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ARTICLE

Failure of chelator-provoked urine testing results to predict heavy metal toxicity in a prospective cohort of patients referred for medical toxicology evaluation

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ABSTRACT

Introduction: Provoked urine testing (PUT), involving chelating agent administration prior to measuring urine metal excretion levels, is used by some alternative health care practitioners to diagnose patients with heavy metal poisoning. Multiple medical societies have advised against this practice due to its presumed unreliability, expense, and lack of validation. However, no prospective study of the predictive value of PUT for heavy metal poisoning has been undertaken.

Methods: This study utilized the Toxicology Consortium's prospective case registry to evaluate the reliability of PUT for diagnosing heavy metal poisoning. Inclusion criteria were toxicology clinic patients with PUT results who were subsequently evaluated by a board-certified medical toxicologist and had a determination made regarding whether their signs and symptoms were likely related or unrelated to toxicologic exposures. The primary outcome was the positive predictive value of PUT for heavy metal toxicity as diagnosed by the evaluating medical toxicologist. Patients presenting to participating toxicology clinics without PUT served as a comparison group.

Results: 74 of 106 cases presenting with PUT results met inclusion criteria and were analyzed. 15 cases were determined by the examining toxicologist to be likely related to a toxicologic exposure. Only three cases were found to be related to heavy metal exposure, giving a positive predictive value of 4.3%. 20.2% of patients with PUT were found to have signs or symptoms related to any toxicologic exposure, compared to 14.3% of clinic patients without PUT. Demographics of toxicology clinic patients with and without PUT results were not significantly different except for age.

Discussion: Our results provide empiric support that PUT is an inaccurate predictor of a diagnosis of heavy metal poisoning by a board-certified medical toxicologist. Given the inability to properly interpret PUT results along with the increased cost burden and risk of false positives, PUT should not be performed.

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Introduction

Provoked urine testing (PUT) describes a diagnostic procedure in which a patient suspected of heavy metal poisoning is first administered a chelating agent and subsequently provides a urine sample that is quantitatively assayed for urinary metal concentrations [1]. However, because of the absence of validation of this type of testing, PUT is not utilized by most medical practitioners, including medical toxicologists.

There are several theoretical and practical concerns regarding PUT. First, post-chelation urine collections are generally done for substantially fewer than 24 h, meaning that when the results are expressed as metal concentrations per gram of urinary creatinine, this can result in inflated values because the effect of chelators is maximal in the first several hours after their time of administration [1–4]. Second, there are no validated reference ranges for chelated urines, and the results of PUT are often inappropriately compared to unprovoked norms. This can create false-positive results, as chelators will increase urinary metal concentrations irrespective of exposure status [1–9]. Third, most often PUT involves determining more than 20 metal levels simultaneously, thus increasing the statistical likelihood of producing an abnormal result based solely upon chance [1,10–13]. Finally, the use of PUT may have adverse effects on the patient because of the significant cost burden, positive results setting off unnecessary cascades of further testing, potential allergic reactions to the administered chelator, increased patient anxiety, and potential false diagnoses [5,7,14–17].

The American College of Medical Toxicology has therefore issued a formal position statement concluding that the evidence does not support the use of PUT for the diagnosis of heavy metal poisoning [11]. This position is also promulgated by the American Board of Internal Medicine's Choosing Wisely campaign [18]. Several published commentaries have also noted the lack of data validating PUT for the diagnosis of heavy metal poisoning [1,5,9,10,12]. However, despite these concerns, no formal prospective evaluation of the

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Supplemental data for this article can be accessed here.

ability of PUT to detect heavy metal toxicity has been undertaken.

Although many patients who obtain PUT present to alternative medicine practitioners for further care such as chelation treatment, some seek care at mainstream medical clinics. When these patients present to medical toxicology clinics, this provides an opportunity for evaluation of possible excessive metal exposures, patient education, and shared decision-making regarding the need for further testing utilizing scientifically validated techniques [12,15].

We utilized a multi-center prospective medical toxicology case registry that collected data on patients presenting to medical toxicology clinics with PUT results obtained due to suspected heavy metal poisoning. Our hypothesis was that a prior PUT would not be predictive of actual heavy metal toxicity or correlate with the end diagnosis of metal toxicity by board-certified medical toxicologists.

Methods

The Toxicology Investigators Consortium (ToxIC) maintains a multi-center prospective case registry whereby all medical toxicologists at participating institutions enter a prespecified set of deidentified patient data for every inpatient and outpatient they evaluate or treat into a secure online database [19,20]. The registry is password-protected and requires two-factor authentication for access. Every record entered into the case registry is quality controlled by review by a ToxIC staff member, and inconsistencies or blank field entries are clarified with the entering toxicologist [19,21].

The majority of medical toxicology clinical services and teaching programs in the United States participate in the ToxIC Registry. As of the end of 2018, there were 40 sites comprising 73 facilities participating in the case registry [21]. The ToxIC case registry operates after review by the Western Institutional Review Board (IRB) and with the consent of the IRBs of participating institutions [19]. The registry is compliant with the Health Insurance Portability and Accountability Act (HIPAA), and no protected health information is collected.

For cases in which, after full evaluation by the treating medical toxicologist, a specific toxicological exposure is identified as a likely cause of the patient's presenting signs and/or symptoms, that substance is recorded in the ToxIC database by selecting it from a detailed dictionary of potential exposures. In the absence of an appropriate choice in the dictionary, alternative entries can be made by utilizing free-text fields. A full description of the methods and structure of the case registry has been previously published [19,21].

In January 2012, the ToxIC registry added a data field identifying all outpatients seen and evaluated at medical toxicology clinics at participating sites in whom the results of a chelator-PUT were supplied by the patient when they presented for toxicologic evaluation. The current study identified all records of cases in which the patient presented to the clinic with results from their PUT that were entered into the registry between January 2012 and June 2019. Since none of the medical toxicologists participating in ToxIC perform PUTs, all PUT testing was done by other providers.

As a component of ToxIC's routine data collection for all patients presenting to participating medical toxicology clinics, the evaluating toxicologist rated the patient's signs and symptoms as likely exposure-related, likely exposure-unrelated, or unknown if exposure-related. Because this is a secondary analysis of previously collected data, the evaluating medical toxicologists had no prior knowledge of this study when evaluating the patients in the clinic and making a determination of relatedness.

Our inclusion criteria were all patients presenting to a ToxIC-participating medical toxicology clinic with the results of a previous PUT analysis, and for whom a formal determination of the relatedness of their signs and/or symptoms to a toxicologic exposure was made after toxicologic evaluation. Patients in whom the determination of the relatedness of their signs and/or symptoms to a toxicologic exposure was not recorded were excluded.

Our primary analysis was an assessment of the positive prediction value (PPV) of a PUT for the determination of relatedness of the patient's presenting signs or symptoms to a heavy metal exposure determined by a medical toxicology evaluation. We defined a True Positive (TP) as a patient meeting inclusion criteria with a medical toxicologist's diagnosis of heavy metal poisoning after a clinical evaluation. A patient who came to a medical toxicology clinic with a positive PUT testing result but who was not ultimately diagnosed with heavy metal poisoning by the evaluating medical toxicologist was defined as a False Positive (FP). PPV was calculated using the equation:

$$\mathrm{PPV} = \mathrm{TP}/(\mathrm{TP} + \mathrm{FP})$$

Patients for whom the relatedness was rated as unknown were not included in this calculation.

Demographics were abstracted for included patients from their records in the registry, including age, gender, race, and Hispanic ethnicity. Other variables were whether patient signs and symptoms were judged to be exposure-related, and their ultimate toxicologic diagnosis or diagnoses, if any. Race and ethnicity data were collected starting in 2014.

For a secondary analysis, the characteristics of patients presenting with PUT were compared to the population of patients in the ToxIC registry presenting to medical toxicology outpatient clinics over the same time period who did not have prior PUT. Patients who presented to medical toxicology clinics for the treatment of substance use disorders were excluded from this analysis, as these patients have a known chronic condition that did not require a toxicologic diagnostic workup.

Age was expressed as mean and range. Because age >89 years old is HIPAA-protected, any patients in this category were characterized as only age >89 years. For averaging purposes, these patients were treated as if they were 90 years old.

Statistical analyses were conducted comparing patients with a PUT versus those with no PUT. Statistical significance was defined *a priori* as $p < 0.05$. Differences in the two

groups were submitted to mean difference analysis for the one continuous variable, age, as determined by the *F*-test, and to Chi-square analysis using the Pearson's Chi-square statistic for the categorical demographics. Relative risk and absolute risk were calculated for categorical demographic variables. In the case of variables with multiple levels, the group having the lowest frequency was selected as the referent group. All analyses were conducted using IBM-SPSS v23 except in the case of relative and absolute risks, which were determined using Epi-Info 7.2.2.6.

This observational cohort study is compliant with Strobe Guidelines for Cohort Studies. See Supplemental Figure 1.

Results

Between January 2012 and June 2019, 106 patients presented to 17 participating medical toxicology clinics with the results of PUT (See Figure 1). Of these, 32 (30.1%) were excluded because a determination of the relatedness of the patient's complaints to a toxicologic exposure was not recorded. The characteristics of the remaining 74 cases (69.8%) are shown in Table 1. There were no statistically significant differences between the demographics of the included versus the excluded patients presenting with PUT. See Supplemental Tables and Supplemental Figure 2. Also shown in Table 1 and Supplemental Figure 3 is the demographic information of patients who presented to ToxIC network clinics for evaluation of potential health effects from known or suspected toxicologic exposures but who did not present with prior PUT results.

After medical toxicology outpatient evaluation, 15 of the 74 patients (20.2%) with PUT data were found to have signs or symptoms determined to be related to a toxicologic exposure. This contrasts with 408 (14.3%) of 2844 patients who presented for toxicologic evaluation without prior PUT who were found to have their presentations related to a toxicologic exposure (Chi-square = 16.1, $p = 0.000$; OR = 3.62, 95% CI = 1.87–7.08). For the 15 PUT cases where it was determined that the cause of a patient's signs or symptoms was related to a toxicologic exposure, the responsible agents are enumerated in Table 2. In three cases, a heavy metal related to PUT was implicated as the diagnosis after completion of the toxicologic evaluation. Thus, the PPV of a PUT is 0.043 (4.3%).

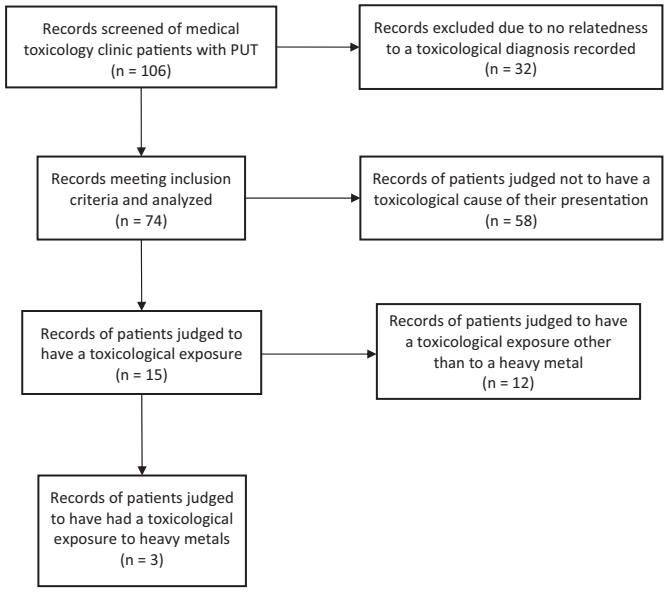

Figure 1. PRISMA flow diagram of ToxIC patients presenting with PUTs.

As shown in Table 1, a total of 2844 patients presented for toxicologic evaluation with no PUT. Of these, 2693 (94.7%) were retained and 151 (5.3%) excluded since toxicological exposure was not recorded. Chi-square analyses, including relative risk estimates, of demographics for those presenting with PUT results versus those without PUT results, found no statistically significant differences except for age. For age, statistically significant mean differences were found [$F(1, 2536) = 7.32$, $p = 0.007$]. Mean and median ages for patients with PUT were 50.4, and 51.0 respectively, and for patients without PUT were 44.7 and 47.0, respectively. See Supplemental Figure 4 for graphic and statistical support of the approximate normality of age for the two groups.

Discussion

The current study evaluated the reliability of PUT for the diagnosis of heavy metal poisoning. The PPV of such testing is 0.043, which is well within the range expected for random chance. Given the 4.3% concordance between PUT and a diagnosis of heavy metal poisoning, our data show that such testing is markedly unreliable. Our results are consistent with previous literature reports that PUT does not reflect the body burden of mercury from prior long-term exposure [2,4,6]. However, even if PUT did validly assess body metal burdens, exceeding a population reference level based upon measured toxin concentrations in a representative sample of a given population does not equate with reaching a threshold value of toxicological significance that presents a health hazard [9,15]. A formal diagnosis of heavy metal poisoning traditionally requires a detailed patient history and physical examination, an exposure history, and reliance on validated biomarkers of exposure such as a 24 h collection of creatinine-adjusted non-chelator provoked urine testing [9,13,17].

We found that the average age of patients who presented to medical toxicology clinics for evaluation of PUT results was statistically significantly older than the age of general non-addiction medical toxicology clinic patients (50.4 versus 44.7 years, respectively). However, this is not of clinical significance. Fifty-four percent (54.1%) of the patients with PUT testing were female. Although not statistically significant, the relative percentages are in keeping with the female-predominant results for inappropriate testing modalities including PUT found by other groups around the world, including one study in Germany [15]. Interestingly, this group did not note a difference in age between patients who presented with inappropriate testing results including PUT and patients who did not [15]. The reasons for the possible female predominance of PUT have not been well studied.

Of the 74 cases that presented with PUT and met our inclusion criteria, only 15 (20.2%) had a confirmed toxicologic

Table 1. Demographics and sources of referral of patients presenting to participating medical toxicology clinics with or without chelator-provoked urine heavy metal testing.

	Characteristic, *n*	Patients with PUT testing	Patients without PUT testing	*p*-Value	Relative risk	Risk difference
Overall	2767	74	2693			
Age					NA	NA
Mean age in years[a] (range)		50.4 (5–90^{+})	44.7 (0.2–90^{+})	0.007		
Median		51.0	47.0			
Gender	2766	74	2692			
Male (%)		34 (45.9)	1273 (47.3)	Chi-square = 0.54, $p = 0.817$	RR = 1.03 95% CI = 0.80–10.5	R Diff = 0.17 95% CI = −0.96 to 1.31
Race	1369	47	1322	Chi-square = 2.41 $p = 0.300$		
White (%)		42 (89.4)	1126 (85.2)		RR = 2.56, 95% CI = 0.63–21.56	R Diff = 1.98 95% CI −2.24 to 9.79
Black (%) reference group		2 (4.3)	141 (10.7)			
Asian (%)		3 (6.4)	55 (4.2)		RR = 3.70 95% CI = 0.61–20.56	R Diff = 3.77 95% CI = −2.05 to 8.45
Other race or unknown[c] (%)		27 (37.0)	1379 (4.0)	NA		
Ethnicity	1428	49	1379	Chi-square = 0.76 $p = 0.385$		
Hispanic (%)[b]		2 (4.1)	103 (7.5)		RR = 0.54 95% CI = 0.13–2.18	R Diff = −1.64 95% CI = −4.45 to 1.15
Not Hispanic		47 (95.9)	1276 (92.5)			
Referral source	2766	74	2692			
Self-referred (%)		17 (23.0)	728 (27.0)		RR = 1.06 95% CI = 0.44–2.78	RR Diff = 0.21 95% CI = −1.67 to 2.10
Occupational (%) reference group		6 (8.1)	282 (10)	Chi-square = 0.04 $p = 0.385$		
Other referral source (%)		51 (68.9)	1682 (62.5)		RR = 1.38 95% CI = −0.60 to 3.20	R Diff = 0.77 95% CI = −0.98 to 2.52

All demographic percentages reflect the percent of total patients for which demographic data were known.
[a]Note: all patients of age ≥90 were counted as age 90 and patients with unknown age were removed – patient age was known for $n = 74$ patients with PUT testing and $n = 2464$ patients without PUT testing.
[b]Given as percent of patients where the ethnicity was known.
[c]Excluded from this analysis due to race unknown.

Table 2. Agents determined to be responsible for presenting signs and symptoms in the 15 patients given a toxicologic diagnosis by the examining medical toxicologist.

Agent	Frequency	Percent
Mercury	3	20.0
Mold	3	20.0
Desvenlafaxine	1	6.7
Dichloroethane	1	6.7
Ethylene oxide	1	6.7
Isocyanates	1	6.7
Oxycodone	1	6.7
Tetrachloroethylene	1	6.7
Zinc oxide	1	6.7
Unknown substances	2	6.7
Total	15	100

diagnosis. Of these, three cases (4.3%) had a diagnosis of metal toxicity. In all three of these cases, the metal was mercury. Mercury exposure can be due to elemental, inorganic, or organic sources, with nonoccupational organic methylmercury exposure primarily due to dietary intake of mercury-containing fish [13,17]. It is important to note that organic mercury is predominantly fecally excreted, and urinary levels of mercury from this source would not be significantly increased via PUT [17]. Thus, the mercury exposures of interest here are primarily from elemental or inorganic sources such as industrial processes, thermometers, and mercury-containing consumer products such as skin lightening creams [4,8,13].

Evaluation of elevated mercury levels after PUT does not appear to improve diagnostic accuracy over standard unprovoked urinary mercury testing. In one published study, the urine mercury concentrations of three patients who presented to an environmental clinic with elevated PUT mercury testing were found to be normal when the preferred non provoked urine mercury retesting was performed [13].

Multiple studies have shown that unprovoked urine mercury excretion rates correlate with both mercury exposure as well as correlating highly with provoked urine mercury excretion rates [2–4,6,22]. Thus, there is no further information to be gained by performing PUT over performing the standard unprovoked testing, and interpretation of PUT is impossible due to the lack of validated reference ranges. In addition, as shown by our data, the use of PUT increases the risk of false-positive results.

Mercury is ubiquitous, and humans are constantly exposed to it in various forms through ambient air, seafood,

and in small amounts from mercury-containing dental amalgams [4,13,17]. Some degree of urine mercury excretion is therefore expected in all people who are tested. The administration of a renally cleared mercury chelating agent, such as succimer, dimercaptopropanesulfonate, or edetate calcium disodium, further increases mercury excretion in both mercury-overexposed and non-overexposed subjects [4,6,8]. One study that attempted to establish norms for PUT and unprovoked urine testing in both mercury-overexposed and non-overexposed subjects suggested an upper urine mercury limit of 12 μg/24 h in unprovoked urine testing and 20 μg/24 h after PUT with two doses of the chelator [6]. However, the use of these values has not been studied or validated. Nor is it known whether the addition of a chelator improves diagnostic accuracy using these values [9]. Data from our study indicates that chelator-provoked urine sampling is not of any diagnostic value and, if relied on, leads to inaccurate diagnoses.

Our study utilized diagnoses that were made by medical toxicologists. We made no attempt to independently review their records or to verify their diagnostic assessment. However, medical toxicologists possess particular expertise in the diagnosis of heavy metal poisoning making their diagnostic conclusions a logical endpoint for comparison with PUTs.

Several studies have questioned whether PUT can distinguish between levels of mercury in the general population versus in more exposed cohorts, all of which concluded that PUT cannot be used for this purpose [1,4–6]. We, therefore, hypothesized that the results of PUT would not correlate with the final diagnoses given to patients after evaluation by board-certified medical toxicologists, which was supported by these results. However, prior to the current study, the actual clinical utility of PUT had not been empirically evaluated.

Medical toxicology is a highly specialized discipline, and the formal outpatient evaluation of patients with potentially consequential toxicologic exposure is relatively uncommon. This is evidenced by the fact that the participating site clinics reported seeing a total of only 2946 non addiction clinic patients over a time period of 7.5 years. Although medical toxicology clinics do occasionally encounter patients who present with the results of PUT, these patients are seen relatively infrequently by mainstream medical practitioners, including medical toxicologists. The ToxIC case registry, aggregating the prospective experience of medical toxicologists from dozens of different sites, allowed for the accumulation of a relatively large number of cases of patients who have been evaluated and had their diagnoses ascertained by a board-certified medical toxicologist.

In three of the 15 cases with PUT that had a toxicologic diagnosis, the patients had signs or symptoms which were judged to be due to mold exposure. Although concern about mold exposure has been overstated, particularly on non-peer-reviewed public websites, mold-related illness does occur, with immunocompromised or atopic individuals being at higher risk [23,24]. However, the concern that immunocompetent members of the public are commonly falling ill with nonspecific, multisystemic illnesses due to exposure to ubiquitous environmental fungi including mold has limited credible supporting scientific evidence [23,24]. Given these patients' mold-related diagnoses, a PUT would have been unnecessary even if PUT were a validated test. This type of prior "shotgun" testing protocol is commonly seen in patients presenting to medical toxicology clinics after being evaluated by alternative medicine practitioners.

Limitations of the current study are that our patient population only includes patients with PUT that presented to medical toxicology clinics for evaluation. As such, they may not be completely typical of all patients who have PUTs done. However, there is no obvious reason why these patients should be markedly different from the entire population of patients for whom a PUT was done. In addition, some patient demographic data such as age or race were missing, especially early in the registry before these fields became required, and 32 of the 106 registry patients with PUT did not have a recorded answer to the question of whether their signs and symptoms were thought to be related to a toxicological cause. Excluding these patients may have biased our results. However, we did not find any significant differences between these patients and those who were included in our analysis.

Conclusion

Our results demonstrate that in clinical practice, PUT is not an accurate assessment of toxic heavy metal exposure and should not be used as a diagnostic aid. These findings support the position statement on this topic promulgated by the American College of Medical Toxicology[11] and the larger medical community as adopted by the American Board of Internal Medicine's Choosing Wisely campaign [18]. The goal of quaternary prevention, which entails protecting patients from being harmed physically, emotionally, and financially by inappropriate and excessive testing or treatment [15], is also consistent with avoiding the use of unproven diagnostic modalities such as PUT.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[1] Ruha A-M. Recommendations for provoked challenge urine testing. J Med Toxicol. 2013;9(4):318–325.
[2] Sällsten G, Barregård L, Schütz A. Clearance half life of mercury in urine after the cessation of long term occupational exposure: influence of a chelating agent (DMPS) on excretion of mercury in urine. Occup Environ Med. 1994;51(5):337–342.
[3] Roels H, Boeckx M, Ceulemans E, et al. Urinary excretion of mercury after occupational exposure to mercury vapour and

influence of the chelating agent meso-2,3-dimercaptosuccinic acid (DMSA). Br J Ind Med. 1991;48(4):247–253.
[4] Molin M, Schütz A, Skerfving S, et al. Mobilized mercury in subjects with varying exposure to elemental mercury vapour. Int Arch Occup Environ Health. 1991;63(3):187–192.
[5] Felton DJ, Kales SN, Goldman RH. An update and review of unconventional metals testing and treatment. Toxics. 2014;2(3):403–416.
[6] Frumkin H, Manning CC, Williams PL, et al. Diagnostic chelation challenge with DMSA: a biomarker of long-term mercury exposure? Environ Health Perspect. 2001;109(2):167–171.
[7] Archbold G, McGuckin RM, Campbell N. Dimercaptosuccinic acid loading test for assessing mercury burden in healthy individuals. Ann Clin Biochem. 2004;41(3):233–236.
[8] Hibberd Rmhah A. Mercury from dental amalgam fillings: studies on oral chelating agents for assessing and reducing mercury burdens in humans. J Nutr Environ Med. 1998;8(3):219–231.
[9] Hoet P, Haufroid V, Lison D. Heavy metal chelation tests: the misleading and hazardous promise. Arch Toxicol. 2020;94(8):2893–2896.
[10] McKay CA. Jr. Medical toxicology case presentations: to chelate or not to chelate, is that the question? J Med Toxicol. 2013;9(4):373–379.
[11] Toxicology ACoM. ACMT recommends against use of post-chelator challenge urinary metal testing. J Med Toxicol. 2017;13:352–354.
[12] Brent J. Commentary on the abuse of metal chelation therapy in patients with autism spectrum disorders. J Med Toxicol. 2013;9(4):370–372.
[13] Kales SN, Goldman RH. Mercury exposure: current concepts, controversies, and a clinic's experience. J Occup Env Med. 2002;44(2):143–154.
[14] Zajac L, Johnson SA, Hauptman M. Doc, can you test me for "toxic metals"? Challenges of testing for toxicants in patients with environmental concerns. Curr Probl Pediatr Adolesc Health Care. 2020;50(2):100762.
[15] Greiner A, Drexler H. Unnecessary investigations in environmental medicine: a retrospective cohort study. Dtsch Arztebl Int. 2016;113(46):773–780.
[16] Jamoulle M. Quaternary prevention, an answer of family doctors to overmedicalization. Int J Health Policy Manag. 2015;4(2):61–64.
[17] Risher JF, Amler SN. Mercury exposure: evaluation and intervention the inappropriate use of chelating agents in the diagnosis and treatment of putative mercury poisoning. Neurotoxicology. 2005;26(4):691–699.
[18] AACT Aa [Internet]. Don't administer a chelating agent prior to testing urine for metals, a practice referred to as "provoked" urine testing. Philadelphia (PA): Choosing Wisely; 2013 [2020 March 21]. Available from: https://www.choosingwisely.org/clinician-lists/american-college-academy-medical-toxicology-chelating-agents-prior-to-urine-test/
[19] Wax PM, Kleinschmidt KC, Brent J. The toxicology investigators consortium (ToxIC) registry. J Med Toxicol. 2011;7(4):259–265.
[20] Spyres MB, Farrugia LA, Kang AM, et al. The Toxicology Investigators Consortium Case Registry-the 2019 annual report. J Med Toxicol. 2020;16(4):361–387.
[21] Spyres MB, Farrugia LA, Kang AM, et al. The Toxicology Investigators Consortium Case Registry-the 2018 annual report. J Med Toxicol. 2019;15(4):228–254.
[22] (ATSDR) AfTSaDR. Toxicological profile for Mercury. Atlanta (GA): U.S. Department of Health and Human Services PHS; 1999.
[23] Bush RK, Portnoy JM, Saxon A, et al. The medical effects of mold exposure. J Allergy Clin Immunol. 2006;117(2):326–333.
[24] Hardin BD, Kelman BJ, Saxon A. Adverse human health effects associated with molds in the indoor environment. J Occup Environ Med. 2003;45(5):470–478.