



A fresh look at reflexive urine testing

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Learning objectives

- Compare the correlative performances of urinalysis, urine microscopy, and urine culture
- Describe motivations for and clinical outcomes associated with urine reflexive testing
- Contrast various laboratory workflows and operational considerations for implementing reflexive urine testing

Urinalysis – the world's oldest lab test



Physician holding matula into the light for inspection



A chart used to categorize urine

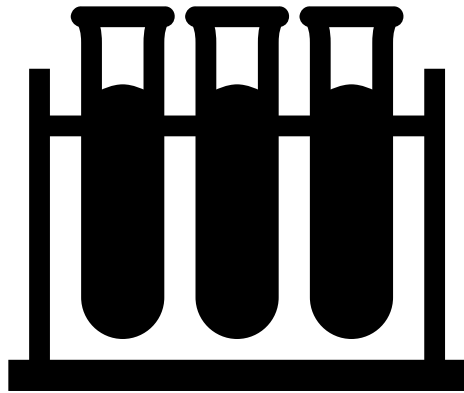
Utility of urinalysis today

- Kidney disorders
- Diabetes mellitus
- Liver disease
- Hypertension of pregnancy
- Urinary tract infections

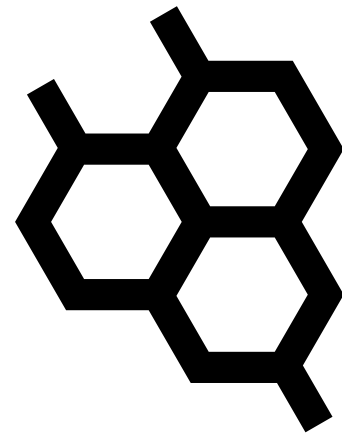


Urinalysis may represent 30% of all lab samples received

Modern urinalysis



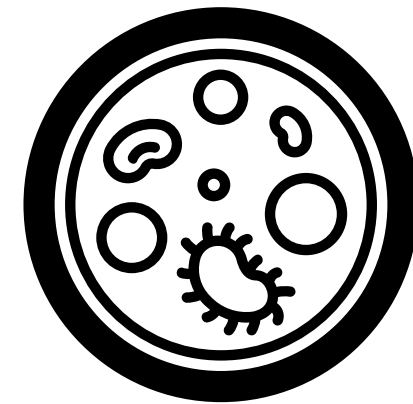
macroscopic
and physical



chemical



microscopic



culture

POCT

Micro Lab

Core Lab

Chemical/dipstick urinalysis



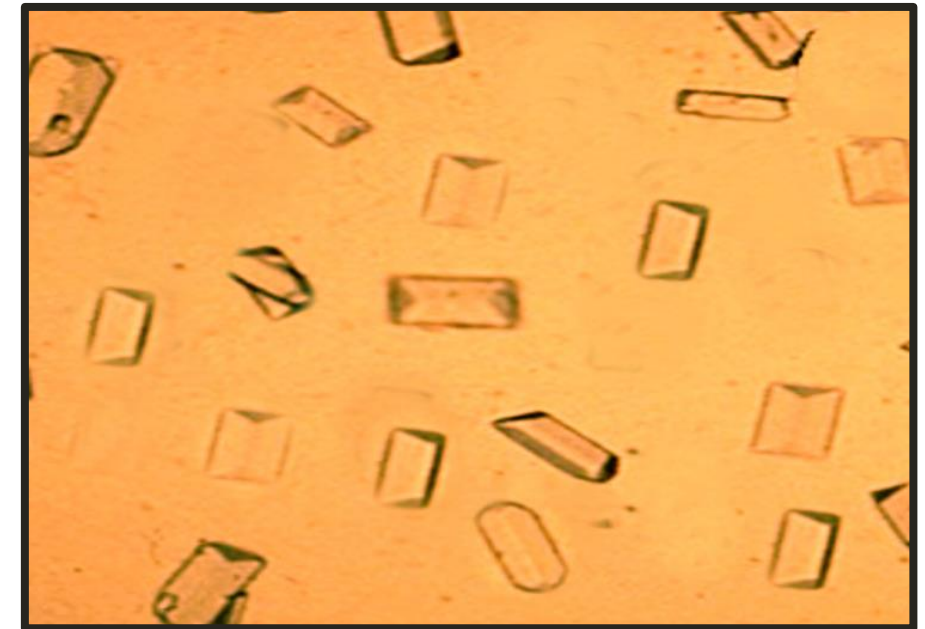
ketones • protein • glucose • leukocyte esterase • blood
• nitrite • bilirubin • pH • urobilinogen • specific gravity

Automated analyzers:

- Standardize color interpretation
- Eliminate variance from timing
- Remove operator subjectivity
- High throughput
- May offer sample transfer automation

Microscopic urinalysis

- RBC, WBC, bacteria, yeast, epithelial cells, casts, crystals,...
- Manual
- Particle analyzers
 - Impedance, flow cytometry, digital imaging, light scatter,...
 - Abnormal findings may necessitate manual review
 - Sensitivity limitations in populations with high prevalence of renal disease



Is microscopy always necessary?



CLSI GP16-A3:2009 Urinalysis, 3rd Edition

“The decision to perform microscopic examinations should be made by each individual laboratory based on its specific patient population.

- *When requested by the physician*
- *When determined by laboratory protocol*
- *When any abnormal physiochemical result is obtained”*

Screening with urine dipstick

- Debated heavily in literature in 1980s
- Overall sensitivity 95%, specificity 74%
- Most false negatives associated with bacteriuria
- Positive chemical strip test “can be safely and effectively used as a prerequisite for routine urine microscopic examination.”

Table 1. Association of Biochemical and Microscopic Abnormalities n=1000

Indicator/Condition	Sensitivity	Specificity	Chi-Square
Leuk Ester/pyuria	0.82	0.77	$P < 0.0002$
Nitrite/bacteriuria	0.02	0.99	$P < 0.009$
Leuk Ester/bacteriuria	0.51	0.62	$P < 0.002$
Protein/bacteriuria	0.85	0.33	$P < 0.05$
Hgb/hematuria	0.70	0.92	$P < 0.001$

Chemical vs. microscopic urinalysis

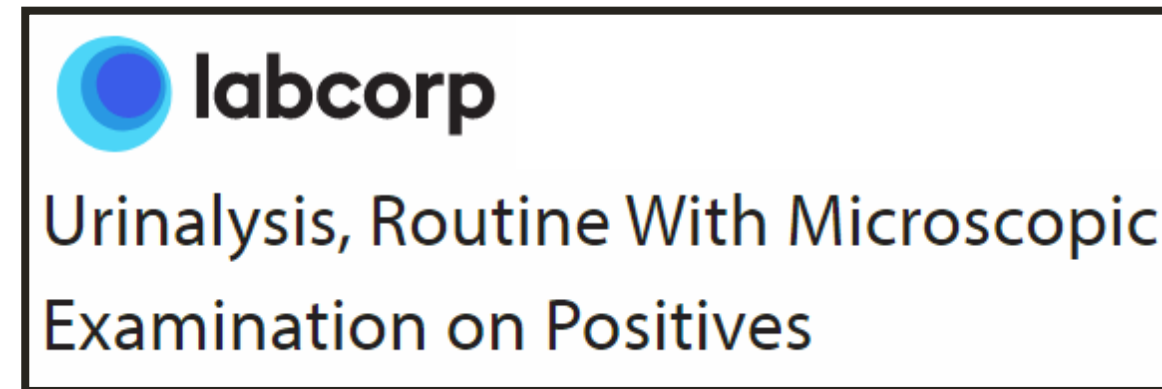
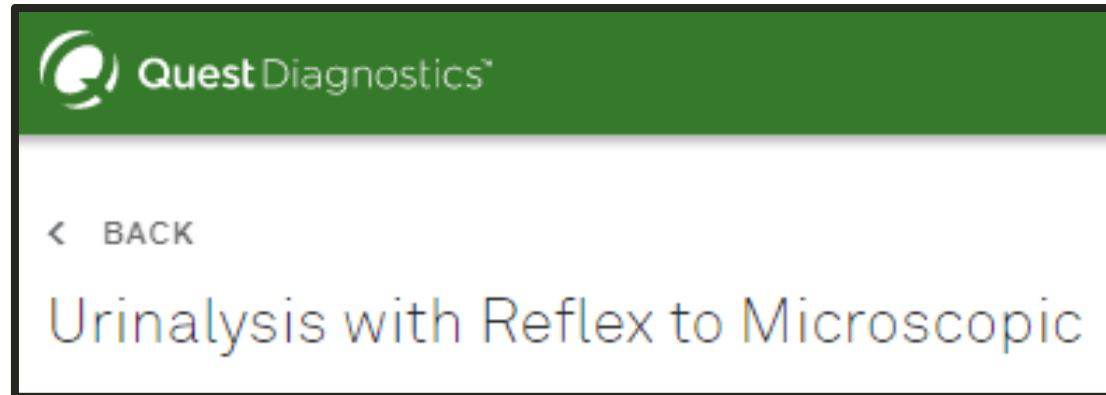
Table 1. Comparison of Urine Results Obtained Using Chemstrip® 8 and 9 with Microscopic Examination n=1000

Part A Chemstrip 8				Part B Chemstrip 9 + leukocyte esterase			
		Microscopic				Microscopic	
		+	-			+	-
Dipstick	+	476	182	Dipstick	+	476	245
	-	131	211		-	101	178
Sensitivity = 78% Specificity = 54%				Sensitivity = 82% Specificity = 42%			

Positive microscopic defined as:

- ≥ 6 WBC, RBC, or renal tubular cells per hpf
- $\geq 2+$ bacteria
- Presence of casts, pathologic crystals

Urinalysis with reflex to microscopic



Urinalysis, Routine (CHLA Laboratory Guide)

Test Includes

Color, appearance, specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, leukocyte and nitrite. A microscopic sediment examination will automatically be performed if positive for hemoglobin, protein, nitrite, and/or leucocyte esterase. Request a microscopic sediment examination separately since a microscopic test is not reflexed on normal macroscopic UAs.

Common reflex criteria for microscopy

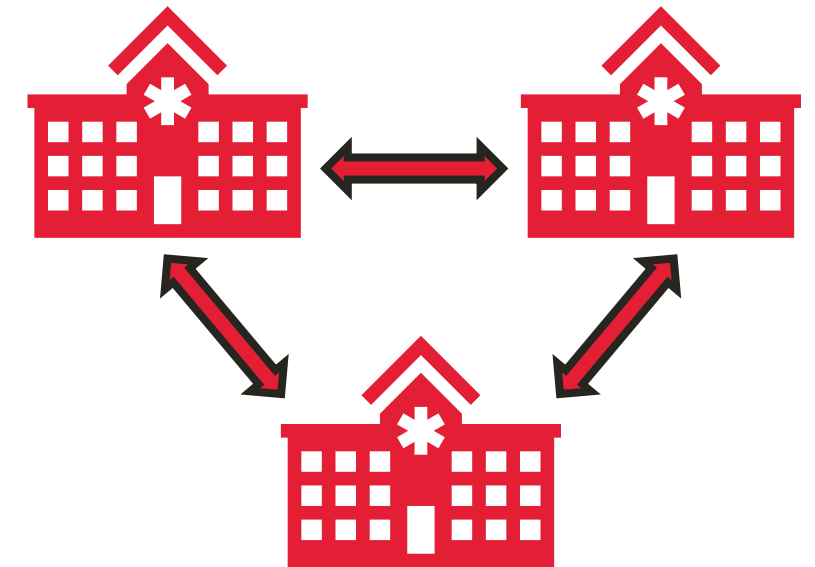
2008 CAP Q-Probes study (n=82 labs):

- Proteins present (99%)
- Leukocyte esterase positive (98%)
- Nitrite present (95%)
- Heme compound present (94%)
- Turbid appearance (80%)
- Bloody appearance (70%)

At the time, only 15% of labs used an automated microscopic analyzer

LAC+USC urinalysis practices

- Part of a multi-hospital network with varying practices
- Desire to:
 - Evaluate and standardize to a UA chemical with reflex to microscopic approach
 - Implement UA with reflex to urine culture as part of a broader effort to decrease CAUTIs



LAC+USC microscopy reflex criteria

Microscopy to be performed if:

- Clarity = Cloudy or turbid
- Glucose \geq 1000 mg/dL
- Blood or protein positive
- Nitrite or leukocyte esterase positive
- Age <30 days
- Violence Intervention Program locations

Chemical vs. microscopic urinalysis

An updated assessment

Patient demographics.	
Total number of unique patients	7607
Age at time of testing	
Mean (range), years	46 (0-105)
Median, years	48
Patient location	
Emergency department	3355 (44.1%)
Outpatient	3293 (43.3%)
Inpatient	959 (12.6%)

Chemical vs. microscopic urinalysis

An updated assessment

Contingency table correlating chemical urinalysis results to microscopic urinalysis results.

		Microscopic urinalysis		
		+	-	Total
Chemical urinalysis	+	3892	2128	6020
				64.7% PPV
	-	295	2812	3107
				90.5% NPV
	Total	4187	4940	9127
	93.0% sensitivity	56.9% specificity		

PPV, positive predictive value; NPV, negative predictive value.

Microscopy positive defined as:

- RBC \geq 4/hpf
- WBC \geq 4/hpf
- Any bacteria

Chemical vs. microscopic urinalysis

An updated assessment

Microscopic findings in 295 samples negative by chemical urinalysis but positive by microscopic urinalysis.

	RBC (/HPF)	WBC (/HPF)	Bacteria (/HPF)
285 (96.6%)	<4		
10 (3.4%)	≥4		
272 (92.2%)		<4	
23 (7.8%)		≥4	
21 (7.1%)			Negative
198 (67.1%)			Trace
50 (16.9%)			1+
15 (5.1%)			2+
5 (1.7%)			3+
6 (2.0%)			4+

Can UA help reduce urine cultures?

NEWS RELEASE

March 21, 2019

BACTERIA IN URINE DOESN'T ALWAYS INDICATE INFECTION
Testing, Antibiotic Treatment Often Unnecessary, Say IDSA Guidelines

Society for Healthcare Epidemiology of America

[View all recommendations from this society](#)

Released October 1, 2015; Revised December 2, 2019

Don't perform cultures (e.g. urine, blood, sputum cultures) or test for *C. difficile* unless patients have signs or symptoms of infection. Tests can be falsely positive leading to over diagnosis and overtreatment.



An initiative of the ABIM Foundation

The American Society for Microbiology

[View all recommendations from this society](#)

August 5 2020



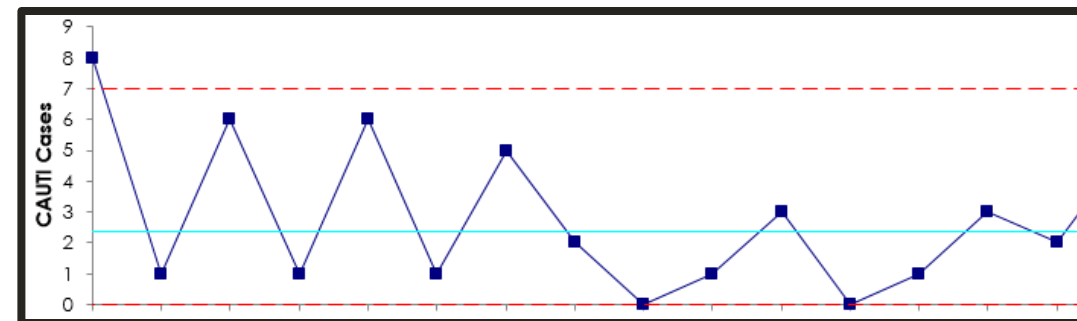
Do not order urine cultures unless patients have symptoms consistent with urinary tract infection (UTI).

Urine cultures should only be requested on patients who have clinical signs of UTI. Routine culture of urine in asymptomatic individuals may detect asymptomatic bacteriuria (ASB) which is commonly found in certain populations. Screening for ASB has no clinical benefit and may result in harm (1, 2).

Testing for ASB should only be pursued in specific populations such as pregnant women and individuals who are about to undergo urologic procedures that involve mucosal disruption (2).

How does over-ordering affect CAUTIs?

- Catheter-associated Urinary Tract Infection
- Reportable data (CDC/NHSN)
- Positive urine culture \neq UTI
 - Especially with the absence of pyuria
 - Catheterized and non-catheterized patients
 - But still can be defined as CAUTI
- Fewer cultures = fewer CAUTIs?



How can the lab help with compliance?

- Implement urinalysis reflex approaches (?)
- Evaluate and/or define reflex criteria
 - Lack of evidence-based guidance
- Offer various electronic order options
- Clarify which orders are appropriate for which patient populations

Urine culture criteria:

What does the literature tell us?

- Multiple studies show high NPV for pyuria
- WBC > 5 or 10/hpf
- Including studies using automated microscopy
- Positive LE and nitrite can increase sensitivity
 - May decrease specificity
- Reflex may eliminate 40-70% of urine cultures
- Performance depends on patient population

Leukocyte esterase reaction

- Surrogate for WBCs
- Catalyzes hydrolysis of esters → color reaction
- Strip sensitivity: ~ 5-15 WBC/hpf
 - Typically considered clinically significant

False negatives	Elevated glucose or protein, presence of some antibiotics, high conc. of ascorbic acid
False positives	Contamination by vaginal discharge

Nitrite reaction

- Most bacteria reduce urine nitrate to nitrite
 - Griess reaction forms purple-pink azo product
- Increases as specimen is retained in bladder
 - 4 hrs recommended (e.g., first morning void)

False negatives	Ascorbic acid, short bladder incubation, low dietary nitrate; will not detect gram-positive bacteria and <i>Pseudomonas</i> infections
False positives	Contamination (may occur in old specimens)

What does our own data tell us?

Chemical UA vs. urine culture

Contingency table correlating chemical urinalysis results to urine culture results.

		Urine culture		Total
		+	-	
Chemical urinalysis	+	645	1610	2255
				28.6% PPV
	-	55	817	872
				93.7% NPV
	Total	700	2427	3127
		92.1% sensitivity	33.7% specificity	

PPV, positive predictive value; NPV, negative predictive value.

What does our own data tell us?

Chemical UA vs. urine culture

Association of urine culture results with chemical urinalysis results.

Urine culture result	Number of samples	Positive leukocyte esterase (%)	Positive nitrite (%)	Positive blood (%)	Positive protein (%)	Positive glucose (%)
Negative	1164	205 (17.6)	11 (0.9)	398 (34.2)	353 (30.3)	53 (4.6)
Contaminant	1263	455 (36.0)	22 (1.7)	437 (34.6)	389 (30.8)	62 (4.9)
Positive	700	526 (75.1)	184 (26.3)	419 (59.9)	339 (48.4)	56 (8.0)
Total	3127	1186 (37.9)	217 (6.9)	1254 (40.1)	1081 (34.6)	171 (5.5)

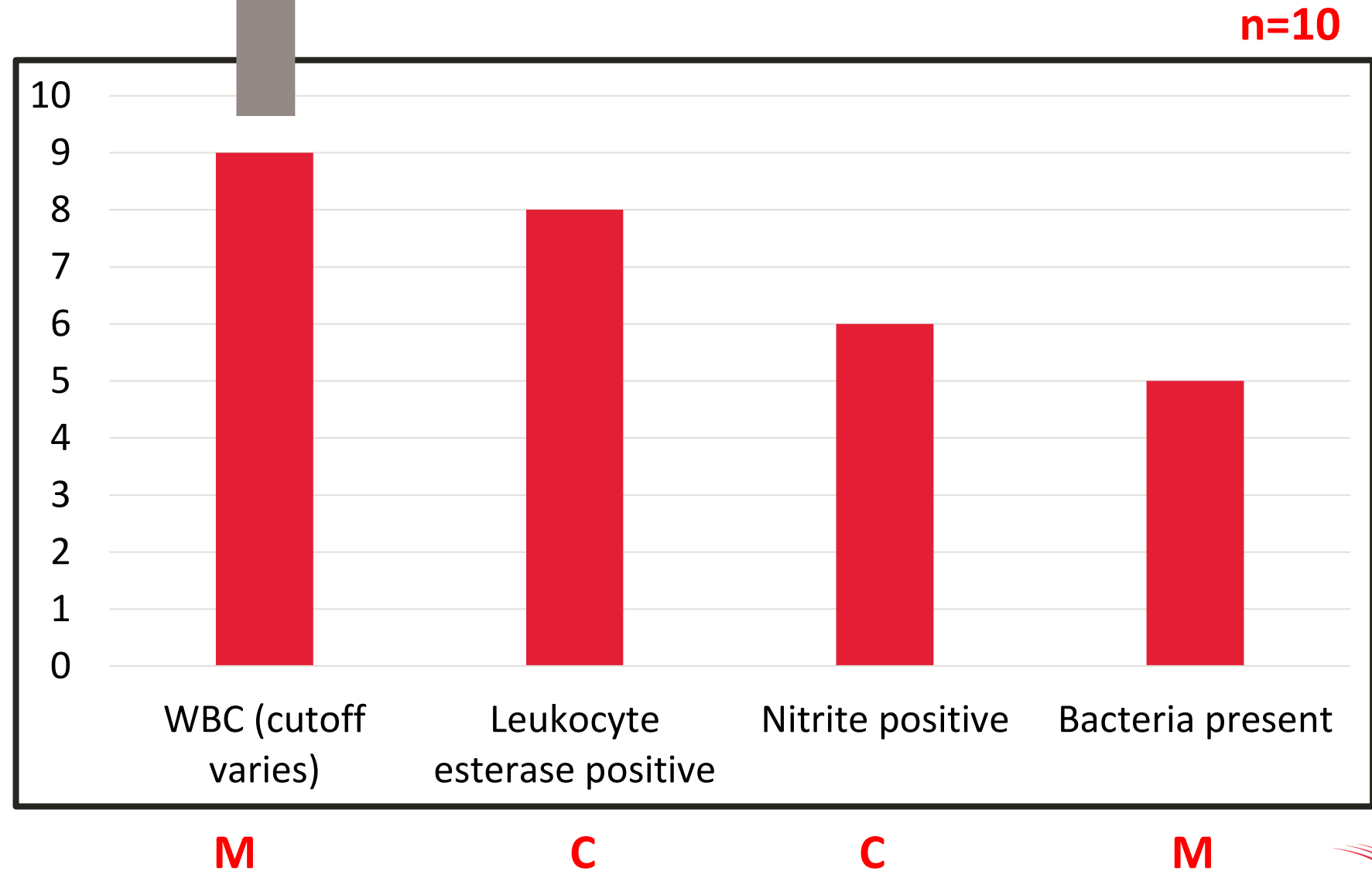
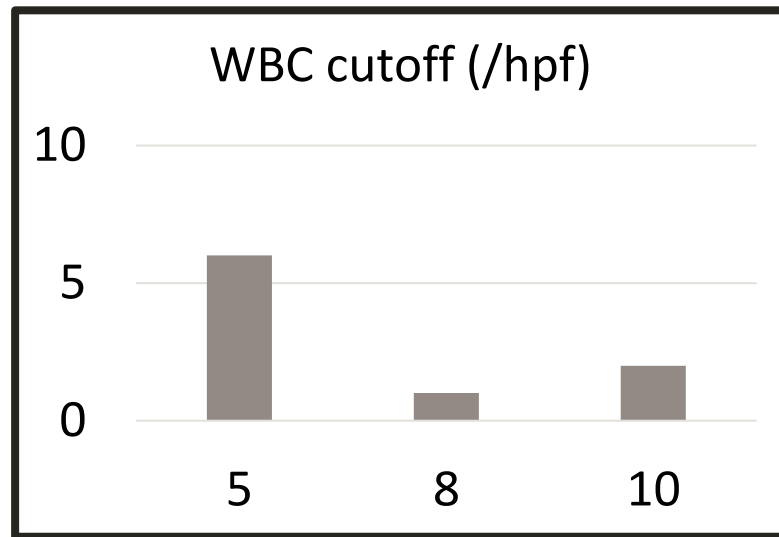
What does our own data tell us?

Chemical UA vs. WBC count

Association of WBC count with chemical urinalysis and urine culture results.

Chemical UA (n = 9127)							Positive culture (%) (n = 700)
WBC/HPF	Number of samples	Positive leukocyte esterase (%)	Positive nitrite (%)	Positive blood (%)	Positive protein (%)	Positive glucose (%)	
0	2819	22 (0.8)	14 (0.5)	274 (9.7)	421 (14.9)	313 (11.1)	43 (6.1)
1-5	4241	637 (15.0)	63 (1.5)	908 (21.4)	1325 (31.2)	499 (11.8)	157 (22.4)
6-10	631	480 (76.1)	39 (6.2)	204 (32.3)	241 (38.2)	78 (12.4)	73 (10.4)
11-20	411	381 (92.7)	28 (6.8)	157 (38.2)	190 (46.2)	50 (12.2)	51 (7.3)
21-50	396	383 (96.7)	61 (15.4)	176 (44.4)	215 (54.3)	57 (14.4)	100 (14.3)
>50	629	618 (98.3)	159 (25.3)	422 (67.1)	461 (73.3)	97 (15.4)	276 (39.4)
Total	9127	2521 (27.6)	364 (4.0)	2141 (23.5)	2853 (31.3)	1094 (12.0)	700 (100.0)

Informal survey of culture reflex criteria



What's common in other major labs?

Reference Laboratory	UA macroscopic only	UA microscopic only	Complete UA (macroscopic + microscopic)	UA with reflex to microscopic	Criteria for reflex to microscopic	Complete UA with reflex to culture	Criteria for reflex to culture
ARUP Laboratories (University of Utah Health)	X		X		N/A	X	WBC >5/HPF
LabCorp			X	X	+ protein; + LE; + blood; + nitrite	X	+ nitrite; + LE; WBC >5/HPF; bacteria ≥ moderate
Quest Diagnostics	X	X	X	X	not specified	X	+ LE; WBC >5/HPF; + yeast; + bacteria AND WBC >5/HPF OR + LE; + nitrite AND WBC >5/HPF OR + LE
Cleveland Clinic	X		X		N/A		N/A
Johns Hopkins Hospital	X	X	X		N/A	X	not specified
New York Presbyterian	X	X	X	X	not specified	X	WBC ≥ 10/HPF
Massachusetts General Hospital				X	+ protein; + LE; + blood		N/A
UCSF Health	X		X		N/A	X	+ protein, LE, or blood; AND WBC >10/HPF

Do reflexive algorithms yield better clinical outcomes?

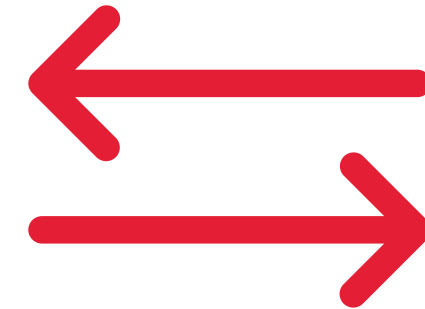
Some studies have reported:

- 40-70% reduction in urine culture orders
 - Associated cost savings
- Reduction of inappropriate antibiotics
- Decreased CAUTIs, and increased CAUTIs!

Why the conflicting results?

Variability in:

- UA and urine culture practices
- Reflexive algorithm design
- Patient populations
- Adherence to algorithms
 - e.g., ability to order culture despite UA results



A success story at Washington University

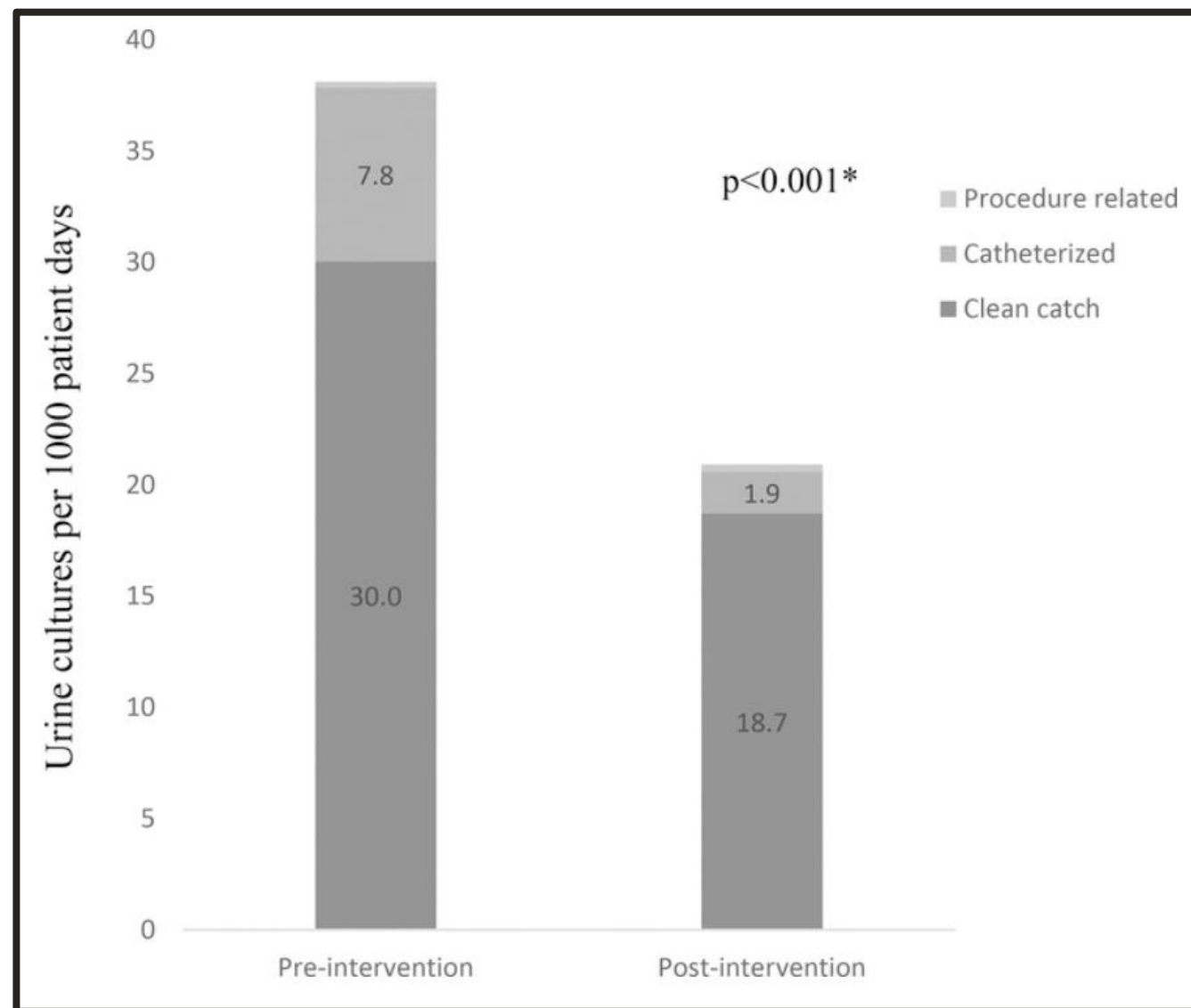
- Algorithm tweaked over 5+ years
- Now only reflex culture off of 10 WBC/hpf
 - Initially included blood, protein, LE, nitrite
- Pre-packaged 2-tube collection kit
 - Allows culture stability up to 48 h
- Multiple orders for different patient populations
 - Strategically place in order sets



Multiple EHR order options

Test name	Definition
UA Reflex to Microscopy WITH Culture *new	If urinalysis is positive for nitrites OR leukocyte esterase, then microscopy and urine culture will automatically be performed
UA Reflex for Neutropenic Patients	If urinalysis is positive for protein (>trace), blood, nitrites, OR leukocyte esterase, then microscopy and urine culture will automatically be performed
UA Reflex to Microscopy WITHOUT Culture	If urinalysis is positive for protein (>trace), blood, nitrites, OR leukocyte esterase, then microscopy will automatically be performed
UA Dip Macroscopic	Macroscopic Dipstick Urinalysis only
UA Microscopy	Urine Sediment Examination only

Intervention of new reflex orders decreased urine cultures and increased culture positivity rate




	Pre-	Post-
Urine cultures per 1000 patient days	38.1	20.9
Percent positive cultures	25.5%	29.7%
CAUTIs per 1000 patient days	0.30	0.30

Workflow considerations

- LIS order
- Specimen containers x 2
- Label printing
- What triggers Micro to start culture?
- Where are tubes stored/held?
- Provider education/clinical decision support

Clinical decision support (example)

Discern: (1 of 1)

 **Urinalysis with Culture, if ind**

This reflex-to-culture test is not appropriate for some special populations. DO NOT order for: Pregnant women, renal transplant patients, neonates <2 months of age, and severely immunocompromised patients (including chemotherapy induced neutropenia with an ANC <1000). Order direct urine culture separately for these patients

Alert Action:

Cancel Urinalysis with Culture, if Indicated

Continue ordering Urinalysis with Culture, if Indicated

Add orders for:

Urine Culture -> Routine collect, T;N

OK

Final considerations for reflexive algorithms

- Multiple stakeholders
 - In lab: Core, Micro, possibly POCT
 - Outside of lab: ID, Primary Care, Nephrology, Urology, OBGYN, Pediatrics...
- Consider your patient population(s)
- Design and position EHR orders intelligently
 - Most effective way to change behavior
- May reduce cultures, but clinical/reportable outcomes remain questionable/controversial

Emerging technologies for UTI

Method	Advantages	Challenges
Urinalysis	<ul style="list-style-type: none"> • fast • cheap 	<ul style="list-style-type: none"> • not specific to UTI
Urine culture	<ul style="list-style-type: none"> • allows for susceptibility testing • cheap 	<ul style="list-style-type: none"> • slow • limited by type of bacteria that will grow • must differentiate between contamination and true infection
Rapid molecular detection	<ul style="list-style-type: none"> • fastest • potentially higher detection rates 	<ul style="list-style-type: none"> • may be limited by genetic targets • must differentiate between contamination and true infection • more expensive

Acknowledgements

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