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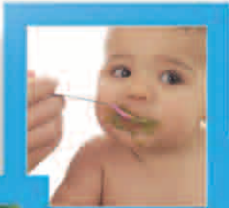
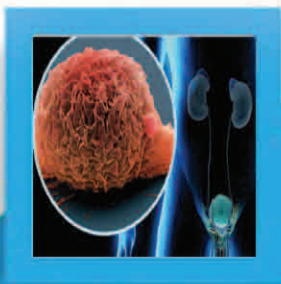
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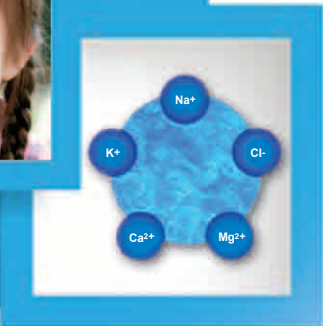
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# the SQUARE

Healthcare bulletin



- ▀ *Down Syndrome*
- ▀ *Diarrhea in Children*
- ▀ *Electrolyte Imbalance*
- ▀ *Bladder Cancer*



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### Editorial



Dear Doctor

It gives us a great pleasure to introduce the latest edition of "the SQUARE"!

In this issue we bring you the details on "Down Syndrome" which is by far the most common and best known chromosomal disorder in humans. A topic on "Diarrhea in Children", a leading cause of childhood mortality and morbidity in the world has been incorporated in this issue. We have also published a feature on "Electrolyte Imbalance" that can be caused by a deficiency or an overabundance of minerals in the body leading to disruption of the overall balance and functioning of the nerves, cardiovascular system, and muscles. Besides, we have highlighted on "Bladder Cancer", a common urologic cancer that has the highest recurrence rate of any malignancy. The incidence of bladder cancer varies considerably among countries, with the highest incidence rates seen in Western countries and the lowest rates in Asian countries.

We hope that you will find this healthcare bulletin both interesting and informative.

On behalf of the management of SQUARE, we wish you and your family a healthy and blissful life!

Thank you!



*Omar Akramur Rab*

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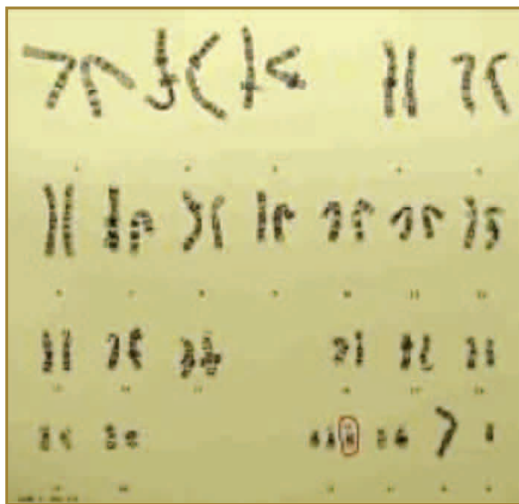
**Product Management Department**

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Key title: The square (Dhaka)

Abbreviated key title: Square (Dhaka)

Down syndrome is by far the most common and best known chromosomal disorder in humans and the most common cause of intellectual disability. It is primarily caused by trisomy of chromosome 21, which gives rise to multiple systemic complications as part of the syndrome. However, not all defects occur in each patient; there is a wide range of phenotypic variation.



*G-banded karyotype showing trisomy 21 (47,XY,+21).*

### Background

For centuries, people with Down syndrome have been alluded to in art, literature and science. It wasn't until the late nineteenth century, however, that John Langdon Down, an English physician, published an accurate description of a person with Down syndrome. It was this scholarly work, published in 1866, that earned Down the recognition as the "father" of the syndrome. Although other people had previously recognized the characteristics of the syndrome, it was Down who described the condition as a distinct and separate entity.

In recent history, advances in medicine and science have enabled researchers to investigate the characteristics of people with Down syndrome. In 1959, the French physician Jérôme Lejeune identified Down syndrome as a chromosomal condition. Instead of the usual 46 chromosomes present in each cell, Lejeune observed 47 in the cells of individuals with Down syndrome. It was later determined that an extra partial or whole copy of chromosome 21 results in the characteristics associated with Down syndrome. In the year 2000, an international team of scientists successfully

identified and catalogued each of the approximately 329 genes on chromosome 21. This accomplishment opened the door to great advances in Down syndrome research.

### Signs and symptoms

When recording the history from the parents of a child with Down syndrome, the clinician should include the following:

- ❑ Parental concern about hearing, vision, developmental delay, respiratory infections and other problems
- ❑ Feeding history to ensure adequate caloric intake
- ❑ Prenatal diagnosis of Down syndrome
- ❑ Vomiting secondary to gastrointestinal tract blockage by duodenal web or atresia
- ❑ Absence of stools secondary to Hirschsprung disease
- ❑ Delay in cognitive abilities, motor development, language development (specifically expressive skills), and social competence
- ❑ Arrhythmia, fainting episodes, palpitations or chest pain secondary to a heart lesion
- ❑ Symptoms of sleep apnea, including snoring, restlessness during sleep, difficulty awaking, daytime somnolence, behavioral changes and school problems

On physical examination, patients with trisomy 21 have characteristic craniofacial findings, such as the following:

- ❑ Flat occiput and a flattened facial appearance
- ❑ Brachycephaly
- ❑ Epicanthal folds
- ❑ Flat nasal bridge
- ❑ Upward-slanting palpebral fissures
- ❑ Brushfield spots
- ❑ Small nose and small mouth
- ❑ Protruding tongue
- ❑ Small and dysplastic ears
- ❑ Generous nuchal skin
- ❑ Diastasis recti
- ❑ Single transverse palmar crease
- ❑ Short fifth finger with clinodactyly
- ❑ A wide space between the first and second toes.

General physical features in patients with Down syndrome may include the following:

- ❑ Shortened extremities
- ❑ Short, broad hands, with short fifth middle phalanx and single transverse palmar creases (~60% of patients)
- ❑ Joint hyperextensibility or hyperflexibility
- ❑ Neuromuscular hypotonia
- ❑ Dry skin
- ❑ Premature aging
- ❑ Wide range of intelligence quotients
- ❑ Congenital heart defects

### Risk factors

#### Maternal Age

As a woman's eggs age, there is a higher risk of the chromosomes dividing incorrectly. Therefore the risk of Down syndrome increases with a woman's age.

Mother's age	Chances of having child with Down syndrome
20	1 in 1,600
25	1 in 1,300
30	1 in 1,000
35	1 in 365
40	1 in 90
45	1 in 30

#### Previous child with Down syndrome

Generally, couples who have had one child with Down syndrome have a slightly increased risk (about 1%) of having a second child with Down syndrome.

#### A carrier parent

Parents who are carriers of the genetic translocation for Down syndrome have an increased risk depending on the type of translocation, therefore prenatal screening and genetic counseling are important. People with Down syndrome rarely reproduce. Fifteen to thirty percent of women with trisomy 21 are fertile and they have about a 50% risk of having a child with Down syndrome. There is no evidence of a man with Down syndrome fathering a child. While the incidence of births of children with Down syndrome increases with maternal age, more children are born to women under the age of 35 due to higher fertility rates. Eighty percent of children with Down syndrome are born to women under the age of 35 years.

### Pathophysiology

The extra chromosome 21 affects almost every organ system and results in a wide spectrum of phenotypic consequences. These include lifethreatening complications, clinically significant alteration of life course (eg, intellectual disability) and dysmorphic physical features. Down syndrome decreases prenatal viability and increases prenatal and postnatal morbidity. Affected children have delays in physical growth, maturation, bone development and dental eruption.

Two different hypotheses have been proposed to explain the mechanism of gene action in Down syndrome: developmental instability (ie, loss of chromosomal balance) and the so-called gene-dosage effect. According to the gene-dosage effect hypothesis, the genes located on chromosome 21 have been overexpressed in cells and tissues of Down syndrome patients and this contributes to the phenotypic abnormalities.

The extra copy of the proximal part of 21q22.3 appears to result in the typical physical phenotype, which includes the following:

- ❑ Intellectual disability-Most patients with Down syndrome have some degree of cognitive impairment, ranging from mild (intelligence quotient [IQ] 50-75) to severe impairment (IQ 20-35); patients show both motor and language delays during childhood
- ❑ Characteristic facial features
- ❑ Hand anomalies
- ❑ Congenital heart defects- Almost half of affected patients have congenital heart disease, including ventricular septal defect and atrioventricular canal defect

Molecular analysis reveals that the 21q22.1-q22.3 region, also known as the Down syndrome critical region (DSCR), appears to contain the gene or genes responsible for the congenital heart disease observed in Down syndrome.

A new gene, DSCR1, identified in region 21q22.1-q22.2, is highly expressed in the brain and the heart and is a candidate for involvement in the pathogenesis of Down syndrome, particularly with regard to intellectual disability and cardiac defects.



Abnormal physiologic functioning affects thyroid metabolism and intestinal malabsorption. Patients with trisomy 21 have an increased risk of obesity. Frequent infections are presumably due to impaired immune responses and the incidence of autoimmunity, including hypothyroidism and rare Hashimoto thyroiditis, is increased.

Patients with Down syndrome have decreased buffering of physiologic reactions, resulting in hypersensitivity to pilocarpine and abnormal responses on sensory-evoked electroencephalographic (EEG) tracings. Children with leukemic Down syndrome also have hyperreactivity to methotrexate.

Decreased buffering of metabolic processes results in a predisposition to hyperuricemia and increased insulin resistance. Diabetes mellitus develops in many affected patients. Premature senescence causes cataracts and Alzheimer disease. Leukemoid reactions of infancy and an increased risk of acute leukemia indicate bone-marrow dysfunction.

Children with Down syndrome are predisposed to developing leukemia, particularly transient myeloproliferative disorder and acute megakaryocytic leukemia. Nearly all children with Down syndrome who develop these types of leukemia have mutations in the hematopoietic transcription factor gene, GATA1. Leukemia in children with Down syndrome requires at least 3 cooperating events: trisomy 21, a GATA1 mutation, and a third undefined genetic alteration.

Musculoskeletal manifestations in patients with Down syndrome include reduced height, atlanto-occipital and atlantoaxial hypermobility, and vertebral malformations of the cervical spine. These findings may lead to atlanto-occipital and cervical instability, as well as complications such as weakness and paralysis.

About 5% of patients with Down syndrome have gastrointestinal (GI) manifestations, including duodenal atresia, Hirschsprung disease and celiac disease. Many patients with trisomy 21 have otorhinolaryngologic manifestations, including hearing loss and recurrent ear infections. About 60% of patients have ophthalmic manifestations.

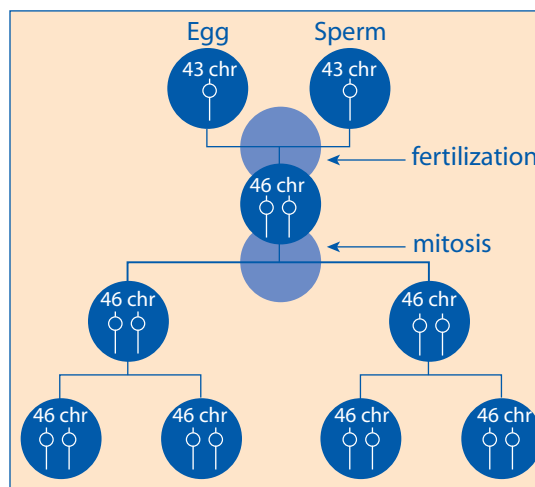
## Types

There are three types of Down syndrome: trisomy

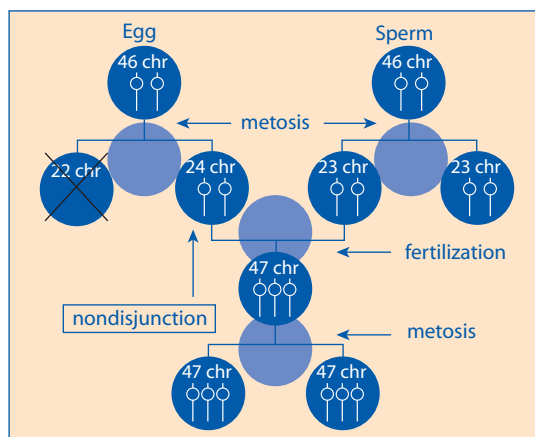
21 (nondisjunction), translocation and mosaicism.

### Trisomy 21 (nondisjunction)

Down syndrome is usually caused by an error in cell division called "nondisjunction." Nondisjunction results in an embryo with three copies of chromosome 21 instead of the usual two. Prior to or at conception, a pair of 21st chromosomes in either the sperm or the egg fails to separate. As the embryo develops, the extra chromosome is replicated in every cell of the body. This type of Down syndrome, which accounts for 95% of cases, is called trisomy 21.



Typical cell division

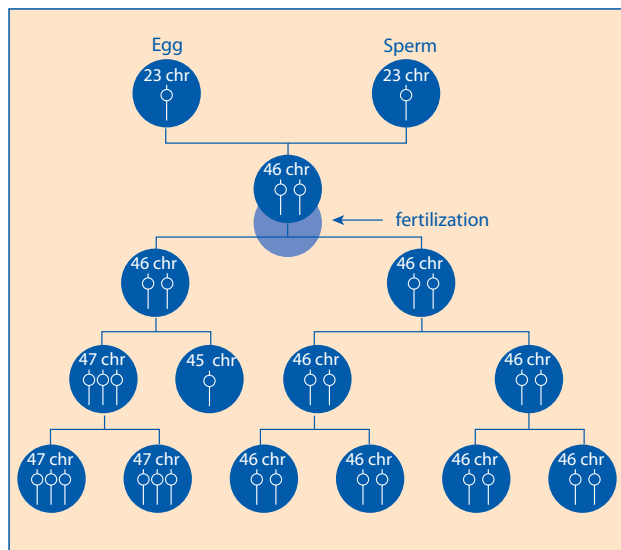


Trisomy 21 (nondisjunction) cell division

### Mosaicism

Mosaicism occurs when nondisjunction of chromosome 21 takes place in one - but not all - of the initial cell divisions after fertilization. When this occurs, there is a mixture of two types of cells, some containing the usual 46 chromosomes and others containing 47. Those cells with 47 chromosomes contain an extra chromosome 21.

Mosaicism accounts for about 1% of all cases of Down syndrome. Research has indicated that individuals with mosaic Down syndrome may have fewer characteristics of Down syndrome than those with other types of Down syndrome.



*Mosaic cell division*

However, broad generalizations are not possible due to the wide range of abilities people with Down syndrome possess.

## Translocation

Translocation accounts for about 4% of all cases of Down syndrome. In translocation, part of chromosome 21 breaks off during cell division and attaches to another chromosome, typically chromosome 14. While the total number of chromosomes in the cells remain 46, the presence of an extra part of chromosome 21 causes the characteristics of Down syndrome.

## Diagnosis

Laboratory studies that may be helpful include the following:

- ❑ Complete blood count with differential
- ❑ Bone marrow examination to rule out leukemia
- ❑ Thyroid-stimulating hormone (TSH) and thyroxine (T4) to rule out hypothyroidism
- ❑ Papanicolaou smears every 1-3 years in sexually active women
- ❑ Cytogenetic studies (karyotyping) for diagnosis of trisomy 21
- ❑ Interphase fluorescence in situ hybridization

(FISH) for rapid diagnosis of trisomy 21

- ❑ Assessment of mosaicism for trisomy 21 (lymphocyte preparations, buccal mucosa cellular preparations, FISH, scoring frequency of trisomic cells)
- ❑ Immunoglobulin G
- ❑ Maternal serum biochemical markers

Current evidence does not support performing routine screening radiographs for the assessment of potential atlantoaxial instability in asymptomatic children. However, imaging studies that may be considered include the following:

- ❑ Echocardiography in every newborn suspected of having trisomy 21 to identify congenital heart disease

- ❑ Ultrasonography

Postnatal diagnostic tests that may be warranted include the following:

- ❑ Auditory brainstem response (ABR), or brainstem auditory evoked response (BAER)
- ❑ Pediatric ophthalmic examination
- ❑ Growth charts specifically for children with Down syndrome
- ❑ Rigorous dental hygiene and dental evaluation

## Management

There are no medical treatments for intellectual disability associated with Down syndrome, but improved medical care has greatly enhanced quality of life and increased life expectancy. Elements of medical care include the following:

- ❑ Genetic counseling
- ❑ Standard immunizations and well child care
- ❑ Management of specific manifestations of Down syndrome and associated conditions (eg, endocrine, infectious, cardiac, respiratory, neurologic, psychiatric, dermatologic or dental disorders)
- ❑ Early intervention programs

Special considerations in adolescents are as follows:

- ❑ Ongoing monitoring measures, including annual audiologic evaluation and annual ophthalmologic evaluation
- ❑ Ongoing management of manifestations of the syndrome and associated conditions
- ❑ Discussion of issues related to the transition to adulthood

Appropriate surgical management of associated conditions should be provided, as follows:

- ❑ Timely surgical treatment of cardiac anomalies is crucial for optimal survival
- ❑ Prompt surgical repair is necessary for GI anomalies, most commonly, duodenal atresia and Hirschsprung disease
- ❑ Surgical intervention may be necessary to stabilize the upper segment of the cervical spine if neurologic deficits are clinically significant
- ❑ Congenital cataracts must be extracted soon after birth and subsequent correction with glasses or contact lenses provided
- ❑ Careful anesthetic airway management is needed because of the associated risk of cervical spine instability
- ❑ Adenotonsillectomy may be performed to manage obstructive sleep apnea

### Possible Complications

- ❑ Airway blockage during sleep
- ❑ Compression injury of the spinal cord
- ❑ Endocarditis
- ❑ Eye problems
- ❑ Frequent ear infections and increased risk of other infections
- ❑ Hearing loss
- ❑ Heart problems
- ❑ Gastrointestinal blockage
- ❑ Weakness of the back bones at the top of the neck

### Prognosis

The overall outlook for individuals with Down syndrome has dramatically improved. Many adult patients are healthier, are better integrated into society, and have increased longevity than before. However, their life expectancy is still reduced.

Approximately 75% of concepti with trisomy 21 die in embryonic or fetal life. Approximately 25-30% of patients with Down syndrome die during the first year of life. The most frequent causes of death are respiratory infections (bronchopneumonia) and congenital heart disease. The median age at death is 49 years. However, some patients reach their sixth decade.

Congenital heart disease is the major cause of morbidity and early mortality in patients with Down syndrome. In addition, esophageal atresia with or

without transesophageal (TE) fistula, Hirschsprung disease, duodenal atresia, and leukemia contribute to mortality. The high mortality later in life may be the result of premature aging.

In elderly persons with Down syndrome, relative preservation of cognitive and functional ability is associated with better survival. Clinically, the most important disorders related to mortality in this population are dementia, mobility restrictions, visual impairment, and epilepsy (but not cardiovascular disease). In addition, the level of intellectual disability and institutionalization are associated with mortality.

Individuals with Down syndrome have a greatly increased morbidity, primarily because of infections involving impaired immune response. Large tonsils and adenoids, lingual tonsils, choanal stenosis, or glossoptosis can obstruct the upper airway. Airway obstruction can cause serous otitis media, alveolar hypoventilation, arterial hypoxemia, cerebral hypoxia, and pulmonary arterial hypertension with resulting cor pulmonale and heart failure.

Leukemia, thyroid diseases, autoimmune disorders, epilepsy, intestinal obstruction and increased susceptibility to infections (including recurrent respiratory infections) are commonly associated with Down syndrome.

The aging process seems to be accelerated in patients with Down syndrome. Many patients develop progressive Alzheimer-like dementia by age 40 years, and 75% of patients have signs and symptoms of Alzheimer disease.

A delay in recognizing atlantoaxial and atlanto-occipital instability may result in irreversible spinal-cord damage. Visual and hearing impairments in addition to intellectual disability may further limit the child's overall function and may prevent him or her from participating in important learning processes and developing appropriate language and interpersonal skills. Unrecognized thyroid dysfunction may further compromise central nervous system (CNS) function.

### References :

- ❑ [www.emedicine.medscape.com](http://www.emedicine.medscape.com)
- ❑ [www.ndss.org/down syndrome](http://www.ndss.org/down%20syndrome)
- ❑ [american pregnancy association](http://americanpregnancy.org)
- ❑ [medlineplus](http://medlineplus)

**D**iarrheal disease is a leading cause of child mortality and morbidity in the world and mostly results from contaminated food and water sources. Worldwide, 780 million individuals lack access to improved drinking water and 2.5 billion lack improved sanitation. Diarrhea due to infection is widespread throughout developing countries.

In developing countries, children under three years old experience on average three episodes of diarrhea every year. Each episode deprives the child of the nutrition necessary for growth. As a result, diarrhea is a major cause of malnutrition, and malnourished children are more likely to fall ill from diarrhea.

## Definition

The normal frequency and consistency of bowel movements varies with a child's age and diet and the definition of diarrhea varies accordingly.

**Frequency** - It is normal for young infants to have up to 3 to 10 stools per day, although this varies depending upon the child's diet (breast milk versus formula; breastfed children usually have more frequent stools). Older infants, toddlers and children normally have one to two bowel movements per day. Diarrhea can usually be defined as an increase in stool frequency to twice the usual number per day in infants, or three or more loose or watery stools per day in older children. But frequent passing of formed stools is not diarrhea, nor is the passing of loose, "pasty" stools by breastfed babies.

**Consistency and color** - The consistency and color of a child's stool normally changes with age. Young infants, especially those who are breastfeeding, usually have soft stools. Their stools may be yellow, green, or brown, and/or appear to contain seeds or small curds.

All children's stools can vary as a result of their diet. Development of stools that are runny, watery, or contain mucus is a significant change that should be monitored. The presence of visible blood or black stools is never normal and always requires medical attention.

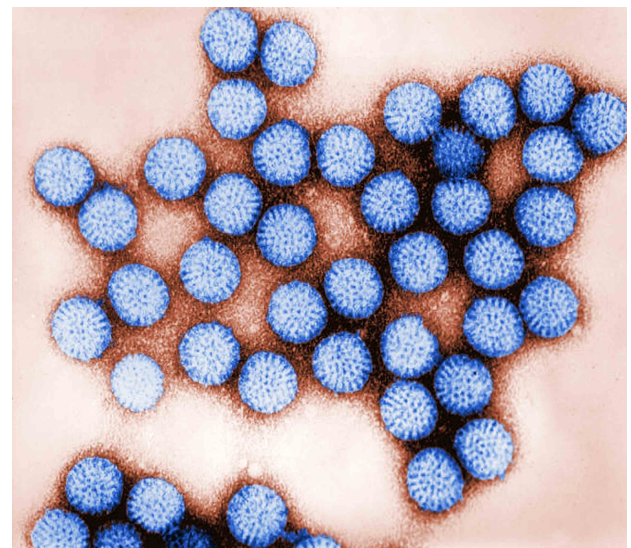
**Duration** - A prolonged history of diarrhea (lasting 14 days or longer) is evaluated and treated differently than an acute case of diarrhea (lasting usually several hours to days).

## Pathophysiology

Mechanisms of diarrhea may include the following: Osmotic, Secretory, Inflammatory and Malabsorptive.

**Osmotic diarrhea** results from the presence of nonabsorbable solutes in the GI tract, as with lactose intolerance. Fasting for 2 to 3 days stops osmotic diarrhea.

**Secretory diarrhea** results from substances (e.g., bacterial toxins) that increase secretion of chloride ions and water into the intestinal lumen. Secretory diarrhea does not stop with fasting.



*One of the common cause of childhood diarrhea is Rota virus*

**Inflammatory diarrhea** is associated with conditions that cause inflammation or ulceration of the intestinal mucosa (eg, Crohn disease, ulcerative colitis). The resultant outpouring of plasma, serum proteins, blood, and mucous increases fecal bulk and fluid content.

**Malabsorption** may result from osmotic or secretory mechanisms or conditions that lead to less surface area in the bowel. Conditions such as pancreatic insufficiency and short bowel syndrome and conditions that speed up transit time cause diarrhea due to decreased absorption.

## Etiology

The causes and significance of diarrhea differ depending on whether it is acute (<2 wk) or chronic (> 2 wk). Most cases of diarrhea are acute.



Some causes of diarrhea		
Cause	Suggestive findings	Diagnostic Approach
<b>Acute</b>		
Antibiotics (eg, broad-spectrum antibiotics, multiple concomitant antibiotics)	Temporal relationship of onset of diarrhea with taking of antibiotics	Clinical evaluation
Bacteria (eg, <i>Campylobacter</i> sp, <i>Clostridium difficile</i> , <i>Escherichia coli</i> [can cause hemolytic-uremic syndrome], <i>Salmonella</i> sp, <i>Shigella</i> sp, <i>Yersinia enterocolitica</i> )*	<ul style="list-style-type: none"> <li>● Fever, bloody stool, abdominal pain</li> <li>● Possibly petechiae or pallor (in patients with hemolytic uremic syndrome)</li> <li>● History of contact with animals (<i>E. coli</i>) or reptiles (<i>Salmonella</i>)</li> <li>● History of eating undercooked food (<i>Salmonella</i>)</li> <li>● Recent (&lt; 2 mo) antibiotic use (<i>C. difficile</i>)</li> <li>● Day care center outbreak</li> </ul>	<ul style="list-style-type: none"> <li>● Stool culture</li> <li>● Fecal leukocytes</li> <li>● If patients appear ill, CBC, renal function tests, and blood culture</li> <li>● If patient has recently been given antibiotics, stool testing for <i>C. difficile</i> toxin</li> </ul>
Food (allergy or poisoning)	<ul style="list-style-type: none"> <li>● <b>Allergy:</b> Urticarial rash, lip swelling, abdominal pain, vomiting, diarrhea, difficulty breathing within minutes to several hours after eating</li> <li>● <b>Poisoning:</b> Nausea, vomiting, abdominal pain, diarrhea several hours after ingestion of contaminated food</li> </ul>	Clinical evaluation
Parasites (eg, <i>Giardia intestinalis</i> [lamblia], <i>Cryptosporidium parvum</i> )*	<ul style="list-style-type: none"> <li>● Abdominal bloating and cramping, foul-smelling stools, anorexia</li> <li>● Possibly history of travel, use of contaminated water source</li> </ul>	<ul style="list-style-type: none"> <li>● Microscopic examination of stool for ova and parasites</li> <li>● Stool antigen tests</li> </ul>
Viruses (eg, astrovirus, calicivirus, enteric adenovirus, rotavirus)*	<ul style="list-style-type: none"> <li>● 5 days of diarrhea with no blood</li> <li>● Often vomiting</li> <li>● Possibly fever</li> <li>● Contact with infected people</li> <li>● Appropriate season for the infection</li> </ul>	Clinical evaluation
<b>Chronic</b>		
Hirschsprung enterocolitis	<ul style="list-style-type: none"> <li>● Delayed passage of stool &gt; 48 h after birth</li> <li>● Possibly long-standing history of constipation</li> <li>● Billious vomiting, abdominal distention, ill appearance</li> </ul>	<ul style="list-style-type: none"> <li>● Abdominal x-ray</li> <li>● Barium enema</li> <li>● Rectal biopsy</li> </ul>
Short bowel syndrome	History of bowel resection (eg, for necrotizing enterocolitis, volvulus, or Hirschsprung disease)	Clinical evaluation
Lactose intolerance	<ul style="list-style-type: none"> <li>● Abdominal bloating, flatus, explosive diarrhea</li> <li>● Diarrhea after ingestion of dairy products</li> </ul>	<ul style="list-style-type: none"> <li>● Clinical evaluation</li> <li>● Sometimes hydrogen breath test</li> <li>● Sometimes test for reducing substances in stool (to check for carbohydrates) and stool pH (&lt; 6.0 indicates carbohydrates in stool)</li> </ul>

Cause	Suggestive findings	Diagnostic Approach
Cow's milk protein intolerance (milk protein allergy)	<ul style="list-style-type: none"> <li>● Vomiting</li> <li>● Diarrhea or constipation</li> <li>● Hematochezia</li> <li>● Anal fissures</li> <li>● Failure to thrive</li> </ul>	<ul style="list-style-type: none"> <li>● Symptom resolution when cow's milk protein is eliminated</li> <li>● Sometimes endoscopy or colonoscopy</li> </ul>
Excessive juice intake	History of excessive juice or sugary drink intake (4-6 oz/day)	Clinical evaluation
Chronic nonspecific diarrhea of childhood (toddler's diarrhea)	<ul style="list-style-type: none"> <li>● Age 6 months-5 yr</li> <li>● 3-10 loose stools/day typically during the day while awake and sometimes immediately after eating</li> <li>● Sometimes undigested food visible in stool</li> <li>● Normal growth, weight gain, activity and appetite</li> </ul>	Clinical evaluation
Immunodeficiency (eg, HIV infection, IgA or IgG deficiency)	<ul style="list-style-type: none"> <li>● History of recurrent skin, respiratory tract, or intestinal infections</li> <li>● Weight loss or poor weight gain</li> </ul>	<ul style="list-style-type: none"> <li>● HIV test</li> <li>● CBC</li> <li>● Immunoglobulin levels</li> </ul>
Inflammatory bowel disease (eg, Crohn disease, ulcerative colitis)	<ul style="list-style-type: none"> <li>● Bloody stools, crampy abdominal pain, weight loss, anorexia</li> <li>● Possibly arthritis, oral ulcerations, skin lesions, rectal fissures</li> </ul>	Colonoscopy
Eosinophilic gastroenteritis	Abdominal pain, nausea, vomiting, weight loss	<ul style="list-style-type: none"> <li>● CBC for peripheral blood (eosinophilia)</li> <li>● Sometimes IgE level</li> <li>● Endoscopy and/or colonoscopy</li> </ul>
Celiac disease (gluten enteropathy)	<ul style="list-style-type: none"> <li>● Symptom onset after introduction of wheat into diet (typically after age 4-6 mo)</li> <li>● Failure to thrive</li> <li>● Recurrent abdominal pain</li> <li>● Bloating</li> <li>● Diarrhea or constipation</li> </ul>	<ul style="list-style-type: none"> <li>● CBC</li> <li>● Serologic screening for celiac disease (IgA antibody to tissue transglutaminase)</li> <li>● Endoscopy for duodenal biopsy</li> </ul>
Cystic fibrosis	<ul style="list-style-type: none"> <li>● Repeated episodes of pneumonia or wheezing</li> <li>● Fatty and foul-smelling stools</li> <li>● Bloating, flatus</li> </ul>	<ul style="list-style-type: none"> <li>● Sweat test</li> <li>● Genetic testing</li> </ul>
Acrodermatitis enteropathica	Sometimes psoriasiform rash, angular stomatitis	Zinc levels
Constipation with encopresis	<ul style="list-style-type: none"> <li>● History of hard stools</li> <li>● Fecal incontinence</li> </ul>	Abdominal x-ray

\*Can also cause chronic diarrhea.

## Evaluation

### History

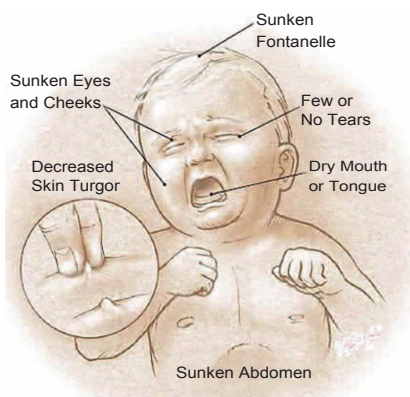
**History of present illness** focuses on quality, frequency, and duration of stools, as well as on any accompanying fever, vomiting, abdominal pain, or blood in the stool. Parents are asked about current or recent (within 2 mo) antibiotic use. Clinicians should establish elements of the diet (eg, amounts of juice, foods high in sugars or sorbitol). Any history of hard stools or constipation should be noted. Clinicians should also assess risk factors for infection (eg, recent travel; exposure to questionable food sources; recent contact with animals at a petting zoo, reptiles, or someone with similar symptoms).

**Review of systems** should seek symptoms of both complications and causes of diarrhea. Symptoms of complications include weight loss and decreased frequency of urination and fluid intake (dehydration). Symptoms of causes include urticarial rash associated with food intake (food allergy); nasal polyps, sinusitis, and poor growth (cystic fibrosis); and arthritis, skin lesions, and anal fissures (inflammatory bowel disease).

**Past medical history** should assess known causative disorders (eg, immunocompromise, cystic fibrosis, celiac disease, inflammatory bowel disease) in the patient and family members.

### Physical examination

Vital signs should be reviewed for indications of dehydration (eg, tachycardia, hypotension) and fever.



*Lookin for Signs of dehydration is very important*

General assessment includes checking for signs of

lethargy or distress. Growth parameters should be noted.

Because the abdominal examination may elicit discomfort, it is advisable to begin the examination with the head. Examination should focus on the mucous membranes to assess whether they are moist or dry. Nasal polyps; psoriasiform dermatitis around the eyes, nose, and mouth; and oral ulcerations should be noted.

Examination of the extremities focuses on skin turgor, capillary refill time, and the presence of petechiae, purpura, other skin lesions (eg, erythema nodosum, pyoderma gangrenosum), rashes, and erythematous, swollen joints.

Abdominal examination focuses on distention, tenderness, and quality of bowel sounds (eg, high-pitched, normal, absent). Examination of the genitals focuses on presence of rashes and signs of anal fissures or ulcerative lesions.

### Red flags

The following findings are of particular concern:

- Tachycardia, hypotension, and lethargy (significant dehydration)
- Bloody stools
- Bilious vomiting
- Extreme abdominal tenderness and/or distention
- Petechiae and/or pallor

### Interpretation of findings

Antibiotic-related, post-infectious, and anatomic-related causes of diarrhea are typically clear from the history. Determination of the time frame helps establish whether diarrhea is acute or chronic. Establishing the level of acuity is also important. Most cases of acute diarrhea have a viral etiology, are low acuity, and cause fever and non-bloody diarrhea. However, bacterial diarrhea can lead to serious consequences; manifestations include fever, bloody diarrhea, and possibly a petechial or purpuric rash.

Symptoms associated with chronic diarrhea can vary and those of different conditions can overlap. For example, Crohn disease and celiac disease can cause oral ulcerations, a number of conditions can cause rashes and any condition can lead to a poor growth pattern.

If the cause is unclear, further tests are done based on clinical findings (see Some Causes of Diarrhea).

## Investigation

Testing is unnecessary in most cases of acute self-limited diarrhea. However, if the evaluation suggests an etiology other than viral gastroenteritis, testing should be directed by the suspected etiology (see Some Causes of Diarrhea).

## Treatment

Specific causes are treated (eg, gluten-free diet for children with celiac disease).

General treatment focuses on hydration, which can usually be done orally. IV hydration is rarely essential.

## Rehydration

Oral rehydration solution (ORS) is a mixture of clean water, salt and sugar. ORS is absorbed in the small intestine and replaces the water and electrolytes lost in the faeces. Sports drinks, sodas, juices, and similar drinks do not meet these criteria and should not be used. They generally have too little Na and too much carbohydrate to take advantage of Na/glucose cotransport, and the osmotic effect of the excess carbohydrate may result in additional fluid loss. ORS is recommended by the WHO and is widely available in the pharmacies without a prescription.

Small, frequent amounts are used and increasing gradually as tolerated. The patient is reassessed. If signs of dehydration persist, the same procedure is repeated.

## Zinc supplements

World Health Organization (WHO) recommends routine use of zinc supplementation, at a dosage of 20 milligrams per day for children older than six months or 10 mg per day in those younger than six months, for 10-14 days beside ORS. Supplementary zinc benefits children with diarrhea because it is a vital micronutrient essential for protein synthesis, cell growth and differentiation, immune function, and intestinal transport of water and electrolytes.

## Diet and nutrition

There has been much confusion and folklore about optimal foods for children with diarrhea. Fortunately,

a number of studies have examined recommendations that are proven to be effective.

Children who are not dehydrated should continue to eat a regular diet and infants who are breastfeeding should continue to do so unless the parent(s) is told otherwise by their clinician. Dehydrated children require rehydration (replacement of lost fluid) and suitable oral rehydration solutions are the most physiologic. After being rehydrated, severely affected children will be able to resume a normal diet.

For chronic nonspecific diarrhea of childhood (toddler's diarrhea), dietary fat and fiber should be increased, and fluid intake (especially fruit juices) should be decreased.

For other causes of chronic diarrhea, adequate nutrition must be maintained, particularly of fat-soluble vitamins.

Specific suggestions for children who are tolerating a regular diet include the following:

- ❑ Most children with diarrhea tolerate full strength cow's milk products. It is not necessary to dilute or avoid milk products, except in children with known allergies to cow's milk.
- ❑ Recommended foods include a combination of complex carbohydrates (rice, wheat, potatoes, bread), lean meats, yogurt, fruits, and vegetables. High fat foods are more difficult to digest and should be avoided.
- ❑ The unnecessary restriction of a child's diet to clear liquids or the BRAT diet (bananas, rice, applesauce, toast) results in inadequate intake of nutrients (calories and/or protein). Giving only clear liquids for several days can actually prolong diarrhea (called "starvation stools").
- ❑ Apple, pear and cherry juice and other beverages with high sugar content should be avoided. Soft drinks or sports drink should also be avoided because they have too much sugar and have inappropriate electrolyte levels for the patient with diarrhea. When clear liquids are recommended, the best choices are the commercially prepared oral rehydration solutions.

## Drug

Medications such as antibiotics and antidiarrheal agents are generally not necessary and could be harmful for infants or children with diarrhea.



Antibiotic therapy is nearly always inappropriate in view of the usual viral etiology. Inappropriate use of antibiotics will not improve diarrhea. Furthermore, antibiotics can cause side effects and lead to development of antibiotic resistance. Rarely, antibiotics may be needed in cases of bacterial infection when a specific cause of the diarrhea has been found or is strongly suspected, particularly after recent travel. When required, antibiotic regimes will be determined by the results of stool culture and sensitivities and local guidelines

Antidiarrheal agents (eg. Loperamide) are not recommended for infants or children, since the benefits do not outweigh the risks. One risk of using an antidiarrheal agent is that it could mask worsening symptoms and delay treatment.

"Racecadotril" is an intestinal antisecretory enkephalinase inhibitor. It inhibits the breakdown of endogenous enkephalins and so reduces the hypersecretion of water and electrolytes into the intestine. It does not modify the duration of intestinal transit. It is licensed (outside USA) for the complementary symptomatic treatment of acute diarrhoea together with oral rehydration (and the usual support measures) when these measures alone are insufficient and it is not possible to treat the cause.

#### Consider hospital admission if:

- ❑ There is any concern regarding the underlying diagnosis.
- ❑ There are signs of dehydration, especially if aged under 6 months.
- ❑ There is inability to comply with oral rehydration - eg, vomiting, poor social circumstances.
- ❑ There is a pre-existing medical condition which may worsen with diarrhoea (eg, diabetes).

#### Prevention

Key measures to prevent diarrhoea according to WHO include:

- ❑ Access to safe drinking water
- ❑ Use of improved sanitation
- ❑ Hand washing with soap

- ❑ Exclusive breastfeeding for the first six months of life
- ❑ Good personal and food hygiene



*Handwashing with soap is an effective way to prevent diarrhea*

- ❑ Health education about how infections spread
- ❑ Rotavirus vaccination.

Globally, there are nearly 1.7 billion cases of diarrheal disease every year. Among children under 5 years old diarrhea is the 2nd leading cause of death and is responsible for killing around 760,000 per year. It is also a leading cause of malnutrition in children under five years old. But a significant proportion of diarrheal disease can be prevented through safe drinking water and adequate sanitation and hygiene.

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**E**lectrolytes are essential minerals in the body that regulate important physiological functions. They are necessary for nerve and muscle function, the body-fluid balance and other critical processes. When dissolved in water, electrolytes separate into positive and negatively charged ions and can carry an electrical charge. These particles are present in blood, plasma, urine and other body fluids. Electrolytes exist in the form of sodium, potassium, calcium, chloride and magnesium and that can be obtained from fluids, supplements and foods.

Electrolytes must exist in the body within a narrow concentration range in order to effectively serve a variety of critical functions. The normal range is measured per liter of blood.

too little water. This water loss can occur from illnesses with vomiting, diarrhea, excessive sweating and fever or from drinking fluid that has too high concentrations of salt.

**Hyponatremia** is caused by water intoxication (drinking so much water that it dilutes the sodium in the blood and overwhelms the kidney's compensation mechanism) or by a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). SIADH can be associated with illnesses like pneumonia, brain diseases, cancer, thyroid problems and some medications.

**Potassium (K):** Potassium is most concentrated inside the cells of the body. The gradient or the difference in concentration from within the cell

Electrolyte	Functions in the body	Normal adult range*
Calcium	Necessary for muscle contraction, nerve function, blood clotting, cell division, healthy bones and teeth.	4.5-5.5 mEq/L
Chloride	Maintains fluid balance in the body.	97-107 mEq/L
Potassium	Regulates heart contraction, helps to maintain fluid balance.	3.5-5.3 mEq/L
Magnesium	Necessary for muscle contraction, nerve function, heart rhythm, bone strength, generating energy and building protein.	1.5-2.5 mEq/L
Sodium	Maintains fluid balance and necessary for muscle contraction and nerve function.	136-145 mEq/L

\*Values may vary from laboratory to laboratory.

**Sodium (Na):** Commonly found outside the cell, in the plasma of the bloodstream. It plays significant role of water regulation in the body. If there is too much sodium in the body, perhaps due to high salt intake in the diet, it is excreted by the kidney and water follows. Sodium is an important electrolyte that helps with electrical signals in the body, allowing muscles and brain to work. It is half of the electrical pump at the cell level that keeps sodium in the plasma and potassium inside the cell. Too much or too little sodium can cause cells to malfunction.

**Conditions of Sodium Imbalance:**

**Hypernatremia** is usually associated with dehydration and instead of having too much sodium, there is

compared to the plasma, is essential in the generation of the electrical impulses that allow muscles and the brain to function.

**Conditions of Potassium Imbalance:**

Hyperkalemia can causes abnormal electrical conduction in the heart may lead to cardiac arrhythmia, a potentially life-threatening situation. High potassium levels are most often associated with kidney failure, in which potassium levels build up and cannot be excreted in the urine. Medications can be used to lower potassium levels until the kidneys are able to excrete the excess of potassium in the urine. However, emergency dialysis may be required to remove the potassium if kidney function is poor.

**Hypokalemia** is most often seen when the body loses too much potassium due to vomiting, diarrhea, sweating and medications like diuretics or laxatives. It is often seen in diabetic ketoacidosis, where potassium is excessively lost in the urine. Since chemicals in the body are related in their metabolism, low magnesium levels can be associated with hypokalemia.

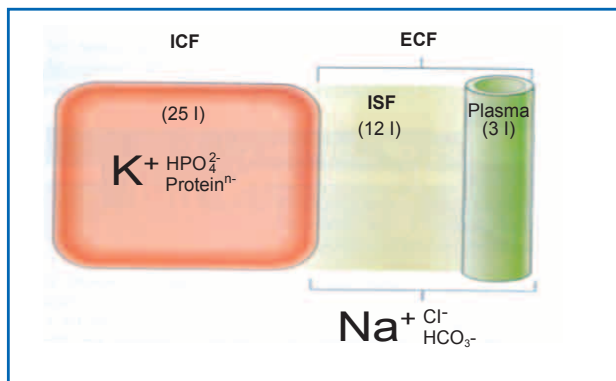
**Calcium (Ca):** Calcium is bound to the proteins in the bloodstream, so the level of calcium is related to the patient's nutrition as well as the calcium intake in the diet. Calcitonin promotes bone growth and decreases calcium levels in the blood and parathyroid hormone, which does the opposite. Calcium metabolism in the body is also closely linked to magnesium levels. Often, the body's magnesium status needs to be optimized before the calcium levels can be treated.

#### Conditions of Calcium Imbalance:

**Hypercalcemia** is associated with "moans, stones, abdominal groans"; symptoms include kidney stones, abdominal pain, and depression. Also, too much calcium can be associated with heart rhythm disturbances. Causes of hypercalcemia include parathyroid tumors, other tumors including breast cancer, excess amounts of Vitamin A or D, Paget's disease and kidney failure.

**Hypocalcemia** is usually associated with eating disorders or lack of parathyroid hormone. Symptoms include weakness, muscle spasms, and heart rhythm disturbance.

#### Electrolyte balance:



*Normal distribution of body water and electrolytes.*

The kidneys play a critical role in regulating electrolyte balance. The concentration of electrolytes

in the body is controlled by a variety of hormones like renin (from kidney), angiotensin (from the lungs, brain and heart), aldosterone (from the adrenal gland) and anti diuretic hormone (ADH, from the pituitary) that keep the electrolyte balance within those normal limits. Sensors in specialized kidney cells monitor the amount of sodium, potassium, and water in the bloodstream. They control the levels of chloride in the blood and "flush out" potassium, magnesium and sodium. Therefore, a disturbance in blood levels of these electrolytes may be related to kidney function. Keeping electrolyte concentrations in balance also includes stimulating the thirst mechanism when the body gets dehydrated.

#### Causes of electrolyte imbalance:

The balance of electrolytes is constantly shifting due to fluctuating fluid levels in our body.

Excessive sweating as a result of exercise, hot weather or high fever some electrolyte levels may be low. Prolonged vomiting, diarrhea are other commonest causes of electrolyte imbalances, as they result in excessive fluid loss. All of these may be side effects of chemotherapy treatment. Electrolyte imbalances can also be caused by a deficiency or an overabundance of minerals in the body. Hyperkalemia and hypercalcemia are indicative of excess amounts of potassium and calcium, respectively, which can disrupt the overall balance and functioning of the nerves, cardiovascular system and muscles. Fluid and electrolyte imbalance can lead to dehydration. Replenish these fluids and electrolytes in order to prevent dehydration, a potentially life-threatening condition.

#### Electrolyte imbalances can be caused by medical conditions including:

- Loss of body fluids from prolonged vomiting, diarrhea
- Sweating, Heat exhaustion
- High fever
- Inadequate diet and lack of vitamins from food
- Malabsorption - body may be unable to absorb these electrolytes due to a variety of GIT disorders or medications
- Hormonal or endocrine disorders-DM, Addison's disease

- ❑ Kidney disease
- ❑ Alcoholism, which causes the breakdown of muscle fibers, resulting in potassium being released into the bloodstream

### **Certain medications may cause an electrolyte imbalance such as:**

- ❑ Diuretics which promote fluid excretion by the kidneys (Loop, Thiazide)
- ❑ Chemotherapy drugs (cisplatin)-A complication of chemotherapy known as tumor lysis syndrome.
- ❑ Angiotensin-converting enzyme (ACE) inhibitors
- ❑ Certain hormones & steroids(hydrocortisone) that are potassium-sparing
- ❑ Calcium supplements
- ❑ Potassium supplements
- ❑ Antibiotics (amphotericin B)

### **Symptoms of electrolyte imbalance:**

An electrolyte imbalance may lead to a number of symptoms which vary and depending on the underlying disease, disorder or condition and also depend on which electrolyte is out of balance and whether the level is too high or too low. For example, altered potassium, magnesium, sodium, or calcium levels may cause muscle spasm, weakness, twitching, or convulsions.

### **General symptoms:**

- ❑ Dry mouth
- ❑ Excessive thirst
- ❑ Irregular heart beat
- ❑ Fatigue, Lethargy
- ❑ Irritability
- ❑ Nausea with or without vomiting
- ❑ Dizziness
- ❑ Trembling

### **Other symptoms:**

Electrolyte imbalance may accompany symptoms related to other body systems including:

- ❑ Constipation
- ❑ Dark/cloudy urine
- ❑ Decreased urine output
- ❑ Dry mouth and foul breath
- ❑ Dry skin
- ❑ Muscle weakness, twitching, spasm
- ❑ Poor skin elasticity
- ❑ Stiff or aching joints
- ❑ Lack of perspiration
- ❑ Confusion

### **Life-threatening symptoms including:**

Change in mental status or sudden behavior change such as confusion, delirium, lethargy, hallucinations

or delusions, Dehydration, Rapid heart rate (tachycardia), Sunken eyes, Convulsions, Coma

### **Complications:**

Because electrolyte imbalances can be due to serious diseases, failure to seek treatment in time may result in life threatening complications and permanent damage.

The potential complications including:

Cerebral edema (swelling of the brain), Overheating, Cardiac arrhythmias, Seizures or convulsions, Shock, Unconsciousness and coma

### **Diagnosis:**

An electrolyte imbalance is usually diagnosed based upon detail history, physical examination and presenting clinical features. Blood for electrolytes, Urinalysis and ECG should be done immediately. Serial or repeated measurements of plasma electrolytes are frequently necessary when a marked abnormality has been found. Since the kidney act to maintain the consistency of bodies fluid and electrolytes by adjusting urine volume and composition, it is very helpful to obtain a simultaneous sample of urine (spot or 24 hours collection) at the time of blood analysis to define the nature of the physiological disturbance in relation to homeostatic balance. An ultrasound or x-ray of KUB may also be needed if electrolyte imbalance is due to kidney problem.

### **Management:**

Treatment of electrolyte imbalance depends on identifying and treating the underlying causes. A Minor electrolyte imbalance may be corrected by diet changes. But in serious conditions, intravenous fluids, electrolyte replacement is needed. Correction of sodium imbalance should be relatively slowly. Rapid correction can cause abnormal flow of water into or out of cells. This is especially important to prevent brain cell damage (central pontinemyolysis).

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**B**ladder cancer is a common urologic cancer that has the highest recurrence rate of any malignancy. In North America, South America, Europe, and Asia, the most common type of bladder cancer is transitional cell carcinoma. Other types include squamous cell carcinoma and adenocarcinomas.

#### **Epidemiology:**

The incidence of bladder cancer increases with age, with the median age at diagnosis being 65 years; bladder cancer is rarely diagnosed before age 40 years.

Bladder cancer is about 3 times more common in men than in women. Over the past 2 decades, however, the rate of bladder cancer has been stable in men but has increased in women by 0.2% annually. The male predominance in bladder cancer in the United States reflects the prevalence of transitional cell carcinoma (TCC). With squamous cell carcinoma (SCC)-in contrast to TCC-the male-to-female incidence ratio is 1:2.

Bladder cancer is the fourth most common cancer in men in the United States, after prostate, lung and colorectal cancer, but it is not among the top 10 cancers in women. Accordingly, more males than females are expected to die of bladder cancer in 2013, with 10,820 deaths in males versus 4,390 in females. Nevertheless, women generally have a worse prognosis than men.

The incidence of bladder cancer is twice as high in white men as in black men in the United States. However, blacks have a worse prognosis than whites.

Limited data indicate that small cell carcinoma of the urinary bladder probably has the same epidemiologic characteristics as urothelial carcinoma. Patients are more likely to be male and older than 50 years.

Worldwide, bladder cancer is diagnosed in approximately 275,000 people each year, and about 108,000 die of this disease. In industrialized countries, 90% of bladder cancers are TCC. In developing countries-particularly in the Middle East and Africa-the majority of bladder cancers are SCCs, and most of these cancers are secondary to *Schistosoma haematobium* infection. Recent studies report that urothelial carcinoma is the most common urologic cancer in China.

In Africa, the highest incidence of SCC has been seen in schistosomal-endemic areas, notably Sudan and Egypt, where SCC ranges from two thirds to three quarters of all malignant tumors of the bladder.

In recent years, a few studies from Egypt have shown a reversal of this trend due to the better control of schistosomiasis in the region, whereas in other parts of Africa the association is unchanged. Increased smoking incidence is believed to have contributed to the shift in Egypt toward TCC, which has a stronger smoking association.

#### **Etiology :**

Up to 80% of bladder cancer cases are associated with environmental exposure. Tobacco use is by far the most common cause of bladder cancer in the United States and is increasing in importance in some developing countries. Smoking duration and intensity are directly related to increased risk.

The risk of developing bladder carcinoma is 2-6 times greater in smokers than in nonsmokers. This risk appears to be similar between men and women. Nitrosamine, 2-naphthylamine, and 4-aminobiphenyl are possible carcinogenic agents found in cigarette smoke.

Occupational exposure to aromatic amines or aniline dyes is presumed to be the cause of bladder cancer in up to 25% of cases. Numerous occupations associated with diesel exhaust, petroleum products, and solvents (e.g., auto work, truck driving, plumbing, leather and apparel work, rubber and metal work) have also been associated with an increased risk of bladder cancer. In addition, increased bladder cancer risk has been reported in persons, including the following, who work with organic chemicals and dyes:

- ❑ Beauticians
- ❑ Dry cleaners
- ❑ Painters
- ❑ Paper production workers
- ❑ Rope-and-twine industry workers
- ❑ Dental workers
- ❑ Physicians
- ❑ Barbers

People living in urban areas are also more likely to develop bladder cancer. The etiology in these cases is thought to be multifactorial, potentially involving exposure to numerous carcinogens.

Several medical risk factors are associated with an increased risk of bladder cancer, including the following:

- ❑ Radiation treatment of the pelvis
- ❑ Chemotherapy with cyclophosphamide
- ❑ Spinal cord injuries requiring long-term indwelling catheters

No convincing evidence exists for a hereditary factor in the development of bladder cancer. Nevertheless, familial clusters of bladder cancer have been reported.

### **Pathophysiology :**

Bladder cancer is often described as a polyclonal field change defect with frequent recurrences due to a heightened potential for malignant transformation. However, bladder cancer has also been described as resulting from implantation of malignant cells that have migrated from a previously affected site. The latter occurs less often and may account for only a small percentage of cases.

Use of the common term superficial bladder cancer should be discouraged. The term implies a harmless nature, which is misleading in many instances. Because it was used to describe the disparate disorders of low-grade papillary bladder cancer and the markedly more aggressive form, carcinoma in situ (CIS), the World Health Organization (WHO) has recommended it be abandoned.

In its place, the term non-muscle-invasive bladder cancer should be used and qualified with the appropriate American Joint Committee on Cancer stage (ie, Ta, T1, Tis). Stage T1 cancer invades lamina propria but not the muscle of the bladder. High-grade T1 tumor associated with CIS carries a relatively high risk for disease recurrence and progression (approximately 60%).

The WHO classifies bladder cancers as low grade (grades 1 and 2) or high grade (grade 3). Tumors are also classified by growth patterns: papillary (70%), sessile or mixed (20%), and nodular (10%).

### **Transitional cell carcinoma**

Transitional cell carcinoma (TCC) arises from stem cells that are adjacent to the basement membrane of the epithelial surface. Depending on the genetic alterations that occur, these cells may follow different pathways in the expression of their phenotype.

The most common molecular biologic pathway for TCCs involves the development of a papillary tumor that projects into the bladder lumen and, if untreated, eventually penetrates the basement membrane, invades the lamina propria, and then continues into the bladder muscle, where it can metastasize. Nearly 90% of transitional cell bladder tumors exhibit this type of behavior.

This progression occurs with high-grade cancers only. Low-grade cancers rarely, if ever, progress and are thought to have a distinct molecular pathway, different from the high-grade cancers and CIS.

The remaining 10% of TCCs follow a different molecular pathway and are called CIS. This is a flat, noninvasive, high-grade urothelial carcinoma tumor that spreads along the surface of the bladder and, over time, may progress to an invasive form of cancer that behaves the same as invasive TCC.

Many urothelial tumors are primarily composed of TCC but contain small areas of squamous differentiation, squamous cell carcinoma (SCC), or adenocarcinoma.

### **Squamous cell carcinoma**

SCC of the urinary bladder is a malignant neoplasm that is derived from bladder urothelium and has a pure squamous phenotype. SCC of the bladder is essentially similar to squamous cell tumors arising in other organs. Because many urothelial carcinomas contain a minor squamous cell component, a diagnosis of SCC of the bladder should be rendered only when the tumor is solely composed of squamous cell components, with no conventional urothelial carcinoma component.

Reportedly, SCC has less of a tendency for nodal and vascular distant metastases than does urothelial carcinoma.

### **Rare forms of bladder cancer**

Adenocarcinomas account for less than 2% of primary bladder tumors. These lesions are observed

most commonly in exstrophic bladders and are often associated with malignant degeneration of a persistent urachal remnant.

Other rare forms of bladder cancer include leiomyosarcoma, rhabdosarcoma, carcinosarcoma, lymphoma and small cell carcinoma. Leiomyosarcoma is the most common sarcoma of the bladder. Rhabdomyosarcomas most commonly occur in children. Carcinosarcomas are highly malignant tumors that contain a combination of mesenchymal and epithelial elements. Primary bladder lymphomas arise in the submucosa of the bladder. Except for lymphomas, all these rare bladder cancers carry a poor prognosis.

Small cell carcinoma of the urinary bladder is a poorly differentiated, malignant neoplasm that originates from urothelial stem cells and has variable expression of neuroendocrine markers. Morphologically, it shares features of small cell carcinoma of other organs, including the lung.

#### **Genetic factors in pathogenesis**

Divergent, yet interconnected and overlapping, molecular pathways are likely responsible for the development of noninvasive and invasive bladder tumors. Somatic mutations in fibroblast growth receptor3 (FGFR-3) and tumor protein p53 (TP53) in tumor cells appear to be important early molecular events in the noninvasive and invasive pathways, respectively.

FGFR-3, Ras and PIK3CA mutations occur with high frequency in noninvasive tumors, leading to upregulation of Akt and mitogen-activated protein kinase (MAPK). Loss of heterozygosity (LOH) on chromosome 9 is among the most frequent genetic alterations in bladder tumors and is considered an early event.

Large numbers of genomic changes have been detected using karyotyping and comparative genomic hybridization (CGH) analysis in urothelial carcinoma. Numerically common are losses of 2q, 5q, 8p, 9p, 10q, 18q, and Y. Gains of 1q, 5p, 8q, and 17q are frequently present, and high-level amplifications can be found; however, the target genes in the regions of amplifications have not been conclusively identified.

Alterations in the TP53 gene are noted in approximately 60% of invasive bladder cancers.

Progression-free survival is significantly shorter in patients with TP53 mutations and is an independent predictor of death among patients with muscle-invasive bladder cancer.

Additionally, alterations in retinoblastoma (Rb), PTEN, and p16 are common in high-grade invasive cancers. Over expression of JUN, MAP2K6, STAT3, and ICAM1 and molecules associated with survival (Bcl-2, caspase-3, p53, survivin), as well as insensitivity to antigrowth signals (p53, p21, p16, pRB), has been demonstrated.

In advanced disease, multiple mechanisms may lead to tumor progression. These include those that promote proliferation, survival, invasion, and metastasis, as well as those that involve deficiencies in DNA damage repair and the finding of stem like cells.

In addition to tumor cell alterations, the microenvironment may promote tumor growth by paracrine influences, including vascular endothelial growth factor (VEGF) production and aberrant E-cadherin expression.

Finally, a growing body of research over the last decade indicates that epigenetic alterations may silence tumor suppressor genes and that they represent important events in tumor progression.

#### **Signs and symptoms:**

Clinical manifestations of bladder cancer are as follows:

- ❑ Painless gross hematuria - Approximately 80-90% of patients; classic presentation
- ❑ Irritative bladder symptoms (e.g., dysuria, urgency, frequency of urination) - 20-30% of patients
- ❑ Pelvic or bony pain, lower-extremity edema, or flank pain - In patients with advanced disease
- ❑ Palpable mass on physical examination - Rare in superficial bladder cancer

#### **Diagnosis:**

- ❑ Urine studies include the following:
  - ❑ Urinalysis with microscopy
  - ❑ Urine culture to rule out infection, if suspected
  - ❑ Voided urinary cytology
  - ❑ Urinary tumor marker testing

## Urinary cytology

- ❑ Standard noninvasive diagnostic method
- ❑ Low sensitivity for low-grade and early stage cancers
- ❑ Fluorescence in situ hybridization (FISH) may improve the accuracy of cytology

## Cystoscopy

- ❑ The primary modality for the diagnosis of bladder carcinoma
- ❑ Permits biopsy and resection of papillary tumors

## Upper urinary tract imaging

- ❑ Necessary for the hematuria workup
- ❑ American Urologic Association Best Practice Policy recommends computed tomography (CT) scanning of the abdomen and pelvis with contrast, with preinfusion and postinfusion phases
- ❑ Imaging is ideally performed with CT urography, using multidetector CT
- ❑ Ultrasonography is commonly used, but it may miss urothelial tumors of the upper tract and small stones

The diagnostic strategy for patients with negative cystoscopy is as follows:

- ❑ Negative urine cytology and FISH - Routine follow-up
- ❑ Negative urine cytology, positive FISH-Increased frequency of surveillance
- ❑ Positive urine cytology, positive or negative FISH - Cancer until proven otherwise

No blood tests are specific for bladder cancer, but a general evaluation is necessary prior to initiating therapy with intravesical Bacillus Calmette-Guérin (BCG) vaccine. Laboratory tests include the following:

- ❑ Complete blood count (CBC)
- ❑ Liver function tests
- ❑ Bony fraction of alkaline phosphatase assay (if bone metastasis suspected)
- ❑ Kidney function studies

## Differential Diagnoses :

- ❑ Hemorrhagic Cystitis: Noninfectious

- ❑ Nephrolithiasis
- ❑ Renal Cell Carcinoma
- ❑ Renal Transitional Cell Carcinoma
- ❑ Ureteral Trauma
- ❑ Urinary Tract Infection, Females
- ❑ Urinary Tract Infection, Males

## Management :

The treatment of non-muscle-invasive bladder cancer (Ta, T1, carcinoma in situ [CIS]) begins with transurethral resection of bladder tumor (TURBT). Subsequent treatment is as follows:

- ❑ Small-volume, low-grade Ta bladder cancer - An immediate single, postoperative dose of intravesical chemotherapy
- ❑ High-risk Ta, T1, and CIS urothelial carcinoma - Intravesical BCG vaccine
- ❑ Persistent or recurrent high-risk disease - Repeat resection prior to additional intravesical therapy (e.g., interferon alfa or gamma); consider cystectomy for high-risk disease

The treatment of muscle-invasive bladder cancer is as follows:

- ❑ Radical cystoprostatectomy in men
- ❑ Anterior pelvic exenteration in women
- ❑ Bilateral pelvic lymphadenectomy (PLND), standard or extended
- ❑ Creation of a urinary diversion
- ❑ Neoadjuvant chemotherapy-May improve cancer-specific survival

Chemotherapeutic regimens for metastatic bladder cancer include the following:

- ❑ Methotrexate, vinblastine, doxorubicin (Adriamycin) and cisplatin (MVAC)
- ❑ Gemcitabine and cisplatin (GC)

## Prognosis:

Untreated bladder cancer produces significant morbidity, including the following:

- ❑ Hematuria
- ❑ Dysuria
- ❑ Irritative urinary symptoms
- ❑ Urinary retention
- ❑ Urinary incontinence



- ❑ Pelvic pain
- ❑ Ureteral obstruction

The recurrence rate for superficial TCC of the bladder is high. As many as 80% of patients have at least 1 recurrence.

The most significant prognostic factors for bladder cancer are grade, depth of invasion, and the presence of CIS. In patients undergoing radical cystectomy for muscle-invasive bladder cancer, the presence of nodal involvement is the most important prognostic factor. To date, there is no convincing evidence of genetic factors affecting outcome.

Non-muscle invasive bladder cancer has a good prognosis, with 5-year survival rates of 82-100%. The 5-year survival rate decreases with increasing stage, as follows:

- ❑ Ta, T1, CIS - 82-100%
- ❑ T2 - 63-83%
- ❑ T3a - 67-71%
- ❑ T3b - 17-57%
- ❑ T4 - 0-22%

Prognosis for patients with metastatic urothelial cancer is poor, with only 5-10% of patients living 2 years after diagnosis.

The risk of progression, defined as an increased tumor grade or stage, depends primarily on the tumor grade, as follows:

- ❑ Grade I - 2-4%
- ❑ Grade II - 5-7%
- ❑ Grade III - 33-64%

#### *Prognosis in carcinoma in situ*

CIS in association with T1 papillary tumor carries a poorer prognosis. It has a recurrence rate of 63-92% and a rate of progression to muscle invasion of 50-75% despite intravesical BCG. Diffuse CIS is an especially ominous finding; in one study, 78% of cases progressed to muscle-invasive disease.

#### *Prognosis in squamous cell carcinoma*

Tumor stage, lymph node involvement, and tumor grade have been shown to be of independent prognostic value in SCC. However, pathologic stage is the most important prognostic factor. In one relatively large series of 154 cases, the overall 5-year survival rate was 56% for pT1 and 68% for pT2 tumors. However, the 5-year survival rate for pT3 and pT4 tumors was only 19%.

Several studies have demonstrated grading to be a significant morphologic parameter in SCC. In one

series, 5-year survival rates for grade 1, 2, and 3 squamous cell carcinoma was 62%, 52%, and 35%, respectively. In the same study of patients undergoing cystectomy, the investigators suggested that a higher number of newly formed blood vessels predicts unfavorable disease outcome.

In SCC, the survival rate appears to be better with radical surgery than with radiation therapy and/or chemotherapy. In locally advanced tumors, however, neoadjuvant radiation improves the outcome. Sex and age have not been prognostically significant in SCC.

#### *Prognosis in small cell carcinoma*

Patients with small cell carcinoma of the bladder usually have disease in an advanced stage at diagnosis, and they have a poor prognosis. Overall median survival is only 1.7 years. The 5-year survival rates for stage II, III, and IV disease are 64%, 15%, and 11%, respectively.

#### **Prevention:**

A study concluded that "specific fruit and vegetables may act to reduce the risk of bladder cancer". Fruit and yellow-orange vegetables, particularly carrots and those containing selenium are probably associated with a moderately reduced risk of bladder cancer. Citrus fruits and cruciferous vegetables were also identified as having a possibly protective effect. However an analysis of 47,909 men in the Health Professionals Follow-Up Study showed little correlation between cancer reduction and high consumption of fruits and vegetables overall or yellow or green leafy vegetables specifically, compared to the statistically significant reduction among those men who consumed large amounts of cruciferous vegetables.

In a 10-year study involving almost 49,000 men, researchers found that men who drank at least 1.44 L of water (around 6 cups) per day had a significantly reduced incidence of bladder cancer when compared with men who drank less. It was also found that: "the risk of bladder cancer decreased by 7% for every 240 mL of fluid added".

#### **References:**

- ❑ <http://reference.medscape.com>
- ❑ [https://en.wikipedia.org/wiki/Bladder\\_cancer](https://en.wikipedia.org/wiki/Bladder_cancer)

## Test Yourself - 37

### Correct Answers :

1. b   2. c   3. a   4. d   5. c   6. b

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## Test Yourself - 38

- The followings are true for "Diarrhea in Children" except:
  - The causes and significance of diarrhea differ depending on whether it is acute or chronic.
  - Rota virus is one of the common causes of childhood diarrhea.
  - Fever, bloody stool are usual findings in viral diarrhea.
  - Tachycardia, hypotension and lethargy are among the particular concern in case of diarrhea.
- All the followings are correct for "Down Syndrome" except:
  - Children with this syndrome are predisposed to develop leukemia.
  - Nondisjunction results in an embryo with two copies of chromosome 21 instead of usual one.
  - In translocation, part of chromosome 21 breaks off during cell division and attaches to chromosome 14.
  - About 75% of concepti with trisomy 21 die in embryonic or fetal life.
- All the below are true for "Electrolyte imbalance" except:
  - Prolonged vomiting, diarrhea are among the commonest causes of this condition.
  - ACE inhibitors may cause an electrolyte imbalance.
  - Sodium imbalance should be rapidly corrected.
  - A sudden behavior change is one of the life threatening symptoms.
- All the followings are correct for "Bladder Cancer" except:
  - Painless gross hematuria occurs in about 60-70% of patients.
  - The recurrence rate for superficial Transitional Cell Carcinoma of bladder is high.
  - In Squamous Cell Carcinoma, the survival rate appears to be better with radical surgery.
  - The WHO classifies bladder cancers as low grade (grades 1 and 2) or high grade (grade 3).
- The followings are right for "Diarrhea in Children" except:
  - Supplementary zinc is used routinely in children with diarrhea.
  - Antidiarrheal agents and antibiotics are generally needed in diarrhea in children.
  - Access to safe drinking water is one of the key measures to prevent diarrhea.
  - It is a leading cause of malnutrition in children under 5 years old.
- All the followings are correct for "Bladder Cancer" except:
  - The risk of developing bladder cancer is 2-6 times greater in smokers than in nonsmokers.
  - Up to 80% of bladder cancer cases are associated with environmental exposure.
  - Adenocarcinomas account for more than 2% of primary bladder tumors.
  - The most common molecular biologic pathway for Transitional Cell Carcinoma involves the development of a papillary tumor.

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