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HYPOTHESIS REVIEW

# Chronic arsenic intoxication diagnostic score (CAsIDS)

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## Abstract

Arsenic and its compounds are well-established, potent, environmentally widespread and persistent toxicants with metabolic, genotoxic, mutagenic, teratogenic, epigenetic and carcinogenic effects. Arsenic occurs naturally in the Earth's crust, but anthropogenic arsenic emissions have surmounted the emissions from important natural sources such as volcanism. Inorganic arsenicals exhibit acute and chronic toxicities in virtually all cell types and tissues, and hence arsenic intoxication affects multiple systems. Whereas acute arsenic intoxication is rare and relatively easy to diagnose, chronic arsenic intoxication (CAsI) is common but goes often misdiagnosed. Based on a review of the literature as well as our own clinical experience, we propose a chronic arsenic intoxication diagnostic score (CAsIDS). A distinctive feature of CAsIDS is the use of bone arsenic load as an essential criterion for the individual risk assessment of chronic arsenic intoxication, combined with a systemic clinical assessment. We present clinical examples where CAsIDS is applied for the diagnosis of CAsI, review the main topics of the toxicity of arsenic in different cell and organ systems and discuss the therapy and prevention of disease caused or aggravated by chronic arsenic intoxication. CAsIDS can help physicians establish the diagnosis of CAsI and associated conditions.

KEYWORDS

arsenic, bone, CAsIDS, chronic, intoxication, risk assessment

## 1 | INTRODUCTION

Arsenic and its compounds are well-established, potent, environmentally widespread and persistent toxicants with metabolic, genotoxic, mutagenic, teratogenic, epigenetic and carcinogenic effects (Bjørklund, Aaseth, Chirumbolo, Urbina, & Uddin, 2017; Mandal & Suzuki, 2002; Tapio & Grosche, 2006).

Arsenic occurs naturally in the Earth's crust, but anthropogenic inorganic arsenic emissions from activities such as metal mining, burning of fossil fuels and pumping of contaminated groundwater for industrial, agricultural, animal and human uses have quantitatively surmounted the emissions from important natural sources such as volcanism on a planetary scale, thus introducing a global issue of sizeable stature (Dani, 2010a; Hong et al., 2009; Wai, Wu, Li, Jaffe, & Perry, 2016). Estimates based solely on the known reserves of arsenic in exploitable gold, coal and oil deposits indicate a 9- to 236-fold increase in annual anthropogenic arsenic emission in the next decades, i.e., more anthropogenic arsenic will be emitted within a couple of decades, than had been emitted during more than two centuries of the past Industrial Age (Figure 1).

Worldwide, hundreds of millions of people are chronically exposed to clinically meaningful inorganic arsenic concentrations (Mandal & Suzuki, 2002; Naujokas et al., 2013), and humans are more susceptible to the toxic effects of arsenic than any other mammal so far studied (Dani, 2009a). Whereas symptomatic arsenic poisoning is not often seen in occupational exposure settings, attempted homicide, deliberate long-term poisoning as well as chronic environmental exposure have resulted in chronic toxicity and chronic arsenic intoxication (CAsI) (Argos et al., 2010; Grobe, 1976; Grobe, 1977; Grobe, 1980; Grobe, 1982; Hall, 2002; Kawasaki, Yazawa, Ohnishi, & Ohi, 2002; Misra & Kalita, 2009).

Chronic arsenic exposure (CAsE) and CAsI have primarily been associated with an increased risk of various types of cancer, skin lesions and vascular disorders. It is now clear that CAsE can also cause metabolic, endocrine, hematologic, immunologic, gastrointestinal, hepatic, respiratory, cardiovascular, renal and neurologic diseases. In addition, CAsE and CAsI can negatively affect human fecundity and reproduction. The leading causes of morbidity and mortality worldwide – vascular diseases (including cardiovascular and cerebrovascular diseases), infectious diseases, cancer (particularly lung cancer), diabetes, diseases of the liver and kidneys, Alzheimer's disease and other dementias (WHO, 2017) – can also be caused or aggravated by long-term arsenic exposure.

  

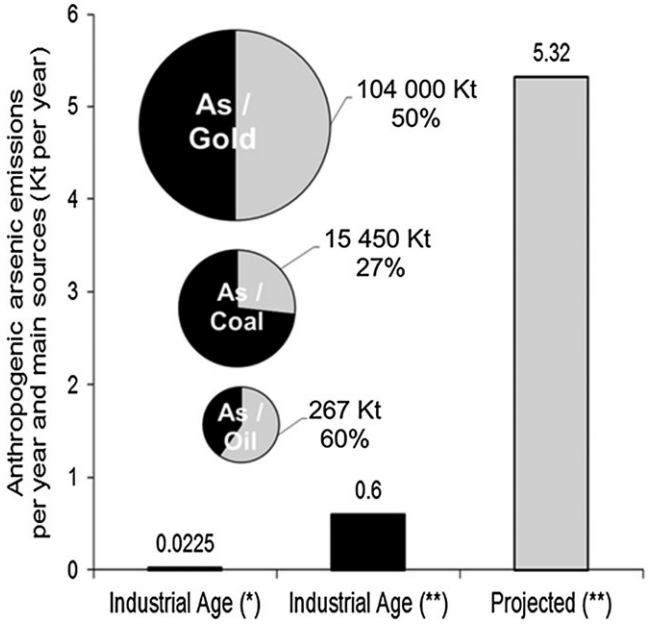


**FIGURE 1** Estimates of past (in black) and future (in gray) anthropogenic arsenic emissions from known reserves of the three selected arsenic sources: gold, coal and oil deposits. Here we compare the conservative estimate of the total (cumulative) anthropogenic arsenic in the industrial age as of the year 2000 as obtained by (*) Han et al. (2003), with estimates based on the average amounts of arsenic in exploited and exploitable gold, coal and oil deposits, as reviewed in (**) Dani (2010a). The former amount to $4.5 \times 10^3$ Kt, as for the year 2000, whereas the latter amount to $120 \times 10^3$ Kt and $266 \times 10^3$ Kt, as for the years 2000 and 2050, respectively. To calculate the average yearly anthropogenic arsenic emissions, we divided the estimates by the number of years in the periods concerned, i.e., 200 years for the Industrial Age (1800–2000), and 50 years for the period 2000–2050. These estimates indicate a 9- to 236-fold increase in annual anthropogenic arsenic emission in the next decades, based solely on the estimated arsenic content in known reserves of gold, coal and oil.

Although CAsI is common, it goes often misdiagnosed, perhaps because no systemic approach to the diagnosis of CAsI has been devised so far. To our knowledge, there is one published guide for the diagnosis of arsenicosis (Saha, 2003), but this is a clinical staging guide based on skin changes rather than a systemic diagnosis guide. Based on a review of the literature and our own clinical experience we propose a CAsI diagnostic score (CAsIDS). We postulate that three elements taken together are necessary and sufficient to confirm a suspected CAsI: (i) documented or suspected CAsE with (ii) presence of arsenic in the bone compartment and (iii) at least one documented subclinical or clinical arsenic toxicity sign or symptom. A distinctive feature of CAsIDS is the use of bone arsenic load (BAsL) as an essential criterion for the individual risk assessment of CAsI, combined with a systemic clinical assessment. The degree of diagnosis certainty is related to the arsenic concentration in the bone compartment as well as the number of simultaneous arsenic toxicity signs and symptoms. We review the toxicity of arsenic in different cell and organ systems and discuss the therapy and prevention of disease caused by CAsI.

## 2 | CHRONIC ARSENIC INTOXICATION DIAGNOSTIC SCORE METHODOLOGY

Known or suspected CAsE and quantification of BAsL are fundamental and essential conditions for CAsI diagnosis, respectively. Arsenic exposure is the sum of exposure through all routes including inhalation, ingestion, dermal contact and through osteoresorption (Dani, 2013). The excretion of arsenic occurs mainly through the urine. Under conditions of chronic intake the concentrations of arsenic in the body reach equilibrium after about 100 days; if the intake of arsenic is suspended then the organ content rapidly falls for all organs except bone – only bone continues to accumulate arsenic throughout life (Adeyemi, Garelick, & Priest, 2010).

Associations between urinary arsenic above certain thresholds and increased morbidity and mortality have been described for a number of diseases. The threshold for diabetes has been found to be 12 μg $g^{-1}$ creatinine (Feseke et al., 2015), whereas the threshold for cardiovascular diseases has been reported to be 7 μg $g^{-1}$ creatinine (Moon et al., 2013). Yet for various cancer types including cancer of the lung, prostate and pancreas, the associations between urinary arsenic and morbidity and mortality have been described as dose-dependent, without threshold (García-Esquinas et al., 2013). In fact, arsenic concentrations associated with increased cancer risk have been found to be near the arsenic detection limit, e.g., 1.77 ng $m^{-3}$ in air (Yoshikawa, Aoki, Ebine, Kusunoki, & Okamoto, 2008) and 3 μg $l^{-1}$ in drinking water (NCS, 2001). The general conclusion is that there is no such thing as a safe chronic exposure level for a carcinogenic substance such as arsenic. In addition, chronic exposure to high concentrations of arsenic in drinking water results in the highest known increases in mortality attributable to any environmental exposure (Smith, Steinmaus, Yuan, Liaw, & Hira-Smith, 2007).

Here we use the following reference values (RFs) for CAsE (total inorganic arsenic exposure is the summation of exposures through all routes and compartments): 1.77 ng $m^{-3}$ in air (Yoshikawa et al., 2008); 3 μg $l^{-1}$ in drinking water (NCS, 2001); 7 μg $g^{-1}$ creatinine in urine (Moon et al., 2013). These RFs are not meant to imply that they are safe, as there is no such thing as a safe environmental exposure level for a carcinogenic substance such as arsenic. They simply are consistent with the evidence that CAsE may require environmental arsenic concentrations as low as at the part per billion level (1 ppb = 1 μg $kg^{-1}$) to affect negatively human health (Eisler, 1994; Eisler, 2004; Marshall et al., 2007; Meliker, Wahl, Cameron, & Nriagu, 2007; Moon et al., 2013; Valentine, Reisbord, Kang, & Schluchter, 1985).

The RFs should be compared to the WHO provisional maximum tolerable daily intake of inorganic arsenic (0.002 mg $kg^{-1}$ of body weight, i.e., 2 μg $kg^{-1}$ $day^{-1}$) (WHO, 2001a); the FAO/WHO maximum allowed arsenic concentration in rice (0.2 mg $kg^{-1}$) (WHO, 2014); the arsenate dose that is active in the treatment of acute promyelocytic leukemia (APL), 60 μg $kg^{-1}$ $day^{-1}$ (Soignet et al., 1998); the human $LD_{50}$ for arsenate, 1 mg $kg^{-1}$ (i.e., 1 μg $g^{-1}$ or 1 part per million, 1 ppm) (Dart, 2004) and the total arsenic concentrations in air of rural and remote areas, 0.02–4 ng $m^{-3}$ (WHO, 2001b).

As to CAsE grading over time we start from the minimal time required for arsenic to reach equilibrium in the body compartments, as predicted by the Middlesex University multicompartment model

(Adeyemi et al., 2010), and refer to the latency periods between the onset of CAsE and the clinical manifestation of CAsI as reported in a series of reports by Grobe (1976, 1977, 1980, 1982) where the latency time varied from 3 to 50 years (average: 26 years), depending on the level of CAsE (Table 1).

To grade the individual CAsE, we establish BAsL intervals based on the median bone arsenic concentration reported for 160 autopsy and 92 surgical specimens (Brodziak-Dopierała, Kwapulinski, & Kowol, 2011; Mari et al., 2014; Yoo et al., 2002) as well as the estimated BAsL in a number of our own patients presenting with arsenic neuropathy. BAsL can be estimated non-invasively as osteoresorptive arsenic in two consecutive urine samples as described elsewhere (Dani, 2013).

To grade the clinical manifestation of CAsI, we include known systemic manifestations of CAsI encompassing cutaneous disorders; hematologic and/or immunologic disorders; gastrointestinal disorders; metabolic, endocrine and reproductive disorders; chronic pulmonary disease; cardiovascular disorders; renal disorders; pre-malignancy and malignancy; neuropathy and encephalopathy or mental disease.

A score is assigned for each of the above CAsE and CAsI criteria and the CAsIDS result or total score is obtained by the sum of all partial scores. More weight is given to CAsE and BAsL because they are considered as fundamental and essential for diagnosis, respectively. Based on the CAsIDS result, CAsI is excluded, suspected or confirmed (Table 2).

## 3 | EXAMPLES OF CHRONIC ARSENIC INTOXICATION DIAGNOSTIC SCORE IN PATIENTS EXAMINED IN TWO COUNTRIES

### 3.1 | Example 1

A 50-year-old woman of Afro-Brazilian origin with a history of chronic arsenic exposure in a traditional gold mining area, whole body dermatitis, urticaria, irritating bullous eruptions on the plantar and side surfaces of her feet. She developed multiple hypopigmented spots on her skin, myocardial infarction, refractory poikilocytic anemia, fatigue, loss of appetite, low weight, mental slowing, Hashimoto thyroiditis, vitamin D insufficiency with secondary hyperparathyroidism, osteoporosis and elevated BAsL in the context of osteoresorptive arsenic intoxication (ORAI). Details of this patient have been reported elsewhere (Dani, 2013). CAsIDS: 69 (CAsI confirmed with a high degree of certainty) (Figure 2).

### 3.2 | Example 2

This German patient was born in 1926 and died in 2013 at the age of 87 years after long years of chronic polymorbidity. He had been chronically contaminated by inorganic arsenic as a World War II prisoner working in the Sociéte Chimique de Gerland, a pesticide factory in Lyon, France. There he used to produce at least two arsenic-based pesticides: “Arséniate de Chaux” and “Acéto-Arsénite de Cuivre.” He developed chronic tonsillitis, bronchitis, hyperuricemia, chronic anemia, low weight, arterial hypertension, atrioventricular block and atrial fibrillation, mitral insufficiency, melanosis and hyperkeratosis. The diagnosis of “arsenism” was only confirmed in 1991, based on the anamnesis and presence of multiple skin cancers over his entire body (squamous cell carcinoma, Bowen's disease). He finally developed ureter and bladder tumor, liver dysfunction with ascites, chronic kidney disease (CKD) with the need of regular dialysis culminating in terminal renal failure, coma and death. No urinary arsenic determination could be performed due do the patient's anuria at the time of examination a few hours preceding his death. CAsIDS (without BAsL): 47 (CAsI confirmed) (Figure 3).

### 3.3 | Example 3

This German patient was born in 1933. He was chronically contaminated with inorganic arsenic from pesticides while working as a winegrower in the Rhineland-Palatinate region in Southern Germany. He developed chronic anemia, an unclear myeloproliferative disease, arterial hypertension, prolonged QTc interval, peripheral vascular disease, diffuse hyperkeratosis, multiple in situ carcinomas of the skin (Bowen's disease), glaucoma, latent hypothyroidism, CKD, bulbitis–duodenitis–duodenal ulcer, Parkinson's disease and dementia. A screening test (Merckoquant®; Merck, Darmstadt, Germany) revealed a urinary arsenic concentration of 100 μg $l^{-1}$ in the morning urine, equivalent to an arsenic/phosphor ratio (As/P) of 6.3 μg $mmol^{-1}$. CAsIDS: 64 (CAsI confirmed with a high degree of certainty) (Figure 4).

### 3.4 | Example 4

This 49-year-old woman lives in Paracatu town, Brazil, less than 200 m away from the southern border of the open pit gold mine operated by Canadian Kinross Gold Corporation (Henderson, 2006). During the last 30 years (i.e., since the beginning of the mining activities in 1987), this patient has been chronically exposed to the inorganic arsenic released from the rocks of the gold mine. The already meaningful CAsE since 1987 increased from 2007 with the controversial expansion of the mine operations (Acangau Foundation, 2009; Boudaoud & France TV, 2017; Dani, 2009b, 2009c, 2009d, 2009e; Dani, 2011a, 2011b; Dani, 2012; Dani, 2014; Dani & Santos, 2014; Enríquez, 2007; KGC, 2006, 2010, 2012, 2014, 2015, 2016a, 2016b; Lisboa, 2015; Lukacs & Groves, 2013; Minas Gerais, 2007; Moura, Rezende, Nascentes, Costa, & Windmoeller, 2008; MPF, 2009; MPT, 2008; Neiva & Silveira, 2008; Ono et al., 2011; Ono, Tappero, Sparks, & Guilherme, 2016; Rezende, 2009; Rezende, Costa, & Windmöller, 2015; Santos, 2012; Santos & Dani, 2016; Terrier, 2011). The patient complained of chronic headache, abdominal pain, pruriginous dark skin lesions of the feet, poor vision, symmetrical numbness and tingling of her hands and feet, bronchitis, arterial hypertension and malaise. In 2011, the concentration of arsenic in her spot urine as determined by inductively coupled plasma mass spectrometry (ICP-MS) was 30.9 μg $l^{-1}$ (Castilhos, 2016). In 2016, she had a stroke and as result of which she showed a M4-hemiparesis of the left side. The physical examination also revealed melanosis of the palms; spotted and diffuse hyperkeratosis and melanosis of the soles, and cutaneous changes typical of blackfoot disease (i.e., peripheral vascular disease). In February, 2017, the analysis of her BAsL according to the Δ As/P method (Dani, 2013) using AAS revealed an estimated BAsL/skeletal weight of 10.8 μg $g^{-1}$. This concentration is increased by 70-fold compared to the median of the bone arsenic

**TABLE 1** Quantitative epidemiological information of arsenic exposure and exposure duration relative to onset and severity of intoxication symptoms in representative human populations

| Arsenic exposure level | Exposure duration and onset of symptoms | Severity of observed effects | Reference |
|---|---|---|---|
| 0.015 mg $kg^{-1}$ $day^{-1}$ per os (reference value) | Short term (hours to days), in children | Acute poisoning. Gastrointestinal, neurological and skin disorders, facial edema, cardiac arrhythmia. | Tsuji, Benson, Schoof, and Hook (2004) |
| Estimated 53 g of inorganic arsenic (mostly $As_2O_3$) over a 13 year period, on average (i.e., 11 mg $day^{-1}$, or 0.157 mg $kg^{-1}$ $day^{-1}$, on average). Obs.: Development of tolerance (habituation) to arsenic possible at this level of chronic exposure. | An estimated over 1000 German wine growers were chronically exposed to inorganic arsenicals during the period 1920–42. Exposure was mainly from the consumption of draft wine, produced for own use, as house drink, containing 2–30 mg arsenic $l^{-1}$ (estimated 47 g/13 years), and from direct uptake during application of arsenicals as pesticides (estimated 3–30 mg arsenic inhaled per day when spraying pesticides without a proper mask, i.e., 6 g per 13 years). Latency time for the manifestation of symptoms varied from 3 to 50 years, depending on the arsenic exposure level (average: 26 years). | Chronic food and occupational poisoning. Skin alterations (acrodermatitis chronica atrophicans, endangiitis obliterans with atrophy of the cutis) in 60–70% of the 50–60-year-old patients, 80–90% of the 60–70-year-old patients and 90–95% of the 70–80-year-old patients. Peripheral circulatory disturbances, cyanosis of the lips, dyspnea and emphysema, together with cardiac insufficiency. Age-related increase in melanosis, precancerous skin lesions, carcinomas, palmo-plantar hyperkeratosis and porphyria cutanea tarda. Significant increase in Dupuytren's contracture in the age groups between 50 and 80; growing progression of arsenic horned pearls on the palms of the hands and soles of the feet. Pathoanatomical changes: Liver cirrhosis, multiple carcinomas, lung cancers, pre-carcinogenic and carcinogenic alterations of the skin including arsenic hyperkeratosis, melanosis, Morbus Bowen and skin carcinomas. Lung cancers in 66% of all wine growers affected. | Grobe (1976, 1977, 1980, 1982) |
| 0.005 mg $kg^{-1}$ $day^{-1}$ per os (reference value) | Months to years, in children. | Subchronic, low-level environmental intoxication. Dermatoses. | Tsuji et al. (2004) |
| >7 μg $l^{-1}$ in drinking water | More than 8 years of chronic arsenic exposure through drinking water in Bangladesh. | Chronic environmental intoxication. Concentration-related increase in prevalence odds ratio for proteinuria. | Chen et al. (2011) |
| >50 μg $l^{-1}$ in drinking water | Tube well water consumption in Bangladesh for more than 24 years in about 50% of patients with cutaneous manifestations of chronic arsenic intoxication. | Chronic environmental intoxication. Average subject age: 36 years. Median duration of arsenic symptoms: 3 years. Melanosis (97% of subjects) and conjunctivitis as earlier symptoms; keratosis (68.7% of subjects), bronchitis, loss of appetite and wasting as prolonged symptoms. | Hossain et al. (2005) |
| >115 μg $l^{-1}$ in drinking water | Chronically exposed populations in Chile region II and Bangladesh. | Chronic exposure to high concentrations of arsenic in drinking water results in the highest known increases in mortality attributable to any environmental exposure. | Smith et al. (2007) |
| Urinary arsenic concentration of 7 μg $g^{-1}$ creatinine | Long-term exposure to low to moderate arsenic levels in 3575 American Indian men and women aged 45–74 years living in Arizona, Oklahoma, and north and South Dakota, USA | Threshold for cardiovascular diseases | Moon et al. (2013) |
| Urinary arsenic concentration of 12 μg $g^{-1}$ creatinine | Association between low to moderate level arsenic exposure, as measured by total arsenic concentration in urine, and the prevalence of T2D in 3151 adult participants in cycle 1 (2007–09) of the Canadian health measures survey. | Threshold for diabetes (T2D) | Feseke et al. (2015) |
| Mean urinary arsenic concentration of 141.2 μg $l^{-1}$ | Children exposed since pregnancy until early childhood to an average water arsenic concentration of 152.13 μg $l^{-1}$ | Chronic environmental intoxication. Forced vital capacity significantly decreased and negatively associated with the percentage of inorganic arsenic. Restrictive spirometric pattern in more than 57% of the children. | Recio-Vega et al. (2015) |
| No threshold | Low to moderate exposure to inorganic arsenic was prospectively associated with increased mortality for cancers of the lung, prostate and pancreas in 3932 American Indians, 45–74 years of age, from Arizona, Oklahoma, and north/South Dakota (the strong heart study). | For various cancer types including cancer of the lung, prostate and pancreas, the associations between urinary arsenic and morbidity and mortality have been described as dose-dependent, without threshold. | García-Esquinas et al. (2013) |

(Continues)

**TABLE 1** (Continued)

| Arsenic exposure level | Exposure duration and onset of symptoms | Severity of observed effects | Reference |
|---|---|---|---|
| >1.77 ng $m^{-3}$ in the air | Monitoring survey data on arsenic concentrations published by the Ministry of the Environment of Japan. | The standardized mortality ratio of lung cancer is significantly higher in areas with arsenic concentrations of 1.77 ng $m^{-3}$ or more. | Yoshikawa et al. (2008) |
| >100 ng $m^{-3}$ in the air | Hispanic women exposed to environmental arsenic from months to years. | Chronic environmental intoxication. Stillbirth prevalence odds ratio for Hispanics: 8.4 (95% confidence interval of 1.4–50.1). | Ihrig, Shalat, and Baynes (1998) |
| Topsoil arsenic concentrations between 7 and 18 mg $kg^{-1}$ | Meta-analysis using arsenic data from the FOREGS project. | First indication that the environmental concentration of total arsenic in topsoils is exponentially related to the prevalence and mortality of Alzheimer's disease and other dementias in European countries. | Dani, 2010a, 2010b) |
| Mean soil arsenic concentration: 3.3 mg $kg^{-1}$ dry weight (range 0.2–22.7 mg $kg^{-1}$ dry weight) | Mother–child pairs ($n$ = 12 798), retrospective cohort, mean follow-up to 6.7 years | First trimester exposure to elevated soil arsenic increased odds of intellectual disability diagnosis. | McDermott, Bao, Marjorie Aelion, Cai, and Lawson (2012) |

T2D, type 2 diabetes.

concentrations reported for surgical and autopsy specimens that had been analyzed by ICP-MS in different populations across the globe (Brodziak-Dopierała et al., 2011; Mari et al., 2014; Yoo et al., 2002). CAsIDS: 53 (CAsI confirmed with a high degree of certainty) (Figure 5).

## 4 | DISCUSSION

Our CAsIDS combines fundamental and essential conditions of CAsI – known or suspected CAsE and BAsL, respectively – with clinically relevant systemic manifestations of CAsI. In the following sections, we discuss important aspects that pose challenges as well as solutions to CAsI diagnosis. Finally, we briefly review what is currently known about arsenic toxicity and discuss the therapy and prevention of disease caused or aggravated by CAsI.

### 4.1 | Estimating the chronic arsenic exposure by environmental monitoring

Estimation of CAsE by environmental monitoring of arsenic concentration in drinking water and food as well as total suspended particles in air is interesting in environmental surveys but it is of limited clinical utility because assessment of bioavailable arsenic in environmental matrices can be very inaccurate and biased and do not reflect the individual's exposure. Recently, it has been shown in a long-term observational study that evidence for health effects of inhaled arsenic derives mainly from occupational studies that are subject to unique biases that may attenuate or obscure such associations (Keil & Richardson, 2017). Most assays do not capture the whole range of exposure pathways and routes and the results of particular assays cannot be extrapolated. For example, gastrointestinal bioavailability indexes cannot be reasonably applied to the respiratory tract, as the half-life of arsenic compounds in the lungs is considerably higher than that in the gastrointestinal tract (Rhoads & Sanders, 1985). Certain arsenic compounds may remain in the lungs for several years, even after the exposure to environmental arsenic has ceased (Brune, Nordberg, & Wester, 1980). Although particles deposited in the upper airways and swallowed after mucociliary clearance result in gastrointestinal tract absorption, smaller particles are deposited more deeply in the respiratory tract, and the fraction of arsenic absorbed by inhalation is thought to be within 60–90% of inhaled arsenic (NIOSH, 2005; Yip & Dart, 2001), which is more than generally indicated by gastrointestinal assays. In addition, the usual methods of environmental monitoring capture neither the highly bioavailable arsenic nanoparticles suspended in air, nor the volatile (gaseous) arsenic forms that are clinically relevant, and neither the gastrointestinal nor the dermal bioavailability assays account for highly bioavailable nanoparticles or gaseous forms such as arsines, which are primarily or secondarily absorbed through the inhalative route (Kinoshita, Hirose, Tanaka, & Yamazaki, 2004; Tian et al., 2014).

To complicate matters, environmental arsenic concentrations are subject to wide variations, which may further reduce the usefulness of environmental monitoring for health risk assessment. For example, depending on the environmental conditions and the microbial flora

**TABLE 2** Chronic arsenic intoxication diagnostic score (CAsIDS)

| Fundamental condition (must be fulfilled with at least a "1" score) | Score |
|---|---|
| 1. Known or suspected exposure to inorganic arsenic at concentrations above the reference values for given time periods | |
| 100 days | 0 |
| 3–12 months | 1 |
| 1–3 years | 2 |
| 3–26 years | 4 |
| 26–50 years | 8 |
| >50 years | 10 |
| **Essential condition (must be fulfilled with at least a "5" score)** | **Score** |
| 2. Bone inorganic arsenic load (μg $g^{-1}$) | |
| ≤0.060 | 0 |
| 0.061–0.153 | 5 |
| 0.154–1.530 | 10 |
| 1.531–15 | 20 |
| 15.1–150 | 30 |
| >150 | 40 |
| **Typical systemic manifestations of chronic arsenic toxicity** | **Score** |
| 3. Cutaneous disorders (at least four of the following): | 5 |
| itching; | |
| erythema or cutaneous rash; | |
| conjunctival congestion (it is sometimes observed but not associated with any signs of pain or inflammation in the affected eyes); | |
| palmo-plantar hyperkeratosis (it is manifested as gradual thickening of soles and palms that leads to cracks and fissures); | |
| dorsal keratosis (it may appear on dorsum of hands and feet); | |
| Dupuytren's contracture; | |
| melanosis (diffuse, abnormal deposition or development of black or dark pigment in the tissues, typically fine spotted melanosis or raindrop pigmentation is found in palms or skin over the chest, back and sometimes on hands and legs); | |
| leukomelanosis (it can be manifested as simultaneous appearance of pigmented as well as depigmented spots on legs, trunk or other parts of body – The combined features of melanosis with keratosis in palms or soles are the cardinal features of arsenical dermatitis, ASD); | |
| mucous membrane pigmentation (it is found in some cases on the tongue, inner side of lips, gums or buccal mucous membrane); | |
| Mee's lines (white lines in the nails). | |
| 4. Hematologic and/or immunologic disorder (at least one of the following): Leukopenia; eosinophilia; anemia including poikilocytic anemia and megaloblastic anemia; splenomegaly and hypersplenism; relapsing infections (chronic infection or more than 2 infections per year); atypical infections (e.g., relapsed tuberculosis). | 5 |
| 5. Gastrointestinal disorders (at least two of the following): a metallic taste; jaundice; hepatomegaly; hepatic steatosis; liver disease, e.g., non-cirrhotic portal fibrosis with or without portal hypertension with bleeding esophageal varices and splenomegaly and hypersplenism; incomplete septal cirrhosis. Loss of appetite, nausea, vomiting, abdominal pain, diarrhea and increased thirst are common in acute arsenic poisoning but may be also observed in acute-on-chronic arsenic intoxication, as in osteoresorptive arsenic intoxication. | 5 |
| 6. Metabolic, endocrine and reproductive disorders (at least one of the following): Insulin resistance and diabetes mellitus; obesity; low weight; thyroid, parathyroid, gonadal or adrenal dysfunction; osteoporosis; abnormal fecundity; spontaneous abortion. | 5 |
| 7. Chronic pulmonary disease (at least two of the following): Lung function impairment; chronic cough; chronic bronchitis and acute respiratory tract infections; pulmonary nodule; diffuse interstitial lung disease and chronic obstructive pulmonary disease; bronchiectasis; bullous-emphysema. | 5 |
| 8. Cardiovascular disorders (at least two of the following): Peripheral vascular disease (including blackfoot disease); Raynaud's phenomenon and acrocyanosis; non-pitting edema of hands/feet; cardiomyopathy; ventricular tachycardia; QTc interval prolongation; arterial hypertension; ischemic heart disease; stroke. | 5 |
| 9. Renal disorders (at least one of the following): Fanconi syndrome (phosphaturia, glucosuria, aminoaciduria and low-molecular weight proteinuria); albuminuria; chronic kidney disease with progressive deterioration of renal function are clinical characteristics associated with chronic arsenic exposure. Glomerular sclerosis and severe acute tubular necrosis involving all the nephron segments as well as acute tubuleinterstitial nephritis may be observed in acute arsenic poisoning. | 5 |
| 10. Pre-malignancy or malignancy (any pre-cancerous, primary or metastatic neoplasia involving any organ, cell or tissue type including, though not restricted to, skin, bladder and lung). | 5 |
| 11. Neuropathy (at least one of the following): Symmetric neuropathy, polyneuropathy, phrenic paresis, fatigue, hearing loss, blindness, Guillain–Barré syndrome or Guillain–Barré-like syndrome. | 5 |
| 12. Encephalopathy or mental disease (at least two of the following): | 5 |
| chronic asthenia, insomnia, fatigue, weakness, malaise or dizziness; | |

(Continues)

**TABLE 2** (Continued)

| Typical systemic manifestations of chronic arsenic toxicity | Score |
|---|---|
| mental slowing, difficulty concentrating, light-headedness, disorientation or confusion; | |
| mood and/or behavioral disorder, depression or anxiety; | |
| delirium, psychosis; | |
| cognitive impairment, memory impairment or dementia. | |
| **TOTAL** | **100** |
| **Interpretation of CAsIDS results** | |
| CAsI confirmed with a high degree of certainty | >51 |
| CAsI confirmed | 41–50 |
| CAsI highly probable | 31–40 |
| CAsI probable | 21–30 |
| CAsI cannot be excluded (patient should be re-evaluated) | 7–20 |
| CAsI excluded with certainty | ≤6 |

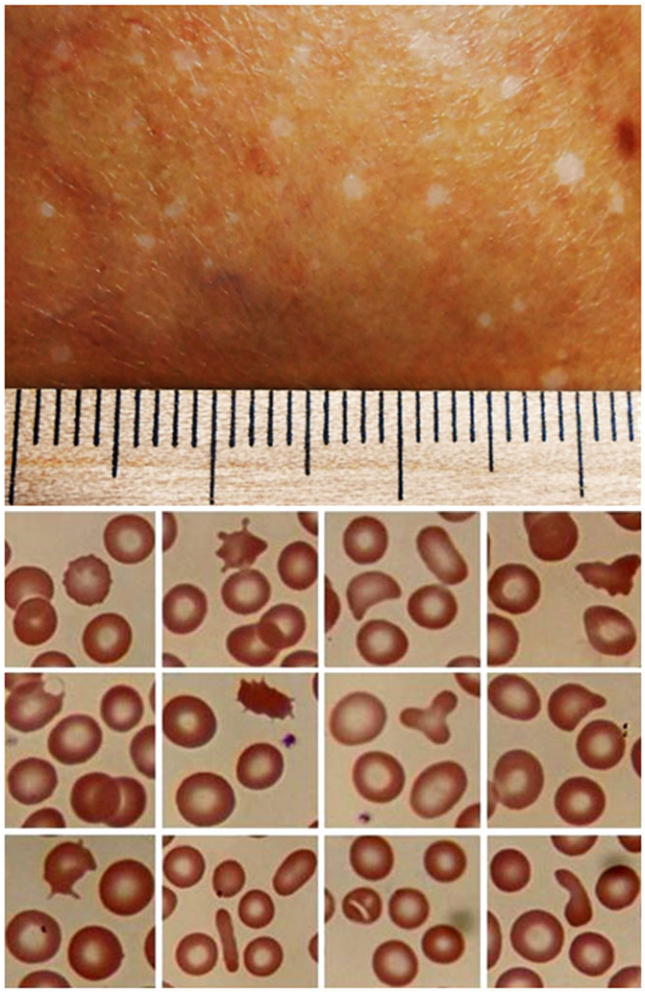

**FIGURE 2** Arsenic-related disorders in a female patient with ORAI examined in 2012 in Heidelberg, Germany (Dani, 2013). Image of the skin shows multiple hypopigmented spots of up to 2 mm in diameter on the patient's leg; also visible are erythematous patches with light hyperkeratotic scaling. Micrograph shows poikilocytic anemia: Hemoglobin of 10.3 g $dl^{-1}$, hematocrit of 32%, anisochromia, hypochromia, anisocytosis and 10% of the erythrocytes showing anomalous forms: Elliptocytes, drepanocytes, dacryocytes, acanthocytes, echinocytes, schizocytes, stomatocytes and target cells. CAsIDS: 69 (CAsI confirmed with a high degree of certainty). Photograph and micrograph by S. U. Dani, April 2012, reproduced with permission of Elsevier

present in the soil, 0.05% to almost 100% soil inorganic arsenic is volatilizated to arsines (Turpeinen, Pantsar-Kallio, & Kairesalo, 2002). It has been shown that arsine and methylarsines are stable in the air in concentrations at the µg $l^{-1}$ gas level and can travel considerable distances in the atmosphere from a point source before converting into non-volatile, oxidized compounds (Mestrot, Merle, Broglia, Feldmann, & Krupp, 2011; Mestrot et al., 2011). Arsine decomposes on heating and under the influence of light and moisture, producing toxic arsenic fumes, whereby NIOSH recommends that persons 9.5 km downwind must be protected during the night (NIOSH, 2015), a recommendation that is hardly practicable. Environmental monitoring is not intended to assess arsenic exposure at the individual level; therefore, it is essential to determine arsenic in the human compartments.

## 4.2 | Assessing the individual risk by bone arsenic load

We chose the BAsL as a reliable method to assess the individual CAsE and related risks in our CAsIDS for the following reasons.

### 4.2.1 | Arsenic accidentally replaces phosphorus in a number of metabolic pathways and physiological processes

Arsenic accidentally replaces phosphorus in a number of metabolic pathways and physiological processes, including bone growth and remodeling (Dani, 2011c). Replacement of phosphorus with arsenic in the calcium phosphate hydroxylapatite (HAP) molecule in the bone mineral matrix generates arsenate HAP (AsHAP) (Lee et al., 2009), the main arsenic storage form in bone. The bones are the main body reservoir of phosphorus (Shaker & Deftos, 2014), and hence the skeleton is the main arsenic storage compartment in the body. In addition, bone is the only body compartment that steadily accumulates arsenic over long exposure periods (Adeyemi et al., 2010).

### 4.2.2 | Sustained arsenate hydroxylapatite dissolution and solubilization and arsenic release from the bones

Sustained AsHAP dissolution and solubilization (Zhang et al., 2011a) and arsenic release from the bones during bone resorption may cause ORAI (Dani, 2013) in a number of physiologic and pathologic conditions. Bone resorption follows a circadian rhythm (Mautalen, 1970;

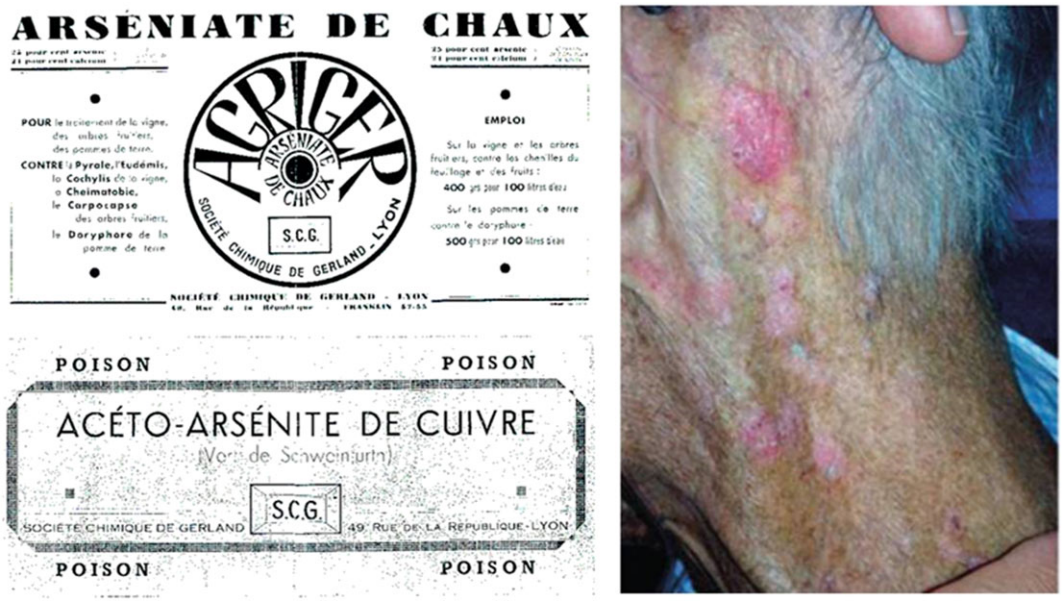


**FIGURE 3** Arsenic-related melanosis and multiple squamous cell carcinomas (Bowen's disease) in a moribund patient examined in 2013 in Worms, Germany. He had been chronically contaminated by inorganic arsenicals ("Arséniate de Chaux" and "Acéto-Arsénite de Cuivre") as a world war II prisoner working in a pesticide factory in Lyon, France. Although the patient had developed a number of signs and symptoms of CAsI, the confirmation of "arsenism" was only made in 1991, more than four decades after cessation of the occupational arsenic exposure. CAsIDS (without BAsL): 47 (CAsI confirmed). Photograph by M. Kaess and S.U. Dani, September 2013, reproduced with permission of Ciencia Hoje

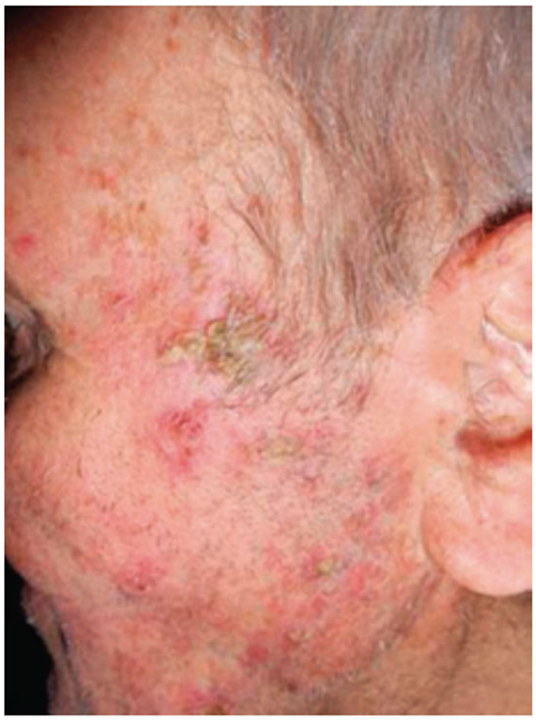

**FIGURE 4** Arsenic-related skin changes including erythematous patches, hyperkeratosis and Bowen's disease in a patient examined by the author in Worms, Germany. CAsIDS: 64 (CAsI confirmed with a high degree of certainty). Photograph by S.U. Dani, October 2013, reproduced with permission of Ciencia Hoje

Takarada et al., 2017) and bone turnover occurs at different rates in anatomically heterogeneous bone structural units called osteons (Cohen & Harris, 1958; Lukas et al., 2011; Robling & Stout, 1998; Tappen, 1977). Bone turnover rates vary at 5–30% per year (Martin, Burr, & Sharkey, 1998; Parfitt, 1983, 1994) while the median rate of bone loss at multiple skeletal sites have been reported at −0.4% per year in young adult women and men (Riggs et al., 2008). In addition, approximately 20% of adult bone surface is undergoing remodeling at any time (Shaker & Deftos, 2014). Chronic exposure to arsenic via the osteoresorptive mechanism may render people susceptible to elevated arsenic exposure years or even decades after an environmental exposure has decreased or even ceased. Osteoresorption increases over osteoanabolism in a number of physiological and pathological conditions, meaning that ORAI may be a common outcome in patients chronically exposed to arsenic. Conditions or agents known to increase the osteoresorption rate include: pregnancy (Sanz-Salvador, García-Pérez, Tarín, & Cano, 2015); bone remodeling during growth (Szulc, Seeman, & Delmas, 2000); prolonged bed rest (Morgan et al., 1985); stress as in physically demanding exercise with energy restriction and sleep deprivation (Hughes et al., 2014); malnutrition (Kerstetter, O'Brien, & Insogna, 2003; Trebble, 2005); diabetes (Kasperk, Georgescu, & Nawroth, 2017); high-salt intake (Buehlmeier et al., 2012) as well as chronic hyponatremia (Barsony, Manigrasso, Xu, Tam, & Verbalis, 2013); vitamin D [25(OH)D] insufficiency or deficiency (Need, 2006), as well as excess of 1,25(OH)2D as in granulomatous diseases such as sarcoidosis and tuberculosis (Tebben, Singh, & Kumar, 2016); infection (Amiel et al., 2004; Fukada et al., 2008; Smith et al., 2002) and inflammation (Haworth et al., 2004; Ruscitti et al., 2015); gonadal dysfunction (Ferlin, Selice, Carraro, & Foresta, 2013; Oury, 2012) including decreased testosterone (Mohamad, Soelaiman, & Chin, 2016) and estrogen (De Oliveira, Fighera, Bianchet, Kulak, & Kulak, 2012) production, as in post-castration and post-menopausal states, respectively; hyperthyroidism (Bassett & Williams, 2016); hyperparathyroidism (Bandeira et al., 2014); long-term corticosteroid therapy (Clarke, 2012); endogenous hypercortisolism (Chiodini,

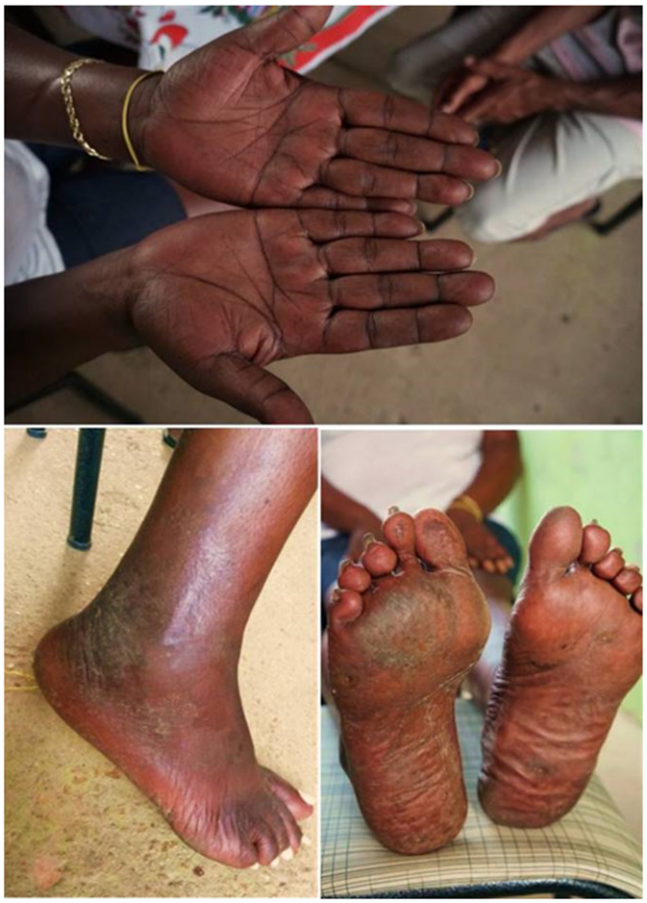

**FIGURE 5** Cutaneous signs of chronic arsenic intoxication in a 49-year-old woman in Paracatu, MG, Brazil (clockwise from the top): Melanosis of the palms; spotted and diffuse hyperkeratosis and melanosis of the soles; blackfoot disease (peripheral vascular disease). CAsIDS: 53 (CAsI confirmed with a high degree of certainty). Photographs by S.U. Dani and H. A. Zschokke, February 2017

Torlontano, Carnevale, Trischitta, & Scillitani, 2008); cancer (Goldner, 2016) and bone metastases (Coleman, 1997).

#### 4.2.3 | Immunomodulatory agent and strong osteoimmunological link between arsenic, inflammation and the immune response

The bone and immune system are functionally interconnected, for immune and bone cells derived from the same progenitors in the bone marrow, they share a common microenvironment and are being influenced by similar mediators. The evidence on increased bone resorption associated with inappropriate activation of T cells such as during inflammation is well established (Zupan, Jeras, & Marc, 2013). The inflammatory milieu favors recruitment and activation of osteoclasts, a process mediated by a number of cytokines and chemokines, which, directly or indirectly, activate osteoclast precursors and enhance their differentiation potential, thus mediating osteoresorption (Hess, 2006; Sućur et al., 2014). Experimental exposure to arsenic at environmentally realistic concentrations has been shown to compromise the cellular and humoral immune responses in avian (Aggarwal, Naraharisetti, Dandapat, Degen, & Malik, 2008; Sattar et al., 2016) and murine (Kozul, Ely, Enelow, & Hamilton, 2009; Kozul et al., 2009) species, thereby making them prone to illnesses. Arsenic has been shown to attenuate the T-cell-mediated immunity by suppressing the proliferation of T cells and cytokine release and increasing the frequency of CD4(+) CD25(+) Foxp3(+) regulatory T cells (Song et al., 2015). Interestingly, increased numbers of CD4(+) cells predispose to autoimmune neuritis when these cells are stimulated by proinflammatory mediators such as interferon-γ (IFN-γ) (Brunn et al., 2014).

#### 4.2.4 | Arsenic exerts both stimulating and inhibiting effects on osteoblast function

Arsenic exerts both stimulating and inhibiting effects on osteoblast function, thereby modulating bone resorption in a concentration-dependent manner (Jia & Jin, 2006; Lever, 2002; Tang, Chiu, Huang, Chen, & Chen, 2009; Xu et al., 2014). At arsenic concentrations found in tissues of individuals exposed to geochemical $AsO_2$, osteoclasts underwent differentiation in vitro, leading to the conclusion that chronic exposure to low-level amounts of arsenic can result in increased bone resorption and contribute to bone-related pathologies (Szymczyk, Kerr, Freeman, Adams, & Steinbeck, 2006).

#### 4.2.5 | Arsenic accumulation in bone varies with environmental exposure

Arsenic accumulation in bone varies with environmental exposure through ingestion or inhalation (Lindh, Brune, Nordberg, & Wester, 1980) and age (Kuor, Kuo, Chou, & Lee, 2000). Information on the arsenic concentration in human bone tissue is limited to a few studies using different analytical procedures to analyze different bones of different people of different ages from different geographical origins and times. These studies indicate arsenic concentrations in bone ranging from 0.04 to 13 000 μg $g^{-1}$ (Aras & Ataman, 1999; Kabata-Pendias & Pendias, 1999; Oakberg, Levy, & Smith, 2000; Rasmussen, Bjerregaard, Gommesen, & Jensen, 2009; Rasmussen & Gwozdz, 1999; Smith, 1957). However, the extremely low arsenic concentrations may result from using low sensitive analytical methods, and the extremely high bone arsenic concentrations, i.e., in the milligram range, as reported for some buried or fossilized bones are believed to be of diagenetic origin. Therefore, we rely on the results of three ICP-MS studies performed on surgical or autopsy bone specimens (Brodziak-Dopierała et al., 2011; Mari et al., 2014; Yoo et al., 2002) in our CAsIDS.

#### 4.2.6 | Osteoresorptive arsenic versus arsenic in hair and nails

The arsenic detection limit for hair samples in spectrometry studies varies between 2 and 10 ng $g^{-1}$ (Rahman, Corns, Bryce, & Stockwell, 2000). Non-exposed people show an average hair arsenic concentration of 0.06 μg $g^{-1}$ (Hirner, Rehage, & Sulkowski, 2000), whereas exposed people can have concentrations as high as 12.4 μg $g^{-1}$ (Schmitt et al., 2002). Values higher than 1.2 μg $g^{-1}$ indicate chronic exposure (Anke, 1986), whereas WHO (2001c) considers 0.4–0.8 μg $g^{-1}$ as normal and sets a minimal critical limit of 1 μg $g^{-1}$. As organic species of arsenic are not incorporated into keratin, hair only reflects exposure to inorganic arsenic (Vahter, 1998). The distribution of arsenic in cross-sections or along the length of a shaft of hair cannot distinguish external contamination from arsenic derived from ingestion (Hindmarsh, 2002). In comparison to hair, exogenous

contamination is not a confounding factor for fingernails; therefore, fingernails have been recommended as a biomarker to arsenic exposure (Agahian, Lee, Nelson, & Johns, 1990; Brima et al., 2006; Mandal, Ogra, & Suzuki, 2003). However, neither hair nor fingernails are long-term arsenic storage compartments, and therefore we prefer osteoresorptive arsenic as a biomarker to CAsE.

### 4.3 | Estimate of the bone arsenic load/skeleton weight by the two-spot-urine (Δ As/P) method

We assume that the dynamic release of phosphorus and arsenic from calcium phosphate HAP and AsHAP in the bone matrix and the net As/P ratio (Δ As/P) in two consecutive spot urine samples reflect the net rate at which bone-bound arsenic is released and can be detected in urine at any time and hence we use the Δ As/P in our estimates of BAsL as described elsewhere (Dani, 2013), with slight modifications.

To estimate the concentration of arsenic in the skeleton we assume that the As/P ratio of the metabolically active bones reflects the average As/P ratio in the skeleton. We multiply the Δ As/P with the estimated skeleton phosphate content, divided by the skeleton weight (SW) as a percentage of the ideal body mass for a given body height [the fat-free skeleton comprises about 3% of the body weight in the fetus and newborn and about 6–7% of body mass in the adult (Heymsfield, Lohman, Wang, & Going, 2005). In the fetus, we use the SW as published by the ICRP for Reference Man (ICRP, 2002). To control for inconsistencies, we check our SW estimates against the Reference Man values. We express the BAsL as estimated (average) arsenic concentration in bone, in μg $g^{-1}$, by dividing BAsL by the skeletal weight (BAsL/SW).

Our method requires 3 days of abstinence of rice and fish consumption before the urine collection as well as two consecutive urine samples with different arsenic concentrations, to differentiate the diet arsenic from the osteoresorptive arsenic. An adequate phosphorus excretion (i.e., urinary phosphorus concentration equal or above the age-specific estimated average requirement) is important to reduce artifact due to arsenic-for-phosphorus swap (Dani, 2011c) or hungry bone syndrome (Witteveen, van Thiel, Romijn, & Hamdy, 2013).

The urine samples are dissolved in $HNO_3$ in the microwave and the elemental analysis can be performed by ICP-MS (Amarasiriwardena, Lupoli, Potula, Korrick, & Hu, 1998) or atomic absorption spectrometry (Aggett & Aspell, 1976). Useful screening methods include the Merckoquant® colorimetric system (Merck, Darmstadt, Germany) based on the Marsh test (Marsh, 1836), Gutzeit test (Gutzeit, 1915; Kinniburgh & Kosmus, 2002) and a bioluminescence assay (Stocker et al., 2003).

### 4.4 | Estimate of the bone arsenic load/skeleton weight according to the Middlesex University multicompartment model

To estimate the BAsL/SW in patients that do not present a circadian variation in urinary arsenic concentration, we use the urinary arsenic concentration to calculate the fraction of the arsenic retained in the bone according to the multicompartment model of the Middlesex University (Adeyemi et al., 2010). This model states that under conditions of chronic intake the concentrations of arsenic in the body reach equilibrium after 100 days – only bone continues to accumulate arsenic. If the oral intake of arsenic is suspended then the predicted organ content rapidly falls for all organs except bone. The Middlesex University Model (herein referred to as "MUM") adequately predicts the measured behavior of arsenic in the body and its excretion in urine/feces following the single administration of $^{74}$As and $^{76}$As. It also produces an estimate of tissue content of $^{76}$As shortly after administration and following assumed chronic intake that is consistent with the measured distribution of arsenic in human tissues collected at necropsy. To estimate the fractional absorption of arsenic by the skeleton, we use the power function as described in the MUM for the whole body:

$$P_t = 108.9\, t^{-0.7321} \quad (1)$$

or "MUM Equation" where $P_t$ is the retained percentage of intake at time $t$.

To calculate the arsenic fraction retained by the skeleton, we establish $t$ = 100 in the MUM Equation days because this is the time at which the arsenic content of all tissues except bone reach steady state. The resulting fraction, 3.7% is multiplied by the patient's soft tissue compartment arsenic load as predicted by the MUM's model:

$$\text{BAsL} : \text{SW} = (\text{STAsL} \times 0.037) : \text{SW} \quad (2)$$

where SW is the skeletal weight, based on the Reference Man (ICRP, 2002) and STAsL the soft tissue arsenic load as predicted by the MUM. We consider the estimated level of arsenic exposition for the fetus as equal to its mother.

### 4.5 | Cutaneous disorders are important, though not mandatory in chronic arsenic intoxication

Although arsenic-related skin lesions such as hyperkeratosis and melanosis are common, skin changes are not mandatory manifestations of CAsI, and a large part of the population chronically exposed to arsenic may have high levels of arsenic in urine, hair and nails, even without showing apparent clinical symptoms, such as skin lesions (Kapaj, Peterson, Liber, & Bhattacharya, 2006). In the classic studies, only 11–15% of people chronically exposed to high arsenic concentrations of 100 ppb and above in drinking water exhibited such skin changes (Fatmi, Abbasi, Ahmed, Kazi, & Kayama, 2013; Tseng et al., 1968).

### 4.6 | Hematologic disorders

CAsE has been associated with depression of hematopoiesis and varying degrees of pancytopenia (Cheng et al., 2004; Vernhet et al., 2008; Woods & Fowler, 1977) and immune dysfunction (Kozul et al., 2009, 2009; Ragib et al., 2009).

Chronic eosinophilia and leukopenia have been reported in CAsI (Feussner, Shelburne, Bredehoeft, & Cohen, 1979; Groch & Heck, 1955; Sengupta, Saha, Jash, & Bandyopadhyay, 2012; Vrotsos, Martinez, Pizzolato, Martinez, & Sriganeshan, 2014). Arsenic may

increase the frequency of CD4(+) CD25(+) Foxp3(+) regulatory T cells (Song et al., 2015), and increased numbers of CD4(+) cells predispose to autoimmune neuritis when these cells are stimulated by proinflammatory mediators such as IFN-γ (Brunn et al., 2014). This is of special interest to the discussion of arsenic-related neuropathy, Guillain–Barré syndrome (GBS) and GB-like syndrome (GBLS), and ORAI. The frequency of peripheral blood mononuclear cells secreting IFN-γ and perforin has been shown to be significantly increased in human papillomavirus (HPV)-vaccinated versus non-vaccinated volunteers (Luckau, Wehrs, Brandau, Horn, & Lindemann, 2016), and IFN-γ has been shown to convert CD4(+) CD25(−) T cells in CD4(+) CD25(+) T cells in patients with GBS (Huang, Li, Liang, & Wang, 2009). The evidence on increased bone resorption associated with inappropriate activation of T cells such as during inflammation is well established (Zupan et al., 2013).

Anemia – including hemolytic, poikilocytic and megaloblastic anemia – has been frequently observed in environmental, nutritional, iatrogenic, osteoresorptive as well as experimental arsenic intoxication (Biswas, Sen, & Biswas, 2010; Bollini et al., 2010; Correia et al., 2009; Dani, 2013; Heck et al., 2008; Hopenhayn, Bush, Bingcang, & Hertz-Picciotto, 2006; Lee et al., 2004; Westhoff, Samaha, & Barnes, 1975). Arsenite causes extensive damage to red blood cells, which impairs their antioxidant system and alters the major cellular metabolic pathways (Maheshwari, Khan, & Mahmood, 2017). Splenomegaly with hypersplenism may be present in association with arsenic-related liver disease (Nevens et al., 1990).

### 4.7 | Gastrointestinal disorders

Loss of appetite, a metallic taste, nausea, vomiting, abdominal pain, watery diarrhea and increased thirst are common in acute arsenic poisoning (Campbell & Alvarez, 1989) but may be also observed in varying degree in acute-on-CAsI, as in ORAI (Dani, 2013). Jaundice, hepatomegaly, hepatic steatosis and liver disease like non-cirrhotic portal fibrosis and incomplete septal cirrhosis, with or without portal hypertension with bleeding esophageal varices and splenomegaly and hypersplenism have been associated with CAsE (Guha Mazumder, 2001; Liu & Waalkes, 2008; Nevens et al., 1990).

### 4.8 | Metabolic, endocrine and reproductive disorders

Arsenic is a known metabolic disruptor (Bernstam & Nriagu, 2000; Tseng, 2004), which is listed as an endocrine disruptor chemical by the World Health Organization (WHO, 2013).

Arsenate, the pentavalent arsenic species ($As^{5+}$) in high concentrations can substitute phosphate and interfere with a number of metabolic pathways. In the classic studies, sodium arsenate was used as a glycolytic inhibitor. Among the studies on the effects of arsenate on enzymes are the pioneering works of the most notable enzymologists of the twentieth century such as Otto Warburg (1883–1970), Frank Weistheimer (1912–2007) and Henry B. F. Dixon (1928–2008).

On the other hand, arsenite, the trivalent arsenic species ($As^{3+}$) has a high affinity for sulfhydryl groups and thus can form covalent bonds with the disulfide bridges in several enzymes, receptors and transporters involved in metabolism, thereby hampering the normal functions of these molecules. Arsenite in physiologically relevant concentrations can induce oxidative stress, and interferences in signal transduction or gene expression by arsenic or by its methylated metabolites are the most possible causes to arsenic-induced diabetes mellitus through mechanisms of induction of insulin resistance and beta cell dysfunction. Arsenite at physiologically relevant concentrations also shows an inhibitory effect on the expression of peroxisome proliferator-activated receptor γ, a nuclear hormone receptor important for activating insulin action (Tseng, 2004). In fact, CAsE has been associated with diabetes mellitus type 2 (Navas-Acien et al., 2006) as well as with obesity (Ceja-Galicia et al., 2017).

CAsE has been also associated with thyroid, gonadal and adrenal dysfunctions (Sun et al., 2016). CAsE is dose-related to poor reproductive outcomes such as abnormal fecundity and spontaneous abortion (Susko et al., 2017; Vahter, 2009; Zubair, Ahmad, & Qureshi, 2017).

Concentration-related increases of fetal loss and infant death have been observed in pregnant women chronically exposed to anthropogenic arsenic-contaminated drinking water (Ahmad et al., 2001; Rahman et al., 2007; Sohel et al., 2010). Arsenic easily passes the placenta, and human studies indicate a moderately increased risk of impaired fetal growth and increased fetal and infant mortality in CAsE (Vahter, 2009).

Fetal death in connection with CAsE during pregnancy may be indicative of ORAI. During normal pregnancy, bone resorption is increased to meet the fetus's needs for calcium (Black, Topping, Durham, Farquharson, & Fraser, 2000; Kovacs, 2012; Sanz-Salvador et al., 2015). Approximately 30 g of calcium is required for the successful mineralization of the fetal skeleton, and 80% of that amount is transferred during the third trimester, when placental calcium transport averages 110–120 mg $kg^{-1}$ $day^{-1}$ (Kovacs, 2012). The arsenic amounts released during the third trimenon from the bones of a pregnant woman who had been chronically exposed to environmental arsenic may be high enough to induce ORAI, because the fetus is more vulnerable to CAsI than its mother is (Laine et al., 2015; Vahter, 2008). Therefore, there is a causal nexus between CAsE → increased bone resorption rates during pregnancy → increased release of bone-bound arsenic → sublethal arsenic intoxication of the mother → transplacental passage of osteoresorptive arsenic to the fetal compartments → sublethal to lethal arsenic intoxication of the fetus.

Natural selection for arsenic tolerance may have increased the frequency of protective variants of the *As3MT* gene in some indigenous human populations exposed to this environmental risk over historical time (Schlebusch et al., 2013). This reproductive fitness adaption may have consequences to a number of other hardly won, nicely balanced human-specific adaptednesses (Dani, 2010a).

### 4.9 | Pulmonary disease

There is strong evidence of a general association between inorganic arsenic and non-malignant respiratory illness, including lung function impairment, chronic cough, chronic bronchitis and acute respiratory tract infections, pulmonary nodule, diffuse interstitial lung disease and chronic obstructive pulmonary disease, bronchiectasis, bullous-emphysema, as well as non-malignant lung disease mortality (Ergün

et al., 2017; Milton & Rahman, 2002; Smith et al., 2011). Some reports and studies have documented marked pulmonary as well as other negative health effects of early life arsenic exposure (i.e., in utero and/or early childhood) throughout the lifespan (Ragib et al., 2009; Sanchez, Perzanowski, & Graziano, 2016; Smith et al., 2006; Srivastava, D'Souza, Sen, & States, 2007; Steinmaus et al., 2016; Vahter, 2008). At least some forms of arsenic are well-established lung carcinogens in humans (Nemery, 1990; Smith, Goycolea, Haque, & Biggs, 1998; Yoshikawa et al., 2008).

### 4.10 | Cardiovascular disorders

Cardiovascular diseases including arterial hypertension (Abhyankar, Jones, Guallar, & Navas-Acien, 2012), blackfoot disease (Tseng, 1977; Yu et al., 1984) and stroke (Chiou et al., 1997; Navas-Acien et al., 2005) are dose-related to CAsE. Cardiomyopathy can be a result of arsenic intoxication (Ghariani et al., 1991; Hall & Harruff, 1989) or the combined cardiotoxic effect of alcohol and arsenic (Bao & Shi, 2010). Microcirculatory assessments revealed that deficits of capillary blood flow and permeability exist in clinically normal skin of patients with chronic arsenical poisoning (Yu, Lee, & Chen, 2002). The pathogenesis of non-pitting edema in CAsI is unclear but may involve a capillary leak syndrome with inflammation and maybe other capillary and interstitial changes (Prasad & Sinha, 2017; Unnikrishnan et al., 2004; Whiting & McCready, 2016).

Various arsenic compounds can induce ventricular tachycardia and prolongation of the QTc interval (Barbey & Soignet, 2001; Ducas, Seftel, Ducas, & Seifer, 2011; Goldsmith & From, 1980; Ohnishi et al., 2000; Zhou et al., 2004). The frequency of electrocardiographic changes that usually precede ventricular tachycardia and prolongation of the QTc interval are directly related to the dose of cumulative exposure to arsenic (Shen, Liu, Jiang, Lu, & Lu, 2004). Arsenic-mediated tachycardia is more frequent in patients with concomitant hypokalemia (Barbey, Pezzullo, & Soignet, 2003).

### 4.11 | Arsenic-mediated nephrotoxicity and nephropathy

Arsenic exposure as a risk factor for renal disease has been recognized as early as 1970 (Levy, Lewin, Ninin, Schneider, & Milne, 1979; Robles-Osorio, Sabath-Silva, & Sabath, 2015; Uldall, Khan, Ennis, McCallum, & Grimson, 1970; Zheng et al., 2015). However, the use of biomarkers such as KIM-1 (Kidney Injury Molecule-1) in studies on arsenic-mediated nephrotoxicity is recent (Cárdenas-González et al., 2016).

Arsenic-mediated nephrotoxicity is thought to involve uncoupled oxidative phosphorylation causing reductions in sodium, phosphate and glucose transport in the proximal tubule cells, which is manifested clinically as Fanconi syndrome (phosphaturia, glucosuria, aminoaciduria and low-molecular weight proteinuria) (Brazy, Balaban, Gullans, Mandel, & Dennis, 1980). Albuminuria associated with arsenic nephrotoxicity may be related to direct endothelial dysfunction in the podocyte and ascending thick portion of the nephron, with higher doses in the mg $kg^{-1}$ range resulting in moderate glomerular sclerosis and severe acute tubular necrosis involving all the nephron segments; acute tubulointerstitial nephritis has also been described as a clinical manifestation of acute arsenic poisoning (reviewed in Robles-Osorio et al., 2015). Fanconi syndrome and CKD with progressive deterioration of renal function are clinical characteristics associated with CAsE.

### 4.12 | Chronic kidney disease versus diabetes mellitus in chronic arsenic exposure

The precise causative mechanisms for both CKD and diabetes are generally unclear (Levey, Bilous, & Shlipak, 2016). In diabetes, outcomes such as microvascular (nephropathy, retinopathy and neuropathy eventually leading to blindness) and macrovascular (cardiac, cerebral and peripheral) changes are collectively known as diabetic complications because they occur more commonly in people with rather than without diabetes. However, CAsE itself can adversely impact the kidney function in diabetic patients independently from blood glucose levels (Robles-Osorio et al., 2015; Wang et al., 2009), and arsenic can aggravate CKD independently of other factors (Cheng et al., 2017).

Urinary arsenic has been dose-related to vascular disorders (Balakumar & Kaur, 2009; Moon et al., 2013; Navas-Acien et al., 2005; Srivastava et al., 2007; States, Srivastava, Chen, & Barchowsky, 2009; Tseng, 1977; Yu et al., 1984) and diabetes (Feseke et al., 2015; Navas-Acien et al., 2006). In addition, the pathological bone turnover dynamics in diabetes (Kasperk et al., 2017; Koye et al., 2017) as well as the decreased arsenic excretion in CKD may induce a vicious circle featured in increased arsenic release from the bone compartment and decreased arsenic excretion, which ultimately increase the CAsE and cause or aggravate ORAI in patients with diabetes and CKD.

Therefore, it must be considered that microvascular complications leading to CKD and blindness in CAsE may be causally unrelated to diabetes, as both vascular disorders and diabetes may be primarily related to CAsI. Accurate anamnesis, estimation of BAsL and a renal biopsy for diagnosis confirmation are indicated in such circumstances.

### 4.13 | Neoplasia

Arsenic and several of its compounds are listed in the IARC Group 1 of carcinogenic substances (IARC, 1980, 1982, 1987, 2004, 2009). There is no threshold or safe exposure level for arsenic, and the cancer morbidity and mortality effects of arsenic are dose-dependent (García-Esquinas et al., 2013). Chronic exposure to high concentrations of arsenic in drinking water results in the highest known increases in mortality attributable to any environmental exposure (Smith et al., 2007), and increased lung cancer risks are similar whether arsenic is ingested or inhaled (Smith, Weber, & Juhasz, 2009).

The carcinogenic effect of trivalent forms of arsenic is most likely due to their ability to induce oxidative stress responses (Kitchin & Conolly, 2010; Tapio & Grosche, 2006; Thomas, 2007) including the unfolded protein response (Li et al., 2011; Ramadan, Rancy, Nagarkar, Schneider, & Thorpe, 2009; Srivastava et al., 2013; Weng et al., 2014). Trivalent arsenic is able to activate a signaling cascade, which may be linked to the epigenetic reprogramming of the genome and the malignant transformation of cells (Bjørklund et al., 2017; Chen et al., 2013). Trivalent arsenic is capable of converting normal stem cells into cancer stem cells in different experimental settings (Chang, Chen, Thakur, Lu,

& Chen, 2014; Tokar et al., 2010; Xu, Tokar, Sun, & Waalkes, 2012). Arsenic has been shown to induce mutations in the mitochondrial DNA and this might be one of the mechanisms of arsenic-related tumorigenesis (Lee & Yu, 2016; Liu et al., 2005; Partridge, Huang, Hernandez-Rosa, Davidson, & Hei, 2007).

Although several arsenic compounds are capable of causing cancer, some arsenicals such as arsenic trioxide have been employed as highly effective drugs in the therapy of APL (M3) (Rao, Li, & Zhang, 2013) and some solid tumors (Chen et al., 2002; Subbarayan & Ardalan, 2014), either as a single agent or in combination with other agents.

## 4.14 | Arsenic neuropathy

The onset of arsenic neuropathy can be acute, as in arsenic poisoning or during treatment of APL with arsenic trioxide (Kühn, Sammartin, Nabergoj, & Vianello, 2016); chronic, as in environmental arsenic exposure; or acute-on-chronic, as in ORAI (Dani, 2013). The diagnosis of acute arsenic neuropathy is straightforward and based on the association of gastrointestinal disorders, encephalopathy and mood disorders (Bahiga, Kotb, & El-Dessoukey, 1978; Campbell & Alvarez, 1989; Ratnaike, 2003). Acute arsenic intoxication is strongly related to symmetrical peripheral neuropathy in the upper and lower limbs, so that the causal relation here is clear (Rodríguez, Jiménez-Capdeville, & Giordano, 2003; Vahidnia, van der Voet, & de Wolff, 2007). In addition, phrenic neuropathy with unilateral elevation of the diaphragm (Bansal, Haldar, Dhand, & Chopra, 1991) and fatigue (Bajorin, Halabi, & Small, 2009; Sińczuk-Walczak et al., 2014) have been associated with arsenic.

Yet the diagnosis of chronic arsenic neuropathy is relatively difficult to make, as it presupposes that a diagnosis of CAsI is made in the first place, which may be a difficult task for unprepared physicians. Although neurons as postmitotic cells and the nervous system in general are believed to be highly susceptible to the effects of CAsI, no CAsE threshold level for chronic arsenic neuropathy has yet been firmly established. One explanation for this situation as postulated by Perriol *et al*. (2006), is this: "Acute arsenic poisoning is less frequent and it is most often lethal. Therefore, its consequences are not well known, more precisely its neurological consequences." It is inferred that the low number of survivors of an acute arsenic poisoning preclude systematic clinical studies of CAsI to be performed.

Another explanation is that the more common, chronic, low-level arsenic neurotoxicity develops slowly over years and decades and it is often subclinical in the early stages. In the HEALS study, increased arsenic exposure in adults aged 20–50 years, as measured by both cumulative and urinary measures, was associated with subclinical sensory neuropathy assessed by a vibration sensitivity tester and expressed as toe vibration threshold (Hafeman et al., 2005). For every 50 μg As per mg Cr increase in total urinary arsenic, there was an increase in toe vibration threshold score. Symptoms of arsenic neuropathy last for years and may even increase after the exposure has ceased or following reduction of exposure (Lagerkvist & Zetterlund, 1994; LeQuesne & McLeod, 1977). Long-term cumulative arsenic exposure is a more important predictor of neuropathy than short-term fluctuations (Lagerkvist & Zetterlund, 1994).

Chronic arsenic neuropathy may be misdiagnosed also because CAsI affects multiple systems and a number of conditions caused or aggravated by arsenic such as diabetes mellitus, immune dysfunction and GBS may masquerade the underlying arsenic neurotoxicity. Severe axonal degeneration and loss, and segmental demyelination might be equally prominent pathological features of the neuropathy caused by arsenic, depending on arsenic dosage and duration of exposure (Goddard, Tanhehco, & Dau, 1992; Oh, 1991).

## 4.15 | Arsenic-induced Guillain–Barré-like syndrome

There is a strong, though not straightforward relation of GBS to arsenic neurotoxicity. At the outset, a distinction must be made between GBS and GBLS. The classical GBS is considered the most common and most severe acute paralytic neuropathy with a worldwide overall incidence of about 1.3:100 000 per annum (Willison, Jacobs, & van Doorn, 2016) and about 0.6:100 000 in children <15 years of age (McGrogan, Madle, Seaman, & de Vries, 2009). None the less, a misdiagnosis of GBS in arsenic polyneuropathy is not infrequent, and there are several reports of arsenic-induced sensorimotor neuropathy mimicking GBS with or without any systemic manifestation of arsenic intoxication affecting groups of arsenic-exposed people (Barton & McLean, 2013; Donofrio et al., 1987; Franzblau & Lilis, 1989; Gear, 1984; Jalal, Fernandez, & Menon, 2015; Kim et al., 2012; Mathew, Vale, & Adcock, 2010). In 2011, the crude incidence rate of GBS in Bangladesh, a country where anthropogenic environmental arsenic contamination is endemic, in children <15 years of age, appeared to be 2.5× to 4× higher than that reported in the literature (Islam et al., 2011).

Arsenic neuropathy and arsenic-induced GBLS commonly occur because of environmental arsenic contamination (Misra & Kalita, 2009), stressing the value of accurate environmental and occupational anamneses for a correct diagnosis. Kawasaki and colleagues (Kawasaki et al., 2002) describe the development of predominantly sensory polyneuropathy in patients exposed to anthropogenic arsenic released to the environment during decades of mining activities in the Toroku Valley, Japan. Their study and other surveys conducted on the Toroku Valley (Hotta, Harada, Hattori, et al., 1979; Nakamura et al., 1973a, 1973b) call attention to the long latency period between the beginning of the exposure to arsenic in different matrices (e.g., gaseous effluent, dust, water) and the first medical records of arsenic-related neuropathy.

Arsenic-induced neuropathy must be considered in the differential diagnosis of GBS in the presence of suspected or known CAsE, elevated arsenic in the body compartments including bone, as well as typical signs and symptoms of arsenic intoxication – no matter the presence of typical GBS changes such as albuminocytological dissociation in the cerebrospinal fluid, infectious or parasitic disease and autoimmune disease. The trigger of GBLS might be a cytokine storm (Bartfai et al., 2007; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998) leading to a significant increase in the bone resorption rate thereby causing an acute arsenic release from the bone compartment, accompanied by a polyspecific humoral response with systemic and intrathecal production of immunoglobulins, or a change in the blood–brain barrier permeability

caused by hyperthermia (Sharma & Johanson, 2007), stress (Tomkins et al., 2001) or arsenic itself (Rai, Maurya, Khare, Srivastava, & Bandyopadhyay, 2010).

This sequence of events may also be observed in response to vaccination, making it difficult to tell arsenic toxicity and the immune response to vaccination apart from each other. However, it is interesting that an association between HPV vaccination and GBS is frequently made, in spite of GBS following HPV vaccination being a very rare event (Katoulis et al., 2010; Ojha et al., 2014).

Recent infectious diseases caused by agents such as Zika virus, Dengue virus, Chikungunya virus or influenza virus as primary triggers of GBS can be ruled out if the onset of the neurological signs and symptoms occurs during the dry season, or when no infectious disease outbreak is recorded where the patient lives or the place the patient has visited on travel. Viral infections typically present a seasonality pattern with a peak during the wet season (Cao-Lormeau et al., 2016; Cortese et al., 2012; Oehler et al., 2015; Pastula et al., 2017; Ralapanawa, Kularatne, & Jayalath, 2015; Simon et al., 2016). Other exclusion criteria include a clinical presentation that may not fit completely to infection, e.g., no myalgia, no joint pain, no retrobulbar pain, no sign or symptoms suggestive of *Campylobacter* enteritis or *Mycoplasma* infection as possible triggers of GBS (Ang et al., 2000; Sharma et al., 2011).

Encephalopathy concomitant to GBLS is an important differential diagnosis criterion since it is considered pathognomonic of arsenic neuropathy and arsenic-induced GBLS as opposed to classical GBS and therefore we will review it separately as follows.

### 4.16 | Arsenic encephalopathy

Arsenic-induced encephalopathy characterized by confusion, word-finding difficulty, and mood and behavioral changes helps differentiate classical GBS from arsenic-induced GBLS (Dally & Conso, 1984; Lin et al., 2008; Perriol et al., 2006). Although short-term memory impairment, difficulty concentrating and disorientation associated with occupational exposure to arsenic can be at least partially reversible upon interruption of exposure (Morton & Caron, 1989), it is unclear whether recovery of cortical functions do occur or if compensatory strategies are developed (Bolla-Wilson & Bleecker, 1987). In addition, cognitive impairments can be long lasting in the context of a central neurodegenerative process caused or aggravated by CAsI. In a meta-analysis, arsenic concentrations in topsoils in the 7–18 ppm range have been found exponentially related to the prevalence and mortality of Alzheimer's disease and other dementias in European countries (Dani, 2010b). Even low arsenic concentrations can impair neurological function, causing cognitive dysfunction, including learning and memory deficits and mood disorders such as depression and anxiety (Chang et al., 2015; Tyler & Allan, 2014).

Arsenic reproductive and developmental toxicities can manifest themselves as mental retardation in the offspring of exposed parents (Kim & Kim, 2015; Liu, McDermott, Lawson, & Aelion, 2010). In the HEALS study, arsenic at low to moderate exposure levels (i.e., water arsenic levels >50 μg $l^{-1}$) was associated, in a dose–response manner, with reduced intellectual function in children (Wasserman et al., 2004, 2007).

### 4.17 | Implications for therapy

The most effective therapies of acute arsenic intoxication are removal of the exposure source and adequate ventilation and hydration, with close monitoring of the cardiorespiratory, hematological and renal status. The presently available chelation therapies have questionable value as they may aggravate the clinical status of poisoned patients (Andersen & Aaseth, 2016).

The conditions under which arsenic can be released from proteins in vitro may be too harsh to allow for any clinical application. However, correcting an eventual hypophosphatemia may decrease the As/P ratio by competitively displacing arsenic in the cell, thereby decreasing the arsenic toxicity (Ginsburg & Lotspeich, 1963). Adequate calcium and vitamin D (cholecalciferol) supplementation, as well as anti-osteoresorptive therapy with a bisphosphonate has been shown to be effective in reducing the ORAI (Dani, 2013).

Approaches to boost mitochondrial bioenergetics (Szalárdy, Zádori, Klivényi, Toldi, & Vécsei, 2015), including boosting the pyruvate dehydrogenase activity by thiamine (Costantini et al., 2016) and magnesium (Lonsdale, 2015) as well as using methylene blue as an alternative mitochondrial electron transfer (Yang et al., 2015) await experimental and clinical testing. The use of exogenous and endogenous antioxidants (Chan & Chan, 2015; Kulkarni & Cantó, 2015) is also a concept that deserves experimental and clinical verification. Activation of antioxidant systems and antioxidative agents such as glutathione, manganese superoxide dismutase and *N*-acetyl-cysteine hold promise to mitigate at least part of the deleterious effects of reactive oxygen species and CAsI (Zhang et al., 2011c).

### 4.18 | Implications for disease prevention

Long latency periods of sustained cancer risk, skin lesions and neuropathies are the hallmarks of CAsI. As the bones are the most important arsenic store compartment in the body, CAsE via osteoresorption may sustain the endogenous arsenic exposure for decades after an environmental arsenic exposure has decreased or even ceased. A rise in the osteoresorption rates or a decrease in the renal function or both may temporarily disturb the arsenic steady state in the body, leading to an acute-on-CAsE and ORAI. Cessation of arsenic exposure is the most effective preventative measure, and regular health monitoring, with attention to conditions known to induce ORAI, is necessary during and after arsenic exposure.

## 5 | CONCLUSION

Our CAsIDS can help physicians establish the diagnosis of CAsI and associated conditions. The development of a web-based application of CAsIDS will help make this diagnostic tool globally available to patients and physicians at www.arsenic.clinic, and help further validate it in different locations and clinical settings.

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## CONFLICT OF INTEREST

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