Urine Tests

A Case-Based Guide to Clinical Evaluation and Application

Victoria J. A. Sharp
Lisa M. Antes
M. Lee Sanders
Gina M. Lockwood
Editors

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Preface

Consider a medical environment in which urine tests are not readily available for interpretation. Urinalysis for identification of blood and glucose, urine culture for diagnosis of urinary tract infection, and urine pregnancy and drug screening are just a few of the urine tests that have become mainstays in modern medical practice. More recent technological advances in laboratory testing have allowed for expansion of urine-based testing; they are now considered accurate, noninvasive, and cost-effective options for diagnosis of sexually transmitted infections, renal insufficiency, and even cancer screening.

Urine Tests: A Case-Based Guide to Clinical Evaluation and Application was conceived in response to the recognition that urine tests are essential in both inpatient and outpatient care settings, yet no clinically based resource exists devoted to understanding their nuances. Appropriate collection, analysis, and interpretation of urine for testing are essential for the diagnosis and management of both common and rare patient concerns. Thus, a handbook describing urine collection technique, methods of analyzing urine, specific tests available, and interpretation for simple and complex diagnoses is an essential tool.

This book is a collaborative effort between specialists, primary care providers, administrators, and researchers who have expert knowledge of urine testing. The authors of this book perform urine testing on patients daily and fully understand the advantages and pitfalls of urine-based tests. The

focus of this book is to provide practical knowledge and clinically relevant scenarios for urine-based tests in order to improve overall patient care.

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Abbreviations

AAP	American Academy of Pediatrics
ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin creatinine ratio
ADH	Antidiuretic hormone
AFB	Acid-fast bacillus (bacilli)
AG	Anion gap
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
ANCA	Antineutrophil cytoplasmic antibodies
Anti-dsDNA	Anti-double stranded DNA antibodies
APOL1	Apolipoprotein L1
ARB	Angiotensin II receptor blocker
ARR	Aldosterone:renin ratio
ASO	Anti-streptolysin O
ATN	Acute tubular necrosis
AUA	American Urological Association
BCG	*Bacille Calmette-Guérin*
β-hCG	beta-human chorionic gonadotropin
BMP	Basic metabolic panel
BP	Blood pressure
BPH	Benign prostatic hyperplasia
BUN	Blood urea nitrogen
C	Celsius
C3	Complement C3
C3GN	Complement C3 glomerulonephritis

C4	Complement C4
Ca	Calcium
c-ANCA/PR3	cytoplasmic antineutrophil cytoplasmic antibodies/proteinase 3
CBC	Complete blood count
CBC w/diff	Complete blood count with differential
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CFU	Colony-forming unit
CK	Creatinine kinase
CKD	Chronic kidney disease
Cl	Chloride
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
CPT	Current Procedural Terminology
Cr	Creatinine
CT	Computed tomography
CTU	Computed tomography urography
CVD	Cardiovascular disease
DDAVP	Desmopressin
DDD	Dense deposit disease
DI	Diabetes insipidus
DKA	Diabetic ketoacidosis
dL	deciliter
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DRE	Digital rectal exam
EAU	European Association of Urology
ED	Emergency department
EGPA	Eosinophilic granulomatosis with polyangiitis
ELISA	Enzyme-linked immunosorbent assay
ENaC	Epithelial sodium channel
ESRD	End-stage renal disease
F	Fahrenheit or French size
FDA	Food and Drug Administration
FeNa	Fractional excretion of sodium
FeUrea	Fractional excretion of urea

FISH	Fluorescence in situ hybridization
FSGS	Focal segmental glomerulosclerosis
g	gram
GBM	Glomerular basement membrane
GC-MS	Gas chromatography-mass spectrometry
GFR	Glomerular filtration rate
GI	Gastrointestinal
GPA	Granulomatosis with polyangiitis
GU	Genitourinary
H	Hydrogen (hydronium)
H_2O	Water
H_2O_2	Hydrogen peroxide
HAGMA	High anion gap metabolic acidosis
Hb, Hgb	Hemoglobin
HBV	Hepatitis B virus
HCO_3	Bicarbonate
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hpf	high power field
HPLC/MS	High-performance liquid chromatography mass spectrometry
HPV	Human papilloma virus
HTN	Hypertension
IDSA	Infectious Diseases Society of America
IgA	Immunoglobulin A
IgAN	Immunoglobulin A nephropathy
IgM	Immunoglobulin M
INR	International normalized ratio
IV	Intravenous
K	Potassium
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
KOH	Potassium hydroxide
KUB	Kidney, ureter, and bladder x-ray
L	Liter
LC/MS	Liquid chromatography mass spectrometry
LE	Leukocyte esterase

LMW	Low molecular weight
LN	Lupus nephritis
lpf	low power field
LSD	Lysergic acid diethylamide
MAR	Medication Administration Record
Mb	Myoglobin
MCD	Minimal change disease
mEq	milliequivalent
mg	milligram
Mg	Magnesium
MGN	Membranous nephropathy
mL	milliliter
mm	millimeter
mmol	millimole
mOsm	milliosmole
MPA	Microscopic polyangiitis
MPGN	Membranoproliferative glomerulonephritis
MRI	Magnetic resonance imaging
MRU	Magnetic resonance urography
Na	Sodium
NAAT	Nucleic acid amplification test
NAGMA	Non-anion gap metabolic acidosis
NH_3	Ammonia
NH_4	Smmonium
nm	nanometer
NPV	Negative predictive value
NSAID	Nonsteroidal anti-inflammatory drug
PAC	Plasma aldosterone concentration
p-ANCA/ MPO-ANCA	perinuclear antineutrophil cytoplasmic antibodies/myeloperoxidase antineutrophil cystoplasmic antibodies
Pap	Papanicolaou
PCA3	Prostate cancer antigen 3
PCH	Paroxysmal cold hemoglobinuria
PCN	Percutaneous nephrostomy
PCNL	Percutaneous nephrolithotomy
PCP	Phencyclidine
PCR	Protein creatinine ratio OR polymerase chain reaction

pH	potential of hydrogen
PID	Pelvic inflammatory disease
PIGN	Postinfectious glomerulonephritis
PLA2R	Phospholipase A2 receptor
PNH	Paroxysmal nocturnal hemoglobinuria
PPI	Proton pump inhibitor
PPV	Positive predictive value
PPM	Provider-performed microscopy
PRA	Plasma renin activity
PSA	Prostate-specific antigen
RAS	Renal artery stenosis
RAAS	Renin-angiotensin-aldosterone system
RBC	Red blood cell
RNA	Ribonucleic acid
RTA	Renal tubular acidosis
rTEC	renal tubular epithelial cell
RVU	Relative value unit
SG	Specific gravity
SGLT2	Sodium glucose co-transport protein 2
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SLE	Systemic lupus erythematosus
SPEP/IFE	Serum protein electrophoresis/ immunofixation
STI	Sexually transmitted infection
SWL	Shock wave lithotripsy
TB	Tuberculosis
TCA	Tricyclic antidepressant
THC	Tetrahydrocannabinol
ttg Ab	tissue transglutaminase antibody
TTP	Thrombotic thrombocytopenic purpura
UA	Urinalysis
UPEP/IFE	Urine protein electrophoresis/ immunofixation
US	Ultrasound
USPSTF	United States Preventative Services Task Force
UTI	Urinary tract infection
WBC	White blood cell

Contents

1 Urine: The Golden Elixir of Life 1
M. Lee Sanders and Lisa M. Antes

2 Follow the Money: Costs, Reimbursement and Regulations of Urine Based Testing 11
Matthew A. Uhlman, Victoria J. A. Sharp, Nora Kopping, and Mark S. Uhlman

3 Going with the Flow: Proper Urine Testing Methods for Clinical Practice 25
Gina M. Lockwood and Victoria J. A. Sharp

4 Urine Dipstick: Blood – The Spectrum of Red 49
Alexandra J. Sharp and Victoria J. A. Sharp

5 Urine Dipstick: Proteinuria – Causes, Consequences and Diagnostic Approach 73
Lewis Mann, Lisa M. Antes, and M. Lee Sanders

6 Urine Dipstick: Urinary Nitrites and Leukocyte Esterase – Dipping into Murky Waters 97
A. Ben Appenheimer and Bradley Ford

7 Urine Dipstick: An Approach to Glucosuria, Ketonuria, pH, Specific Gravity, Bilirubin and Urobilinogen – Undeniable Chemistry 117
Puja T. Pape, Victoria J. A. Sharp, and Jessica Rockafellow

8 Urine Microscopy: The Burning Truth – White Blood Cells in the Urine 143
Andrew M. Vitale and Gina M. Lockwood

9 Urine Microscopy: Seeing Red – Understanding Blood in the Urine 167
Christopher Meier and Gina M. Lockwood

10 Urine Microscopy: The Utility of Urinary Casts in Patient Care – Practical and Useful Tips for Busy Clinicians 189
Stephanie J. Houston, M. Lee Sanders, and Lyndsay A. Harshman

11 Urine Microscopy: Clouding Over – Bacteria, Yeast, Parasites and Zika 205
Bradley Ford, Wendy Fiordellisi, Victoria J. A. Sharp, and A. Ben Appenheimer

12 Urine Microscopy – Urine Made Crystal Clear 233
Courtney Yong, Chad R. Tracy, and Lisa M. Antes

13 Urine Testing in Children: Little People, Big Challenges 259
Gina M. Lockwood and Douglas W. Storm

14 Urine Based Tests in the Diagnosis of Genitourinary Cancers 281
Morgan Schubbe, Laila Dahmoush, and Kenneth G. Nepple

15 Kidney Excretions: The Lyter Side of Urine 299
Jeremy Steinman, Carly Kuehn, and Lisa M. Antes

16 Other Common Uses for Urine Screening in Clinical Practice: Substance Use Disorders, Antipsychotic Adherence, Sexually Transmitted Infections 329
Aubrey Chan, Puja T. Pape, and M. Lee Sanders

17 Urine Tests: Solidifying Concepts – Questions and Answers 347
M. Lee Sanders, Lisa M. Antes, Victoria J. A. Sharp, and Gina M. Lockwood

Index 379

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Chapter 1
Urine: The Golden Elixir of Life

M. Lee Sanders and Lisa M. Antes

Objectives

- Understand the basic anatomy of the urinary system
- Discuss glomerular filtration as the process of urine formation
- Describe how urine composition and amount are determined by a series of specialized tubules

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Overview

Many scientists as well as philosophers have recognized the importance of urination and how this basic physiologic function is vital to sustain life. The urinary system and tract are responsible for the production, refinement and elimination of urine from the body. A thorough examination of urine provides valuable information that assists in patient care. This book is dedicated to the clinical application of urine tests; however before test application, one should understand some basic principles of urine production, refinement and elimination.

The kidney presents in the highest degree the phenomenon of sensibility, the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism; a power of adaptation which almost gives one the idea that its component parts must be endowed with intelligence. (Frank Starling, 1909)

Urine Production

The kidney is the organ responsible for urine production. Humans normally have two separate "bean shaped" kidney organs located to the left and right of the spine in the retroperitoneal space. The kidneys are highly vascular organs receiving an average 20–25% of the cardiac output, which is remarkable since the kidneys only comprise 0.5% of total body weight [1, 2].

The basic filtering unit of the kidney is the nephron. The nephron is composed of a glomerulus, a series of tubules and a collecting duct. Exact nephron number across individuals is variable but total number is determined/finalized at birth. After birth, new nephrons cannot be developed and lost nephrons cannot be replaced. Each kidney on average contains approximately one million nephrons [1, 2].

Blood is supplied to the nephron through a series of arteries finally reaching the glomerular capillaries via the afferent arteriole and leaving the capillary bed via the efferent arteriole (Fig. 1.1). The hydrostatic pressure in the capillary bed forces

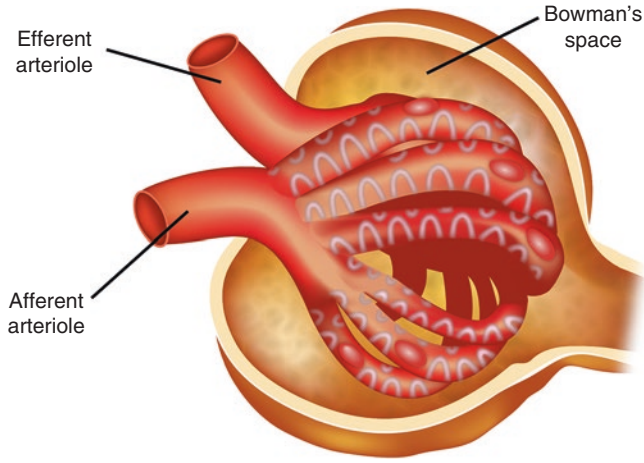

FIGURE 1.1 Capillary bed of the glomerulus. (Courtesy of Teresa Ruggle, University of Iowa.)

fluid to move from the blood compartment across the semi-permeable glomerular membrane into the urinary space (Bowman's space). This ultrafiltrate is essentially the same osmolality as plasma and includes water, small molecules, and ions that easily pass through the filtration membrane [1, 2].

Larger molecules such as proteins and red blood cells are normally prevented from passing through the filtration membrane. This filtration membrane or barrier is comprised of three components: (a) the endothelial cells of the renal capillaries, (b) the basement membrane and (c) the epithelial cells lining the urinary space. Evidence of protein (see Chap. 5) or red blood cells (see Chap. 9) in the urine could therefore be a sign that this barrier is compromised [3–5].

Urine Refinement

The ultrafiltrate in Bowman's space will then pass through a series of tubules and a collecting duct. This refinement process allows for the secretion of additional waste products in

addition to reabsorption of water and solutes from the ultrafiltrate. This refinement process is also required to sustain life. In a typical 70 kilogram individual, the kidney filters approximately 180 liters of fluid daily. Life would cease to exist without the ability to reabsorb solutes and water from the filtrate. The kidneys are very efficient at this process as only 1–2 liters of urine on average are excreted daily while maintaining electrolyte, mineral and pH balance in the blood.

Four major tubular segments of the nephron (Fig. 1.2) determine the final composition and volume of the urine: (a) proximal convoluted tubule, (b) loop of Henle, (c) distal convoluted tubule and (d) collecting duct. Each individual segment of the tubule possesses a unique set of channels and transporters that allow reabsorption and excretion to occur. The main ion that is reabsorbed through these segments is sodium. Filtering 180 liters a day would lead to the theoretical excretion of approximately 25,500 mmol per day of sodium, a

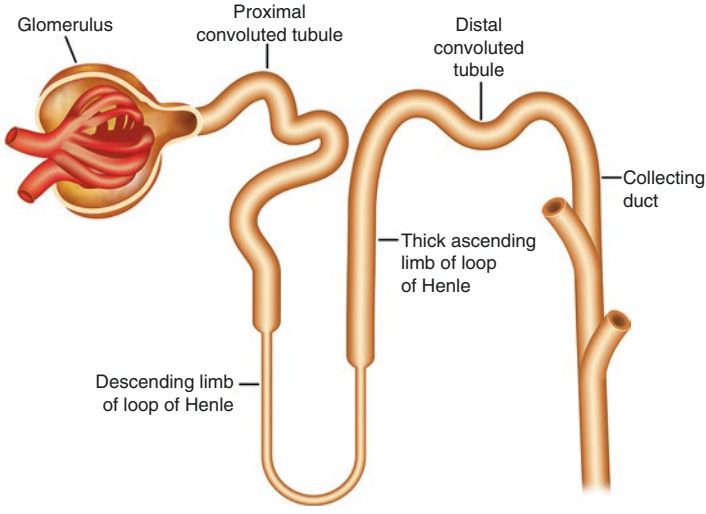

FIGURE 1.2 The nephron of the kidney. (Courtesy of Teresa Ruggle, University of Iowa.)

loss that would be incompatible with life. The efficient reabsorption mechanism of the renal tubules allows for over 99% of this sodium to be reabsorbed, leading to only about 100 mmol per day sodium excretion [1, 2]. Additional examples of the reabsorption efficiency of the kidney are listed in Table 1.1.

The proximal convoluted tubule is the workhorse of the kidney and reabsorbs more solute and water than any other segment of the nephron. Approximately 55–65% of the total ultrafiltrate is reabsorbed in this segment. Almost all of the filtered glucose and amino acids are reabsorbed in this segment along with 90% of the bicarbonate, 65% of the sodium and 55% of the chloride. Since both solutes/ions and water are reabsorbed in the proximal convoluted tubule, the ultrafiltrate leaving the proximal tubule is essentially the same osmolality as the ultrafiltrate that entered. Stated another way, urine is neither concentrated nor diluted in this segment [1, 2].

The loop of Henle is composed of a descending limb and an ascending limb. The descending limb is relatively impermeable to solutes but freely permeable to water. The ascending limb is water impermeable; thus here begins the diluting

Table 1.1 Filtration, excretion, and reabsorption of water, electrolytes, and solutes by the kidney in a normal adult

Substance	Amount	Filtered	Excreted	Reabsorbed	% Filtered amount reabsorbed
H_2O	L/day	180	1.5	178.5	99.2
Na^+	mEq/day	25,200	150	25,050	99.4
K^+	mEq/day	720	100	620	86.1
Ca^{++}	mEq/day	540	10	530	98.2
HCO_3^-	mEq/day	4320	2	4,318	99.9+
Cl^-	mEq/day	18,000	150	17,850	99.2
Glucose	mmol/day	800	0	800	100.0
Urea	g/day	56	28	25	50.0

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segment of the nephron because removal of solutes and not water dilutes the ultrafiltrate concentration. The $Na^+K^+2Cl^-$ symporter on the apical membrane of the thick ascending limb allows for 25% of the filtered sodium and chloride to be reabsorbed in this segment of the nephron [1, 2]. This transporter is the site of action for the class of diuretics known as loop diuretics. Hereditary or acquired dysfunction of this transporter results in Bartter syndrome. This disorder has clinical features (hypokalemia, metabolic alkalosis, hypercalciuria) similar to those seen in patients given a loop diuretic [6–8].

The distal tubule is relatively impermeable to water, continuing the diluting segment of the nephron. The Na^+Cl^- symporter on the apical membrane of the distal convoluted tubule allows for an additional 5–10% of filtered sodium and chloride to be reabsorbed in this segment of the nephron [1, 2]. This transporter is the site of action for the class of diuretics known as thiazide diuretics. Hereditary or acquired dysfunction of this transporter results in Gitelman syndrome. This disorder has clinical features (hypokalemia, metabolic alkalosis, hypocalciuria) similar to those seen in patients given a thiazide diuretic [6–8].

The collecting duct fine tunes sodium reabsorption as well as potassium and acid excretion. The epithelial sodium channel (ENaC) on the apical membrane of the principal cell in the collecting duct allows for an additional 1–3% of the filtered sodium load to be reabsorbed. This channel is upregulated by the mineralocorticoid aldosterone [1, 2]. Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, cause a downregulation of ENaC resulting in sodium diuresis. A hereditary or acquired activating mutation of ENaC results in Liddle syndrome, which is a disorder with clinical characteristics similar to those of a high aldosterone state (excessive sodium reabsorption, hypervolemia, hypertension, hypokalemia) [8–10]. An inactivating mutation has also been described that results in clinical char-

acteristics similar to those of a low aldosterone state (sodium wasting, hypovolemia, hyperkalemia) [11].

The collecting duct is impermeable to water in the absence of antidiuretic hormone (ADH). When ADH is present, the collecting duct becomes permeable to water through the use of aquaporin channels. It is here in the collecting duct that the urine can be further diluted or concentrated depending on the needs of an individual. The major stimuli for ADH secretion are hyperosmolality and effective circulatory volume depletion [1, 2].

Urine Elimination

Urine flows from the collecting duct of the nephron to join a converging system of tubules with other collecting ducts. These ducts then join together to form the minor calyces followed by the major calyces that ultimately converge in the renal pelvis (Fig. 1.3). Urine continues to flow from the renal pelvis into the ureter, transporting urine into the urinary bladder. Urine from both kidneys is stored in the bladder until the process of micturition (urination) occurs.

The first urge to void is felt at a bladder volume of approximately 150 milliliters (mL). A marked sense of fullness is felt at about 400 mL and bladder capacity is approximately 500 mL [12]. Urine is normally excreted voluntarily from the body by flowing through the urethra away from the bladder.

Average daily urine production for adults is usually between 1–2 liters (L) depending on the state of hydration, activity level, and health of the individual. Producing too much or too little urine requires medical attention. Polyuria (see Chap. 15) is a condition of excessive urine production (more than 3 L/day). Oliguria is the production of less than 400–500 mL/day and anuria is the production of less than 50–100 mL/day.

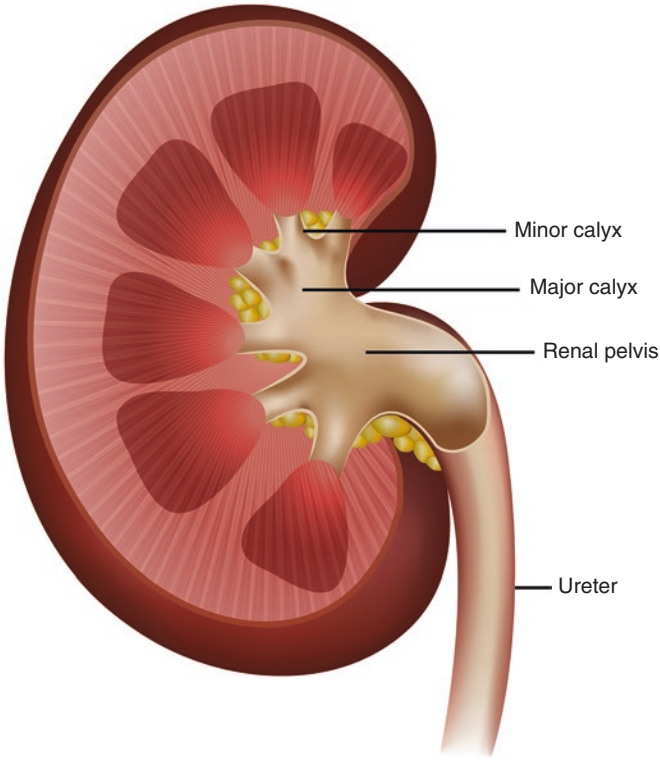

FIGURE 1.3 Anatomy for urine flow through the kidney. (Courtesy of Teresa Ruggle, University of Iowa.)

Summary

Normal urinary system anatomy consists of two kidneys, two ureters, one urinary bladder and one urethra. The urinary system is responsible for urine production, refinement and elimination. The final composition and amount of urine is determined by the specialized actions of glomerular filtration followed by tubular reabsorption and secretion. Urine can be collected from a patient and its contents provide additional clinical information to the provider. This information may be obtained by a urinalysis using a dipstick to determine chemical composition; microscopic analysis to look for cells, casts or

crystals; cultures to assist with infection diagnosis; or specialized tests to assess for cancer, electrolyte abnormalities or substance abuse. Whatever the test, analyzing this golden elixir of life provides a valuable, noninvasive means to assist with patient care.

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Chapter 2
Follow the Money: Costs, Reimbursement and Regulations of Urine Based Testing

Matthew A. Uhlman, Victoria J. A. Sharp, Nora Kopping, and Mark S. Uhlman

Objectives

- Gain an understanding of costs and reimbursement issues related to urine studies
- Recognize regulatory requirements related to obtaining and maintaining accreditation to perform urine-based testing
- Differentiate which urine-based tests are preferable to other testing modalities from financial and quality perspectives

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Overview

Urine-based tests are a critical and increasingly utilized part of the investigative workup for many diseases. As such tests continue to evolve, urine-based diagnostics will increasingly represent a relatively painless and easy-to-collect tool for healthcare providers. While many urine-based tests are available, reimbursement for them may not be, and for others, cost benefit ratios are unacceptable. An understanding of the associated costs, reimbursement and regulatory aspects of such tests is paramount in their successful deployment and utilization. In this chapter we will highlight key financial and regulatory considerations for the clinician considering the use of the urine-based tests currently available.

Costs

Urine-based testing has been a part of medical care since the time of the Sumerian and Babylonian empires [1] and while similarities still exist in urine-based diagnostics, financial considerations are (assumedly) far more complex today. Most clinicians and providers are familiar with urine-based testing in some respect, but far fewer are versed in the financial and regulatory aspects of such tests. Whether the testing is done under a microscope at a provider's office or delivered overnight for analysis at a reference lab, an understanding of the many different considerations surrounding such tests is increasingly important.

In the United States each year, nearly 1 billion physician office visits occur, with over 500 million visits to primary care offices [2, 3]. While only a fraction of patients undergo a urine-based diagnostic test, the number of studies and accrued costs quickly become staggering. In urine-centric specialties such as urology or nephrology, the percentage of patients requiring testing and the number of potential urine-based tests increases drastically.