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Medical Policy

Subject:	**Pooled Antibiotic Sensitivity Testing**		
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Description/Scope

This document addresses pooled antibiotic sensitivity testing (P-AST) of urine in combination with a Multiplex Polymerase Chain Reaction (M-PCR) assay for the identification of susceptible urine pathogens and antibiotic resistance genes. This assay testing is proposed for use in the outpatient setting for treatment of recurrent, persistent, and complicated urinary tract infections (UTI) that have been refractory to conventional antibiotics.

Position Statement

Investigational and Not Medically Necessary:

Pooled antibiotic sensitivity testing is considered investigational and not medically necessary in the outpatient setting for all indications.

Rationale

Urinary tract infections (UTIs) are considered complicated when there is an increased chance for a complicated course, for example in pregnant women, individuals with anatomic or functional abnormalities, those with long-term indwelling urinary catheters, renal diseases, and immunocompromising diseases (Bonkat, 2018). For complicated UTIs, Escherichia coli (E. coli) is the most common cause but other causative uropathogens include other enterobacteriaceae, pseudomonas, enterococci, and staphylococci (methicillin-sensitive staphylococcus aureus [MSSA] and methicillin-resistant S. aureus [MRSA]) (Hooton & Gupta, 2018).

Molecular antimicrobial susceptibility testing with assays, such as the Guidance® UTI (Pathnostics™ Inc., Irvine, CA), is proposed as a patented approach to identification and antibiotic sensitivity testing called

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Pooled Antibiotic Susceptibility Testing (P-AST). This test, in combination with a Multiplex Polymerase Chain Reaction (M-PCR) assay, is intended for use in complicated UTIs where the infection has been resistant to conventional antibiotic therapy for identification of specific pathogens and antibiotic resistance genes. Techniques commonly used to detect bacterial nucleic acid sequences that confer antibiotic resistance include PCR and DNA hybridization. A number of such genotypic assays have been cleared by the United States Food and Drug Administration (FDA), as screening tools for identification of multidrug-resistant bacteria in hospital settings, and for diagnostic purposes. However, to date the number of FDA-cleared assays have been limited to the detection of one or a few specific genetic resistance targets in a given bacterial species. For many bacteria, antimicrobial resistance is complex, and molecular assays that target only a few known resistance genes to predict antimicrobial susceptibility are insufficient and misleading. Detection of specific genetic resistance targets is further complicated by the emergence of genetic variants. Genotypic results do not obviate the need for phenotypic antimicrobial susceptibility testing, which is still necessary to confirm test results and to provide information about other possible therapeutic options. Molecular testing is currently performed in addition to, not in place of, phenotypic antimicrobial susceptibility testing (Ledebedoer, 2011; Mangold, 2016; McGeer, 2016; Sullivan, 2016).

Results from a large multi-national study of 4264 women from ten countries, the Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC), showed that up to 10.3% of E. coli in UTIs are resistant to at least three different classes of antimicrobial agents with ampicillin having the highest degree of resistance (48.3%) (Schito, 2009).

In 2018, the European Association of Urology (EAU) released an update to their Urologic Infections guideline in which they state (all with a 'Strong' strength of rating):

Do not screen or treat asymptomatic bacteriuria in the following conditions:

- **Women without risk factors;**
- **Patients with well-regulated diabetes mellitus;**
- **Post-menopausal women;**
- **Elderly institutionalized patients;**
- **Patients with dysfunctional and/or reconstructed lower urinary tracts;**
- **Patients with renal transplants;**
- **Patients prior to arthroplasty surgeries;**
- **Patients with recurrent urinary tract infections.**

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The EAU document recommends:

- **Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa ('Strong' rating).**
- **Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment ('Weak' strength of rating).**
- **Diagnose recurrent UTI by urine culture ('Strong' rating).**
- **Recurrent UTI indicates that the occurrences are symptomatic.**
- **Use laboratory urine culture to detect bacteriuria in patients prior to undergoing urological interventions breaching the mucosa ('Weak' rating).**

The EAU defines complicated UTI (cUTI) as occurring:

> **In an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection. Other factors associated with cUTIs include: vesicoureteral reflux, recent history of instrumentation, UTI in males, pregnancy, and healthcare-associated infections. Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients suspected of having a cUTI (Bonkat, 2018).**

To date, studies of P-AST and M-PCR urine testing have been insufficient to demonstrate the safety, efficacy and impact on clinical outcomes. In 2020, Daly and colleagues reported on a retrospective study of existing data from 66,383 individuals seen for possible UTI by house-call primary care providers. Trial subjects were divided into two cohorts. One cohort was treated based upon the results from standard urine cultures (SUC). The other cohort was treated in accordance with results from an assay combining Multiplex-Polymerase Chain Reaction (M-PCR) and Pooled Antibiotic Susceptibility Testing (P-AST) of urine specimens. The total number of emergency department visits and hospitalizations were compared between the two cohorts. The investigators found that the use of the combined M-PCR/P-AST was associated with a 13.7% decrease in hospital admissions and/or emergency department utilization when compared to the use of SUC testing (3.27% vs. 3.79%; p=0.003). The investigators concluded that these findings suggest that use of a combined M-PCR/P-AST assay in outpatient management of suspected UTI may improve patient outcomes and reduce emergency department and hospital utilization. The investigators noted that randomized studies are

underway to investigate further the role that M-PCR/P-AST may play to aid in the management of UTI in the elderly population (Daly, 2020).

In 2020, Vollstedt and colleagues collected urine specimens from 3124 individuals with symptoms of UTI. Of these, M-PCR testing detected bacteria in 61.1% (1910) of specimens. Pooled Antibiotic Susceptibility Testing (P-AST) results were available for 70.8% (1352) of these positive specimens. Of these positive specimens, 43.9% (594) were monomicrobial, while 56.1% (758) were polymicrobial. The odds of resistance to ampicillin (p=0.005), amoxicillin/clavulanate (p=0.008), five different cephalosporins, vancomycin (p=<0.0001), and tetracycline (p=0.010) increased with each additional species present in a polymicrobial specimen. In contrast, the odds of resistance to piperacillin/tazobactam decreased by 75% for each additional species present (95% confidence interval [CI], 0.61-0.94; p=0.010). For one or more antibiotics tested, 13 pairs of bacterial species exhibited statistically significant interactions compared with the expected resistance rate obtained with the Highest Single Agent Principle and Union Principle (Vollstedt, 2020).

Background/Overview

Polymerase chain reaction (PCR) testing provides simplified DNA (deoxyribonucleic) analysis by amplification of the targeted gene or DNA sequence. One important prerequisite of PCR is that the sequence of the gene, or at least the borders of the region of DNA to be amplified, must be known. PCR testing may be useful when a culture is difficult due to the low numbers of organisms present in the specimen, for fastidious or lengthy culture requirements, or when there is difficulty in collecting an appropriate sample. Quantification of viral load via PCR has been used as a prognostic indicator and for follow/up of individual response to therapy. To date, PCR amplification techniques have been limited by challenges in the interpretation of test results, potential for false positive results and other confounders including specificities, sensitivities, and positive and negative predictive values for many microorganisms in sufficiently large population groups.

Since 1978, the FDA has approved several urine culture kits and devices (FDA, 2018), and multiple laboratories have developed specific urine culture tests that they must validate and perform in-house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA, '88). Several manufacturers have also developed PCR assays designed to detect multiple pathogens, such as the INFINITI® bacterial vaginosis QUAD assay, designed to detect bacteroides fragilis, gardnerella vaginalis,

mobiluncus mulieris, mobiluncus curtisii, atopobium vaginae and prevotella bivia (AutoGenomics, Bacterial Vaginosis, 2010). The INFINITI candida vaginitis QUAD assay is designed to detect 5 fungal species: C. albicans, C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis (AutoGenomics Candida Vaginitis 2010). Quest Diagnostics has developed the Quest SureSwab, which includes tests for C. trachomatis, N. gonorrhoeae, and T. vaginalis as well as tests for bacterial vaginosis and Candida spp.

Definitions

Antibiotic resistance testing, also known as antimicrobial susceptibility testing: Refers to testing for the purpose of isolating causative microorganisms and guiding treatment decisions regarding antibiotic selection. Testing can be done by conventional methods (phenotypic testing) and newer molecular (genotypic) techniques such as PCR, NAAT and NGS.

Antimicrobial: An agent that kills microorganisms or stops their growth.

Genotypic: The genetic makeup of an organism or group of organisms with reference to a single trait, set of traits or an entire complex of traits.

Molecular testing: Relating to the study of molecules, a group of atoms bonded together, representing the smallest fundamental unit of a chemical compound that can take part in a chemical reaction.

Nucleic acid amplification test (NAAT or NAT): Atype of genetic test used for infectious disease. This technique makes numerous copies (amplification) of any genetic material from the microbes present in a sample so that it can be more easily detected. One type of NAAT is polymerase chain reaction (PCR).

Phenotypic: Relating to the observable characteristics of an individual resulting from the interaction of its genotype with the environment.

Polymerase Chain Reaction (PCR): A laboratory technique used to make multiple copies of a segment of DNA.

Urinary Tract Infection (UTI): Refers to an infection of any part of the urinary system (kidneys, ureters, bladder, urethra).

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Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81479	Unlisted molecular pathology procedure [when specified as a pooled antibiotic sensitivity test with multiplex PCR, such as the Guidance® UTI test]
87999	Unlisted microbiology procedure [when specified as a pooled antibiotic sensitivity test with multiplex PCR, such as the Guidance® UTI test]

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Brubaker L, Wolfe A. The urinary microbiota: a paradigm shift for bladder disorders? Curr Opin Obstet Gynecol. 2016; 28(5):407-412.
2. Cope M, Cevallos ME, Cadle RM, et al. Inappropriate treatment of catheter-associated asymptomatic bacteriuria in a tertiary care hospital. Clin Infect Dis. 2009; 48(9):1182-1188.
3. Daly A, Baunoch D, Rehling K, et al. Utilization of M-PCR and P-AST for diagnosis and management of urinary tract infections in home-based primary care. JOJ Urol Nephrol. 2020; 7(2).
4. Devillé WL, Yzermans JC, van Duijn NP, et al. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. BMC Urol. 2004; 4:4.

5. **Ducharme J, Neilson S, Ginn JL. Can urine cultures and reagent test strips be used to diagnose urinary tract infection in elderly emergency department patients without focal urinary symptoms? CJEM. 2007: 9(2):87-92.**
6. **Schito GC, Naber KFB, Botto HF, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents. 2009; 34(5):407-413. Available at: https://pubmed.ncbi.nlm.nih.gov/?term=ARESC+study. Accessed on January 14, 2021.**
7. **Schmiemann G, Kniehl E, Gebhardt K, et al. The Diagnosis of Urinary Tract Infection: A Systematic Review. Deutsches Ärzteblatt International. 2016; 07(21):361-367.**
8. **Vollstedt A, Baunoch D, Wolfe A, et al. Bacterial interactions as detected by pooled antibiotic susceptibility testing (P-AST) in polymicrobial urine specimens. J Surg Urol. 2020:1(1):1-10.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **Bonkat G, Pickard R, Bartoletti R, et al. European Association of Urology (EAU) Urological Infections Guidelines. 2018. Presented at the EAU Annual Congress Amsterdam the Netherlands 2020. ISBN 978-94-92671-07-3. Available at: http://uroweb.org/guideline/urological-infections/#3. Accessed on January 14, 2021.**
2. **Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011; 52(5):e103-120.**
3. **Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010; 50(5):625-663.**
4. **Price TK, Dune T, Hilt EE, et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. J Clin Microb. 2016; 54(5):1216-1222.**
5. **Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011; 128(3):595-610.**

Websites for Additional Information

American Urological Association (AUA). Guideline: Catheter-Associated Urinary Tract Infections: Definitions and Significance in the Urologic Patient. 2014. Available at:

https://www.auanet.org//guidelines/catheter-associated-urinary-tract-infections. Accessed on January 25, 2021.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	02/11/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

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