Measurement of Thomboxane Metabolites for ASA Resistance AHS – G2107

File Name: measurement_of_thromboxane_metabolites_for_asa_resistance
Origination: 01/01/2019
Last CAP Review: 07/2019
Next CAP Review: 07/2020
Last Review: 12/2019

Description of Procedure or Service
Thromboxane (TXA2) is a prostaglandin metabolite that causes platelet aggregation and vasoconstriction (Lopez, et al, 2014). Aspirin (ASA) is an acetylated salicylate and is classified as a nonsteroidal anti-inflammatory medication (Abramson, 2017). Aspirin resistance is the inability of aspirin to decrease platelet production of thromboxane A2 and thereby platelet activation and aggregation.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
Measurement of thromboxane metabolites in urine (e.g. AspirinWorks) to evaluate aspirin resistance is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

When Measurement of Thomboxane Metabolites for ASA Resistance is covered
N/A

When Measurement of Thomboxane Metabolites for ASA Resistance is not covered
The measurement of thromboxane metabolites in urine (e.g. AspirinWorks) to evaluate aspirin resistance is considered investigational.

Policy Guidelines
Background
Aspirin acts primarily by interfering with the biosynthesis of cyclic prostanoids, including thromboxane. It irreversibly inhibits COX-1, resulting a decrease in production of thromboxane.
Measurement of Thomboxane Metabolites for ASA Resistance AHS – G2107

This results in an antithrombotic effect (Altman, 2004). Low doses of aspirin (typically 75 to 81 mg/day) are sufficient to inhibit platelet production (Abramson, 2017), and is indicated for the primary and secondary prevention of cardiovascular disease (Zehnder, et al., 2017).

Numerous studies show that aspirin resistance affects 15% to 25% of individuals (Alberts, 2010). A systematic review and meta-analysis on aspirin resistance indicated that patients who are resistant to aspirin are at a greater risk (odds ratio [OR]: 3.85) of clinically important cardiovascular morbidity than patients who are sensitive to aspirin (Krasopoulos et al., 2008). The effect of aspirin administration varies considerably among patients at high risk for cardiovascular events. Gum and coworkers (2001) found insufficient inhibition of platelet aggregation by aspirin in 6 to 24 percent of patients with stable coronary artery disease, while other estimates range from 5 to 60 percent (Martin and Talbert, 2005).

Many biochemical tests and several commercially available products have been developed to detect aspirin resistance. Tests used in research laboratories are aggregometry (turbidometric and impedance), tests based on activation-dependent changes in platelet surface, and tests based on activation-dependent release from platelets. Point-of-care tests include PFA-100, IMPACT, and VerifyNow, which can detect platelet dysfunction that may be due to aspirin effect.

It has been proposed that aspirin resistance can also be detected by thromboxane metabolites in urine. Aspirin inhibits platelet activation through the permanent inactivation of the cyclooxygenase (COX) activity of prostaglandin H synthase-1 (referred to as COX-1), and consequently inhibits the biosynthesis of thromboxane A2 (TXA2), a platelet agonist. The urinary concentrations of the metabolite 11-dehydrothromboxane B2(11 dhTxB2) indicate the level of TXA2 generation.

The AspirinWorks Test Kit is an enzyme-linked immunoassay test that can be used to determine levels of 11 dhTxB2 in human urine (Geske, Guyer, & Ens, 2008). The AspirinWorks Test Kit was compared to the Accurnetrics VerifyNow Aspirin Assay as the predicate device. The manual AspirinWorks Test Kit measures urinary 11 dhTxB2, a metabolite of TXA2, a direct inducer of platelet aggregation, while the automated Accurnetrics VerifyNow Aspirin Assay is a turbidimetric-based optical detection system, which measures platelet-induced aggregation in whole blood. Both analyze aspirin's effect through the reduction of TXA2 production or the resulting inhibition of platelet aggregation.

A major limitation of this test is that while serum TxB2 comes primarily from platelets, urinary 11dhTxB2 is not a specific measure of platelet thromboxane formation. Urine 11dhTxB2 reflects systemic thromboxane formation, and up to 30% or more can derive from extra-platelet sources, including monocytes, macrophages, atherosclerotic plaque, and other tissues that contain nucleated cells capable of regenerating functional COX-1, or that contain COX-2 (Smock & Rodgers, 2010).

**Clinical Validity and Utility**

Eikelboom et al. (2002) studied whether aspirin resistance, defined as failure of suppression of thromboxane generation, increases the risk of cardiovascular events in a high-risk population. The authors concluded that in aspirin-treated patients, urinary concentrations of 11 dhTxB2 predict the future risk of myocardial infarction or cardiovascular death and that these findings raise the possibility that elevated urinary 11 dhTxB2 levels identify patients who are relatively resistant to aspirin and who may benefit from additional anti-platelet therapies or treatments that more effectively block in vivo thromboxane production or activity.

However, Altman et al. (2004) reviewed this study and stated that the authors support the view that failure to suppress thromboxane generation defines aspirin resistance and that this hypothesis assumes a direct association between the rise of urinary 11 dhTxB2 levels and increment of
Measurement of Thromboxane Metabolites for ASA Resistance AHS – G2107

vascular events (e.g., myocardial infarction, stroke and cardiovascular death). Altman and colleagues explained that failure of aspirin to produce the expected inhibition of platelet function might be attributed to several mechanisms and that it can not be defined by the level of serum thromboxane or its urinary metabolites because these measurements do not correlate with the reduction of inhibition of platelet aggregation in response to multiple stimuli.

Results from 2 different clinical studies established a cutoff for aspirin effect at less than 1500 pg 11d hTxB2/mg creatinine. Further analysis revealed that 180/204 (88.2 percent) of samples from individuals not taking aspirin were above the cut-off value. Analysis of samples from individuals taking various doses of aspirin revealed that 7/163 (4.3 percent) of 81 mg/day aspirin users indicated a lack of aspirin effect (greater than 1500 pg 11d hTxB2/mg creatinine) and 4/38 (10.5 percent) of the 325 mg/day aspirin users indicated a lack of aspirin effect. In total, 11/201 (5.5 percent) of all aspirin users tested indicated a lack of aspirin effect.

Lordkipanidze et al. (2007) compared the results obtained from six major platelet function tests in the assessment of the prevalence of aspirin resistance in patients with stable coronary artery disease. 201 patients with stable coronary artery disease receiving daily aspirin therapy (80 mg or more) were recruited. Platelet aggregation was measured by: (i) light transmission aggregometry (LTA) after stimulation with 1.6 mM of arachidonic acid (AA), (ii) LTA after adenosine diphosphate (ADP) (5, 10, and 20 microM) stimulation, (iii) whole blood aggregometry, (iv) PFA-100, (v) VerifyNow Aspirin; urinary 11d hTxB2 concentrations were also measured. Eight patients (4%) were deemed resistant to aspirin by LTA and AA. The prevalence of aspirin resistance varied according to the assay used. Results from these tests showed poor correlation and agreement between themselves. The authors concluded that “platelet function tests are not equally effective in measuring aspirin’s anti-platelet effect and correlate poorly amongst themselves and that the clinical usefulness of the different assays to classify correctly patients as aspirin resistant remains undetermined.”

Dretzke et al (2015) examined “whether or not insufficient platelet function inhibition by aspirin (‘aspirin resistance’), as defined using platelet function tests (PFTs), is linked to the occurrence of adverse clinical outcomes, and further, whether or not patients at risk of future adverse clinical events can be identified through PFTs.” The authors found that “Results indicated that some PFTs may have some prognostic utility, i.e. a trend for more clinical events to be associated with groups classified as ‘aspirin resistant’. Methodological and clinical heterogeneity prevented a quantitative summary of prognostic effect. Study-level effect sizes were generally small and absolute outcome risk was not substantially different between ‘aspirin resistant’ and ‘aspirin sensitive’ designations. No studies on the cost-effectiveness of PFTs for ‘aspirin resistance’ were identified.” The authors concluded that “Although evidence indicates that some PFTs may have some prognostic value, methodological and clinical heterogeneity between studies and different approaches to analyses create confusion and inconsistency in prognostic results, and prevented a quantitative summary of their prognostic effect.”

Wang et al (2018) evaluated the association between stable urine metabolites of thromboxane (TxA2-M) and prostacyclin (PGI2-M), circulating levels of cellular adhesion molecules (CAMs: E-selectin, P-selectin), chemokines and C-reactive protein, and the incidence of major adverse cardiovascular events (MACE) in 120 patients with stable ASCVD on aspirin therapy. Urinary TxA2-M levels were significantly correlated with circulating P-selectin (r = 0.319, p < 0.001) and E-selectin (r = 0.245, p = 0.007) levels, and associated with higher risk of MACE (p = 0.043). In contrast, PGI2-M levels were not significantly associated with CAM levels or MACE. These results provide insight into the contribution of TxA2 biosynthesis to ASCVD progression in humans, and suggest that patients with elevated TxA2-M levels may be predisposed to advanced platelet and endothelial activation and higher risk of adverse cardiovascular outcomes.
Measurement of Thomboxane Metabolites for ASA Resistance AHS – G2107

Harrison et al (Harrison et al., 2018) compared 9 platelet function tests to assess responsiveness to three ASA dosing regimens in 24 T2D patients randomized in a three-treatment crossover design to ASA 100 mg/day, 200 mg/day, or 100 mg twice daily for 2-week treatment periods. They found that all cyclo-oxygenase (COX-1)-dependent tests and some COX-1-independent tests (PFA-CEPI, LTA-ADP) demonstrated significant reductions in platelet reactivity with all ASA doses. Two COX-1-independent tests (WBA-ADP and PFA-CADP) showed no overall reduction in platelet reactivity. Overall classifications for detecting all ASA doses, compared to baseline, were as follows: very good–LTA-AA ($k = 0.95$) and VerifyNow™-ASA ($k = 0.85$); good–serum TxB$_2$ ($k = 0.79$); moderate–LTA-ADP ($k = 0.59$), PFA-100™-CEPI ($k = 0.56$), urinary TxB$_2$ ($k = 0.55$), WBA-AA ($k = 0.47$); and poor–PFA-100™-CADP ($k = -0.02$) and WBA-ADP ($k = -0.07$). No significant kappa statistic differences were seen for each test for each ASA dose. Correlations for each test with serum TxB$_2$ measurements were as follows: very good–VerifyNow™-ASA ($k = 0.81$, $R^2 = 0.56$) and LTA-AA ($k = 0.85$, $R^2 = 0.65$); good–PFA-100™-CEPI ($k = 0.62$, $R^2 = 0.30$); moderate–urinary TxB$_2$ ($k = 0.57$, $R^2 = 0.51$) and LTA-ADP ($k = 0.47$, $R^2 = 0.56$); fair–WBA-AA ($k = 0.31$, $R^2 = 0.31$); and poor–PFA-100™-CADP ($k = 0.04$, $R^2 = 0.003$) and WBA-ADP ($k = -0.04$, $R^2 = 0.0005$). The platelet function tests we assessed were not equally effective in measuring the antiplatelet effect of ASA and correlated poorly amongst themselves, but COX-1-dependent tests performed better than non-COX-1-dependent tests.

Applicable Federal Regulations

AspirinWorks received 510(k) marketing clearance from the FDA in May, 2007 and is intended to aid in the qualitative detection of aspirin in apparently healthy individuals post ingestion.

Guidelines and Recommendations

UpToDate

In a review on nonresponse and resistance to Aspirin, Zehnder et al (Zehnder, Tantry, & Gurbel, 2017) stated that “different laboratory methods for detecting "aspirin resistance" correlate poorly with one another, if at all, suggesting that they are sensitive to different parameters of ex vivo platelet function, including pre-existing platelet hyperreactivity. This variability has been shown in normal volunteers as well as in patients with coronary artery.” Regarding screening, the authors stated that they “do not recommend routine testing of patients for aspirin resistance/nonresponsiveness. Aspirin nonresponsiveness is rare in compliant patients and is not strongly associated with clinical outcomes in published studies.”

International Society on Thrombosis and Haemostasis

The Working Group on Aspirin Resistance (Michelson et al., 2005) published a position paper which concluded that other than in research trials it is not appropriate to test for aspirin resistance or change therapy based on such tests. There are no published studies which address the clinical effectiveness or data linking aspirin dependent laboratory test to clinical outcomes in patients.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

**Applicable service codes: 84431**

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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Lip, Gregory Y H. A contemporary viewpoint on 'aspirin resistance'. Annals of Medicine. 3/1/2012

Measurement of Thomboxane Metabolites for ASA Resistance AHS – G2107


Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

**Policy Implementation/Update Information**

1/1/2019 New policy developed. BCBSNC will not provide coverage for the measurement of thromboxane metabolites in urine (e.g. AspirinWorks) to evaluate aspirin resistance because it is investigational. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)


12/10/2019 Reviewed by Avalon 3rd Quarter 2019 CAB. Added code 82750 to Coding/Billing section; no other changes to policy. Medical Director review 12/2019. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.