Volatile organic compounds for urinary tract infection

Clinical Policy ID: CCP.1504

Recent review date: 12/2021

Next review date: 4/2023

Policy contains: Electronic noses, spectroscopy, urinary tract infection, volatile organic compounds.

Coverage policy

Volatile organic compounds for diagnosing urinary tract infection are investigational/not clinically proven and, therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Standard laboratory culture.
Dipstick test.

Background

Bacteria are present in the tissues around the urethral opening and often colonize the urine. Because bacteria are more likely to ascend to the female bladder, which has a shorter urethral length, rates of urinary tract infection are higher among women. Various gram-positive and gram-negative bacteria, principally *Escherichia coli*, cause most urinary tract infections. Common infections include cystitis, pyelonephritis, and catheter-associated urinary tract infection (Flores-Mireles, 2015; Foxman, 2014).

Risk factors include female sex; prior infection; advanced age; recent sexual intercourse; use of a condom, diaphragm, or spermicide; vaginal infection; trauma/manipulation; diabetes; obesity; genetic susceptibility; or anatomic abnormalities. The estimated lifetime risk of urinary tract infection for women, based on self-reported history of diagnosis by a physician, is 60.4%. Recurrence is common. Most complicated infections are attributed to indwelling catheters (Flores-Mireles, 2015; Foxman, 2014).

Antibiotics are the standard treatment for urinary tract infections. Rising rates of resistance to antibiotics, along with high recurrence rates are of concern to care givers, and underline the need for alternative therapies less susceptible to resistance (Flores-Mireles, 2015). An estimated 10% of urinary tract infections are resistant to antibiotics (Smart, 2019).

The effort to develop alternative therapies can be enhanced by better diagnosis. Current diagnosis of urinary tract infection relies on two options. One is a dipstick test, which is rapid but often not accurate; one study places sensitivity and specificity, compared to lab culture, at 75.7% and 68.9% (Najeeb, 2015). The alternative is culturing to identify a pathogen, which takes 24 – 72 hours; during this delay, broad-spectrum antibiotics may be prescribed, leading to resistance. Tests that avoid over-prescription are needed (Dospinescu, 2020).

Volatile organic compounds are carbon-based compounds that can originate from microbial pathogens or a host response to infection and inflammation; many are associated with common urinary tract pathogens. These compounds can improve diagnosis of urinary tract infections. Several technologies have been developed, including gas chromatography, proton transfer reaction mass spectrometry, ion mobility spectrometry, selected ion flow tube mass spectrometry, field asymmetric ion mobility spectrometry, gas chromatography flame ionization detection, and electronic noses (Dospinescu, 2020).

In 2001, the U.S. Food and Drug Administration granted premarket approval for use of the Osmetech Microbial Analyser for diagnosis of urinary tract infection. The product uses “electronic nose” (odor sensor) technology to measure the presence of bacteria by semiquantitative analysis of volatile compounds (U.S. Food and Drug Administration, 2003).

Findings

The American Academy of Family Physicians practice guidelines on urinary tract infection for children/infants and adults only mentions urine microscopy and dipstick testing as diagnostic methods (Michels, 2015; Veauthier, 2020). No other guideline mentions volatile organic compound testing for urinary tract infection.

An early study of 534 urine samples found the Osmetech Microbial Analyser had good sensitivity and specificity (83.5% and 87.6%), compared to conventional culture, to detect bacteruria, defined as $\geq 10^5$ colony-forming units of one or more strains of bacteria per milliliter. Authors described the Analyser as promising for rapid screening of urine specimens to identify probable negatives (Aithithan, 2001).

A review of electronic nose technology found 20 of 25 patients with a diagnosis of urinary tract infection were correctly identified as positive. In addition, of 45 samples, with 14 having unknown urinary tract infection status, all but one of those 14 were correctly identified (Pavlou, 2002).

One review concludes that of the existing models, electronic noses and ion mobility spectrometry systems are still the most suitable candidates in the diagnosis of urinary tract infection, since they are easy to use, portable, relatively low-cost, and have methods which can be automated (Dospinescu, 2020).

A study of 84 urine samples that tested for 85 volatile organic compounds identified five isolates positively associated with *Escherichia coli*-resistant strains, and two with sensitive strains of urinary tract infections. The accuracy of identifying resistant and sensitive strains was 91.1% and 79.5%, respectively (Hewett, 2020).

A study of 39 samples (38 high-risk children) showed that urinary volatile organic compound analysis (electronic nose technology) correctly identified patients with and without urinary tract infection (P = .048; sensitivity/specificity 67% and 70%). Authors suggest this test could be used as an adjuvant to diagnose child urinary tract infection (Visser, 2020).

A study used thermal desorption-gas chromatography-mass spectrometry to 'smell' antibiotic-resistant bacteria in 18 bacterial isolates (*Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*). The isolates were grown with and without the presence of antibiotic. Nine and 22 compounds differed significantly between cephalexin and ciprofloxacin sensitive/resistant isolates, respectively ($P < .05$) (Smart, 2019).

Efficacy of volatile organic compounds varies by study. One review of 101 urine samples using ion mobility spectrometry-based electronic nose documented sensitivity of 95% and specificity of 97% (Roine, 2014). Other studies showed limited accuracy.

Volatile organic compounds have also been proposed as a diagnostic or screening tool for other conditions; the most commonly cited of these is cancer. The medical literature contains several large literature reviews on the efficacy and usefulness of volatile organic compounds for cancer. However, medical necessity is not established, due to limited studies, small study sizes, limited accuracy, and lack of standardization (Brusselmans, 2018; Catino, 2019; Oakley-Girvan, 2017; Zhou, 2020).

References

On September 20, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “electronic noses,” “spectroscopy,” “urinary tract infection,” and “volatile organic compounds.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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