

2024

Effective Test Utilization Best Practices Recommendations

- 1** Use Immature Granulocyte (IG) count rather than manual band count in sepsis evaluation.
- 2** Do not routinely monitor breast cancer patients with both CA 15-3 and CA 27.29.
- 3** Do not order urine eosinophils for acute interstitial nephritis (AIN) or when evaluating acute kidney injury (AKI).
- 4** Do not routinely order Thyroid Hormone Binding Ratio (e.g., T3 Resin Uptake or T-Uptake) assays to determine the free T4 index. Use free T4 assays instead.
- 5** Consider molecular-based testing for diagnosis of arboviral disease within first seven days of symptom onset.
- 6** Do not order bacterial culture (genital culture) for the diagnosis of Bacterial Vaginosis (BV).

1. Use Immature Granulocyte (IG) count rather than manual band count in sepsis evaluation

The use of immature neutrophils (>10%) has long been incorporated into the diagnostic criteria of Systemic inflammatory response syndrome (SIRS) and Sepsis. This traditionally manifests in the reliance on manual band counts. Because this procedure is plagued with significant interobserver variability and limited sampling (only 100 leukocytes are evaluated), the manual band count is an imprecise and non-specific data point that offers little diagnostic information.

A superior option is the immature granulocyte (IG) count. This is a fast, cheap and reproducible parameter on commercial hematology analyzers. Via the use of fluorescent flow cytometry, the size and nuclear characteristics of over 30,000 nucleated cells are determined from a standard blood draw. The IG count includes metamyelocytes, myelocytes, and promyelocytes. These cells are early markers of the marrow response and have a higher sensitivity and specificity than manual band count in detecting infection.

References:

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med.* 1992 Jun;20(6):864-74. PMID: 1597042.
2. Ansari-Lari, M., et al. Immature granulocyte measurement using the Sysmex XE-2100: Relationship to infection and sepsis. *Am J Clin Pathol.* 2003. 120:795-799.
3. Bhansaly P, Mehta S, Sharma N, Gupta E, Mehta S, Gupta S. Evaluation of Immature Granulocyte Count as the Earliest Biomarker for Sepsis. *Indian J Crit Care Med.* 2022 Feb;26(2):216-223. doi: 10.5005/jp-journals-10071-23920. PMID: 35712744; PMCID: PMC8857719.
4. Cornbleet PJ. Clinical utility of the band count. *Clin Lab Med.* 2002 Mar;22(1):101-36. doi: 10.1016/s0272-2712(03)00069-6. PMID: 11933571.

2. Do not routinely monitor breast cancer patients with both CA 15-3 and CA 27.29

CA 15-3 and CA 27.29 are antigens from the same gene, MUC-1. Studies demonstrate high concordance between the two markers; there is no evidence of added value in performing both tests routinely for individual patients. For breast cancer monitoring, if medically necessary, consistently use either CA 15-3 or CA 27.29, not both.

References:

1. Lin DC, Genzen JR. Concordance analysis of paired cancer antigen (CA) 15-3 and 27.29 testing. *Breast Cancer Res Treat.* 2018 Jan;167(1):269-276.
2. CMS National Coverage Determination (NCD) 190.29: "Tumor Antigen by Immunoassay - CA 15-3/CA 27.29."

3. Do not order urine eosinophils for acute interstitial nephritis (AIN) or when evaluating acute kidney injury (AKI)

Historically, the presence of urine eosinophils has been used as a biomarker for acute interstitial nephritis (AIN). Support for eosinophiluria as a marker for AIN originally came from two studies, only nine patients each, that found urine eosinophils present in patients with biopsy-confirmed AIN (1,2). However, subsequent studies with more robust populations have not supported eosinophiluria as a sensitive or specific marker for AIN (3,4).

These findings are best illustrated in a 2013 retroactive study by Muriithi et al. of 566 patients that found urine eosinophils demonstrated only 30% sensitivity and 68% specificity for AIN compared to all other diagnoses – with only 15.6% positive and 85.7% negative predictive values (5), concluding that eosinophiluria exists in many kidney diseases and is no better at distinguishing AIN from acute tubular necrosis or other kidney diseases (5). Per Muriithi et al, most diagnoses of AIN are determined by clinical history, physical examination and laboratory findings. Renal biopsy is the gold standard for atypical cases or those where definitive confirmation is required for therapy.

In 2021, the Association for Diagnostics and Laboratory Medicine published a guidance document for laboratory investigation of acute kidney injury (AKI) recommending diagnostic thresholds, the role of new biomarkers, and discontinuation of wasteful testing (eg, urine eosinophils) (6). The guidance recommends against using urinary eosinophils to confirm or exclude AIN nor should it be considered in the evaluation of AKI (6).

References:

1. Galpin JE, Shinaberger JH, Stanley TM, Blumenkrantz MJ, Bayer AS, Friedman GS, Montgomerie JZ, Guze LB, Coburn JW, Glasscock RJ. Acute interstitial nephritis due to methicillin. *Am J Med.* 1978 Nov;65(5):756-65. doi: 10.1016/0002-9343(78)90793-3. PMID: 707534.
2. Linton AL, Clark WF, Driedger AA, Turnbull DI, Lindsay RM. Acute interstitial nephritis due to drugs: Review of the literature with a report of nine cases. *Ann Intern Med.* 1980 Nov;93(5):735-41. doi: 10.7326/0003-4819-93-5-735. PMID: 7212486.
3. Perazella MA, Bomback AS. Urinary eosinophils in AIN: farewell to an old biomarker? *Clin J Am Soc Nephrol.* 2013 Nov;8(11):1841-3. doi: 10.2215/CJN.08620813. Epub 2013 Sep 19. PMID: 24052220; PMCID: PMC3817912.
4. Gau N, Jackups R. Urine Eosinophils (UEs) Have No Practical Value for the Diagnosis of Acute Interstitial Nephritis (AIN). *American Journal of Clinical Pathology.* 2018 Oct; 150(1): S148–S149. doi: 10.1093/ajcp/aqy112.351.
5. Muriithi AK, Nasr SH, Leung N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. *Clin J Am Soc Nephrol.* 2013 Nov;8(11):1857-62. doi: 10.2215/CJN.01330213. Epub 2013 Sep 19. Erratum in: *Clin J Am Soc Nephrol.* 2018 Jul 6;13(7):1079. PMID: 24052222; PMCID: PMC3817898.
6. El-Khoury JM, Hoenig MP, Jones GRD, Lamb EJ, Parikh CR, Tolan NV, Wilson FP. AACC Guidance Document on Laboratory Investigation of Acute Kidney Injury. *J Appl Lab Med.* 2021 Sep 1;6(5):1316-1337. doi: 10.1093/jalm/jfab020. Erratum in: *J Appl Lab Med.* 2024 Feb 02;: PMID: 33973621.

4. Do not routinely order Thyroid Hormone Binding Ratio (THBR, e.g., T3 Resin Uptake or T-Uptake) assays to determine the free T4 index. Use free T4 assays instead.

Before free T4 assays, the Thyroid hormone binding ratio (THBR) was part of a two-test procedure to estimate the free T4 index (FT4I). Modern FT4 assays are now faster, more accurate, and less expensive than this two-test index approach. When ordered with free T4, the THBR does not add value in routine evaluations. THBR retains limited utility in rare patients with inconsistent results attributed to the presence of abnormal binding proteins.

References:

1. Spencer CA. Laboratory thyroid tests: A historical perspective. *Thyroid*. 2023;33(4):407-419.
2. Guber HA, Farag AF. Evaluation of Endocrine Function. In: McPherson RA, Pincus MR. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 23rd Edition. St. Louis: Elsevier, Inc; 2017.

5. Consider molecular-based testing for diagnosis of arboviral disease within the first seven days of symptom onset

Testing for arboviral disease diagnosis should be based on the patient's clinical presentation, duration of symptoms, exposure history, and information regarding circulation of endemic viruses. Molecular diagnosis is the method of choice, when available, to diagnose acute arboviral infection. Serologic testing is recommended in patients presenting beyond 5 days of initial symptoms. For patients tested earlier, serological testing may be negative due to an underdeveloped immune response.

References:

1. Sharp TM, Fischer M, Muñoz-Jordán JL, Paz-Bailey G, Staples JE, Gregory CJ, Waterman SH. Dengue and Zika Virus Diagnostic Testing for Patients with a Clinically Compatible Illness and Risk for Infection with Both Viruses. *MMWR Recomm Rep*. 2019 Jun 14;68(1):1-10. doi: 10.15585/mmwr.rr6801a1. PMID: 31194720; PMCID: PMC6581290.
2. Section 5: Travel-Associated Infections & Diseases – Viral. Jeffrey B. Nemhauser (ed.), *CDC Yellow Book 2024: Health Information for International Travel* (New York, 2023; online edn, Oxford Academic, 23 Mar. 2023), accessed 13 Mar. 2024.
3. Lustig Y, Mannasse B, Koren R, Katz-Likvornik S, Hindiyeh M, Mandelboim M, Dovrat S, Sofer D, Mendelson E. Superiority of West Nile Virus RNA Detection in Whole Blood for Diagnosis of Acute Infection. *J Clin Microbiol*. 2016 Sep;54(9):2294-7. PMID: 27335150; PMCID: PMC5005505
4. Miller JM, Binnicker MJ, Campbell S, Carroll KC, Chapin KC, Gonzalez MD, Harrington A, Jerris RC, Kehl SC, Leal SM Jr, Patel R, Pritt BS, Richter SS, Robinson-Dunn B, Snyder JW, Telford S 3rd, Theel ES, Thomson RB Jr, Weinstein MP, Yao JD. *Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2024 Update by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)*. *Clin Infect Dis*. 2024 Mar 5:ciae104. doi: 10.1093/cid/ciae104. Epub ahead of print. PMID: 38442248.

6. Do not order bacterial culture (genital culture) for the diagnosis of Bacterial Vaginosis (BV)

Bacterial vaginosis (BV) is a vaginal dysbiosis, but there is no consensus on the group of bacterial species that cause BV. Although *Gardnerella vaginalis* can be recovered using routine culture methods, it not a specific marker of disease and therefore culture is not a recommended diagnostic tool. To diagnose BV nucleic acid amplification based testing (NAAT) is more sensitive and specific than other available methods. Gram stain with Nugent scoring is acceptable if NAAT testing is not available.

References:

1. Miller JM, Binnicker MJ, Campbell S, Carroll KC, Chapin KC, Gonzalez MD, Harrington A, Jerris RC, Kehl SC, Leal SM Jr, Patel R, Pritt BS, Richter SS, Robinson-Dunn B, Snyder JW, Telford S 3rd, Theel ES, Thomson RB Jr, Weinstein MP, Yao JD. Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2024 Update by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). Clin Infect Dis. 2024 Mar 5:ciae104. doi: 10.1093/cid/ciae104. Epub ahead of print. PMID: 38442248.
2. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187. doi: 10.15585/mmwr.rr7004a1. PMID: 34292926; PMCID: PMC8344968.
3. Muzny CA, Balkus J, Mitchell C, et al. Diagnosis and management of bacterial vaginosis: summary of evidence reviewed for the 2021 Centers for Disease Control and Prevention sexually transmitted infections treatment guidelines. Clin Infect Dis. 2022;74(Supplement_2):S144-S151. doi:10.1093/cid/ciac021
4. Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215. Obstet Gynecol. 2020 Jan;135(1):e1-e17. PMID: 31856123.