LABORATORY DIAGNOSTIC ASPECTS OF URINARY TRACT INFECTION – POTENTIAL IMPACT ON ANTIMICROBIAL STEWARDSHIP

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Disclosure

None

OBJECTIVES

1. Describe pre-analytical laboratory strategies for the diagnosis of UTI that support antimicrobial stewardship
2. Describe analytical laboratory strategies for the diagnosis of UTI that support antimicrobial stewardship
3. Describe post-analytical laboratory strategies for the diagnosis of UTI that support antimicrobial stewardship

INTRODUCTION

- UTI - common reason for seeking medical care; 50% of females ≥ 1 UTI in life
- 8 million office visits/year; 1 million hospital admissions
- 7 million cases of cystitis; 250K of pyelo
- UTI – cystitis, pyelonephritis, urethritis
  - Bacteriuria – symptomatic vs asymptomatic
  - Complicated vs uncomplicated (normal UT)

CLINICAL MANIFESTATIONS

- Infants - failure to thrive, vomiting, fever, non-specific
- Children - frequency, urgency, dysuria, flank or abdominal pain
- Adults (cystitis) - frequency, urgency, dysuria, turbid urine, suprapubic heaviness or pain, hematuria, pyuria

CLINICAL MANIFESTATIONS

- Adults (pyelonephritis) - fever, chills, flank pain, frequency, urgency, dysuria, pyuria
- Elderly – problematic; may be asymptomatic, pyuria may be absent, typical symptoms may occur; mortality from bacteremic UTI 10-30%

ETIOLOGY

- Uncomplicated - *E. coli* (75-90%), others - *S. saprophyticus* (5-15%), *Klebsiella, Proteus, Enterococcus, Pseudomonas*
- Complicated/HAI - *E. coli* (50%), other *Enterobacteriaceae, Pseudomonas, Acinetobacter, Enterococcus,* staphylococci

ETIOLOGY

- Elderly (males) - *Proteus = Providencia, E. coli, Pseudomonas;* (females) - *E. coli, Proteus, Klebsiella*
- Anaerobes - rare; requires SPA
- *Salmonella* - associated with bacteremia
- *Candida* - indwelling catheters, Ab Rx
- *S. aureus* - invades kidney from blood
- SCN - males w/ structural abnormality

RARE ORGANISMS

- *Corynebacterium urealyticum* – possesses strong urease – struvite stones; obstructive uropathy, renal transplant
- *Aerococcus* – similar to *Enterococcus;* elderly males w/ underlying urologic problems
- *Gardnerella vaginalis & Haemophilus influenzae* – rare pathogens
- *Candida* – healthcare associated; DM, neoplasms, catheterization, antibiotic/steroid use, neonates; often asymptomatic; no quantitative criteria

LABORATORY DIAGNOSIS

- Indication is key
- May not be indicated for non-pregnant otherwise healthy females with frequency, urgency, dysuria
- Indicated for infants, males, asymptomatic pregnant females, catheter or instrument associated HAI UTI, renal transplant, urologic disorders, diabetes, suspected pyelonephritis, prostatitis, epididymitis, relapse

LABORATORY DIAGNOSIS

- If indicated – perform
  - Results can aid management
- If not indicated – “don’t do it!”
  - Positive results - Ab Rx, CDI, resistance
- If uncertain - “UA with culture if indicated”
  - Use stringent criteria – WBC >10/hpf
  - Other criteria – low specificity

SPECIMENS

- First morning specimen
- SPA – gold standard/safe; infants, some adults, pregnant females; anaerobic culture
- Straight catheter – discard 1st few mLs, aseptic technique; 1-5% risk of infection
- Pediatric bag – negative culture rules out UTI; positive are often due to contamination

SPECIMENS

- Foley catheter
  - Use collection port
  - Clamp tubing
  - Do not culture catheter or bagged urine
  - **MUST** change Foley if >72 hrs
  - CAUTI

SPECIMENS

Straight catheter

Foley catheter

Pediatric bag

SPECIMENS

- CCMS urine; collection technique critical
  - Cleanse with towelettes as follows:
    - Males – hold foreskin back; clean urogenital meatus;
    - Females - **separate the labia**; clean urogenital meatus; keep the labia separated while collecting urine
  - Urinate a small amount into toilet
  - Place cup under urine stream; when full, finish urinating into toilet; recap cup

SPECIMENS

- Transport/Storage
  - Urine is excellent growth medium
  - Culture ASAP
  - If delayed > 2 hours
    - 4ºC up to 24 hours
    - Borate preservative - works well (24-48 hrs), toxic to bacteria if ≤ 3 mL collected

SPECIMEN COLLECTION

SCREENING METHODS

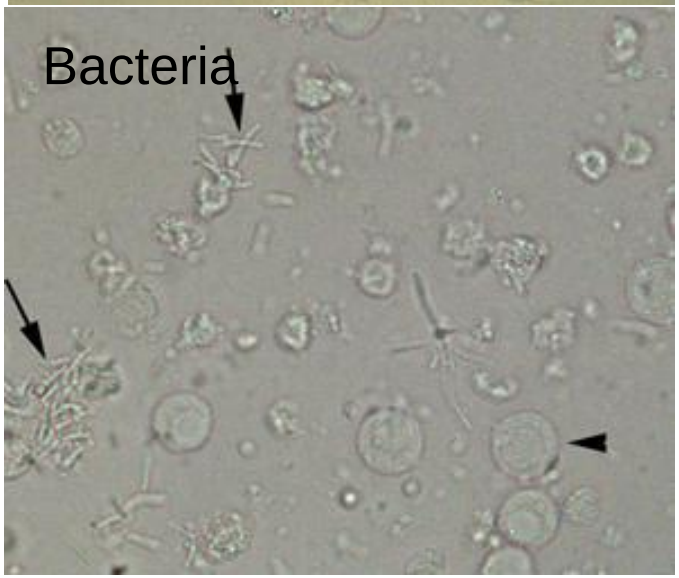
- Microscopic/dipstick UA
- Gram stain
- Bioluminescence - bacterial ATP - light
- Filtration/Staining - Bac-T-Screen
- Growth dependent/flow cytometry
- All the above perform better @ $\geq 10^5$ CFU/mL

URINALYSIS

- Non-specific – cloudiness, blood tinged
- Pyuria – leukocyte esterase or >5-10 WBC/hpf of unspun urine; sensitivity/specificity (>5) - 80-85%
  - Reflex - “UA with culture if indicated”; WBC >10/hpf
- Nitrituria – nitrate reducing bacteria; sensitivity – 39-69%; specificity 90-93%
- Leukocyte esterase + nitrites (either); 86%/67%
- Hematuria/proteinuria/bacteriuria - not sensitive or specific
- White cell casts - pyelonephritis

URINALYSIS

Dipstick UA



CULTURE

- **Must have** signs/symptoms of UTI e.g. frequency, urgency, dysuria, fever, etc., or other well established indication
- Normal flora - urine sterile; urine specimens may not be - contaminated w/ urethral/rectal/vaginal flora (6-38%) including potential pathogens
- If culture performed w/o indication
  - Growth a good possibility
  - Unnecessary treatment – CDI, resistance
  - CAUTI increased

CULTURE

- Symptomatic - 1 spec; asymptomatic* – 2
- Noninvasive (CCMS, foley, pedi bag) - 1 µL
- Invasive specimens (SPA, SC) – 10 µL
- Media - monomicrobial & gram negative bacteriuria the rule - BAP + MAC (EMB) ± PEA (CNA); chromogenic media
- Incubation - 35ºC; 18-48 hours

CULTURE

- Quantitative culture - separate true UTI from contamination
- Classically - $\geq 10^5$ CFU/mL - UTI; $< 10^5$ CFU/mL contamination
- Reculture as test-of-cure – not recommended except for pregnant women, high risk patients

GUIDELINES - NONINVASIVE

# Isolates	CFU/mL	Workup
1	< 10,000	MMI (minimal morphologic identification)
	≥ 10,000	ID/AST (identification/antimicrobial susceptibility testing)
2	Both < 10,000	MMI (both)
	Both ≥ 10,000	ID/AST (both)
	1 < 10,000	MMI
	1 ≥ 10,000	ID/AST
≥3	1 ≥ 100,000	ID/AST
	2 < 10,000	MMI
	Any other	MMI; “mixed culture; recollect if indicated”

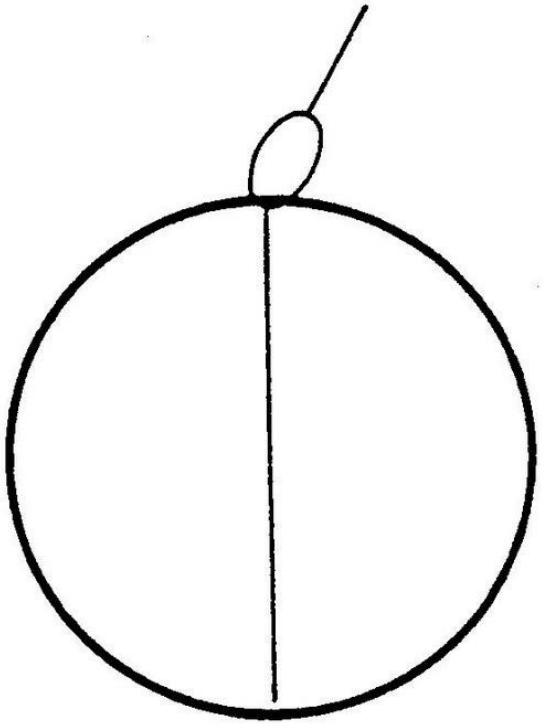
Noninvasive – CCMS, foley, pedi bag
Culture 1 µL; incubate 16-24 hrs
ID/AST – as appropriate

GUIDELINES - INVASIVE

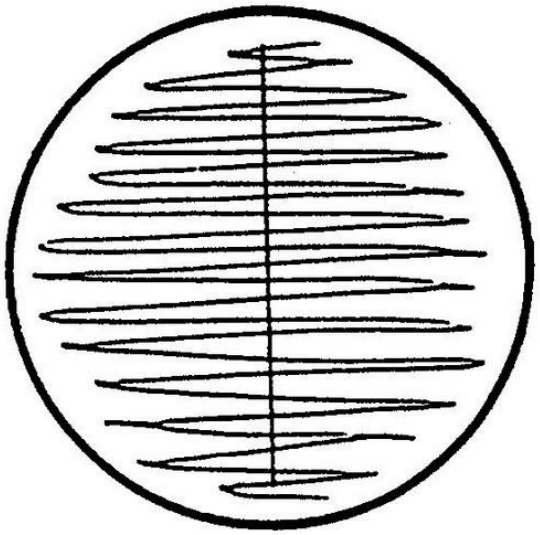
# Isolates	CFU/mL	Workup
1	< 1000	MMI (minimal morphologic identification)
	≥ 1000	ID/AST (identification/antimicrobial susceptibility testing)
2	Both < 1000	MMI (both)
	Both ≥ 1000	ID/AST (both)
	1 < 1000	MMI
	1 ≥ 1000	ID/AST
3	1 ≥ 10,000	ID/AST
	2 < 1000	MMI
	Any other	MMI

Invasive – straight cath, SPA, cystoscopy, nephrostomy
Culture 10 µL; incubate 48hrs
ID/AST – as appropriate

INOCULATION/CULTURE

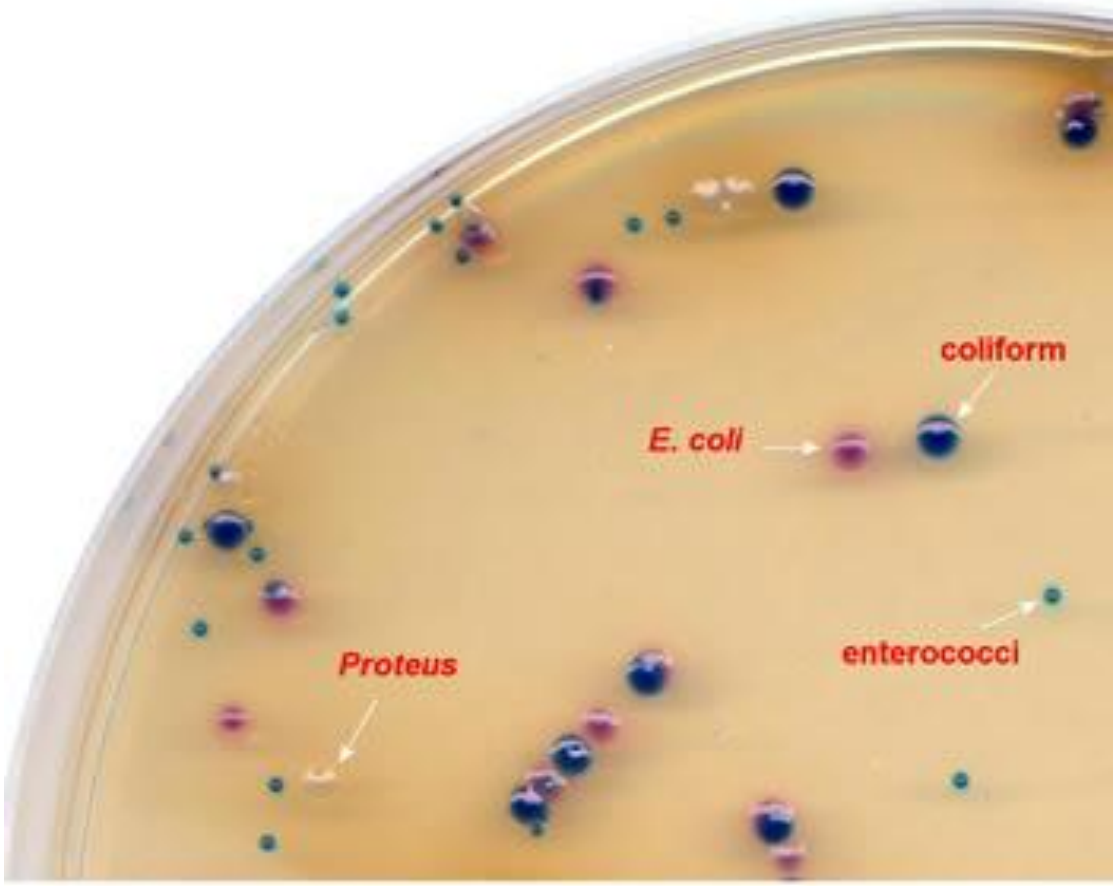


1
Primary Inoculation



2
Streak at Right Angles

CHROMOGENIC MEDIA



CULTURE PROBLEMS

- Specimen collection - females, infants
- Chronic catheterization - colonization; symptoms hard to assess; significance of 6-8 organisms?
- Culture+ without appropriate indications

MIXED CULTURE

- ≥ 3 bugs)
  - <5% if collected & transported appropriately
  - Up to 50% are not – usually contamination

CULTURE PROBLEMS

- Nursing home patients - poor positive predictive value
- Symptomatic patients w/ $<10^5$ CFU/mL
  - Females + classic symptoms + coliforms
    - $\geq 10^5$ CFU/mL (50% sens/99% spec)
    - $\geq 10^2$ CFU/mL (95% sens/85% spec)
- Pregnant females with GBS – marker of heavy vaginal/rectal colonization

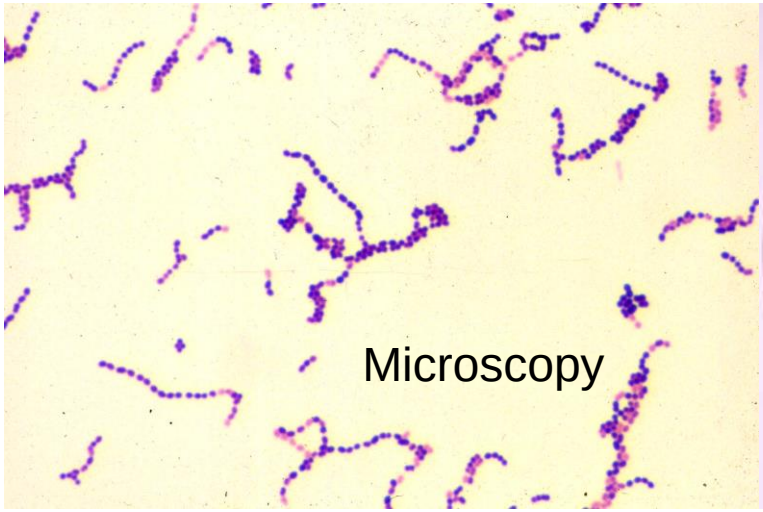
FALSE NEGATIVE CULTURES

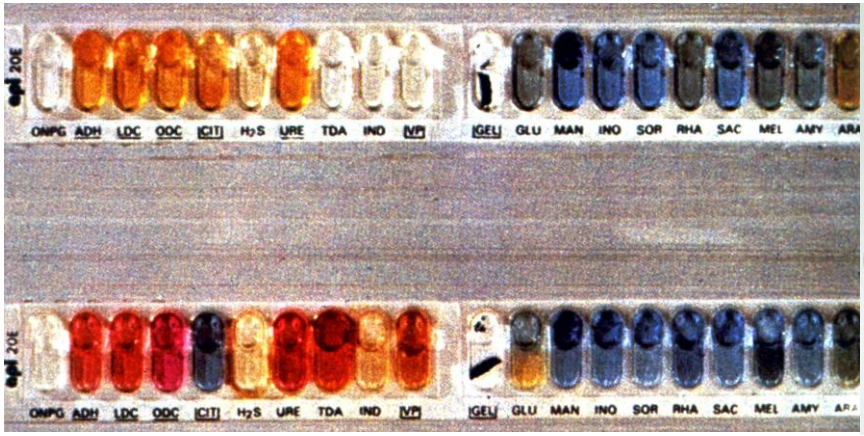
- Dilution - forcing fluids
- Antibiotic therapy - high urine concentration
- “Sterile pyuria” – WBC >5 w/ negative culture
  - Injury to UT, catheterization, vesicoureteral reflux, interstitial cystitis, polycystic kidney disease, tumor, staghorn calculi, stones, abnormal UT, contiguous infection
  - Anaerobes, *Chlamydia trachomatis, Ureaplasma urealyticum, Mycobacterium tuberculosis, Leptospira,* systemic fungal infection

CULTURE ID & AST

- Core function of Microbiology Lab
- No growth - no problem
- Growth - identify isolate(s)
  - Necessary to determine etiology, clinical significance, potential therapy
  - Conventional methods
    - Microscopy/Colony Morphology/Biochemical Reactivity
    - TAT – 24-72 hours after appearance of visible colonies

CONVENTIONAL ID



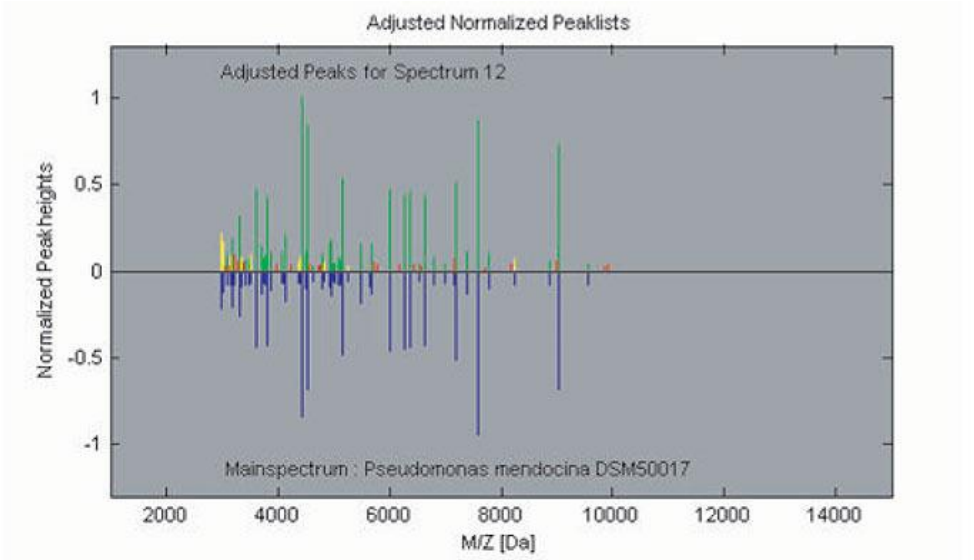


Biochemical Profile

MALDI-TOF

- Matrix-assisted laser desorption/ionization – Time of Flight
- Proteins & peptides arranged in a spectrum of increasing mass
- Pattern or “fingerprint” characteristic for individual organism
- bioMérieux – Vitek MS®; Bruker – Biotyper®
- TAT – 10 minutes

MALDI-TOF



Result Report	Detected Species	Ranking	act Sc	max Sc	Rel Score	PM k	PM b	PM m	Rel P-Num.	I-Corr.	1000*Pro
Spectrum #12	Ps. mendocina DSM50017	1	3813	4271	0.89	41	10	83	0.55	0.88	438
	Ps. oleovorans B396	2	1671	3450	0.48	14	8	83	0.22	0.39	41
	Ps. fluorescens B340	3	868	4186	0.21	6	7	83	0.11	0.19	4
	Ps. veronii DSM11331	4	847	4250	0.20	5	7	83	0.10	0.14	3
	Ps. putida DSM291	5	374	2821	0.13	3	3	83	0.05	0.12	1
	Ps. putida B401	6	329	2638	0.12	3	2	83	0.05	0.11	1

Analyte Name	Analyte ID	Organism (best match)	Score Value	Organism (second best match)	Score Value
D2 (+++)	referenz	Escherichia coli DH5alpha BRL	2.382	Escherichia coli ATCC 25922 THL	2.226
D3 (+++)	MB 20	Burkholderia multivorans LMG 14293 HAM	2.457	Burkholderia dolosa DSM 16088 HAM	1.855
D4 (+++)	MB 20	Burkholderia multivorans LMG 14293 HAM	2.462	Burkholderia dolosa DSM 16088 HAM	1.996

AST - Reminders

- When performed
  - Isolate clinically significant (pathogen)
  - Susceptibility pattern unpredictable
  - Standardized method available
- Utility
  - AST results may not predict clinical efficacy
  - Purpose of AST is to detect phenotypic RESISTANCE - high correlation with clinical failure

AST - TAT

- Conventional AST – 18-24 hours
- Vitek XL AST (bioMérieux) – 6-12 hrs
- MAST (Greiner Bio-One) – 2-4 hrs
- Accelerate (Pheno) – 7 hrs
- Faster time to definitive/directed antibiotic therapy

WORKFLOW

- Faster TAT – nice, but…
- Need to maximize speed advantages
  - Initial read of cultures – 18 hrs
  - If no growth – final
  - If growth – MALDI ID & rapid AST
    - Results for ID in 1 hr
    - Results for AST 6-12 hrs later
  - That the “pitch”, but need a “catcher” (ASP)

What's The Bottom Line?

- Organism identifications on day 1 (18-24 hours after specimen processing) instead of day 2
- Reported AST results (later) on day 1 (4-12 hours after identification) instead of day 2
- Clinical utility of faster results depends on what you do with the information & how fast you do it
- Antibiotic stewardship intervention vital for optimal utilization of faster results

IMPACT

- Shorter time to identification & AST
  - ASP key to getting
    - Shorter time to effective therapy
    - Shorter time to optimal therapy
    - Reduction in length of antimicrobial therapy
    - Reduced LOS
    - Reduction in ICU LOS

Cavalieri SJ 2018. Effect of Antimicrobial Stewardship with Rapid MALDI-TOF Identification and Vitek 2 Antimicrobial Susceptibility Testing on Hospitalization Outcome (ID Week Poster)
Beganovic M et al. 2017. Effect of Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry (MALDI-TOF MS) Alone versus MALDI-TOF MS Combined with Real-Time Antimicrobial Stewardship Interventions on Time to Optimal Antimicrobial Therapy in Patients with Positive Blood Cultures J Clin Microbiol 55(5):1437

SUMMARY

- Key features of laboratory diagnosis of UTI
  - Perform only when indicated
  - Appropriate specimen collection/transport vital
    - “Garbage in → garbage out”
  - Awareness of limitations
  - Rapid ID & AST with robust ASP
    - Significant clinical impact

LABORATORY DIAGNOSTIC ASPECTS OF UTI – POTENTIAL IMPACT ON ASP

Assessment Question

What is the MAJOR purpose behind the strategy of using the presence of pyuria (≥10 WBC/hpf) as the sole criterion for performing a urine culture when “UA with culture if indicated” is ordered?

a. To culture urine only when there is a high likelihood of UTI (specificity)
b. To ensure that no UTIs are missed (sensitivity)
c. To reduce urine cultures for the overworked Microbiology lab
d. To ensure that the lab works up all microoganisms that grow from culture
e. To annoy physicians

Assessment Question

What is the MAJOR purpose behind the strategy of "selective reporting" of antimicrobial susceptibility testing (AST) results?

a. Control pharmacy costs
b. Drive usage toward oral therapy
c. Reduce usage of fluoroquinolones
d. Force physicians to call the lab for AST results
e. Preserve the utility of currently available broad spectrum antibiotics

Assessment Question

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