How to Recognize and Treat Heavy Metal Poisoning from Occupational and Non-occupational Exposures

A focus on Lead, Mercury and Arsenic

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Presentation Outline

- Heavy Metals
- Sources of Exposure
- Clinical Manifestation of Toxicity
- Evaluation
- Management

Heavy Metals: Commonalities

- Natural components of the earth's crust
  - Lead
  - Mercury
  - Arsenic
- Sources of Exposure
  - Natural sources
  - Industrial processes
  - Commercial products
  - Folk remedies
  - Contaminated food and herbals
- All heavy metals are toxic in sufficient quantities
- Route of Exposure:
  - Food
  - Water
  - Air
- Toxicity
  - Complexes with critical proteins and enzyme systems containing sulfur, oxygen and nitrogen
  - Cellular dysfunction and death
  - Vulnerable organs include CNS, GI, CVS, Hematopoietic, Renal and PNS
- Toxicity Manifestations Vary
  - Heavy metal involved
  - Exposure level
  - Chemical and valance states
  - Acute vs. Chronic
  - Age of the individual
- Management Principles
  - Exposure mitigation
  - Supportive Care
  - Enhanced elimination (chelation)

LEAD

Lead: Characteristics

- Properties
  - Grey-silver heavy metal ~ 0.002% earth's crust
  - No physiologic role
  - Stored mainly in bone (95%) with half-life ~ 30 years
- History
  - Human use in paint 40,000 BC
  - Industrial Revolution
    - Leaded gasoline (stopped 1990)
    - Leaded paint (banned 1972)
  - Reports of toxicity
    - Ancient Egyptians
    - Leaders of Rome
      - Personality changes
      - Still Births
      - Sterility

- Sources of Exposure:
  - Occupational (inhalation)
    - Battery plant workers
    - Metal Welders
    - Painters
    - Construction workers
    - Crystal glass makers
    - Firing-range operator
    - Shipbuilders
    - Lead miners
  - Leaded-paint
    - Houses built before 1978
    - Lead dust
  - Commercial Products
    - Retained lead bullets
    - Curtain weights
    - Lead-glazed ceramics
  - Folk Remedies
    - Azarcon and greta

Lead: Chronic Toxicity in Adults

- Most commonly from occupational respiratory exposure
- Toxicity Manifestations
  - Hypertension
  - Anemia
  - Abdominal colic
  - Muscle and joint pain
  - Decreased fertility
  - Renal failure
  - Peripheral motor neuropathy (wrist drop)
  - Subtle neurological symptoms: lethargy and emotional liability
  - Encephalopathy (blood lead level > 100 mcg/dl)
- Important Considerations
  - Stored mainly in bone (95%) with half-life ~ 30 years
  - Blood lead level may increase with increased bone metabolism
  - Lead objects retained within the body releases lead
    - Acidic environment like synovial and stomach
    - Mechanical stress

Lead: Diagnosis

- Exposure History
- Unexplained Clinical Presentation
  - Hypertension, abdominal colic, wrist drop, renal failure, encephalopathy
- Blood lead level is the gold standard
- Other laboratory tests
  - CBC: hypochromic microcytic anemia and basopholic stippling
  - Basic metabolic panel
  - Urinalysis
  - X-ray fluorescence
- Occupational Monitoring
  - OSHA: periodic screening for exposure to air lead of 30 mcg/m3
  - Blood lead level check and follow up

Lead: Management

- Exposure mitigation
- Workplace
  - PPE
  - Safe work practices
  - Improving industrial engineering
- Chelation
  - Symptomatic
  - Blood lead level greater than 70 mcg/dl
- Choice of Chelating Agent
  - Oral Succimer (DMSA)
    - Mild symptoms
    - Blood lead level 70 – 100 mcg/dl
  - Intravenous CaNa2EDTA plus oral Succimer (or IM Dimercaprol)
    - Encephalopathy
    - Blood lead level > 100 mcg/dl

MERCURY

Mercury: Characteristics

- Properties
  - Liquid silvery appearance
  - No physiologic role
  - Three distinct forms with distinct toxicities
    - Elemental
    - Inorganic
    - Organic
- History
  - Human use
    - Décor Egypt1500 BC
    - Cosmetic Greece and Rome
    - Medicinal East Asia
    - Syphilitic Western Europe 1400 "two minutes with Venus, two years with Mercury"
  - Industrial Revolution
    - Workplace exposure
    - Hat makers in felt production (carroting)
  - Reports of toxicity
    - Hatters
    - "mad as a hatter"

Mercury: Elemental Mercury

- Heavy liquid that volatilize to an odorless gas at room temperature
- Sources of Exposure
  - Industrial processes and commercial applications
    - Thermometers, thermostats, barometers
    - Electronics
  - Dental amalgams
  - Home folk remedies

- Route of Exposure
  - Inhalation
  - Ingestion
- Chronic Toxicity Manifestations (inhalation)
  - GI upset
  - Acrodynia (pink disease)
  - Erethism
  - Hands tremor
  - Renal failure

Mercury: Acrodynia (pink disease)

Mercury: Elemental Mercury

- Diagnosis
  - Exposure history
  - Clinical syndrome
  - 24-urine for mercury is gold standard (<50 mcg)
  - Blood mercury level has limited value (<10 mcg/L)
- Management
  - Exposure mitigation
  - Chelation
    - Symptomatic
    - Elevated body burden of mercury
    - Oral Succimer (DMSA)

Mercury: Inorganic Mercury

- Mercury salts
  - Mercury Sulfide (HgS) Cinnabar
- Sources of Exposure
  - Historic
    - Cosmetics and skin treatments
    - Mercuric chloride in teething powder (calomel)
  - Current
    - Pesticides and herbicides
    - Home folk remedies
- Route of Exposure
  - Ingestion
- Toxicity Manifestations (Ingestion)
  - Corrosive to GI mucosa
  - Pink disease (calomel)
  - Renal failure
  - Nephrotic syndrome

Mercury: Inorganic Mercury

- Diagnosis
  - Exposure history
  - Clinical syndrome
  - 24-urine for mercury is gold standard (<50 mcg)
  - Blood mercury level has limited value (<10 mcg/L)

- Management
  - Exposure mitigation
  - Supportive care
  - Chelation (prompt)
    - Symptomatic
    - Elevated body burden of mercury
    - Dimercaprol IM
    - Oral Succimer (DMSA)
  - Hemodialysis
    - Renal failure

Mercury: Organic Mercury

- Organic mercurial compounds
  - Methyl mercury
  - Ethyl mercury (thimerosal)
  - Bioamplification
    - Microorganisms methylate inorganic and elemental mercury resulting in methylmercury
  - Well-absorbed by GI tract
  - Crosses blood-brain barrier and placenta
- Clinical Toxicity
  - Paresthesia (mouth area)
  - Visual fields constriction
  - Ataxia and tremor

- Sources of Exposure
  - Historic
    - Industrial
      - Minamata Japan 1956
      - 2263 adult poisonings
      - 63 congenital poisoning
      - Methylmercury in seafood
    - Medicinal
      - Iraq 1972
      - 6000 poisonings
      - 459 death
      - Methylmercury fungicide grain
  - Current
    - Dietary consumption of predatory fish (Tuna and sword fish)

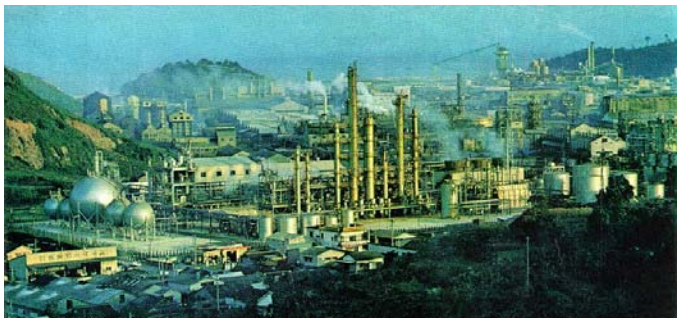
Minamata Bay

Minamata City

- Town of 200,000
- Fishery jobs
- Fish and Shellfish main diet

Minamata Bay

Chisso Factory
1932 - 1968



"Economic" success post WWII

MINAMATA DISEASE
Masazumi Harada (1971), translated by Sachie Tsushima and Timothy S. George, edited by Timothy S. George.

- 1956 Discovery of Minamata Disease
- Cat suicides
- Thousands of people affected and hundreds died
- Permanent brain damage and congenital defects "Minamata Disease"
- Methyl Mercury poisoning
- Seafood

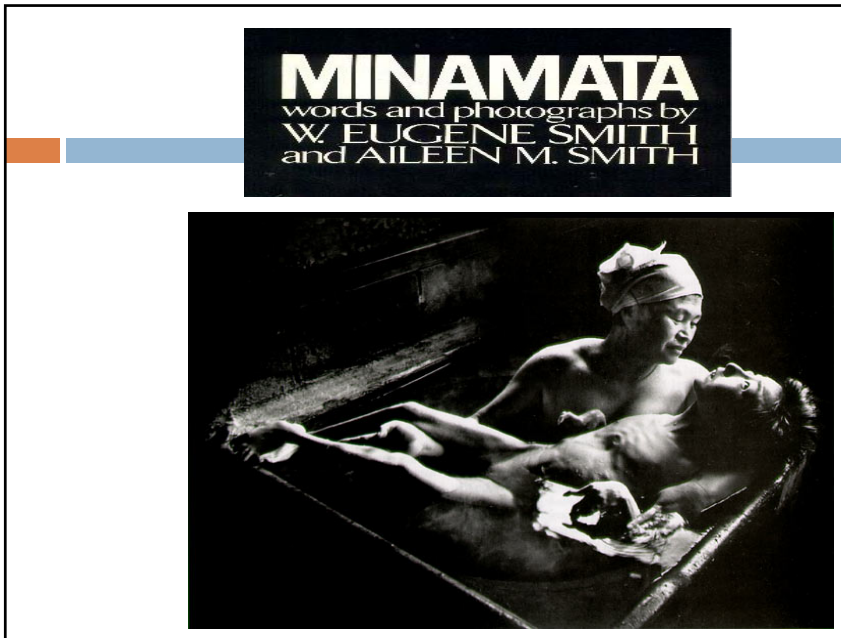
Distribution of Certified Patients (March 31, 2000)

Minamata Disease

- Acquired Minamata Disease, 1956
  - Chronic methyl mercury poisoning
  - Constricted visual fields
  - Hearing loss
  - Ataxia
  - Dysarthria
  - Tremors
  - Peripheral neuropathy
- Congenital Minamata Disease, 1962
  - Methyl mercury crosses the placenta (1ppm in cord blood)
  - Cerebral Palsy - like manifestations
  - Limb deformation

•Harada M: Minamata disease: Methylmercury poisoning in Japan caused by environmental pollution. *Crit. Rev. Toxicol.***25**:1-24 (1995)

•Harada M: Congenital Minamata disease, Intrauterine Methylmercury poisoning. In John L. Sever: Teratogen Update, Environmental birth defects risks, New York, Alan R. Liss, pp123-126 (1986)



Cover up Operation

- 1959 Research Group at Kumamoto University concluded that Mercury most probable cause
- 1959 Company physician banned from revealing animal experiment results linking the plant effluent to disease
- 1965 Discovery of Minamata Disease in Niigata, Agano River Basin
- 1966 Halt of Effluent discharge into the Bay
- 1968 Official government recognition of cause-effect between Methyl mercury and Minamata

"Death Flows from the Pipe"

- Chisso chemical plant dumping Mercury waste into the bay
- Inorganic Mercury *in* the effluent
- Mercury was used as catalyst in PVC and Acetaldehyde production

W. Eugene Smith
Industrial Waste
from the Chisso Chemical Company 1972

Mercury Concentrations in Tissue Samples (ppm)*

Human	
Control	less than 3.0
kidney	3.1-144.0
liver	0.3-70.5
brain	0.1-24.8
hair	96-705

Fish & Shellfish	
Oyster	5.6
Gray mullet	10.6
Short-necked clam	20.0
China fish	24.1
Crab	35.7

Cats	
Control	0.9-3.66
kidney	12.2-36.1
liver	37-145.5
brain	8-18
hair	21-70

•Harada M: Minamata disease: Methylmercury poisoning in Japan caused by environmental pollution. *Crit. Rev. Toxicol.***25**:1-24 (1995)

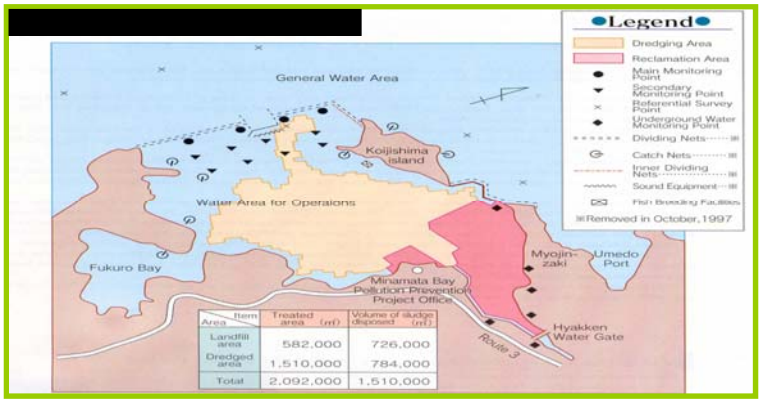
Immediate Actions

"Quarantine" the Bay

Fishing Ban

Clean-up Operation

Removal, Reclamation and Dredging

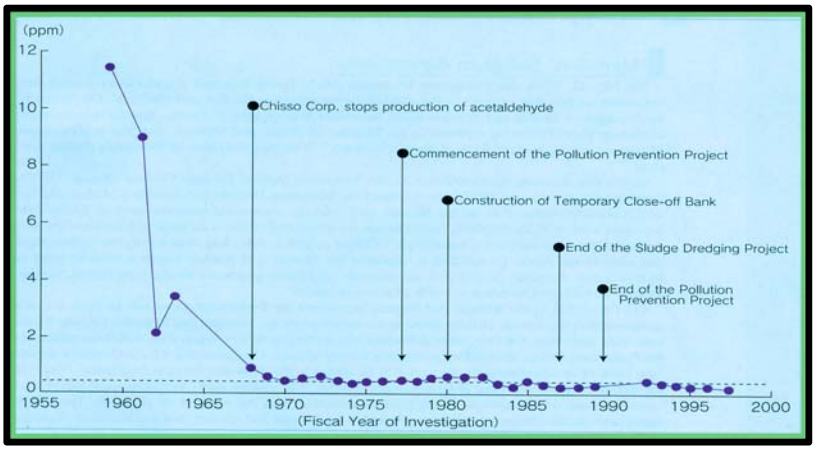


Clean-up Operation
Removal, Reclamation and Dredging

Minamata Bay Declared Safe
July 29, 1997

1997 Removal of a net preventing mercury-polluted fish in Minamata Bay (Kumamoto Pref.) from entering the sea.

Trends in Total Mercury Levels of Fish and Shellfish



Fight goes on …

- Victims appealed their cases to District Court, the High Court, and the Supreme Court, and the latter ruled in their favor.
- ~ 10,000 people awarded payment

Health Facilities for Minamata Victims

Memories

Mercury: Organic Mercury

- Diagnosis
  - Exposure history
  - Clinical syndrome
  - Whole Blood mercury level is the goal standard(<10 mcg/L) since more than 90% of methylmercury is bound to Hb in RBC
  - Urinary mercury is unreliable since methylmercury is eliminated primarily in the bile
- Management
  - Exposure mitigation
  - Supportive care
  - Chelation
    - Symptomatic
    - Elevated body burden of mercury
    - Dimercaprol
    - Oral Succimer (DMSA)

ARSENIC

Arsenic: Characteristics

- Properties
  - Arsenic compounds occur in four chemical forms
    - Inorganic (toxic)
    - Arsine (toxic)
    - Organic (little toxicity)
    - Elemental (non toxic)
  - Toxic arsenic compounds occur in two oxidation states
    - Arsenite is ten times more toxic than arsenate
  - No physiologic role
- Sources of exposure
  - Human use
    - Criminal Poisoning (suspected in Mozart and Napoleon deaths)
  - Industry
    - Paints
    - Pesticide, herbicide, fungicide
    - Wood preservatives
    - Semiconductors
  - Medicinal
    - Arsenic trioxide for leukemia
  - Geological contamination
    - Drinking water
  - Seafood
    - Organic arsenic (little toxicity)

Arsenic: Inorganic Arsenic

- Acute Toxicity
  - GI: nausea, vomiting, bloody rice watery diarrhea
  - Hematologic: bone marrow suppression
  - CVS: QT prolongation and torsade de pointes
  - PNS: peripheral neuropathy
  - CNS: encephalopathy
- Chronic Toxicity
  - Dermatologic: hyperpigmentation and keratosis on palms and soles
  - Nails: Mees lines
  - PNS: peripheral neuropathy
  - CVA: peripheral vascular disease and HTN

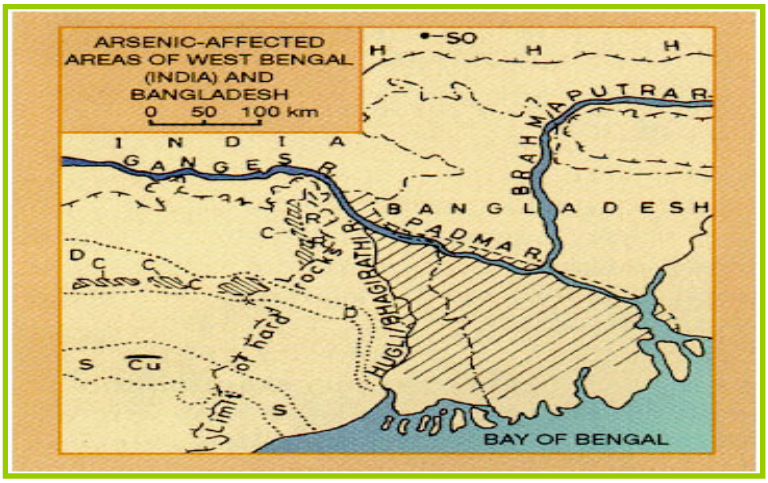
Bangladesh

Arsenic

- Bangladesh. 1970 - 2005
- 3695 with arsenic poisoning
- Tube Well's water
- Groundwater naturally contaminated with arsenic

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)

Bangladesh



Chronic Arsenic Toxicity

Physical Parameters	Bangladesh
Area in sq km	148,393
Population in millions	120
Total number of districts	64
Number of arsenic-affected districts (groundwater arsenic >10 µg/L)	60
Number of arsenic-affected districts (groundwater arsenic >50 µg/L)	50
Area of arsenic-affected districts in sq km	118,849
Population of arsenic-affected districts in millions	104.9
Total number of hand tube well water samples analyzed	34,000
% of samples with arsenic >10-µg/L	56
% of samples with arsenic >50-µg/L	37
Number of arsenic-affected blocks/police stations with arsenic >50 µg/L	178
Number of arsenic-affected villages (est.) with groundwater arsenic >50 µg/L	2000
Population drinking water with arsenic >50 µg/L (in millions)	25
Districts surveyed for arsenic patients	34
Number of districts in which arsenical skin lesions were identified	32
Villages surveyed for arsenic patients	244
Number of villages in which arsenical lesions were identified	217
Persons from affected villages screened for arsenic patients (preliminary survey)	18,000
Number of patients, including children, identified as having clinical manifestations	3695 (20.6%)
% of children with arsenical skin lesions of total patients	6.11

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)

Clinical Stages of Arsenic Chronic Toxicity

- Asymptomatic
- Dermatological manifestations
- Internal stage
  - Anemia and HTN
  - Lungs, Liver and Spleen
- Malignant stage
- Peripheral neuropathy

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)

Dermatologic Signs

- Keratosis
- Melanosis
- Melanokeratosis
- Leucomelanosis
- Mucous membrane pigmentation

Arsenic: Chronic Toxicity

Arsenic Concentrations in Patients

Parameters	Bangladesh			
	As in Hair[a] (µg/kg)	As in Nail[b] (µg/kg)	As in Urine[c] (µg/L)	As in Skin Scale[d] (µg/kg)
No. of observations	4386	4321	1084	705
Mean	3390	8570	280	5730
Median	2340	6400	115.78	4800
Minimum	280	260	24	600
Maximum	28,060	79,490	3086	53,390
Standard deviation	3330	7630	410	9790
% of samples having arsenic above normal	83.15	93.77	95.11	—

[a] Normal levels of arsenic in hair range from 80–250 µg/kg; 1000 µg/kg indicates toxicity (40).
[b] Normal levels of arsenic in nails ranges from 430–1080 µg/kg (41).
[c] Normal excretion of arsenic in urine ranges from 5–40 µg/1.5 L (per day) (42).
[d] Normal value for skin scale arsenic not defined.

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)

Well's Water

Mudur: BMJ, Volume 320(7238).March 25, 2000.822

Wells Water and Arsenic Level

Fig. 2. **Plot showing proliferation of tube wells from 1970 to 2000 in the 21-km² area of Araihazar, Bangladesh, from which samples were collected** (not all the wells installed in 2000 were sampled by the time the survey ended in June 2000)

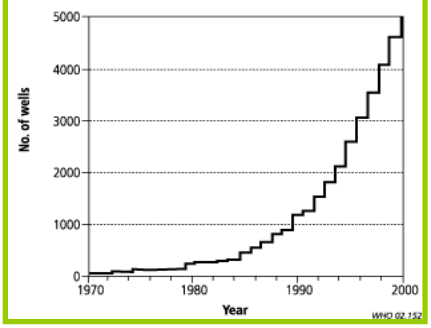
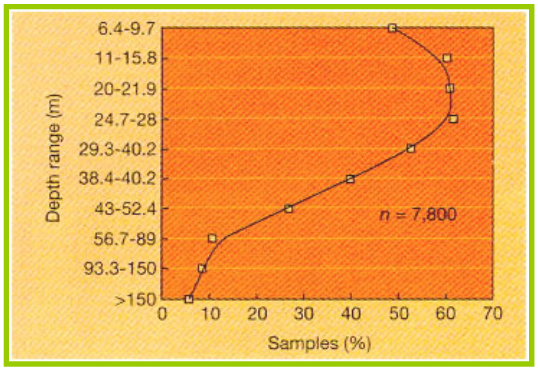


Table 2. Range of concentration of arsenic in water from 4997 tube wells in Araihazar, Bangladesh, 2000

Arsenic concentration (µg/l)	% of wells
<5–10	28
11–50	20
51–100	17
101–900	35

Bulletin of the World Health Organization. 80(9):732-7, 2002

Well's Depth and Arsenic Level

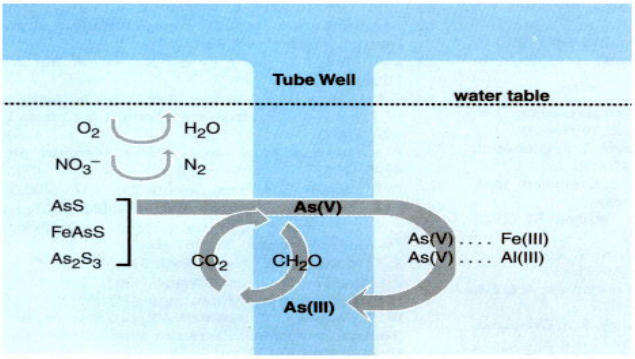


Chowdhury: Nature, Volume 401(6753).October 7, 1999.545-546

Arsenic

- Naturally occurring heavy metalloid
- Often associated with other metals in nature like copper, lead and gold
- Released into environment from volcanoes and erosions from mineral deposits
- Certain bacteria use arsenic salts for energy generation in the absence of oxygen and thus mobilize it from solid to aqueous phase

Contamination of Water Aquifer



Oremland: Science, Volume 300(5621).May 9, 2003.939-944

Promotion of well-switching

Deep Well in West Bengal, LAG©

Arsenic: Inorganic Arsenic

- Diagnosis
  - Exposure history
  - Clinical syndrome
  - 24-urine arsenic is the gold standard (<50 mcg/L)
  - Speciation of urinary arsenic should be done to differentiate inorganic from organic forms
  - Whole blood arsenic level rapidly declines in 24-48 hours (<1 mcg/dl)
  - EKG
  - CBC, CMP
  - Nerve conduction studies
- Management
  - Exposure mitigation
  - Supportive care
  - Chelation
    - Symptomatic
    - Elevated body burden of mercury
    - Dimercaprol
    - Oral Succimer (DMSA)
  - Hemodialysis
    - Renal failure