flow cytometry used together do not appear to increase the diagnostic yield.[22]

Table 4. Medications

- Aminoglycosides
- Amitriptyline
- Analgesics
- Anticonvulsants
- Aspirin
- Busulfan
- Chlorpromazine
- Cyclophosphamide
- Diuretics
- Oral contraceptives
- Pencillins (extended spectrum)
- Quinine (QM-260)
- Vincristine
- Warfarin

The desire to find more noninvasive screening methods has led to the evaluation of newer tests such as urine histochemistry (ImmunoCyt test) and proteomics assays for the nuclear matrix protein NMP22 (NMP22 BladderChek test). These tests may hold more promise in the detection of lower-grade tumors.[23]

Urine histochemistry utilizes three monoclonal antibodies specific for two antigens expressed on the surface of TCC tumor cells. Urine histochemistry appears to be more sensitive than cytology in the detection of lower grade tumors, whereas cytology seems to have a higher sensitivity in detection of higher-grade tumors.[24] However, the sensitivity of the histochemistry test does not seem high enough to replace cystoscopy.

Proteomics involves the analysis of protein expression in tissues, serum, and other biologic samples to identify or characterize malignant tumors on the basis of unique protein expression patterns. In a large study of more than 1300 patients with multiple risk factors for bladder carcinoma, all the patients underwent cystoscopy, with the comparison of urine cytology to the assay for NMP 22. Of the patients diagnosed with bladder carcinoma, the NMP assay was found to be more sensitive than cytology for lower- and intermediate-grade tumors.[23]

Other urinary biomarkers are being evaluated and have been found to have some utility in monitoring for recurrent carcinoma, but have not proven to be useful as a screening technique and have not eliminated the need for cystoscopy. These markers include qualitative fluorescence image analysis, molecular cytogenesis, telomerase expression, tumor associated intracellular or secreted products, oncogene mutations, microsatellite alterations, and markers of apoptosis.[25]

Cystoscopy. The disadvantages of cystoscopy are the discomfort of an invasive procedure and the limited ability to detect carcinoma in situ.[26] However, it is the only accurate method of detecting a transitional cell carcinoma of the bladder and urethra.[27]

Cystoscopy has a lower yield in patients younger than 40 years with no risk factors for malignancy.[28] In these select patients, cystoscopy may be deferred, but urine cytology, given its noninvasiveness, can be considered.

Bilateral ureteral brush biopsy, ultrasound, or endoscopy may be needed when transitional malignancy of the ureter is suspected, such as in a patient with analgesic-associated renal disease.

Glomerular vs. Urologic Hematuria

The differential diagnosis of hematuria is wide and can require management from different specialists, and this has led the attempt to find tests that could categorize asymptomatic microscopic hematuria as a marker for renal or urologic disease. As RBCs enter the urine as a result of glomerular bleeding, they pass through the renal tubules and can be subjected to high transmembrane osmotic gradients. This can lead to shrinking of cells, creating an irregular "crenated" shape in place of the normal biconcave disks of the RBC.[29] The presence of such RBC has been evaluated by phase-contrast microscopy or automated size analysis in a Coulter counter. However, in a double-blind controlled comparison of the findings of two blinded observers using phase contrast microscopy, this technique was not successful.[30] No larger-scale studies have been conducted to validate the use of these techniques in helping exclude causes of hematuria.

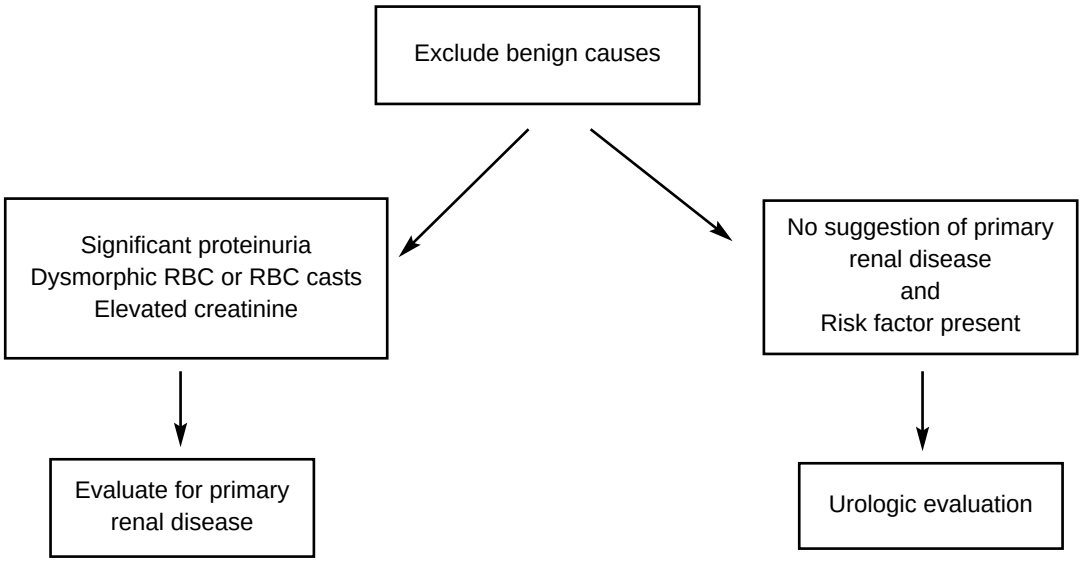
Management of Separate Diagnosis

The management of these patients is dictated by the diagnostic workup. For patients with an initial negative evaluation for asymptomatic microhematuria, most do not develop significant urologic disease. Yet, for a small percentage of patients, hematuria can precede the diagnosis of bladder cancer by many years, and some followup is necessary in higher-risk patients—especially older patients with a history of smoking or occupational exposures.[28] However, because the data regarding follow-up in such patients are sparse, recommendations regarding such follow-up are based on literature-based evidence and are not standardized. Based on AGU guidelines, consideration could be given to repeating urinalysis and urine cytology at six, 12, 24, and 36 months.[2] After three years, the patient does not require further urologic monitoring. If a higher level of suspicion exists, consideration can be given to cystoscopy or further radiologic imaging.

Patients with hypertension, proteinuria, or evidence of glomerular bleeding in the form of red cell casts or dysmorphic red blood cells should be referred to a nephrologist for further monitoring and evaluation.

For patients found to have a suspicious malignancy, both the urologist and medical oncologist share joint management, with the help of radiation oncology in certain situations. Renal masses found to be suspicious for malignancy are removed surgically by urologists, without biopsies in most situations, given concern for tumor cell seeding with needle biopsy. In the last five years, with the availability of targeted receptors, the clinical outcome for patients with advanced renal cell malignancies has improved dramatically. Urothelial malignancies to the ureter, renal pelvis, urethra, and bladder are managed with surgery alone in the early stage, but require surgery, platinum-based chemotherapy, and radiation therapy for more advanced disease.

Figure 2. Initial Evaluation of Asymptomatic Microscopic Hematuria



Renal Malignancies

With approximately 38,000 cases diagnosed per year in the United States, renal cell carcinoma accounts for only about 2.5% of all malignancies.[31] Approximately 25% of patients present with locally advanced invasive or metastatic disease. Approximately 30% of patients with resected disease have a recurrence.[32] Given that the median survival for patients with advanced disease is slightly more than one year, there has been a focus on the development of new treatments.

As noted above, from the office of the primary care physician, hematuria can be the presenting symptom. Other suspicious symptoms include flank pain, fatigue, weight loss, and a palpable abdominal mass on physical examination. About 2% of diagnoses are associated with hereditary syndromes. The peak age of presentation is the 60s to 70s, and a there is an increased incidence in men, with a 1.6:1 ratio of men to women.[31] Risk factors include obesity, smoking, and hypertension.[33] Other adverse prognostic factors after diagnosis include poor functional status, high lactate dehydrogenase, a low hemoglobin level, and a high calcium level.

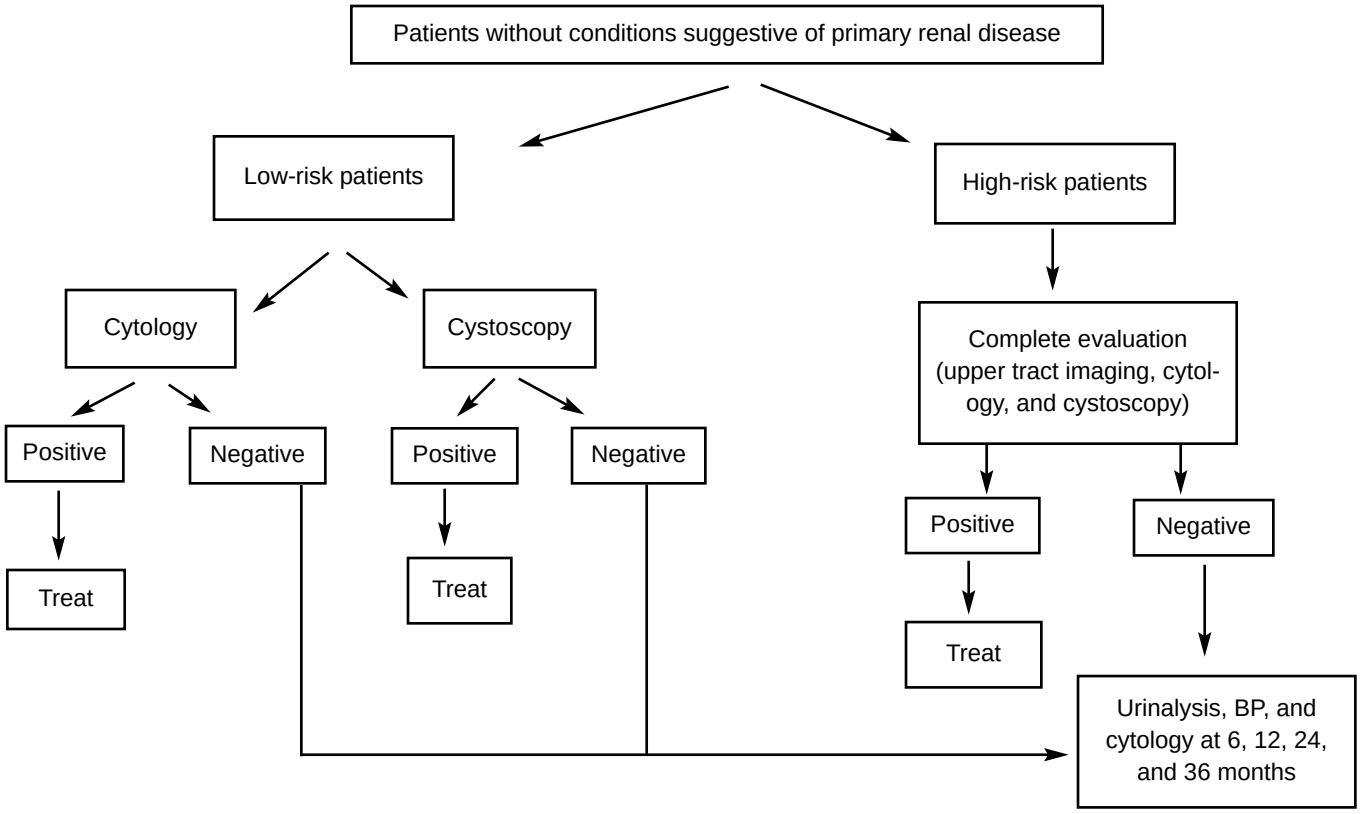
Surgical excision is the primary treatment for early stage renal-cell carcinoma. Radical nephrectomy, which includes removal of the kidney en bloc with Gerota's fascia, the ipsilateral adrenal gland, and regional lymph nodes, has been the standard therapy. The surgical approach is determined by the size and location of the tumor within the kidney, the stage of the tumor, and any other special anatomical considerations. Even in the setting of metastatic disease, there may be a role for nephrectomy. The combination of nephrectomy and interferon alfa has been shown to be superior to interferon alfa alone in advanced disease.[34] In the setting of isolated metastasis, there is a role for resection of both the primary site of disease and of the isolated metastasis.

In the last few years, the treatment of advanced renal cell cancer has been revolutionized by new targeted therapies. Rates of response to chemotherapy alone are low (roughly 4-6%).[35] Prior to this treatment, options were limited mainly to immunotherapy, with IL2 in selected patients with a good performance status with metastatic disease, and with interferon alpha in the adjuvant setting after nephrectomy. In a novel phase III trial, sunitinib, an orally administered inhibitor of tyrosine kinases, including vascular endothelial growth factor receptor (VEGF) and platelet-derived growth factor receptor (PDGFR), was compared to interferon alfa in previously untreated patients with metastatic disease. Progression-free survival, the primary endpoint, was found to be significantly longer with higher response rates in patients receiving sunitinib compared to patients who received interferon alfa.[36] These receptor tyrosine kinases play an important role in the pathogenesis of clear cell carcinoma, the most common histologic diagnosis among renal cell carcinoma. This key role in pathogenesis occurs through involvement of the tumor suppressor gene, the von Hippel-Lindau gene, which is activated in a majority of sporadic cases by deletion, mutation, or methylation.

Following this study, another pivotal phase III study comparing sorafenib to placebo in patients with advanced renal cell carcinoma resistant to standard treatment showed that sorafinib prolonged progression-free survival compared to placebo. Sorafenib is also an orally active multikinase inhibitor, with effects on tumor cell proliferation and angiogenesis.[37]

With the results of these two phase III studies, the oral tyrosine kinase inhibitors have transformed the treatments of metastatic renal cell carcinoma. Currently, these targeted treatments are being studied in the adjuvant setting following surgery. The toxicities associated with these drugs commonly seen by both the oncologist and primary care physicians include diarrhea, hypertension, hand-foot-skin reactions, alopecia, nausea,

Figure 3. Urologic Evaluation of Asymptomatic Microscopic Hematuria



bleeding, and cardiovascular events. Notably, patients receiving sunitinib can have a decline in their ventricular function. However, with discontinuing the medication, the cardiomyopathy is reversible.[38]

Another new agent, temsirolimus, was studied in poor prognosis patients with advanced disease. Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) kinase, a component of intracellular signaling pathways involved in the growth and proliferation of cells. A phase III trial compared temsirolimus to interferon alfa to the combination of both drugs in previously untreated, poor-prognosis metastatic renal-cell carcinoma. Overall survival and progression-free survival were improved in the temsirolimus group compared to interferon alfa alone. The addition of interferon alfa did not improve survival.[39] The primary toxicities of temsirolimus included asthenia, rash, anemia, nausea, dyspnea, diarrhea, peripheral edema, hyperlipidemia, and hyperglycemia. This trial provided a new target, mTOR, in renal cell carcinoma. This drug has yet to be compared to the oral tyrosine kinase inhibitors in advanced carcinoma.

Clear cell histology is the most common histology in renal cell malignancies. These new medications were tested primarily in patients with clear cell histology. However, other histologies, such as papillary renal cell, chromophobe, collecting duct renal cell carcinoma, or oncocytoma, follow a different clinical course. Chromophobe renal cell carcinoma and oncocytoma follow a more benign course, whereas collecting duct carcinomas follow a more aggressive course. Chemotherapy may be more effective for collecting duct carcinoma. Papillary carcinoma follows a more favorable course when localized, but a more aggressive course if metastatic in contrast to clear cell histology. Therefore, the histology must be considered prior to starting the treatments available in renal cell carcinoma. Patients with impaired renal function and a small, well localized renal malignancy may be candidates for partial nephrectomy.

Urothelial Malignancies

Bladder cancer is the most common malignancy of the urinary system and the most common malignancy associated with microscopic hematuria. Transitional cell carcinoma (TCC), also known as urothelial carcinoma, is the predominant histology in the United States and accounts for 90% of bladder carcinoma. The most common risk factors for bladder carcinoma include smoking and occupational exposures. In regions outside the United States where schistosomiasis is more prevalent, nonurothelial histologies are more common. Transitional cell carcinoma also can involve the renal pelvis, ureter, and urethra.

In 2008, it was estimated that approximately 68,000 cases of bladder carcinoma were diagnosed in the United States.[40] Bladder cancer typically is diagnosed in older individuals, with a median age of 69 in men and 71 in women.[41] Although it is rare, bladder cancer can present in younger patients, but it usually is low grade, non-invasive disease.[42] There is a higher risk of

bladder cancer in white men, with roughly twice the incidence as African American and Hispanic men.[43]

Environmental exposures are a risk factor for urothelial carcinoma. The urothelium that lines the mucosal surfaces of the urinary tract is exposed to environmental carcinogens. This "field cancerization" effect is a hypothesis to explain the multifocal nature of carcinomas of the lower and upper urinary tract.[44] Potential occupational carcinogens include benzene, polyaromatic hydrocarbons, and diesel exhausts.

Several agents have been evaluated as chemopreventive agents in the prevention of bladder cancer. Retinoids have been studied in both epidemiologic studies and in clinical trials. In a primary chemoprevention trial, 29,000 male smokers were randomized to beta-carotene, alpha-tocopherol (a vitamin E precursor), both, or placebo in the ATBC study. At a follow-up of 6.1 years, there was no statistical difference in the number of bladder carcinoma diagnoses in each treatment group.[45] Other vitamin A derivatives, pyridoxine, vitamin E, and asorbic acid have been evaluated as chemopreventive agents, but no clear role has been established in either primary or secondary chemoprevention.

TCCs of the renal pelvis and ureter are thought to be due to the same etiologic factors as TCC of the bladder. Given the multifocal nature of these tumors, patients with a urothelial cancer of the upper urinary tract should have close surveillance for a tumor of the lower urothelial tract or the contralateral urinary tract. In a series of 82 patients who had complete resection of a TCC of the renal pelvis or ureter, urothelial carcinoma of the bladder was subsequently diagnosed in 44% of the patients at a median interval of 14 months.[46]

The clinical presentation of bladder cancer can range from superficial disease to invasive or metastatic disease. In the United States, the approach for high-grade, superficial bladder cancer is transurethral resection followed by intravesicular treatment with BCG. For patients with disease refractory to BCG, the treatment would then be radical cystectomy. Some patients with a projected longer survival proceed directly to immediate cystectomy, given the 50% risk of progression to muscle invasive disease.[47]

Approximately 10-20% of patients with invasive bladder cancer have locally advanced, inoperable tumors. These patients can be offered cisplatin-based chemotherapy to try to render patients unresectable.[48] Chemoradiation is an option for patients who desire bladder preservation, with salvage cystectomy reserved for patients who do not respond. Patients with a poorer performance status can be treated with radiation alone or chemotherapy for palliative purposes.

Whereas transitional cell or urothelial carcinoma comprise 90% of bladder cancer in North America and Europe, in areas of the world where infection with *Schistoma haematobium* is prevalent, nonurothelial carcinoma of the bladder is more common. These patients often present with hematuria and irritative symptoms. Nonurothelial carcinomas are classified as epithelial or nonepithelial. The large majority are epithelial, which include squamous cell, adenocarcinoma, and small cell carcinoma. The nonepithelial include sarcomas, pheochromocytomas, melanomas, and lymphomas.

In these areas, squamous cell cancer accounts for approximately 75% of cases, transitional cell carcinoma for 20%, and adenocarcinoma for 5%.[49] Although the pathophysiology behind the development of nonurothelial carcinoma is not understood, both bladder irritation and metaplasia are thought to be contributing factors. Areas with increased incidence of *Schistoma haematobium* have a significant increase of bladder cancer, including squamous cell cancer, adenocarcinoma, mixed histology, and transitional cell carcinoma, with squamous cell being most common. Squamous cell carcinoma without infection usually presents with bulky tumors and locally advanced disease, although metastatic disease is present in only about 10% of patients.[50] Treatment is primarily surgery, given that chemotherapy and radiation have not been shown to be successful in affecting outcome, and these patients have frequent local recurrences. Schistosomal bladder carcinoma usually presents at a younger age, more commonly in men. These tumors are more low- to moderate-grade. The standard management includes radical cystectomy and lymph node dissection. Small studies have shown that chemotherapeutic agents have activity in advanced disease, although these studies have been underpowered to show a clinical significance.

Glomerular Disease and Hematuria

Although malignancy is a strong consideration in the workup of older patients with hematuria who have specific risk factors, hematuria in young adults is more likely to be caused by renal parenchymal disease than malignancy. Unfortunately, given the rare cases of urinary tract malignancies in individuals younger than 40 years, each young patient must be considered individually in determining whether a referral to a urologist, nephrologist, or both is necessary. Several studies have shown that renal biopsy in patients with no urologic explanation of hematuria has shown glomerular disease in a significant number of patients.[51-52]

In a series, 165 patients with microscopic or macroscopic hematuria were referred to nephrologists and underwent renal biopsies. All of these patients had no obvious signs of renal disease: normal serum creatinine, no evidence of significant proteinuria with protein excretion of < 300 mg/24 hours on urine collections. Of these patients, abnormal findings were noted on renal biopsies in 46% of patients.[53] Approximately one-third of the patients had IgA nephropathy, seven patients had thin basement membrane nephropathy, and 20 had various other forms of glomerular disease.

IgA Nephropathy

IgA nephropathy, also known as mesangial IgA disease or Berger's disease, is the most common primary glomerulonephritis in developed areas of the world.[54] There is a peak incidence in the second and third decades of life, with a greater frequency in Asians and Caucasians.[55] This disease can present with a wide spectrum of disease. Given that findings can be noted on renal biopsy, this diagnosis must be considered in otherwise relatively healthy patients with hematuria who have a relatively negative diagnostic workup. The more classic presentation is hematuria—

more commonly gross hematuria—several days within the onset of a respiratory illness. Other presentations include nephrotic syndrome, hematuria and proteinuria, rapidly progressive glomerulonephritis, Henoch-Schoenlein purpura, chronic renal failure, or asymptomatic microscopic hematuria.[56]

The presence of IgA nephropathy is established only by renal biopsy. The pathognomonic finding is seen on immunofluorescence microscopy of the tissue, which demonstrates prominent, globular deposits of IgA (often accompanied by C3 and IgG) in the mesangium and, less often, along the glomerular capillary wall. IgA nephropathy is generally not associated with a marked cellular glomerular infiltration, which suggests that glomerular injury is mediated by resident glomerular cells. As IgG and complement components often are codeposited, IgA alone appears sufficient to provoke glomerular injury in the susceptible individual. This occurs predominantly through IgA-induced activation of mesangial cells and local complement activation.[57]

Some patients with IgA nephropathy have a coexisting diffuse thinning of the glomerular basement membrane that is indistinguishable from thin basement membrane nephropathy. It is not known whether these patients follow a different clinical course of patients with typical IgA nephropathy.[58]

Manifestations of IgA nephropathy are most often restricted to the kidney. However, mesangial IgA deposition can be seen with alcohol-related cirrhosis, celiac disease, and HIV infection.

Patients with IgA nephropathy who do not have evidence of proteinuria seem to have a lower risk of progression of their disease. Despite this, renal insufficiency and proteinuria can still develop in a percentage of patients over the long term, and these patients may progress to end-stage renal disease (ESRD).[57] The possible role of persistent microscopic hematuria in predicting an adverse outcome in this group of patients is debated.[54]

The approach to the treatment of IgA nephropathy is not well standardized. Two approaches include symptomatic treatment of symptoms and manifestations as the disease progresses versus the use of corticosteroids. Attempts to slow progression include the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to control blood pressures and monitoring of proteinuria. Corticosteroids can be used as treatment of underlying inflammatory disease.

Disease typically is monitored serially using the urine sediment, protein excretion (usually estimated from the protein-to-creatinine ratio), and the serum creatinine concentration. Hematuria is thought to mark the presence of persistent immunologic activity, but not necessarily of progressive disease. This finding may be a sign of a "smoldering" segmental necrotizing lesion, suggestive of "capillaritis."[59] The presence of hematuria alone should not necessarily prompt the need for treatment, whereas the presence of moderately severe proteinuria may be an indicator of more severe disease and may mark the need for instituting treatment.

The two main nonimmusuppressive treatments include ACE inhibitors for blood pressure and proteinuria and statin therapy for lowering lipid levels. Small randomized studies have shown that both ACE inhibitors and ARBs are more effective than other antihypertensive drugs in slowing the progressive decline in glomerular filtration rate in IgA nephropathy.[60] The addition of an ARB to an ACE inhibitor in patients with IgA nephropathy may produce a further antiproteinuric effect and has been evaluated in several trials.[61] However, no randomized trials have shown that these combination regimens improve renal outcomes. Yet, given that a more antiproteinuric effect is thought to improve overall outcome, these treatments either alone or in combination continue to be used and studied.

Lipid-lowering with statins has been associated with a slower rate of loss of glomerular filtration rate in patients with mild to moderate chronic kidney disease (CKD).[62] Both this and the association of chronic kidney disease and cardiovascular disease have led to the use of statin therapy as part of the management in patients with IgA nephropathy and manifestations of renal disease.

A variety of treatment regimens using corticosteroids, alone or in combination with other immmunotherapies, has been evaluated. Studies evaluating these treatments have not been conclusive, and often these studies have been small and have limited follow-up with conflicting results.[63] In practice, most nephrologists will not treat mild or stable IgA nephropathy with glucocorticoids or other immunosuppressive therapies, given the limited evidence of benefit and toxicity from chronic use.[64] Steroid therapy in such patients should only be administered when there is clinical and histologic evidence of active inflammation. Corticosteroid therapy for periods of 6 months to two years has been associated with a reduction in proteinuria and perhaps improved renal survival in certain studies, but this has not been a consistent finding.[65] Immunosuppressive therapy should be considered only in patients with more severe disease as noted by a more rapidly progressive clinical course and histologic evidence of severe active inflammation.

Thin Glomerular Basement Membrane

Thin glomerular basement membrane disease, also previously known as benign familial hematuria, can be another common cause of asymptomatic glomerular bleeding. This disease can only be diagnosed by renal biopsy, with electron microscopy showing uniform thinning of the glomerular basement membrane (Lamina Densa). The most common manifestation of this disease is asymptomatic microscopic hematuria. The disease is inherited in an autosomal dominant pattern, and typically these patients have a good prognosis. Hypertension, proteinuria, and progressive renal failure are not common manifestations of this disease. However, progression in certain cases to end-stage renal failure has been reported.[66] Typically these patients are observed and have an excellent prognosis for normal renal function.

Another glomerular disease reported in patients with asymptomatic microscopic hematuria is mesangial proliferative glomerulonephritis, similar to IgA disease, but without the presence of IgA deposits. The prognosis of this disease is similar to IgA nephropathy.

Summary

The implications of hematuria, either gross or microscopic, can be broad and range from renal, urologic, malignant, and

benign causes. Given such a large differential diagnosis, the diagnostic workup can seem overwhelming. The patient's risk factors, history, and physical examination should dictate how to proceed. It is important to note that older patients, even if a renal cause may be suspected, deserve a full evaluation of the upper and lower urinary tract to exclude malignancy, given that these patients can be at increased risk. Also, an abnormality of the upper tract should not preclude an evaluation of the lower tract, given that patients can have anatomic abnormalities in both locations, which both warrant treatment. In patients who have a negative diagnostic evaluation for both renal and urologic disease, certain patients with asymptomatic hematuria warrant continued followup at future intervals to see if their symptoms resolve. This decision should include consideration of the risk factors for each patient and should be evaluated on an individualized basis.

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Physician CME Questions

14. The most common malignancy associated with microscopic hematuria is:
    A. renal cell carcinoma.
    B. bladder cancer.
    C. prostate cancer.
    D. colon cancer.

15. Thorough evaluation of the lower genitourinary tract in the workup of

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

hematuria includes:

A. cystoscopy and cytology.
B. CT and ultrasound of the pelvis.
C. IV pyelogram.
D. colonscopy and cystoscopy.

16. Risk factors for pathologic disease after evaluation for hematuria include all of the following *except*:
    A. smoking.
    B. alcohol.
    C. pelvic irradiation.
    D. analgesic abuse.
    E. chemical exposure.

17. Which of the following studies is useful for evaluation of a smaller renal mass?
    A. IV pyelogram
    B. cystoscopy
    C. CT
    D. ultrasound

18. Screening for microscopic hematuria in the general population has been shown to reduce mortality.
    A. true
    B. false

19. Medications that commonly cause hematuria include all of the following *except*:
    A. aminoglycosides.
    B. penicillins.
    C. analgesics.
    D. cyclophosphamide.
    E. beta blockers.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

CME Answer Key

14. B
15. A
16. C
17. C
18. B
19. E

In Future Issues: ***Management of Headaches***

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Liraglutide: Promise of the Incretin Class

Source: Nauck M, et al. *Diabetes Care* 2009;32:84-90.

GLUCAGON-LIKE PEPTIDE-1 (GLP) IS A recently "rediscovered" endogenous hormone of the incretin class. GLP has diverse favorable metabolic effects that modulate excess glucose excursions, including enhancement of glucose-dependent insulin secretion, slowing of gastric emptying, blunting of glucagon, and increased satiety. "Natural" GLP has a fleeting (2 minutes or less) half-life, precluding its utility as a pharmacotherapeutic tool. Recently, we have captured some of the valuable activity of the incretins by employing agents that block the degradation enzyme of GLP, DPP-4. Subcutaneous liraglutide (LIR) is a synthetic GLP analogue with a half-life of 13 hours, allowing once-daily dosing.

Nauck et al performed a double-blind, controlled trial of LIR vs glimepiride or placebo added to maximum-dose metformin in more than 1000 Type 2 diabetics. Subjects were followed for approximately 6 months.

At the end of treatment, A1c reductions (about 1%) were similar for 2 different doses of LIR or glimepiride. Important differences, however, included changes in body weight and incidence of hypoglycemia. For instance, minor hypoglycemia was seen in only about 3% of LIR subjects, but 17% of glimepiride subjects. LIR was associated with modest weight loss (average 2.3 kg) compared to a 1 kg weight gain in glimepiride subjects. The most common adverse effect noted with LIR was nausea (11-19%), which has been commonly reported with another injectible member of the incretin class, exenatide. ■

Low-glycemic Index Diet in Type 2 Diabetics

Source: Jenkins DJ, et al. *JAMA* 2008; 300:2742-2753.

THE KNOWLEDGE THAT NOT ALL CARbohydrate sources provide a similar rate of glucose rise has been captured with the glycemic index metric; high-glycemic index foods (e.g., bread, potatoes, simple sugars) produce very prompt glucose rise compared with low-glycemic index items (e.g., beans, complex carbohydrate sources like cruciferous vegetables). In Type 2 diabetics, in whom first-phase insulin secretion (that component of insulin secretion intended to respond to prompt glucose rise) is lost, low-glycemic index foods are intuitively preferred. Unfortunately, confirming meaningful benefits from consumption of a low-glycemic index diet has been difficult.

In this trial, Jenkins et al studied Type 2 diabetics (n = 210) assigned to 6 months of a low-glycemic index diet or a high-cereal fiber diet. Both diets achieved A1c reduction, but the low-glycemic index diet was superior (0.5% vs 0.18%). An additional favorable effect of the low-glycemic index diet was a modest HDL increase.

Whether patients can and will sustain a low-glycemic index diet, and whether such A1c reductions will reduce diabetes-related endpoints, remains to be determined. In the meantime, there is no suspicion of any detrimental effect of the low-glycemic index diet: Most short and intermediate term data suggest salutary effects. ■

Glucose Control and Macrovascular Disease

Source: Duckworth W, et al. *N Engl J Med* 2009;360:129-139.

MOST CLINICIANS MAINTAIN A FAIRLY glucose-centric view of diabetes. That is, we have made the assumption that the most visible derangement in diabetes, hyperglycemia, is the culprit producing vascular disease. The next intuitive step is that if glucose is pathogenetic in the development of vascular disease, then glucose modulation should reduce it. Despite consistent favorable clinical trial data confirming the benefits of glucose control upon microvascular disease (retinopathy, nephropathy, neuropathy), no clinical trial (except a single trial with acarbose) has shown reduction in macrovascular risk (myocardial infarction or stroke).

The VA Diabetes Trial (VADT) follows close on the heels of the ACCORD and ADVANCE trials, which not only failed to show reductions in macrovascular disease, but in one trial (ACCORD) demonstrated increased mortality in persons with very tightly controlled diabetes.

The VADT enrolled almost 2000 veterans with Type 2 diabetes and randomly assigned them to standard vs intensive therapy. Since almost half had already sustained a CV event, other tools to reduce CV risk were already widely employed in both groups.

At the 5.6 year endpoint of the trial, the intensive therapy group attained a substantially lower A1c than the standard therapy group: 6.9% vs 8.4%. Disappointingly, there was no discernible reduction in CV risk or microvascular endpoints in this group. There was a reassuring contrast between VADT and ACCORD: No increase in mortality with tight control was seen, despite a greater incidence of hypoglycemia. Clinicians will have to rely upon diet, exercise, smoking cessation, lipid modulation, and blood pressure control to reduce CV endpoints in Type 2 diabetics. ■

Risks Associated with the Morning BP Surge

Source: Kario K, White WB. *J Am Soc Hypertens* 2008;2:397-402.

AMBULATORY MONITORING OF BLOOD pressure (BP) has demonstrated a pattern of BP change typified by an overnight reduction in BP of 10-20% and a "morning surge" in BP beginning closely around the time of awakening. Even in patients with hypertension, morning surge in BP is seen. And it's not only BP that surges in the morning: Blood coagulability, plaque vulnerability, platelet aggregability, and blood viscosity also increase at this time. Because CV events (MI, stroke, arrhythmia) also cluster disproportionately around this circadian phenomenon, experts have opined that modulation of the morning BP surge might provide benefits in clinical outcomes.

The relationship between the morning BP surge and CV risk is strengthened by the observation that it correlates with arterial wall stiffness, left ventricular hypertrophy, and carotid intima-media thickness.

Office blood pressure is typically measured several hours after the morning surge. Encouraging more widespread use of at-home BP self-monitoring is a reasonable first step to obtain more information about morning BP. Since we have not yet learned which, if any, antihypertensives might hold special benefits on morning BP, and we do not have a major clinical trial confirming risk reduction through morning BP control, we lack sufficient evidence to mandate control of morning BP surge as a specific entity at this time. ■

Simplifying Dosing for Actinic Keratoses

Source: Zeichner JA, et al. *J Am Acad Dermatol* 2009;60:59-62.

ACTINIC KERATOSES (AK) ARE AT BEST precancerous skin lesions, and at worst (a belief held by many leaders in the skin cancer field) skin carcinoma in situ. In either case, the combination of cosmetic burden, troublesome symptoms, and association with squamous cell cancer motivates their destruction. Although it is commonplace to utilize simple local destructive measures (e.g., cryotherapy) to destroy an individual lesion, it is becoming increasingly clear that field therapy (i.e., treating an entire region to include both evident and subclinical AK lesions) provides a better and more lasting service to the patient.

Imiquimod is an immune system upregulator that has shown excellent efficacy in eradication of AK. As with all other topical agents employed for this purpose, local adverse effects and complexity of dosing regimen are limitations for some patients. Typical dose regimens for imiquimod rely upon 2-3 times weekly application of 5% cream for 8-16 weeks. Less frequent dosing, if effective, would reduce cost, enhance compliance, and possibly be better tolerated.

In this small study (n = 20), subjects applied imiquimod 5% cream once weekly for 16 weeks to half of the face, and placebo to the other half. At 16 weeks, 47% of imiquimod recipients showed marked improvement or better. In contrast to 2-3 times weekly dosing regimens, local adverse effects were essentially absent.

Total clearance rates with more frequent dosing are much higher, but so are intolerance and adverse effect rates. The authors suggest that these favorable results should be stimulus for larger, longer-duration studies. ■

Aerobic and Resistance Training Effects in PAD

Source: McDermott MM, et al. *JAMA* 2009;301:165-174.

THE PRESENCE OF PERIPHERAL ARTERIal disease (PAD), confirmed by an ankle-brachial index of < 0.95, is often manifest by limitation in ability to walk, pain with walking, and limitation in performance of normal daily activities. For most patients, smoking cessation is the most important intervention. Pharmacotherapy is of limited value. Exercise training has been suggested as a method to improve oxygen utilization by the tissues and functional ability.

McDermott et al studied PAD patients (n = 156) who were randomized to aerobic training (treadmill), resistance training (weight training), or control. The treadmill group exercised 3 times weekly, beginning at a 2 mph walking speed for 15 minutes, working up to 40 minutes (with increases in treadmill speed and grade as tolerated). The resistance training group exercised 3 times weekly with knee extensions, leg presses, and leg curls. Both groups were followed for 6 months. The primary outcome was distance on the 6-minute walk.

Treadmill exercise improved the primary endpoint, but the control and resistance training groups did not significantly differ. Treadmill exercise also improved distant vascular health, as demonstrated by improvements in brachial artery flow-mediated dilation (no improvement was seen in the control or resistance training groups). ■

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Warning Regarding Topical Anesthetics

In this issue: FDA warning on topical anesthetics; antipsychotics increase sudden cardiac death; the step up vs step down debate; treating pain, fatigue, mood, and sleep in fibromyalgia; FDA Actions.

Something for your pain?

The FDA has issued a warning regarding topical anesthetics and the risk of life-threatening side effects. This is the second warning in 2 years regarding this issue, the first coming in February 2007 following the deaths of two women who used extensive topical anesthetics in preparation for cosmetic procedures. The latest warning was prompted by a study published in *Radiology*, which compared oral acetaminophen or ibuprofen vs lidocaine gel applied to the skin of the breasts to reduce discomfort during mammography. In the study, 4% lidocaine gel was applied by a nurse from the clavicles to the inferior costal margins and laterally to the mid axillary lines and then covered with plastic wrap to ensure consistency of application. Discomfort from mammograms was significantly lower in the lidocaine gel group and the authors postulate that decreased discomfort may improve the likelihood of future mammographic screening (Lambertz CK, et al. *Radiology* 2008;248:765-772). The FDA's previous warning in 2007 followed on the heels of two reports of young women undergoing laser hair removal who applied either lidocaine or tetracaine topical preparations to the lower extremities and then covered the application with plastic wrap. Both women developed seizures, fell into a coma, and eventually died due to excessive blood levels of the topical anesthetic. Many of these topical products are available over the counter. The FDA strongly advises consumers not to: make heavy application of topical anesthetics over large areas of skin, use concentrated formulas, apply to broken or irritated skin, wrap the treated skin with plastic wrap or other dressings, or apply heat to skin treated with these products.

Increase in sudden cardiac death

Antipsychotics, both typical and atypical, are associated with a dose-related increase in sudden cardiac death according to a new study. Typical antipsychotics such as thioridazine (Mellaril®) and haloperidol (Haldol®) block repolarizing potassium currents and prolong QT intervals. Multiple studies have shown a dose-related increased risk of sudden cardiac death associated with these drugs. Less is known about the atypical antipsychotic drugs although many have similar cardiovascular effects. Researchers from Nashville reviewed the records of Medicaid enrollees in Tennessee including the records of 44,218 and 46,089 baseline users of a single typical and atypical antipsychotic, respectively. These were matched with 186,600 nonusers of antipsychotic drugs. Thioridazine and haloperidol were

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the most frequently prescribed typical agents, while clozapine (Clozaril®), quetiapine (Seroquel®), olanzapine (Zyprexa®), and risperidone (Risperdal®) were the most commonly used atypical agents. Both users of typical and atypical antipsychotic drugs had higher rates of sudden cardiac death than nonusers with adjusted incident rate ratios of 1.99 (95% CI, 1.68-2.34) and 2.26 (95% CI, 1.8-2.72), respectively. There was a higher rate for users of atypical antipsychotic drugs vs typical antipsychotics with an incident rate of 1.14 for the comparison (95% CI, 0.93-1.39). For both classes of drugs, the risk for current users increased significantly with increasing dose. The authors conclude that current users of typical and of atypical antipsychotic drugs had similar, dose-related increased risk of sudden cardiac death and that atypical antipsychotic drugs are no safer than the older drugs (Ray WA, et al. *N Engl J Med* 2009;360:225-235). An accompanying editorial suggests that children and the elderly are particularly vulnerable to these drugs and their use in these populations should be "sharply reduced" (Schneeweiss S, Avorn J. *N Engl J Med* 2009;360:294-296).

Step up vs step down

Which is more effective for treating dyspepsia: Starting with aggressive therapy and tapering down, or starting with antacids and progressing to more aggressive therapy depending on symptoms? The so called step-up vs step-down debate has raged for years, particularly in managed-care settings. In a new study from the Netherlands, patients with dyspepsia were randomized to treatment with an antacid, H2-receptor antagonist, and proton pump inhibitor (step up) vs the same drugs in reverse order (step down), with each step lasting 4 weeks. Primary outcome was symptom relief and cost-effectiveness of initial management at 6 months. Treatment success after 6 months was achieved in 72% of patients in the step-up group and 70% of patients with step-down group. The average medical costs were lower for patients in the step-up group (€228 vs €245; P = 0.0008) mainly because of the cost of medication. The rate of adverse effects was the same in both groups and were generally mild. The authors suggest that treatment success is similar in both groups but the step-up strategy was more cost-effective for patients with new onset dyspeptic symptoms (van Marrewijk CJ, et al. *Lancet* 2009;373:215-225). An accompanying editorial suggests that the degree of cost difference between the two groups was overestimated because costs were based on brand name drugs and generics are now available. It furthers suggested that the study may not change practice in primary care as the author recommends a 4-8 week course of a proton pump inhibitor for patients with symptoms of the upper gastrointestinal tract with discontinuation of treatment if patients remain asymptomatic (van Zanten SV. *Lancet* 2009;373:187-189).

Pain, fatigue, mood, sleep and fibromyalgia

Tricyclics work better than other antidepressants for the treatment of fibromyalgia according to new study from Germany. In a meta-analysis of 18 randomized controlled trials of antidepressants for the treatment of fibromyalgia, researchers reviewed studies utilizing tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAO). All antidepressants were associated with a reduction in pain, fatigue, depressed mood, and sleep disturbances. Pain reduction was particularly good for tricyclic antidepressants, while MAO inhibitors showed modest effect and SSRIs and SNRIs showed a small effect. TCAs were effective in low doses of 12.5-50 mg, far below the doses commonly employed to treat depression, and were very effective for reducing pain, fatigue, and sleep disturbance (*JAMA* 2009;301:198-209). Currently duloxetine (Cymbalta®), pregablin (Lyrica®), and milnacipran (Savella™) are the only FDA-approved drugs for the treatment of fibromyalgia.

FDA Actions

The FDA is launching a program to improve the safety of imported drugs to the United States. The pilot program would allow manufacturers of drugs outside United States to apply for 1 of 100 certifications, which would require that companies have a secure supply chain for their product. Criteria would include holding an FDA-approved drug application, guaranteeing that active pharmaceutical ingredients would be imported only to make FDA-approved drugs, complying with Good Manufacturing Practices, and guaranteeing that their drug products use a secure supply chain. This program is in response to concerns about manufacturing processes outside the United States and the embargoing of several foreign manufactured drugs in the last year. ■