Clinical Policy Bulletin: Analysis of Volatile Organic Compounds

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Policy

Aetna considers the analysis of volatile organic compounds experimental and investigational for the following indications (not an all-inclusive list) because the clinical effectiveness of this technique has not been established:

- Detection of bacteriuria
- Detection of cancer (e.g., breast cancer, colorectal cancer, lung cancer and cancer of the pleura, pancreatic cancer; not an all-inclusive list)
- Diagnosis of amyotrophic lateral sclerosis
- Diagnosis of autism spectrum disorders
- Diagnosis of inflammatory bowel disease
- Diagnosis of juvenile idiopathic arthritis
- Diagnosis of non-alcoholic fatty liver disease
- Differential diagnosis of breast diseases (e.g., breast cancer, cyclomastopathy, and mammary gland fibroma)
- Prediction of development of childhood obesity
- Use as markers for monitoring hemodialysis efficiency

Background

Urinary tract infections (UTIs) are a leading cause of morbidity and health care expenditures in persons of all ages. Individuals at increased risk include sexually active young women, the elderly and those undergoing genitourinary instrumentation or catheterization (Orenstein and Wong, 1999). The diagnosis of UTI may be made on the basis of clinical signs and symptoms in combination with
A urinalysis that reveals both bacteriuria and pyuria is considered clinically diagnostic of UTI. Traditionally, confirmatory cultures have been obtained to verify the infection and identify the specific organism(s) involved; however, this standard is evolving. If a culture is obtained, the presence of at least 100,000 colony-forming units (CFU) of bacteria on a voided specimen has classically been used as the culture-based definition of UTI. Lower colony counts (100 CFU or less) may be used to establish a clinical diagnosis in catheterized or aspirated specimens from symptomatic patients (Griebling, 2004).

Research directed towards rapid and early detection of UTI to exclude probable negatives have facilitated the development of sensor technology and the production of devices known as “electronic noses” that can detect and discriminate the production of volatile compounds from microbial infections in situ. Such qualitative and semi-quantitative approaches could play a significant role in the early diagnosis of microbial diseases. Using artificial intelligence and web-based knowledge systems, electronic noses might also have a valuable role in monitoring disease epidemiology (Turner and Magan, 2004).

Aathithan et al (2001) reported on the use of the Osmetech Microbial Analyzer (OMA) (Osmetech plc, Crewe, UK) for the analysis of bacteria in urine. The OMA is an automated headspace (the volume above the liquid sample) analyzer fitted with four polymer sensors that respond to different volatile organic compounds released from microorganisms in urine. The OMA technique is based on the principle that volatile compounds from bacteria are released and can then be detected by gas sensors. The detection of volatile organic compounds in urine by gas-liquid chromatography (GLC) was demonstrated by earlier investigators (Coloe, 1978; Manja and Rao, 1983; Hayward, 1983); however, these methods were only moderately successful in detecting infected and non-infected urine and did not develop into practical diagnostic tools. The OMA consists of a carousel where sample vials are kept at a constant temperature. A co-axial needle is automatically inserted through a sample vial septum and nitrogen gas at 50 % relative humidity is introduced above the surface of the urine via the inner lumen of the needle. The outer needle lumen allows the sample headspace to be delivered across a sensor array for 3 minutes at a flow rate of 60 ml/min. The sensor is then allowed to recover before humid nitrogen gas is passed over the sensor for a 4-min wash. The resistance of each of the polymer sensors is measured during the sampling period, and the change from the initial resistance is calculated. The needle is then removed; the carousel moves the next sample into position, and the process is repeated. The system is computer-controlled, and data are captured on to a computer hard disk. The authors compared the effectiveness of the OMA with standard culture results on 534 urine samples. When bacteriuria was defined as 100,000 CFU/ml, the sensitivity and specificity of the OMA device were reported as 84 % and 88 %, respectively. When bacteriuria was defined as 10,000 CFU/ml, the sensitivity fell and the specificity rose, 72 % and 89 %, respectively.

Aathithan and colleagues (2001) concluded that the OMA shows promise as an automated system for the rapid routine screening of urine specimens; however, the following limitations were reported: (i) it was unclear which of the volatile compounds in the headspace the instrument was responding to; therefore, the present sensors may not be optimized for urine analysis; (ii) the detection of volatile compounds is limited by the present array of sensors; therefore, other
significant volatile compounds could be missed; (iii) bacterial volatile products could be lost, either by adsorption onto urinary cells or protein or by dissipation during delays between specimen collection and analysis; (iv) some bacterial species may not produce volatile compounds; and (v) processing speed is limited by the need for the sensors to recover after each sample. The authors reported that clinical trials with more-refined versions of the instrument are in progress.

The Osmetch Microbial Analyserä - Urinary Tract Infection Detector (OMAä-UTI) (Osmetech plc, Crewe, UK) received 510(k) pre-marketing clearance from the U.S. Food and Drug Administration (FDA) in 2001. The OMA is intended for use by clinical laboratories as an aid to diagnosis UTI. According to the 510(k) summary, the OMA-UTI was compared to an existing device, the Uriscreenä (Diatech Diagnostics, Inc.), to establish substantial equivalence. Urine results with the OMA-UTI were compared to standard culture (a positive culture was defined as 100,000 CFU/ml) in 1,038 urine samples. The sensitivity and specificity of the OMA-UTI were reported as 81.0 % and 83.1 %, respectively. The FDA determined the performance of the OMA-UTI compared favorably with the Uriscreen, which reported a sensitivity of 95 % and specificity of 73 % when compared to standard culture. However, the manufacturer was not required to submit to the FDA the evidence of efficacy that is necessary to support a premarket approval application (PMA).

The analysis of volatile organic compounds in urine to detect bacteria is promising (Aathithan et al, 2001; Pavlou et al, 2002); however, there is inadequate evidence of the clinical effectiveness of this technique. Clinical outcome studies published in the peer-reviewed medical literature are necessary to determine the clinical value of the analysis of volatile organic compounds in urine.

The Work Loss Data Institute's guideline on “Lung cancer and cancer of the pleura: Pulmonary (acute & chronic)” (2013) stated that “Other surveillance techniques include sputum analyses for biomarkers, the presence of volatile organic compounds in the exhaled air, and screens for deoxyribonucleic acid (DNA) alterations. The value of these tests is undergoing research at the current time and their use cannot be recommended”.

Yuan et al (2014) stated that exposures to polycyclic aromatic hydrocarbons (PAHs) from various environmental and occupational sources are considered a primary risk factor for lung cancer among lifelong never smokers, based largely on results from epidemiologic studies utilizing self-reported exposure information. Prospective, biomarker-based human studies on the role of PAH and other airborne carcinogens in the development of lung cancer among lifelong non-smokers have been lacking. These researchers prospectively investigated levels of urinary metabolites of a PAH and volatile organic compounds (VOCs) in relation to lung cancer risk in a nested case-control study of 82 cases and 83 controls among lifelong never smokers of the Shanghai Cohort Study, a prospective cohort of 18,244 Chinese men aged 45 to 64 years at enrollment. These investigators quantified 3 PAH metabolites: r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT), 3-hydroxyphenanthrene (3-OH-Phe) and total hydroxyphenanthrenes (total OH-Phe, the sum of 1-, 2-, 3- and 4-OH-Phe), as well as metabolites of the VOCs acrolein (3-hydroxypropyl mercapturic acid), benzene (S-phenyl mercapturic acid), crotonaldehyde (3-hydroxy-1-
methylpropylmercapturic acid) and ethylene oxide (2-hydroxyethyl mercapturic acid). Urinary cotinine was also quantified to confirm non-smoking status. Compared with the lowest quartile, odds ratios (95 % confidence intervals [CI]) for lung cancer risk for the highest quartile levels of PheT, 3-OH-Phe and total OH-Phe were 2.98 (1.13 to 7.87), 3.10 (1.12 to 7.75) and 2.59 (1.01 to 6.65) (all p trend < 0.05), respectively. The authors concluded that none of the metabolites of the VOCs were associated with overall lung cancer risk.

Jiang et al (2014) stated that amyotrophic lateral sclerosis (ALS) is a rapid progressive motor neuron disease. Currently, there are no specific or reliable biomarkers for the diagnosis of this disease, and there are no effective medical treatments. The early diagnosis and treatment of this disease has the potential to prolong the survival of ALS patients, but typically, approximately 1 year passes between the onset of symptoms and the diagnosis of this disease. Thus, there is an urgent need to find specific biomarkers to enable early diagnosis and therapeutic intervention in this disease. Analyzing the VOCs present in the blood and exhaled breath is a useful and convenient approach for investigating potential biomarkers. These investigators examined the VOCs present in blood samples from copper zinc superoxide dismutase 1 (SOD1) glycine to alanine mutation at position 93 (G93A) mice to determine whether a specific biomarker pattern exists in these transgenic mice. Blood samples from ALS mice and their age-matched littermates were analyzed using gas chromatography-mass spectrometry. A total of 12 independent compounds associated with oxidative stress were identified at the early stage of disease. The data showed that there is a specific pattern of blood VOCs in ALS mice that could potentially be used as biomarkers that could improve the diagnosis of this disease. Furthermore, these compounds could also potentially be used to monitor the response to neuro-protective agents and to better understand the underlying mechanisms of ALS.

Cozzolino and colleagues (2014) stated that autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders which have a severe life-long effect on behavior and social functioning, and which are associated with metabolic abnormalities. Their diagnosis is on the basis of behavioral and developmental signs usually detected before 3 years of age, and there is no reliable biological marker. The objective of this study was to establish the volatile urinary metabolomic profiles of 24 autistic children and 21 healthy children (control group) to investigate VOCs as potential biomarkers for ASDs. Solid-phase micro-extraction (SPME) using DVB/CAR/PDMS sorbent coupled with gas chromatography-mass spectrometry was used to obtain the metabolomic information patterns. Urine samples were analyzed under both acid and alkaline pH, to profile a range of urinary components with different physicochemical properties. Multi-variate statistics techniques were applied to bio-analytical data to visualize clusters of cases and to detect the VOCs able to differentiate autistic patients from healthy children. In particular, orthogonal projections to latent structures discriminant analysis (OPLS-DA) achieved very good separation between autistic and control groups under both acidic and alkaline pH, identifying discriminating metabolites. Among these, 3-methyl-cyclopentanone, 3-methylbutanal, 2-methyl-butanal, and hexane under acid conditions, and 2-methyl-pyrazine, 2,3-dimethyl-pyrazine, and isoxazolo under alkaline pH had statistically higher levels in urine samples from autistic children than from the control group. The authors concluded that further investigation with a higher number of patients
should be performed to outline the metabolic origins of these variables, define a possible association with ASDs, and verify the usefulness of these variables for early-stage diagnosis.

Wang et al (2014a) stated that the association between cancer and volatile organic metabolites in exhaled breaths has attracted increasing attention from researchers. These researchers reported on a systematic study of gas profiles of metabolites in human exhaled breath by pattern recognition methods. Exhaled breath was collected from 85 patients with histologically confirmed breast disease (including 39 individuals with infiltrating ductal carcinoma, 25 individuals with cyclomastopathy and from 21 individuals with mammary gland fibroma) and 45 healthy volunteers. Principal component analysis and partial least squares discriminant analysis were used to process the final data. The volatile organic metabolites exhibited significant differences between breast cancer and normal controls, breast cancer and cyclomastopathy, and breast cancer and mammary gland fibroma; 21, 6, and 8 characteristic metabolites played decisive roles in sample classification, respectively (p < 0.05). Three volatile organic metabolites in the exhaled air, 2,5,6-trimethyloctane, 1,4-dimethoxy-2,3-butanediol, and cyclohexanone, distinguished breast cancer patients from healthy individuals, mammary gland fibroma patients, and patients with cyclomastopathy (p < 0.05).

The authors concluded that the identified 3 volatile organic metabolites associated with breast cancer may serve as novel diagnostic biomarkers.

Wang et al (2014b) noted that many recent studies have focused on the connection between the composition of specific VOCs in exhaled breath and various forms of cancer. However, the composition of exhaled breath is affected by many factors, such as lung disease, smoking, and diet. Volatile organic compounds are released into the bloodstream before they are exhaled; therefore, the analysis of VOCs in blood will provide more accurate results than the analysis of VOCs in exhaled breath. Blood were collected from 16 colorectal cancer (CRC) patients and 20 healthy controls, then solid phase micro-extraction- chromatography-mass spectrometry (SPME-GC-MS) was used to analysis the exhaled VOCs. The statistical methods principal component analysis (PCA) and partial least-squares discriminant analysis (PLSDA) were performed to deal with the final dates. Three metabolic biomarkers were found at significantly lower levels in the group of CRC patients than in the normal control group (P<0.01): phenyl methylcarbamate, ethylhexanol, and 6-t-butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne. In addition, significantly higher levels of 1,1,4,4-tetramethyl-2,5-dimethylene-cyclohexane were found in the group of CRC patients than in the normal control group (p < 0.05). Compared with healthy individuals, patients with CRC exhibited a distinct blood metabolic profile with respect to VOCs. The authors concluded that the analysis of blood VOCs appears to have potential clinical applications for CRC screening.

Alkhouri and colleagues (2014a) examined the association of breath VOCs with the diagnosis of non-alcoholic fatty liver disease (NAFLD) in children. Patients were screened with an ultrasound of the abdomen to evaluate for NAFLD. Exhaled breath was collected and analyzed per protocol using selective ion flow tube mass spectrometry (SIFT-MS). A total of 60 patients were included in the study (37 with NAFLD and 23 with normal liver). All children were over-weight or obese. The mean age was 14.1±2.8 years and 50 % were female. A comparison
of the SIFT-MS results of patients with NAFLD with those with normal liver on ultrasound revealed differences in concentration of more than 15 compounds. A panel of 4 volatile organic compounds can identify the presence of NAFLD with good accuracy (area under the receiver operating characteristic curve [AUC] of 0.913 in the training set and 0.763 in the validation set). Breath isoprene, acetone, trimethylamine, acetaldehyde, and pentane were significantly higher in the NAFLD group compared with normal liver group (14.7 ppb versus 8.9 for isoprene; 71.7 versus 36.9 for acetone; 5.0 versus 3.2 for trimethylamine; 35.1 versus 26.0 for acetaldehyde; and 13.3 versus 8.8 for pentane, p < 0.05 for all). The authors concluded that exhaled breath analysis is a promising non-invasive method to detect fatty liver in children. Isoprene, acetone, trimethylamine, acetaldehyde, and pentane are novel biomarkers that may help to gain insight into pathophysiological processes leading to the development of NAFLD.

Alkhouri and associates (2014b) investigated changes in VOCs in exhaled breath in over-weight/obese children compared with their lean counterparts. Single exhaled breath was collected and analyzed per protocol using SIFT-MS. A total of 60 over-weight/obese children and 55 lean controls were included. Compared with the lean group, the obese group was significantly older (14.1 ± 2.8 versus 12.1 ± 3.0 years), taller (164.8 ± 10.9 versus 153.3 ± 17.1 cm) and more likely to be Caucasian (60 % versus 35.2 %); p < 0.05 for all. A comparison of the SIFT-MS results of the obese group with the lean group revealed differences in concentration of more than 50 compounds. A panel of 4 VOCs can identify the presence of over-weight/obesity with excellent accuracy. Further analysis revealed that breath isoprene, 1-decene, 1-octene, ammonia and hydrogen sulfide were significantly higher in the obese group compared with the lean group (p < 0.01 for all). The authors concluded that obese children have a unique pattern of exhaled VOCs. They stated that changes in VOCs observed in this study may help to gain insight into pathophysiological processes and pathways leading to the development of childhood obesity.

In a prospective cross-sectional, single-center study, Zeft et al (2014) analyzed exhaled VOCs to evaluate for the presence of a unique breath pattern to differentiate pediatric patients with juvenile idiopathic arthritis (JIA) from healthy controls. This study included pediatric JIA patients and healthy controls (age range of 5 to 21 years). The diagnosis of JIA was determined using standard clinical criteria. Exhaled breath was collected and analyzed using SIFT-MS to identify new markers of JIA. A total of 76 patients were included in the study (21 with JIA and 55 healthy controls). Juvenile idiopathic arthritis phenotype was as follows: 12 polyarticular RF-negative, 2 persistent oligoarticular, 4 extended oligoarticular, 2 psoriatic, and 1 enthesitis-related arthritis. Routinely analyzed VOCs for SIFT-MS quantification showed significant differences in 13 VOCs peaked between JIA patients and healthy controls. Discriminant analysis via step-wise variable selection of mass scanning ion peak data demonstrated that 4 VOCs can classify patients with JIA or as healthy controls with only 3 mis-classifications; p < 0.001. Further analysis revealed that breath 1-decene, 1-octene, and 3-methyhexane (all markers of oxidative stress) were significantly higher in the JIA group compared to controls (11.5 ± 6.7 ppb versus 2.1 ± 0.2 for 1-decene; 10.5 ± 2.2 versus 4.5 ± 0.7 for 1-octene; and 17.5 ± 3.7 versus 10.4 ± 1.4 for 3-methyhexane, p value < 0.001 for all). The authors concluded that exhaled breath analysis is a promising non-invasive method to distinguish children with JIA from...
healthy children. These researchers provided pilot data to support the hypothesis that a unique breath-print can be demonstrated for JIA in the exhaled metabolome.

Dawiskiba et al (2014) evaluated the utility of serum and urine metabolomic analysis in diagnosing and monitoring of inflammatory bowel diseases (IBD). Serum and urine samples were collected from 24 patients with ulcerative colitis (UC), 19 patients with the Crohn's disease (CD) and 17 healthy controls. The activity of UC was assessed with the Simple Clinical Colitis Activity Index, while the activity of CD was determined using the Harvey-Bradshaw Index. The analysis of serum and urine samples was performed using proton nuclear magnetic resonance (NMR) spectroscopy. All spectra were exported to Matlab for preprocessing which resulted in 2 data matrixes for serum and urine. Prior to the chemometric analysis, both data sets were unit variance scaled. The differences in metabolite finger-prints were assessed using partial least-squares-discriminant analysis (PLS-DA). Receiver operating characteristic curves and area under curves were used to evaluate the quality and prediction performance of the obtained PLS-DA models. Metabolites responsible for separation in models were tested using STATISTICA 10 with the Mann-Whitney-Wilcoxon test and the Student's t test ($\alpha = 0.05$). The comparison between the group of patients with active IBD and the group with IBD in remission provided good PLS-DA models (p value 0.002 for serum and 0.003 for urine). The metabolites that allowed distinction of these groups were: N-acetylated compounds and phenylalanine (up-regulated in serum), low-density lipoproteins and very low-density lipoproteins (decreased in serum) as well as glycine (increased in urine) and acetoacetate (decreased in urine). The significant differences in metabolic profiles were also found between the group of patients with active IBD and healthy control subjects providing the PLS-DA models with a very good separation (p value < 0.001 for serum and 0.003 for urine). The metabolites that were found to be the strongest biomarkers included in this case: leucine, isoleucine, 3-hydroxybutyric acid, N-acetylated compounds, acetoacetate, glycine, phenylalanine and lactate (increased in serum), creatine, dimethyl sulfone, histidine, choline and its derivatives (decreased in serum), as well as citrate, hippurate, trigonelline, taurine, succinate and 2-hydroxisobutyrate (decreased in urine). No clear separation in PLS-DA models was found between CD and UC patients based on the analysis of serum and urine samples, although 1 metabolite (formate) in uni-variate statistical analysis was significantly lower in serum of patients with active CD, and 2 metabolites (alanine and N-acetylated compounds) were significantly higher in serum of patients with CD when comparing jointly patients in the remission and active phase of the diseases. Contrary to the results obtained from the serum samples, the analysis of urine samples allowed to distinguish patients with IBD in remission from healthy control subjects. The metabolites of importance included in this case up-regulated acetoacetate and down-regulated citrate, hippurate, taurine, succinate, glycine, alanine and formate. The authors concluded that NMR -based metabolomic finger-printing of serum and urine has the potential to be a useful tool in distinguishing patients with active IBD from those in remission.

Patel et al (2014) stated that breath testing is becoming an important diagnostic method to evaluate many disease states. In the light of rising healthcare costs, it is important to develop a simple non-invasive tool to potentially identify pediatric patients who need endoscopy for IBD. In a pilot study, these researchers analyzed exhaled VOCs and investigated the presence of a unique breath patterns
to differentiate pediatric patients with IBD from healthy controls. This single-center study included pediatric IBD patients and healthy controls (age range of 5 to 21 years). The diagnosis of IBD was confirmed by endoscopic, histological and radiographic data. Exhaled breath was collected and analyzed using SIFT-MS to identify new markers or patterns of IBD. A total of 117 patients (62 with IBD and 55 healthy controls) were included in the study. Linear discriminant analysis and principle component analysis of mass scanning ion peak data demonstrated 21 pre-selected VOCs correctly classify patients with IBD or as healthy controls; p < 0.0001. Multi-variable logistic regression analysis further showed 3 specific VOCs (1-octene, 1-decene, (E)-2-nonene) had excellent accuracy for predicting the presence of IBD with an AUC of 0.96 (95 % confidence interval [CI]: 0.93 to 0.99). No significant difference in VOCs was found between patients with CD or UC, and no significant correlation was seen with disease activity. The authors concluded that these pilot data supported the hypothesis that a unique breath-print potentially exists for pediatric IBD in the exhaled metabolome.

In a prospective, cross-sectional study, Navaneethan et al (2014) identified potential VOCs in the headspaces (gas above the sample) of bile in patients with malignant biliary strictures from pancreatic cancer. Bile was aspirated in 96 patients undergoing ERCP for benign and malignant conditions. Selected ion flow tube mass spectrometry (VOICE200R SIFT-MS instrument; Syft Technologies Ltd, Christchurch, New Zealand) was used to analyze the headspace and to build a predictive model for pancreatic cancer. The headspaces from 96 bile samples were analyzed, including 24 from patients with pancreatic cancer and 72 from patients with benign biliary conditions. The concentrations of 6 compounds (acetaldehyde, acetone, benzene, carbon disulfide, pentane, and trimethylamine [TMA]) were increased in patients with pancreatic cancer compared with controls (p < 0.05). By using receiver-operating characteristic curve analysis, these researchers developed a model for the diagnosis of pancreatic cancer based on the levels of TMA, acetone, isoprene, dimethyl sulfide, and acetaldehyde. The model \[10.94 + 1.8229 \times \log \text{(acetaldehyde)} + 0.7600 \times \log \text{(acetone)} - 1.1746 \times \log \text{(dimethyl sulfide)} + 1.0901 \times \log \text{(isoprene)} - 2.1401 \times \log \text{(trimethylamine)} \text{ greater than or equal to 10} \] identified the patients with pancreatic cancer (AUC = 0.85), with 83.3 % sensitivity and 81.9 % specificity. The authors concluded that measurement of biliary fluid VOCs may help to distinguish malignant from benign biliary strictures. Moreover, they stated that further studies are needed to validate these observations.

Queralto et al (2014) noted that cancer diagnosis is typically delayed to the late stages of disease due to the asymptomatic nature of cancer in its early stages. Cancer screening offers the promise of early cancer detection, but most conventional diagnostic methods are invasive and remain ineffective at early detection. Breath analysis is, however, non-invasive and has the potential to detect cancer at an earlier stage by analyzing volatile biomarkers in exhaled breath. These researchers summarized breath sampling techniques and recent developments of various array-based sensor technologies for breath analysis. Significant advancements were made by a number of different research groups in the development of nanomaterial-based sensor arrays, and the ability to accurately distinguish cancer patients from healthy controls based on VOCs in exhaled breath has been demonstrated. Optical sensors based on colorimetric sensor array technology were also discussed, where preliminary clinical studies...
suggested that metabolic VOC profiles could be used to accurately diagnose various forms of lung cancer. The authors concluded that recent studies have demonstrated the potential of using metabolic VOCs for cancer detection, but further standardization and validation is needed before breath analysis can be widely adopted as a clinically useful tool.

Mochalski et al (2014) noted that monitoring VOCs in exhaled breath shows great potential as a non-invasive method for assessing hemodialysis efficiency. These researchers identified and quantified a wide range of VOCs characterizing uremic breath and blood, with a particular focus on species responding to the dialysis treatment. Gas chromatography with mass spectrometric detection coupled with SPME as pre-concentration method. A total of 60 VOCs were reliably identified and quantified in blood and breath of patients with chronic kidney disease. Excluding contaminants, 6 compounds (isoprene, dimethyl sulfide, methyl propyl sulfide, allyl methyl sulfide, thiophene and benzene) changed their blood and breath levels during the hemodialysis treatment. The authors concluded that uremic breath and blood patterns were found to be notably affected by the contaminants from the extracorporeal circuits and hospital room air. Consequently, patient exposure to a wide spectrum of volatile species (hydrocarbons, aldehydes, ketones, aromatics, heterocyclic compounds) is expected during hemodialysis. Whereas highly volatile pollutants were relatively quickly removed from blood by exhalation, more soluble ones were retained and contributed to the uremic syndrome. At least 2 of the species observed (cyclohexanone and 2-propenal) are uremic toxins. Perhaps other volatile substances reported within this study may be toxic and have negative impact on human body functions. They stated that further studies are needed to investigate if VOCs responding to HD treatment could be used as markers for monitoring hemodialysis efficiency.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes not covered for indications listed in the CPB:

0041T

Other ICD-9 codes related to the CPB:

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
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<tbody>
<tr>
<td>041.00 -</td>
<td>Bacterial infection in conditions classified elsewhere and of unspecified site</td>
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<tr>
<td>041.9</td>
<td>Bacterial infection in conditions classified elsewhere and of unspecified site</td>
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<td>V72.6</td>
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The above policy is based on the following references:


