

Arsenicosis: A Review of Its Diagnosis and Treatment

Hye MA¹

Abstract

Prolong ingestion of arsenic contaminated water affects human health severely. More than 67 million people in Bangladesh are exposed to 0.05 mg/ liter or above of arsenic in their drinking water and it is now considering a biggest crisis in health and social sector in the modern world. Arsenicosis affects almost all the vital system of the body. Skin involvement is the earliest and commonest feature. Diagnosis is usually done by history, clinical feature and laboratory analysis. Still there is no international consensus on its diagnosis and treatment. Antioxidant and food supplements are tried with different range of success.

In this article, author describes the extent of arsenicosis and elaborates its diagnosis and treatment.

Keywords: Arsenicosis, Arsenic Contamination, Melanosis, Keratosis, Diagnosis, Treatment, Bangladesh.

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1. Corresponding Author:
Prof. Dr. Mohammad A. Hye
MBBS, M.Sc (University of London), FRCP (Edin)
Professor of Dermatology
Jalalabad Ragib-Rabeya Medical College
Patantula, Sylhet-3100.
E-mail: mohammadhye@hotmail.com
Mobile: 0171173704

Introduction

WHO working group defined Arsenicosis as "a chronic condition arising from prolonged ingestion of arsenic above safe dose for at least six months, usually manifested by characteristic skin lesions of melanosis and or keratosis with or without involvement of internal organs"¹.

The WHO Guideline value for arsenic in drinking water is set at 10 ppb. This is the drinking water standard adopted in many industrialized countries. However, many developing countries have kept the limit at 50 ppb for practical reasons².

Arsenicosis has become a major health problem in Bangladesh and West Bengal of India. It is also identified in many countries, irrespective of geographical or economic situation.

The symptoms and signs of arsenicosis differ in individuals, population groups and geographical areas. There are no internationally recognized criteria for the diagnosis and management of arsenicosis². The purpose of this paper is to review pathogenesis, diagnosis and treatment of this disorder.

Arsenic: Fact Sheet

Basic

Arsenic(As) is a natural component. Concentrations of arsenic in environment are following:

- i) Rock- 1.5-2.0 mg.
- ii) Contaminated soil up to 500 mg/kg.
- iii) Natural water - 0.1-0.4 microgram/L.

Arsenic is also emitted into the atmosphere by high-temperature processes such as coal-fired power generation plants, burning vegetation and volcanic action.

Arsenic combine with both metals and non-metal elements to form mainly following 2 types of compounds:

- i) Inorganic Arsenic (Trivalent, e.g. arsenates, and Pentavalent, e.g. arsenates).
- ii) Organic Arsenic{Mono- methyl arsonic acid (MMA), and Di-methyl arsinic acid (DMA)}.

The organic forms are comparatively non-toxic and mostly present in sea foods. Inorganic forms are toxic to human health and present in almost everywhere including air, water, soil and food.

Historical Background

Arsenic is known to human since from prehistoric era. Hippocrates recommended arsenic for treatment of skin ulcer & boil. In Indian sub-continent during the period of Buddha, it had been used for the treatment of many diseases. Alchemiste Geber-discovered arsenic oxide in 9th century. The poison was transformed into a medicine in the 1700s, when Thomas Fowler developed a solution of arsenic trioxide in potassium bicarbonate (1%w/v) for the treatment of asthma, chorea, eczema, pemphigus, and psoriasis³. It was also used empirically for the treatment of a variety of diseases, including leprosy, syphilis, and yaws⁴. In 1822 arsenic was identified as possible carcinogen. Interestingly enough, the dilemma of its effects and side effects is still going on; in spite of health

crisis due to arsenic poisoning, in many countries, arsenic trioxide (trisenox) has been used in the treatment of patients with acute promyelocytic leukemia⁵ in modern time and has even obtained the FDA approval in September 2000³ for use in the condition.

It is colorless, odourless, and tasteless and these characteristics contributed much to use it as a poison of choice. Arsenic poisoning, accidental or deliberate has been implicated in the illness or death of number of people throughout the history. Recent forensic evidence uncovered the evidences of arsenic poisoning as a cause of death of following prominent people: Francesco I de Medici, Grand duke of Tuscany (1541-1587), Eric VII of Sweden (1533-1577), George III of Great Britain (1738-1820), Theodor Ursinus (1749-1800), Napoleon Bonaparte (1769-1821)^{6,2}.

Arsenicosis: Bangladesh Perspective

"Bangladesh is in the midst of a mass poisoning in history, dangerous level of arsenic have been found in the ground water, entering millions of people sip by sip as they drink from over 4 million tube wells."(7)

Prior to the 1970s, Bangladesh had one of the highest infant mortality rates due to ineffective water purification sewage system. Millions of wells were constructed then to provide drinking water. In result, infant mortality and diarrheal diseases were reduced by 50%. But among 8.4 million wells, approximately 1 in 4 of these wells is now contaminated with arsenic. So far ground water contamination by arsenic is detected in 62 districts out of 64 and about 38200 arsenicosis patients were identified across the country⁸.

Arsenicosis was first reported in Chapai Nawabgonj district in year 1993. Now, it is estimated that between 35 to 77 million Bangladeshi or 28 to 62% of the total population of 125 million are now at risk of chronic arsenic poisoning¹⁹. It is described in world media as the largest known mass poisoning in history⁷.

Global Scenario:

Arsenic contamination of ground water is widespread and there are a number of regions where arsenic contamination of drinking-water is significant. It is now recognized that at least 140 million people in 50 countries have been drinking water containing arsenic at levels above the WHO provisional guideline value of 10 μ /L⁹.

In 1917, arsenicosis through ground water was first identified in Cordoba of Argentina (Bell Ville Disease). High concentrations of arsenic in drinking-water are found in various parts of the world including Argentina, Bangladesh, Chile, China, Hungary, India (West Bengal), Mexico, Nepal, Pakistan, Thailand, USA, and Viet Nam. It may be mentioned that in USA, and many other countries safe level of arsenic is below 0.01mg/l¹⁰.

Pathogenesis

After ingestion, arsenic is absorbed from the gastrointestinal tract; following absorption, arsenic undergoes metabolism through repeated reduction and oxidative methylation. It is widely accepted that methylated metabolites of inorganic arsenic are less reactive and less genotoxic; metabolism is regarded as a bio-inactivation mechanism.

Following metabolism, arsenic is rapidly cleared from blood, and only 0.1% of the arsenic remains in the plasma 24 hours after dosing. Urine is the most common route of elimination. As much as 45% to 75% of the dose is excreted in the urine within a few days to a week^{11,12}. The trivalent state of arsenic (As^{3+}), is widely distributed by virtue of its binding with sulfhydryl groups in keratin filament and has a tendency to accumulate in the skin, hair, nails, and mucosae of the oral cavity, esophagus, stomach, and the small intestine¹³. On the other hand, arsenate (As^{5+}) is the predominant form deposited in the skeleton because of its ability to replace phosphate in the apatite crystal in bones; as a result of this it is retained there for a longer time¹³. Within 30 hours of ingestion, arsenic deposits in the hair.

Daily consumption of water with greater than 50 micrograms per liter of arsenics, usually lead to health problems¹⁴.

Some people may be affected by lower levels of arsenic than others. Young children, the elderly, people with long-term illnesses, and unborn babies are at greatest risk of being affected.

If the exposure is of a large concentration then the progression of the arsenic poisoning event would lead to seizures, electrolyte disturbances and systemic shock and even death.

Trivalent arsenic is believed to be a carcinogen that induces chromosomal abnormalities. However, the exact molecular mechanism of arsenic induced carcinogenesis is less understood¹⁵.

It has been shown to induce sister chromatid exchanges, chromosomal aberrations, and also DNA-protein crosslinks in lymphocytes and in fibroblasts^{8,16} to explain this genotoxicity. Several mechanisms have been put forward, one of which emphasizes the role of reactive oxygen species in inducing the chromatid exchange¹⁷. The other theory highlights the role of arsenic in impairing the DNA repair process. DNA excision repair of thymine dimer in human fibroblast is inhibited by inorganic arsenic¹⁸. As^{+3} is found to inhibit DNA ligase¹⁹ and tubulin polymerization²⁰. It has also been shown that arsenic alters the activity of tumor suppressor gene p53 by DNA methylation.

Dermatological Manifestations

Arsenicosis is a multisystem disorder. Its common features are dermal lesions, peripheral neuropathy, skin cancer, bladder and lung cancers and peripheral vascular disease^{21,22,23,24,25,26}. Usually dermatological manifestations start to appear after minimum exposure periods of approximately 5 years. It may be 80% of them with urinary excretion of arsenic value between 1-3 mg/l²⁷. In one large-scale study, 3695 (20.6%) of 18,000 persons in Bangladesh and 8500 (9.8%) of 86,000 persons in West Bengal living in arsenic-affected districts were found to show dermatological features of arsenicosis²⁷. Pigmentary changes (melanosis) and hyperkeratosis are the predominant cutaneous effects; though at times, Bowen's disease or skin cancers may arise too.

Epidemiological studies in different regions of the world have consistently demonstrated a strong association between long-term inorganic arsenic ingestion and skin lesions, typically in the form of hyperkeratosis, hyperpigmentation or hypopigmentation. Observations of skin lesions following low chronic exposure have suggested that these characteristic dermal changes are sensitive indications of the toxic effects of inorganic arsenic²⁸. These effects have been demonstrated in many studies using different study designs. Exposure-response relationships and high risks have been observed for each of these end-points. The effects have been most thoroughly studied in Taiwan²⁹. In this large study a population of 40 421 was divided into three groups based on the arsenic content of their well water (high, >0.60 mg/l; medium, 0.30-0.59 mg/l; and low, <0.29 mg/l³⁰).

A similar exposure-response pattern was observed in a study in Bangladesh, where prevalence of keratosis was used as a surrogate for arsenic exposure^{31,32}. Dermatological lesions are classified or described different ways in different studies. GuhaMazumdar et al.³³ described skin lesions of arsenic in Table-I:

Table-I: Classification of skin lesions in arsenicosis

Grade-I	Mild	a. Diffuse melanosis. b. Suspicious spotty depigmentation/ pigmentation over trunk/limbs c. Mild diffuse thickening of soles and palms.
Grade-II	Moderate	a. Definite spotty pigmentation /depigmentation on the trunk and limbs, bilaterally distributed. b. Severe diffuse thickening (with/without wart like nodules of the palms and soles).
Grade-III	Severe	a. Definite spotty pigmentation/ depigmentation as above with few blotchy pigmented/ depigmented macular patches over trunks or limbs b. Pigmentation involving the undersurface of tongue and/or buccal mucosa. c. Larger nodules over thickened palms and soles. Diffuse verrucous lesions of the soles with cracks and fissures and keratotic horns over palms/soles.

Followings are the major dermatological manifestations:

1. Melanosis: The earliest and the commonest cutaneous sign is melanosis^{34,35} [Fig-1].



Figure-1: Melanosis.

In a study, conducted in the arsenic-prevalent area of Bangladesh, 100% of the patients of arsenic was showed pigmentary changes³⁵. Prolonged ingestion of arsenic results in pigmentation, most intense on the trunk, which can be diffused^{36,37} or localized, particularly affecting skin folds^{15,36}. Fine freckles of spotted pigmentary changes are also seen, known as 'rain-drop pigmentation'^{15,36} [Fig-2].

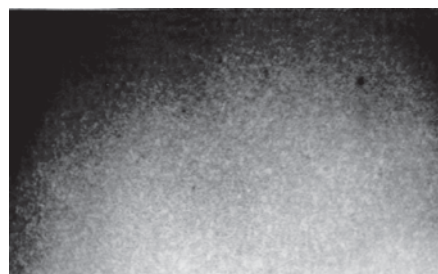


Figure-2: Rain drop pigmentation.

Sometimes macular areas of depigmentation may appear on normal skin or hyperpigmented background producing the distinctive appearance of 'leucomelanosis'^{15,37} [Fig-3].



Figure-3: Leucomelanosis.

Blotchy pigmentation may also involve mucous membranes such as the under surface of the tongue or buccal mucosa^{15,36,37}.

2. Keratosis: Arsenical hyperkeratosis appears predominantly on the palms and soles, and it has been found that keratosis on the soles is the most sensitive marker for the detection of arsenicosis at an early stage³⁸. Keratoses are graded as mild, [Fig-4] moderate, or severe

depending on the extent and severity¹⁵. In the mild variety of keratosis, the involved skin has hardened texture with papules less than 2 mm in size [Fig-4] that can be best felt by palpation. In the moderate variety, the lesions usually advance to form raised, punctate, keratosis, 2-5 mm in diameter [Fig-5]. When the keratosis becomes severe, it may form keratotic elevations more than 5 mm in size and sometimes become confluent and diffuse and sometimes result in cracks and fissures too^{34,39} [Fig-6].



Figure-4: Mild Keratosis.



Figure-5: Moderate Keratosis.



Figure-6: Severe Keratosis with crack and fissure.

Though palms and soles are primarily affected by hyperkeratosis, dorsa of the extremities and trunk may also be affected by it. It is interesting that palmar keratosis usually appears earlier than arsenic-related cancers of bladder and lung; thus it can act as an early marker of carcinogenicity⁴⁰.

3. Skin Cancers: Usually three types of skin cancers are observed: Bowen's disease; basal cell carcinoma and squamous cell carcinoma. In Japan, a study showed that Bowen's disease develop after 10 years, invasive squamous cell carcinoma develop after 20 years and internal malignancy particularly pulmonary malignancy develop after 30 years of arsenic exposure⁴¹.

It has been suggested that human papilloma virus (HPV) infection could constitute an additional risk factor for the development of non-melanoma skin cancer in humans chronically exposed to arsenic⁴². It is also reported that Merkel cell carcinoma⁴³ sometimes co-exist with Bowen's disease^{44,45} in patients with arsenicosis. There is also a study which has demonstrated an increased risk of melanoma in persons with elevated toenail arsenic concentrations⁴⁶, raising the issue relating to the role of arsenic in the development of melanoma. Skin cancer in arsenicosis can arise in the hyperkeratotic areas, as well as on non-keratotic areas of the trunk, extremities, or head^{47,48}.

Skin is thought to be perhaps the most sensitive site for arsenic-induced malignancies⁴⁹. The lesions are frequently multiple and involve covered areas of the body; unlike non-arsenical skin cancer, which usually presents as a single lesion and which occurs frequently on the exposed parts of the body^{29,50}.

Diagnosis:

The diagnosis relies on both laboratory and clinical criteria. A dermatologist or a clinical expert should differentiate the findings with other mimicking findings. A reliable history of consuming drinking water with an elevated concentration of arsenic for at least six months is sufficient to establish exposure. In the absence of adequate information regarding a subject's exposure history, the finding of elevated levels of arsenic in a subject's hair or nails could offer presumptive evidence of elevated arsenic exposure.

A diagnostic algorithm is formulated by WHO to provide a simplified scheme for implementing the case definition and classifying patients under field conditions and in various levels of health care facilities.

The present algorithmic approach for the diagnosis of arsenicosis highlights that the condition can be diagnosed as 'clinically confirmed' by an arsenic expert even without laboratory confirmation of raised arsenic content in drinking water, hair, or nail¹⁵. This algorithmic approach allows for further arsenic estimation if resources permit and a clinically confirmed case is further classified as clinical and laboratory confirmed, if laboratory results favor the diagnosis.

Histopathological Feature

Only few numbers of studies are found in literature regarding the types and patterns of histopathological

changes in skin lesions of arsenicosis. A study from Bangladesh⁵¹ showed that hyperkeratosis, parakeratosis, acanthosis, papillomatosis, hypergranulosis, and dysplastic changes to be the most important and constant findings. However, basal pigmentation and dermal changes were found to be inconstant features.

In another study, hyperkeratotic lesions of 70 patients with arsenicosis were compared with 20 controls⁵². Significant findings included hyperkeratosis (100%), parakeratosis (97%), acanthosis (95.7%), and papillomatosis (74%). The results were found to be significantly more ($P < 0.001$) in the patients than in controls. Basal cell pigmentation was found in 42.8% ($P > 0.05$) and dysplasia and malignant changes in 7% ($P > 0.1$). There is no study about the histopathology of arsenic related pigmentary lesions.

A study on the severe keratotic lesions of arsenicosis revealed that pre-cancerous skin lesions were in 6.6% and cancerous lesions in 0.8% of the patients⁵³.

Laboratory Criteria

1. Water: Consumption of drinking water with an arsenic concentration more than the prevailing national standard for at least 6 months is essential for the establishment of elevated exposure to arsenic. The maximum permissible limit of arsenic in drinking water as per the recent guideline of WHO is 0.01 mg/L. In India and Bangladesh, maximum permissible limit is 0.05 mg/L.

2. Nails and hairs: Both nails and hairs provide circumstantial evidence of arsenic exposure within the preceding 9 months. A hair arsenic concentration of 1 mg/kg is a marker of significant exposure; however, a concentration of 1.5 mg/kg in nail is required to correlate with a diagnosis of chronic arsenicosis. Hair analysis for arsenic is a semi-reliable method for confirming chronic toxicity. It does not discriminate between externally deposited arsenic and arsenic found within the hair shaft. Arsenic levels in hair sections may provide an indication of the time of exposure based on length from growth site. The hair of an individual who died 6 to 8 hours after ingestion of an arsenic overdose generally does not contain arsenic.

The current standard for arsenic analysis is atomic absorption spectroscopy,⁵⁴ which measures total arsenic, does not distinguish between pentavalent, trivalent, or organic arsenic⁵⁵.

Blood arsenic level is less useful than urine level unless exposure occurred on the same day. Serum (or blood) arsenic levels are detectable only during the first 2 to 4 hours after ingestion. The half-life of inorganic arsenic in blood is 2 hours and that of the methylated metabolites is 5 to 20 hours.

Urinary AS^{+3} and AS^{+5} levels present about 10 hours and return to normal in 20 hours. Urinary monomethylarsine and dimethylarsine levels peak at 40 to 60 hours and return to baseline in 6 to 20 days after ingestion. Urine (in absence of intake of seafood) - Level $> 50 \mu g As/L$ is indicative of continuing Exposure⁵⁵.

Treatment

Until now, there is no internationally recognized module to treat patients of arsenicosis. Following guidelines of WHO are now followed in Bangladesh:

Cessation of exposure to drinking water or other items with elevated concentration of arsenic;

- i. Administration of drugs or nutrients directed at hastening recovery or averting disease progression;
- ii. Provision of non-specific supportive care to improve physical symptoms or treat selected complications;
- iii. Secondary prevention of latent effects through medical surveillance, and
- iv. Counseling and education to address psychosocial sequelae of the illness and provision of appropriate rehabilitation.

Administration of non-specific nutritional supplements or anti-oxidants is practicing on many countries. It may hasten recovery or avert the disease progression. Some commonly used anti-oxidants include beta carotene, vitamin E and vitamin C. Still there is lacking of large-scale, randomized-controlled double-blinded trial to evaluate the efficacy of these treatment regimens. Their use depends on the national policy and the recommendations of the concerned medical bodies in respective countries.

In Bangladesh, a small number of clinical trial are done to ascertain the efficacy of mentioned drugs. Momin et al. found Selenium is very effective in a recent double blind study⁵⁶.

In another double blind randomized trial, Dr. Hasina Mamataz et al. found Spirulina as a very effective remedy in treatment of Arsenicosis⁵⁷. Following antioxidants or food supplements are commonly prescribed in Bangladesh:

- i. Retinol
- ii. Beta-carotene
- iii. Ascorbic acid
- iv. Alpha-tocopherol
- v. Selenium
- vi. Spirulina
- vii. Zinc

Symptomatic treatment for patients with keratosis or keratosis and melanosis includes the application of keratolytic agents. Presently, 5-10% of salicylic acid and 10-20% of urea-based ointment for the treatment of keratotic lesions is the most common prevailing practice in Bangladesh.

Counseling and education to combat the psychosocial sequelae of the illness is important. Programs should be implemented on educating patients and other community members about basic public health aspects of arsenicosis and to dispel misconceptions that may lead to stigmatization. It is also needed to provide appropriate rehabilitation.

The patient should be evaluated for the presence of other medical conditions, potentially related to arsenic exposure. Patients should be referred, as appropriate, for further treatment.

Conclusion

Arsenicosis is a public health crisis in Bangladesh and also in a part of India. However, the prevalence of this disease is not confined in this region only but it is prevailing in others countries also.

Still, knowledge an regarding arsenic contamination and its health hazards is less understood. A multidisciplinary approach is urgently needed to combat this high magnitude of health catastrophe.

Acknowledgement

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