Measurement of Renal Function
Typhoid Fever
Oral malodor
Common Pediatric Urological Problems

Fact File
Current Affairs
News from Internet
January 1, 2007

Dear Doctor:

Another year has passed with the twinkling of an eye, and we now find January 2007 on our calendars. In 2006, good things happened and terrible, happy and sad, as usual. However, the most striking news of 2006 was the winning of Bangladesh’s first Nobel Prize that exhilarated a poor nation more accustomed to news of natural disasters, disease and political upheaval. Throughout this ‘Medical Newsletter’ we feel proud to join the people of Bangladesh to congratulate Professor Muhammad Yunus and his brainchild, the Grameen Bank (GB), on their winning of the much-coveted 2006 Nobel Peace Prize. At the beginning of the New Year we also take the opportunity to wish all of you a safe, healthy, and prosperous New Year. Please accept our sincerest thanks for your readership during the year gone by.

Individuals with kidney disease who are able to obtain an early diagnosis and treatment experience a higher quality of life and are able to maintain more of their day-to-day activities, including keeping their jobs. Appropriate measurement of the glomerular filtration rate (GFR) is important for the assessment of renal function. This time an article on renal function reviews the methods used to assess GFR.

In the society we live in today, it’s a sad but true fact that a person is immediately judged by the first impression that he/she makes! If the person has bad breath - constantly or even occasionally, then he/she is immediately prejudged by something that is not his/her fault! May be it’s time to do something about it...An article in this issue therefore urges to drive away the bad breath.

Typhoid is one of the lead articles in this issue. Today, typhoid fever still attacks some 17 million people in poor countries each year, and kills about 600,000 of them. Back before antibiotics such as chloramphenicol, typhoid was very much feared. This is why in New York in the early 1900s, Mary Mallon was vilified and demonized as “Typhoid Mary”. It was claimed that she deliberately and malevolently infected everyone she came near, with typhoid. Today, the term “Typhoid Mary” refers to someone who carries death, doom and destruction with them. However, we couldn’t refrain ourselves from sharing with you the story of “Typhoid Mary”.

“A child is not a small adult”. Their anatomy is often not fully developed. The problems that affect their diminutive organs require understanding, experience and an exceedingly skilled touch to correct. This time we have a luminous article on common pediatric urological problems in Medical Newsletter.

A recent addition in Medical Newsletter i.e. ‘Fact File’ features the ten basic facts of tuberculosis (TB). As usual you will also be enlightened by the up-to-date articles of ‘Current Affairs’ and ‘News From Internet’.

At last we would like to say that we are truly privileged to communicate with you four times a year and will continue to do our very best throughout 2007 to help you enjoy to the fullest. Anticipating your co-operation once again, with best regards,
Renal Function: How to Measure in Clinical Practice

The reliable measurement of renal excretory function is of great importance in clinical practice and in research. Several countries are moving towards population screening for renal impairment to try to reduce the associated increased cardiovascular risk. Accurate measurement is methodologically difficult, so surrogate measures such as serum creatinine levels and prediction formulas (based on factors such as the patient’s age, sex, and serum creatinine level) are more commonly used in routine practice. This article describes routine and more specialized methods of assessing renal function and discusses about estimated glomerular filtration rate (GFR).

The kidney has several interlinked functions (box). These depend on glomerular filtration rate, the unit measure of kidney function. Glomerular filtration rate can be defined as the volume of plasma cleared of an ideal substance per unit of time (usually expressed as ml/min). The ideal substance is one that is freely filtered at the glomerulus and neither secreted nor reabsorbed by the renal tubules.

Markers of Glomerular Filtration Rate

Creatinine
Plasma creatinine is almost exclusively a product of the metabolism of creatine and phosphocreatine in skeletal muscle, but also originates slightly from dietary sources of creatinine such as cooked meat. Creatinine generation from the muscles is proportional to the total muscle mass and muscle catabolism. In people with a relatively low muscle mass, including children, women, the elderly, malnourished patients and cancer patients, the serum creatinine is lower for a given GFR. Therefore, there is a danger of underestimating the amount of renal impairment in these patients.

Serum creatinine is commonly used to screen for renal disease or to investigate urinary sediment abnormalities, hypertension or non-specific symptoms such as tiredness. It is also used to monitor renal function after transplantation, in patients with glomerulonephritis, in chronic renal disease, and in patients with glomerulonephritis taking disease-modifying therapy. Serum creatinine can also be used to monitor the effects of nephrotoxic drugs such as gentamicin or anticancer drugs.

In patients with stable renal function, serum creatinine levels are usually constant, with variability daily of about only 8%. Creatinine is freely filtered at the glomerulus and is not reabsorbed, but up to 15% is actively secreted by the tubules. In advanced renal failure, excretion of creatinine through the gastrointestinal tract increases. There is not a good correlation between serum creatinine and kidney damage early in a disease process. This is because the healthy parts of the kidneys can make up for the damaged parts and so the GFR does not reflect the damage. As a result, by the time the serum creatinine starts to noticeably rise, there is already significant damage.

Creatinine clearance
Measuring the creatinine clearance using serum creatinine level and a timed urine collection gives an estimate of glomerular filtration rate:

Creatinine clearance = (urine creatinine x volume)/serum creatinine

As a result of tubular secretion of creatinine, creatinine clearance tends to overestimate true glomerular filtration rate. This is a systematic error of fairly stable magnitude, however, until advanced renal failure is reached, allowing creatinine clearance to be a reasonable method of following changes of renal function in patients. The main problem with creatinine clearance is the requirement for urine collection over 24 hours; patients find this inconvenient and therefore collections are often inaccurate. Also a 25% daily variation in the values obtained using this method has been reported. Creatinine clearance is therefore no longer much used in clinical practice.
Urea
Serum urea is a less reliable marker of glomerular filtration rate than creatinine because levels are more vulnerable to change for reasons unconnected to glomerular filtration rate. A high protein diet, tissue breakdown, major gastrointestinal hemorrhage, and corticosteroid therapy can lead to an increase in plasma urea whereas a low protein diet and liver disease can lead to a reduction. Also, 40-50% of filtered urea may be reabsorbed by the tubules, although the proportion is reduced in advanced renal failure.

Mean of urea and creatinine clearance
In advanced renal failure the mean of urea and creatinine clearance may give a more accurate estimate of glomerular filtration rate than either clearance alone, as the effects of urea reabsorption and creatinine secretion tend to cancel each other out. It is the recommended method for estimating residual renal function in patients receiving dialysis.

Inulin clearance
No endogenous ideal substance exists for measuring glomerular filtration rate, so the standard method requires infusion of an exogenous agent, such as inulin. Inulin was first used for measuring glomerular filtration rate in 1951. Its use is limited because purified inulin is expensive and difficult to measure, and measuring glomerular filtration rate in this way is time consuming for both for patients and clinicians. A bolus and infusion of inulin are given to achieve a steady plasma level, followed by collection of regular blood and urine samples over several hours for inulin estimation. This method (now-a-days, often using polyfructosan) is only used in research studies when very accurate estimation of renal function is necessary.

Radioisotopic methods
From the late 1960s the use of radionuclides has offered an alternative method of estimating glomerular filtration rate that avoids some of the practical disadvantages of inulin clearance. Estimates using radionuclides correlate closely with inulin clearance. Radionuclides are usually given as a single dose and the glomerular filtration rate is calculated by their rate of disappearance from the plasma, obviating the need for urine tests.

Radioisotopic methods have the disadvantage of precautions being required in handling and disposal of radioactive materials. They are also expensive and not suitable for use during pregnancy. Another important consideration is that the terminal elimination phase is significantly prolonged in advanced renal failure. In patients with moderate renal failure (glomerular filtration rate 30-59 ml/min) samples are taken for up to five hours after injection whereas in patients with advanced renal failure samples are required for up to 24 hours after injection.

Radiocontrast agents
Radiocontrast agents were initially available in the 1960s but difficulties in chemical analysis and unacceptable amounts of free iodine in the preparations limited their use in favor of radioisotopic agents. These problems have largely been resolved and radiocontrast agents now offer the advantages of radioisotopes without the concerns of radioactive substances. Agents currently in use are iothalamate, siatrizoate meglumine, and iohexol. Iohexol may be the agent of choice as it is relatively quick to use and its results are comparable to inulin clearance.

Functions of kidney related to glomerular filtration rate
- Excretion of:
  - Nitrogenous waste
  - Sodium
  - Free water
  - Potassium
  - Phosphate
  - Water soluble medicines (for example, digoxin, gentamicin)
- Control of blood pressure
- Acid-base balance
- Secretion of erythropoietin
- Hydroxylation of vitamin D$_1$ (activation)
- Gluconeogenesis in the fasting state
- Catabolism of peptide hormones (including insulin)
Cystatin C
The past decade has witnessed an upsurge of interest in cystatin C as an endogenous glomerular filtration rate marker. Cystatin C is part of the cystatin “superfamily” of cysteine protease inhibitors. It is freely filtered at the glomerulus. Its use is, however, limited by higher variability of serum levels than creatinine (75% vs. 7%) between patients. Also, serum levels are increased in malignancy, HIV infection, and glucocorticoid therapy. At present cystatin C has no established role, but it may emerge as a useful way of identifying patients with early renal failure as part of screening programs.

Detection of patients not known with a specific renal disease, but at risk for progressive chronic kidney disease (CKD)
As patients with renal failure due to type 2 diabetes, hypertension or generalized vascular disease have in most cases never experienced acute symptoms indicative of renal disease, such as hematuria, severe hypertension or edema (as patients with glomerular or interstitial diseases), programs have to be designed to detect them at an earlier phase. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines defined the five stages of CKD, dependent on the level of glomerular filtration rate (GFR) and the presence of an elevated urinary albumin excretion, defined as microalbuminuria (30-300 mg albumin/24 hours) or macroalbuminuria (>300 mg albumin/24 hours) (Table 1).

Subjects at risk for progressive CKD and cardiovascular disease could be detected by screening for albuminuria. With this approach, it would be possible to detect subjects with stages 1 and 2 CKD, who cannot be detected by screening only for GFR. Various review papers recently described the laboratory methods to measure albuminuria, the way urine samples could be collected, the definitions for an abnormally elevated albuminuria, and the way in which a population screening on albuminuria might be organized.

The second option is screening for GFR, as patients with stages 3 and 4 CKD may have an impaired GFR also without having micro- or macroalbuminuria. It is clear that accurate GFR measurements using inulin or iothalamate infusions cannot be applied in large-scale screening programs. Accurate 24 hours collections necessary for the calculation of a creatinine clearance are also difficult to apply in such programs. That is the reason why in the last decade, much attention was focused on the optimal formula to estimate GFR from just one single plasma creatinine measurement and some indices of creatinine production. As the latter is determined by muscle mass of the subject and also associated with several limitations, most formulas use age (the elderly produce less creatinine), sex (women produce less creatinine), race (Whites produce less creatinine), and weight or height (leaner and smaller subjects produce less creatinine). The most widely used are the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) formula (Table 2).

Prediction Formulas
To circumvent the practical difficulties of formal measurement of clearance, several prediction formulas have been published.

Table 1: Clinical relevance of the five stages of CKD, according to the level of GFR and the presence of an elevated albuminuria

<table>
<thead>
<tr>
<th>GFR</th>
<th>Elevated albuminuria</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>&gt;90</td>
<td>yes</td>
</tr>
<tr>
<td>Stage 2</td>
<td>60-89</td>
<td>yes</td>
</tr>
<tr>
<td>Stage 3</td>
<td>30-59</td>
<td>yes/no</td>
</tr>
<tr>
<td>Stage 4</td>
<td>15-29</td>
<td>yes/no</td>
</tr>
<tr>
<td>Stage 5</td>
<td>&lt;15</td>
<td>yes/no</td>
</tr>
</tbody>
</table>

* Patients with estimated glomerular filtration rate >60 ml/ min/ 1.73 m² should be regarded as normal unless they have evidence of kidney disease (persistent proteinuria or hematuria, or both, microalbuminuria in patients with diabetes, structural kidney disease such as polycystic kidney disease in adults or reflux nephropathy).
**Cockcroft and Gault equation**

In 1976, Cockcroft and Gault introduced an equation to predict creatinine clearance. The equation was derived from an investigation of 249 men with creatinine in a steady state; the subsequent companion equation for women was based on their 15% lower muscle mass. The equation tends to overestimate renal function at lower levels, particularly when obesity or fluid overload is present, as the resultant increase in weight does not reflect an increase in muscle mass. However, as with creatinine clearance, this is largely a systematic error and the equation remains useful for following changes in renal function in a patient.

**Modification of diet in renal disease formula**

More recently Levey et al introduced a formula derived from data on patients with advanced renal failure in the modification of diet in renal disease study. This is referred to as the “6-variable MDRD” or “6-v MDRD” formula. This formula gives an estimate of glomerular filtration rate in millilitres per minute adjusted for body surface area of 1.73 m² and is based on a patient’s age, sex, race, and levels of serum urea, serum creatinine, and serum albumin. By avoiding inclusion of weight, the formula is less prone to errors from fluid overload and obesity.

In 2000 a simplification of the modification of diet in renal disease formula using only patient’s age, sex, race, and serum creatinine level was derived from the original data. This is referred to as the “4-variable MDRD” or “4-v MDRD” formula. With the exception of race, the other variables required are normally provided routinely when a sample is submitted to the laboratory. It is therefore much easier for laboratories to report estimated glomerular filtration rate using this formula.

One important issue concerning the use of prediction formulas is that different laboratories use different methods for creatinine estimation. Some assays are more sensitive than others. However, some of the difference in assay methods can be corrected for and there are plans to adopt correction factors throughout the United Kingdom. When using a correction factor, the formula used is a slightly modified form of the 4-v MDRD formula.

The modification of diet in renal disease formulas have been validated in an ever increasing number of patient groups, including elderly patients and recipients of renal transplants, although concern has been expressed over reliability in different ethnic groups such as Chinese and Indian patients. Also, as advanced renal failure, their validity has been questioned in patients with normal or near normal glomerular filtration rates. It is therefore recommended that they are not used routinely at levels greater than 60 ml/min/1.73 m². It should be stressed that these formulas are not valid in certain clinical settings such as acute renal failure, pregnancy, severe malnutrition, diseases of skeletal muscle, paraplegia, and quadriplegia, in children, or when renal function is changing rapidly.

**Limitations of estimated GFR measurements**

Although GFR estimates are easy to apply, the Cockcroft-Gault and MDRD formula as well all the other published formulas have their limitations. It is only if one is aware of these limitations that a good use of the formulas can be expected.

There are fundamental differences between the Cockcroft-Gault and the MDRD formula to estimate GFR. First, the Cockcroft-Gault formula has

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**Table 2: Commonly used formulas for estimating renal function**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cockcroft and Gault equation</strong></td>
<td>Estimated creatinine clearance (ClCr) = ( \frac{(140 - \text{age}) \times \text{weight} \times 1.2 \times (0.85 \text{ if female})}{\text{SCr}} )</td>
</tr>
<tr>
<td><strong>6-variable MDRD</strong></td>
<td>( 170 \times \left( \frac{\text{SCr}}{88.4} \right)^{-0.999} \times \text{age}^{-0.176} \times \left( \frac{\text{SU}}{0.357} \right)^{-0.170} \times \left( \frac{\text{SAlb} \times 10}{0.762 \text{ if female}} \right) \times \left( 1.180 \text{ if Black} \right) )</td>
</tr>
<tr>
<td><strong>4-variable MDRD</strong></td>
<td>( 186.3 \times \left( \frac{\text{SCr}}{88.4} \right)^{-1.154} \times \text{age}^{-0.203} \times \left( 0.742 \text{ if female} \right) \times \left( 1.21 \text{ if Black} \right) )</td>
</tr>
<tr>
<td><strong>Modified 4-variable MDRD</strong></td>
<td>( F \times 175 \times \left( \frac{\text{SCr}}{88.4} \right)^{-1.154} \times \text{age}^{-0.203} \times \left( 0.742 \text{ if female} \right) \times \left( 1.21 \text{ if Black} \right) )</td>
</tr>
</tbody>
</table>

where F = correction factor, SCr = serum creatinine in µmol/l, and age is expressed in years.
Originally been validated against creatinine clearance as the gold standard, whereas the MDRD formula was developed against iothalamate-measured GFR. As creatinine, but not iothalamate, is excreted not only by filtration but also by secretion, creatinine clearance always exceeds iothalamate clearance. Consequently, the Cockcroft-Gault-based GFR estimates tend to exceed MDRD-based GFR estimates in most subjects. Second, the Cockcroft-Gault formula (which includes weight in the formula) is expressed in milliliters per minute, while the MDRD formula (which does not include weight in the formula) is expressed in milliliters per minute per 1.73 m$^2$. This difference makes a direct comparison between the two difficult. In general, clinicians are not used to expressing GFR normalized for standard body surface area.

**Conclusion**

Prediction formulas using serum creatinine levels are by far the most widely used methods of measuring renal excretory function in routine clinical practice. One of these, the modified 4-v MDRD estimated glomerular filtration rate formula is now being used for direct reporting of estimated glomerular filtration rates by laboratories and has become the standard method used to identify and monitor patients with reduced renal function in the United Kingdom and elsewhere. It is anticipated that recognition and appropriate management of patients with chronic kidney disease will reduce cardiovascular events and slow further deterioration in renal function in these patients.

**References**

1. Traynor J. How to measure renal function in clinical practice. *BMJ* 2006; 333: 733-737
3. Lipps B. Serum Creatinine and Kidney Disease. About.com

**READERS’ COMMENTS**

"Thank you very much for sending me your well circulated Newsletter. It is really helpful to keep health professionals up-to-date with current knowledge."

- Dr. (Major) Bashidul Islam  
  MBBS, MPH, MCPS, FCPS  
  21 Field Ambulance, Bogra Cantonment

"I am very happy and grateful to you for sending your valuable Newsletter, containing latest and up-to-date information about Medical Science."

- Dr. Subir Bhattacharjee, MBBS  
  Senior Medical Officer, Ami Tea Garden  
  Duncan Brothers (BD) Ltd., Chandpur Bagan, Habigonj"
Oral Malodor (Halitosis)

In medical literature, bad breath is usually referred to as halitosis or oral malodor. The word “halitosis” comes from the Latin halitus, which means “breath,” and the Greek suffix osis, to specify a condition or a process. Concern about bad breath goes back to ancient times. One of the earliest discussions of offensive breath can be found in the Ebers papyrus, which dates from around 1550 BC. This document identified various aromatic substances such as myrrh and frankincense which could be used to overcome mouth odor. Pliny the Elder (23-79 AD) wrote that bad teeth, old age, and some foods could cause bad breath. His observations are still valid, although much more is known about the problem. In Shakespeare’s Midsommer-Night’s Dream, Bottom exhorts the other characters in the play to “eat no onions or garlick, for we are to utter sweet breath . . . .”

Oral malodor (halitosis) is common and can affect people of all ages. Most people have some element of transient unpleasant oral odor at some time. In the developed world, 8-50% of people perceive that they have persistent recurrent episodes of oral malodor. While ordinary healthy breath has been described as smelling like “blooming chestnuts,” offensive breath manifests itself in a variety of ways depending on the cause. Mouth odors have been described as “smelling like rotten eggs” or “smelling fishy”.

What is the most likely cause of halitosis?

Oral malodor on awakening is common and generally not regarded as halitosis. Longstanding oral malodor is usually caused by oral, or sometimes nasopharyngeal, disease. The most likely cause of oral malodor is the accumulation of food debris and dental bacterial plaque on the teeth and tongue, resulting from poor oral hygiene and resultant gingival and periodontal inflammation. Although most types of gingivitis and periodontitis can give rise to malodor, acute necrotizing ulcerative gingivitis (Vincent’s disease, trench mouth) causes the most notable halitosis. People with gingivitis or periodontal disease have higher bacterial counts in their saliva than do people with healthy mouths.

Lack of oral cleansing because of xerostomia (dryness of the mouth) also has the potential to cause or enhance malodor, and some evidence indicates that wearing dentures may sometimes cause oral malodor, possibly by virtue of increased tongue coat deposits.

What other causes of halitosis exist?

Mild transient oral malodor often arises after sleep and is sometimes termed “morning halitosis.” This may be more likely in people with nasal obstruction - for example, due to upper respiratory tract infection - or when people sleep in a hot, dry atmosphere.

As one might assume, diet can sometimes cause bad breath. For example, physicians often reported that a patient with a vegetarian diet complained of a strong vegetable odor on his breath. Garlic and onions have long been implicated in halitosis. When someone indulges in such odor-producing foods, the volatile substances dissolve in the blood and are transferred to the expired air in the lungs. An improperly balanced or “fad” diet can cause bad breath as well. Individuals on the Atkins Diet or on the Doctor’s Quick Weight Loss Diet, which are high in protein and low in carbohydrates, can suffer halitosis. Stomach odors can taint the breath during belching, or by regurgitation, as with a “nervous,” nauseated stomach.

It is well known that cigarette smoke and alcohol can cause unpleasant breath. Like garlic and onions, these substances yield volatile by-products which pass into the breath through the lungs. “Nicotine” breath is well known, as is the telltale sign of drinking beer, wine, or whiskey. The breath tests police perform on drivers suspected of excess drinking use a “photometric colorimeter.” This device contains a mixture of potassium dichromate and sulfuric acid. Breath passes through this mixture, which changes color in proportion to the amount of alcohol present.

Some studies have linked bad breath in women to the menstrual cycle. In 1970, R.E. S. Prout and Rosamund Hopps, University of Sheffield, England, pointed out...
Towards a Fresh Breath

that the bacteria count in saliva increases during both menstruation and ovulation. This occurs because hormonal changes during these times cause the gums to become edemic, or bloated. This swelling traps bacteria between the gums and teeth, which in turn can cause gingivitis.

In 1978, Tonzetich and colleagues performed follow-up research in which they found a definite tendency for volatile sulfur compounds to increase up to four times the normal level around mid-cycle at or near ovulation, and during menstruation. The researchers speculated that increases in these compounds may be related to increases in estrogen levels. The study confirms the often noticed symptom of bad breath during menstruation. Taking this study one step further, James G. Kostelc and colleagues, in the University City Science Center, have recently suggested that measurement of the volatile sulfur compounds involved in mouth odor may help to predict the time of ovulation. This could be helpful to couples who are trying to conceive. Bad breath is also common during pregnancy. At that time, as during ovulation, the gums become edemic, a finding reported by Harald A. Lee, University of Connecticut, School of Dental Medicine.

Respiratory tract infections can cause oral malodor as a consequence of nasal or sinus secretions passing into the oropharynx or in people who breathe predominantly through their mouth. Tonsillitis may also be causes of halitosis. Foreign bodies in the nose can likewise produce a striking odor to the breath. Bronchiectasis and other lung infections, such as in cancer, may also cause halitosis. A study by Bennet Lorber, Temple University, Philadelphia, implicated anaerobic organisms as the cause of fetid breath odor in some patients with lung infection.

Chronic renal failure, for example, causes the patient to emit a “fishy” or “fetid” odor. A group at Thomas Jefferson University, Philadelphia, confirmed that the odor in these patients is caused by either dimethylamine or trimethylamine. Their findings suggested that intestinal bacteria rather than oral bacteria were involved in the increase in breath amines.

One of the symptoms of gonorrhea is bad breath. Lesions may spread from the primary site of infection to the mouth, causing tissues to become inflamed or ulcerated. At the same time, the saliva thickens, and the victim develops bad breath. Syphilis of the nose can cause halitosis due to gumma formation, the soft gummy tumor characteristic of tertiary syphilis. Cold sores caused by herpes simplex virus are also associated with a foul odor and acute gingivitis. Symptoms tend to disappear after 10 to 14 days.

A range of systemic disorders may rarely cause oral malodor (Box 1). In some cases, patients may have no alternative to accepting bad breath, especially when needed medication is a cause (Box 2). Also drugs can alter the senses of taste and smell which can cause “subjective halitosis.”

More importantly, some patients complain of oral malodor yet do not have confirmable halitosis, even with objective testing. This symptom may be attributable to a form of delusion or monosymptomatic hypochondriasis (self-oral malodor, halitophobia). Such people often wrongly interpret the actions of others as an indication that their breath is offensive, and with time these patients can adopt a variety of behaviors to minimize their perceived problem (such as covering the mouth when talking, avoiding or keeping a distance from other people, or avoiding social interactions). People with halitophobia often become fixated with teeth cleaning.

**Box 1: Possible systemic causes of oral malodor**

- Acute febrile illness
- Respiratory tract infection (usually upper)
- Helicobacter pylori infection (?)
- Pharyngo-esophageal diverticulum
- Gastro-esophageal reflux disease
- Pyloric stenosis or duodenal obstruction
- Hepatic failure (fetor hepaticus)
- Renal failure (end stage)
- Diabetic ketoacidosis
- Leukemias
- Trimethylaminuria
- Hypermethioninemia
- Menstruation (menstrual breath)
and tongue cleaning and frequently use chewing gums, mints, mouthwashes, and sprays in the hope of reducing their distress.

**What is the oral source of halitosis?**

Scientists now concur that ordinary mouth odor is primarily caused by volatile sulfur-bearing compounds - such as hydrogen sulfide and methylmercaptan. These substances are generated through the metabolic activities of microorganisms in the mouth. Food and proteins remaining in the mouth after eating are degraded by the microorganisms into peptides and constituent amino acids. These further degrade into the highly volatile sulfur compounds.

The species of microorganisms implicated most often in oral odor are Fusobacterium, Bacteroides, and Klebsiella, although other species can also be involved. These anaerobic organisms multiply in the mouth where the lack of oxygen favors their survival. They thrive on dental plaque, the sticky substance which accumulates on teeth. Plaque also accumulates in mouth areas such as the gingival crevice (the space between the surface of a tooth and the overlapping gum) and the tongue. They also multiply in any saliva that becomes trapped in periodontal defects, or in any area outside of the mainstream of salivary flow.

Oral malodor can also arise from the posterior dorsal tongue (and this explains why oral malodor may sometimes occur in people with good oral hygiene). As a consequence of its large and papillary surface area, the dorsum of the tongue can retain large amounts of desquamated cells, leucocytes, and microorganisms (and presumably salivary constituents). The microbial content on the tongue may be greater, but not necessarily different, in people with periodontal disease than in others.

**How is halitosis diagnosed and assessed?**

One’s own breath odor is often undetectable due to habituation, although many people will have an accompanying bad taste (metallic, sour, fecal, etc.) depending on oral dryness and the degree of breath odor.

A somewhat effective home method to determine the presence of bad breath is to lick the back of the wrist, let the saliva dry for a minute or two, and smell the result. Another way would be to lightly scrape the posterior of the tongue with an inverted spoon or a piece of dental floss, and to smell the dried residue. A spouse, family member, or close friend may be willing to smell one’s breath and provide honest feedback. Highly reliable home tests are now available which use a chemical reaction to test for the presence of polyamines and sulfur compounds on tongue swabs. It should be remembered that breath odor changes in intensity throughout the day depending on many factors, so test should be performed several times.

The clinical assessment of oral malodor is usually subjective and is based on smelling the exhaled air of the mouth and nose and comparing the two (organoleptic assessment). Odor detectable from the mouth but not from the nose is likely to be of oral or pharyngeal origin. Odor from the nose alone is likely to be coming from the nose or sinuses. In rare instances when the odor from the nose and mouth are of similar intensity, a systemic cause of the malodor may be likely. Assessment of the quality of the odor (the hedonic method) relies on the use of trained clinical judges.

Objective measurement of the breath components is rarely used in routine clinical practice, as it is expensive and time consuming.

**What is the treatment of halitosis?**

Treatment is primarily directed towards educating the patient as to the cause and prevention and lessening the accumulation of oral bacteria. Brushing after meals and flossing at least once daily is necessary to remove rotting food debris from between the teeth, especially at the gumline. Gently cleaning the tongue surface twice daily with a tongue-brush, tongue scraper, or tongue cleaner will reduce this primary source of breath odor. An inverted teaspoon is also effective; a toothbrush less so, as the size and angle of
the head do not allow it to reach as far as necessary. One should be careful to avoid scraping the V-shaped row of taste buds found at the extreme back of the tongue. Brushing a small amount of antibacterial mouth rinse or tongue gel onto the tongue surface will further inhibit bacterial action.

Since dry mouth can increase bacterial buildup and cause or worsen bad breath, chewing sugarless gum can help with the production of saliva, and thereby help to reduce bad breath. Some gums, toothpaste, sprays, and gels that combat dry mouth for several hours have recently been marketed over the counter. Maintain water levels in the body by drinking several glasses of water a day. Adding lemon juice to water is refreshing and also beneficial. Some studies have shown that eating yogurt, drinking green tea, or chewing cinnamon or sugarless cinnamon gum can reduce bad breath.

The range of mouthwashes suggested for the treatment of oral malodor act by reducing either the bacterial load or the associated odoriferous compounds. Unfortunately, few randomized controlled trials have looked at the effectiveness of these. Chlorhexidine gluconate produces a fall in bacteria that produce volatile sulfur compounds, and the mouthwash or spray can be more effective at reducing oral malodor for several hours. A mouthwash of chlorhexidine/cetylpyridinium chloride and zinc lactate also reduces oral malodor. Patients may, however, be reluctant to use chlorhexidine long term as it has an unpleasant taste, can give rise to a burning sensation of the oral mucosa if used too frequently, and can cause (reversible) staining of the teeth. A two-phase oil-water mouthwash can reduce oral malodor for several hours, without adverse effects. Other mouthwashes that can reduce oral malodor for several hours include cetylpyridinium chloride, chlorine dioxide, and zinc chloride.

Triclosan has both a direct action against volatile sulfur compounds and an antibacterial effect; used in mouthwashes and toothpastes, it may reduce oral malodor. The action of triclosan against volatile sulfur compounds, however, seems to depend mainly on the solubilising agent with which it is delivered. A formulation of triclosan/co-polymer/sodium fluoride seems to be particularly effective in reducing volatile sulfur compounds, oral bacteria, and oral malodor.

Experimental methods of reducing oral malodor include the use of glycosylation inhibitors (such as D-galactosamine), probiotic placement of bacteria (such as Streptococcus salivarius) that replace the bacteria causing oral malodor, light exposure that directly inhibits bacteria that produce volatile sulfur compounds, or lethal photosensitization. Patients with halitophobia require referral for clinical psychological investigation and treatment. Unfortunately, few of these people are willing to follow this course of treatment.

References
2. Halitosis, the Silent Affliction: A Profile of Bad-Breath Research. Essays of an Information Scientist 1981-82; 5: 742-748
3. Halitosis. Answers.com
5. Halitosis (Bad Breath). University of Maryland Medical Center
6. The Truth About Halitosis. usenature.com
TB is a disease of poverty; virtually all TB deaths occur in the developing world, affecting mostly young adults in their most productive years. TB especially affects the most vulnerable, such as the poorest and malnourished.

Global TB incidence is still growing at 1% every year because of the rapid increase in Africa; intense control efforts are helping incidence fall or stabilize in other regions.

HIV/AIDS, TB and malaria kill 6 million people every year; nearly 2 million deaths are caused by TB.

TB is curable, but kills 5000 people every day.

TB is a leading killer among HIV-infected people with weakened immune systems; a quarter of a million TB deaths are HIV-associated - most of them in Africa.

10 facts about tuberculosis (TB)
2 billion people - one third of the world's population - are infected with TB bacilli, the microbes that cause TB. 1 in 10 people infected with TB bacilli will become sick with active TB in their lifetime; people with HIV are at a much greater risk.

TB is contagious and spreads through the air; if not treated, each person with active TB infects on average 10 to 15 people each year.

TB is a worldwide pandemic; though the highest rates per capita are in Africa (29% of all TB cases), half of all new cases are in 6 Asian countries - Bangladesh, China, India, Indonesia, Pakistan and the Philippines.

Almost 9 million new TB cases occurred in 2004 - 80% of them in 22 countries.

Multidrug-resistant TB (MDR-TB) is a form of TB that does not respond to the standard drug treatment. MDR-TB is present in virtually all 109 countries recently surveyed by WHO and partners.

Source: World Health Organization
Typhoid fever is among the most common febrile illnesses encountered by practitioners in developing countries. Although advances in public health and hygiene have led to the virtual disappearance of typhoid fever from much of the developed world, the disease still remains endemic in many developing nations. Today, typhoid fever has appeared as a global health problem and a matter of deep concern. The ongoing confusions in the diagnosis and treatment of typhoid fever among physicians have led to a critical situation. This is mainly because of the changed clinical picture of this disease that continues to grow more and more confusing with those of many other febrile illnesses. The advent of antibiotic treatment has led to a change in the presentation of typhoid fever. The classic mode of presentation with a slow and “stepladder” rise of temperature and toxicity is now rarely observed. The current situations have created a global urgency and necessity to have a clinical review of this disease condition in order to combat this new pattern of typhoid fever.

Magnitude of The Problem

The actual impact and the true burden of typhoid fever are very difficult to estimate globally as the existence of established surveillance systems are numbered particularly in developing countries. The recent revisions in the global estimates of typhoid fever from the US Centers for Disease Control and Prevention estimate that there are 21.6 million typhoid cases annually, with the annual incidence varying from 100 to 1000 cases per 100,000 populations. And in

Typhoid Mary: Villain or Victim?

Mary Mallon, the most infamous typhoid carrier in medical history was born in Ireland in 1869 and worked as a cook for wealthy New Yorkers. In 1906 she was hired by a banker living in a rented house in Oyster Bay, Long Island. When typhoid fever struck 6 of its 11 occupants, the property’s owner hired George Soper, a sanitary engineer, to investigate. Salmonella typhosa had been identified in the 1880s. Soper was aware that it spread through contaminated water and suspected the possibility of carriers. He traced Mallon’s employment history and discovered that typhoid had struck in 7 of the 8 families she had worked for, with 22 cases between 1900 and 1907.

In March 1907 Soper told Mallon she was spreading typhoid and demanded samples of feces, urine and blood. She refused. Soper enlisted the help of the New York City Health Department but it could not persuade Mallon either. Finally, under police escort, Mallon found herself in the Willard Parker Hospital, where high concentrations of typhoid bacilli were confirmed in a stool specimen.

She was quarantined in an isolation cottage on the grounds of Riverside Hospital in North Brother Island, NY. She stayed there for three years, in relative isolation. It was during that time that she was dubbed Typhoid Mary. In 1909 she sued the health department for her release, but it was not granted. However, a year later a new health commissioner released Mallon, based on her promise not to work as a cook. She didn’t keep the promise. She disappeared from health department view and returned to cooking. She resurfaced again in 1915, using the name Mrs. Brown and working as a cook in Sloane Maternity Hospital in Manhattan. During her three months there, she had spread typhoid to at least 25 doctors, nurses and staff, two of whom had died. She was sent again to North Brother Island, where she lived the rest of her life, 23 years, alone in a one-room cottage.
Bangladesh, the incidence is approximately 2000 per 100,000 in one year. Another recent population based studies from South Asia suggest that the incidence is highest in children aged less than five years, with higher rates of complications and hospitalization. Furthermore, typhoid fever also has a very high social and economic impact because of the hospitalization of patients with acute disease and the complications and loss of income attributable to the duration of the clinical illness. Nevertheless, clinically apparent bacteremic S. typhi infection in children aged less than three years has been described in Bangladesh, India, Jordan, Nigeria, and elsewhere. In Chile, single blood cultures for all children below two years presenting with fever, regardless of other clinical symptoms, showed that 3.5% had unrecognized bacteremic infections caused by S. typhi or S. paratyphi. It is important to note that reports from some provinces in China and Pakistan have indicated more cases of fever caused by S. paratyphi A than by S. typhi. All these clinical data reveals the patterns of typhoid fever that greatly varies regionwise and also posses no similarity while affecting different age groups. The incidence seems to be high among children in some areas whereas it appears quite low in other places.

### Changing Epidemiology and Development of Drug Resistances

There may be several factors that affect the changing epidemiology of typhoid. Although the overall ratio of disease caused by S. typhi to that caused by S. paratyphi is about 10 to 1, the proportion of S. paratyphi infection is increasing in some parts of the world. In contrast to the Asian situation, Africa has been associated with the concomitant increase in community acquired bacteremia due to non-typhoidal Salmonellae such as S. typhimurium- an illness that may be clinically indistinguishable from typhoid. The presentation of typhoid fever may be altered by coexisting morbidities and early administration of antibiotics. In areas where malaria is endemic and where schistosomiasis is common the presentation of typhoid may be atypical. This may often confuse the picture with neuropsychiatric manifestations, and often may be mistaken for encephalitis, meningitis, cerebral malaria, phychosis etc.

Another alarming development has been the emergence of multi drug resistant (MDR) typhoid. Till 1948, chloramphenicol was considered the gold standard antimicrobial for treating typhoid. Then the

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### Recommended Antibiotic Treatments For Typhoid Fever

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>Drug</th>
<th>Daily Dose (mg/ kg)</th>
<th>Course (Days)</th>
<th>Drug</th>
<th>Daily Dose (mg/ kg)</th>
<th>Course (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncomplicated Typhoid Fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully sensitive</td>
<td>Fluoroquinolones (ofloxacin or ciprofloxacin)</td>
<td>15</td>
<td>5-7*</td>
<td>Chloramphenicol Amoxicillin</td>
<td>50-75</td>
<td>14-21</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone or Cefixime</td>
<td>15</td>
<td>7-14</td>
<td>Penicillin G</td>
<td>500-750</td>
<td>8-40</td>
</tr>
<tr>
<td></td>
<td>Azithromycin or Ceftriaxone</td>
<td>8-10</td>
<td>7</td>
<td>Azithromycin Cefixime</td>
<td>8-10</td>
<td>14</td>
</tr>
<tr>
<td>Multi drug resistance</td>
<td></td>
<td>15-20</td>
<td></td>
<td>Cefixime</td>
<td>20</td>
<td>7-14</td>
</tr>
<tr>
<td>Quinolone resistance</td>
<td></td>
<td>7-14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe Typhoid Fever Requiring Parenteral Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully sensitive</td>
<td>Fluoroquinolone (ofloxacin)</td>
<td>15</td>
<td>14</td>
<td>Chloramphenicol Amoxicillin</td>
<td>100</td>
<td>14-21</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone</td>
<td>15</td>
<td>14</td>
<td>Penicillin G</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>Multi drug resistance</td>
<td></td>
<td>60</td>
<td>14</td>
<td>Ceftriaxone or Cefotaxime</td>
<td>80</td>
<td>10-14</td>
</tr>
<tr>
<td>Quinolone resistance</td>
<td>Ceftriaxone or Cefotaxime</td>
<td>60</td>
<td></td>
<td>Fluoroquinolone</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>

*Three day courses also effective, particularly so in epidemic containment
**TMP/SMX=trimethoprim/sulfamethoxazole

Optimum treatment for quinolone resistant typhoid fever has not been determined. Azithromycin, third generation cephalosporins or 10-14 days course of high dose fluoroquinolone is effective.
resistant strains of *S. typhi* developed which was first reported from Britain in 1950 and from India in 1972. After sporadic outbreaks of chloramphenicol resistant typhoid between 1970 and 1985, many strains of *S. typhi* developed MDR to the three primary antimicrobials- ampicillin, chloramphenicol and co-trimoxazole. The first major epidemic of MDR *S. typhi* was reported from Mexico in 1972. Since then an increasing frequency of MDR has been reported from all parts of the world predominantly from the developing countries. This imposed a serious threat towards public health and was countered by the advent of oral quinolones. But quinolone resistance in *S. typhi* and *S. paratyphi* has recently been described in various parts of Asia. It may be possibly related to the widespread and indiscriminate use of this drug.

The changing pattern of multi drug resistance in typhoid fever was studied in Delhi in 1993. Out of 76 patients, 12 patients responded to a combination of chloramphenicol and gentamicin, 51 to ciprofloxacin while the remaining 9 responded to combination of cefotaxime and amikacin. This study re-emphasizes the changing pattern, and the role of quinolone especially ciprofloxacin in the management of drug resistant typhoid fever; but at the same time it indicates that ciprofloxacin is not the drug of choice in all cases of typhoid fever and resistance to it may be seen in some cases, where alternatives are required.

One hundred children with positive blood culture for *S. typhi* were studied for clinical profile in Ahmedabad in 2000. Eighty percent Salmonella isolates were resistant to amoxicillin, chloramphenicol and co-trimoxazole, but all were sensitive to ciprofloxacin and ceftriaxone. In another study, out of 5410 blood samples, 715 samples were found positive of *S. typhi*. The number of MDR strains of *S. typhi* constituted almost 16.1% of the

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sensitivity Range (%)</th>
<th>Specificity Range (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microbiological Tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td>40-80</td>
<td>NA</td>
<td>Widely regarded as the gold standard, but sensitivity may below in endemic areas with high rates of antibiotic use hence true specificity is difficult to estimate</td>
</tr>
<tr>
<td>Bone marrow cultures</td>
<td>55-67</td>
<td>30</td>
<td>Greater sensitivity but invasive and thus of limited clinical value, especially in ambulatory management</td>
</tr>
<tr>
<td>Urine cultures</td>
<td>0-58</td>
<td>NA</td>
<td>Variable sensitivity</td>
</tr>
<tr>
<td>Stool culture</td>
<td>30</td>
<td>NA</td>
<td>Sensitivity lower in development countries and not used routinely for follow-up</td>
</tr>
<tr>
<td><strong>Molecular Diagnostics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymerase chain reaction</td>
<td>100</td>
<td>100</td>
<td>Promising, but initial reports indicated similar sensitivity to blood cultures and lower specificity</td>
</tr>
<tr>
<td>Nested polymerase chain reaction</td>
<td>100</td>
<td>100</td>
<td>Promising and may replace blood culture as the new &quot;gold standard&quot;</td>
</tr>
<tr>
<td>Widal test (tube dilution and slide agglutination)</td>
<td>47-77</td>
<td>50-92</td>
<td>Classic and inexpensive. Despite mixed results in endemic areas, still performs well for screening large volumes. May need standardization and quality assurance of reagents</td>
</tr>
<tr>
<td>Typhidot</td>
<td>66-88</td>
<td>75-91</td>
<td>Lower sensitivity than Tyhidot-M</td>
</tr>
<tr>
<td>Typhidot-M</td>
<td>73-95</td>
<td>68-95</td>
<td>Higher sensitivity and specificity than classic Typhidot in some series, but other evaluations suggest that the performance may not be as robust in community settings as in hospital</td>
</tr>
<tr>
<td>Tubex</td>
<td>65-88</td>
<td>63-89</td>
<td>Promising initial results but has yet to be evaluated in larger trials in community settings</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine antigen detection</td>
<td>65-95</td>
<td>NA</td>
<td>Preliminary data only</td>
</tr>
</tbody>
</table>

*NA= Not Available.*
Infectious Disease

Diagnosing Typhoid: A Rising Challenge

Although the mainstay of diagnosing typhoid fever is a positive blood culture, it is positive in only 40-60% of cases. In many developing nations, widespread availability of antibiotics and its prescribing is one of the notable reasons for the low sensitivity of blood cultures. And this is also so during the early course of the disease. Stool and urine cultures become positive after the first week of infection but their sensitivity is much lower. Bone marrow cultures are more sensitive but they are difficult to obtain, relatively invasive, and of little use in public health settings. Other hematological investigations are non-specific. The classic Widal test measures antibodies against O and H antigens of S typhi, and is more than 100 years old. But this test lacks sensitivity, and reliance on it alone in areas where typhoid is endemic may lead to over diagnosis.

Newer diagnostic tests have been developed. Typhidot or Tubex directly detects IgM antibodies against a host of specific S. typhi antigens but have not proven to be sufficiently robust in large scale evaluations in community. A polymerase chain reaction using H1-d primers has been used to amplify specific genes of the organisms in the patients’ blood and is a promising means of making a rapid diagnosis. Despite these new developments, the diagnosis of typhoid is critical and poses problems, since it may mimic many common febrile illnesses without localizing signs. In children with multi system features, the early stages of enteric fever may be confused with conditions like acute gastroenteritis, bronchitis and bronchopneumonia. Subsequently, the differential diagnosis includes malaria, sepsis with other bacterial pathogens, tuberculosis, brucellosis, leptospirosis and rickettsial diseases and also some viral infections like dengue fever, acute hepatitis, and infectious mononucleosis. All these reasons have indicated the urgency of developing a newer option that may allow the rapid and specific diagnosis of the common febrile illnesses specially malaria, dengue fever and typhoid.

Drug Resistance Versus Treatment

Early diagnosis of typhoid fever and prompt administration of appropriate antibiotic treatment are essential for optimal management, especially in children. Standard treatment with chloramphenicol or amoxicillin is associated with a relapse rate of 5-15% or 4-8% respectively, whereas the newer quinolones and third generation cephalosporins are associated with higher cure rates.

The MDR typhoid has led to widespread use of fluoroquinolones as the treatment of choice. But in recent years, the quinolone resistance has placed tremendous pressure on public health systems in areas where treatment options are limited. Studies of short course antibiotic treatment for MDR typhoid have shown that fluoroquinolones can achieve satisfactory cure rates, but ceftriaxone was associated with higher rates of relapse. A recent review concludes that there is little evidence to support administration of fluoroquinolones to all cases of typhoid and that satisfactory cure rates can be achieved in drug sensitive cases with first line agents such as chloramphenicol. Given the signs of rapidly increasing resistance of S. typhi to fluoroquinolones, it is imperative that the widespread use of these antibiotics for fever and their availability over the counter should be restricted, although it may already be too late.

Current Treatment Options

The prognosis for a patient of typhoid fever depends on the rapidity of diagnosis and treatment with an appropriate antibiotic. Other factors include the patient’s age, general health status and nutrition, the causative Salmonella serotype and appearance of complications.
Quinolones are highly active against Salmonellae in vitro, effectively penetrate macrophages, achieve high concentrations in the bowel and bile lumina and thus have potential advantages over other antimicrobials. Short course therapy with ofloxacin (10-15 mg/kg two times daily for 2-3 days) appears to be simple, safe, and effective in uncomplicated MDR typhoid fever but this is only so when the strain is susceptible to nalidixic acid. Therefore, all S. typhi isolates should be screened for nalidixic acid resistance and tested against a clinically appropriate quinolone. Ciprofloxacin has also been found to be highly effective therapy against MDR S. typhi and S. paratyphi. But resistance to ciprofloxacin appears to be increasing, particularly in Indian subcontinent. Patients with nalidixic acid-resistant strains may preferably be treated with higher doses of ciprofloxacin (10 mg/kg two times daily for 10 days).

Third generation cephalosporins like cefotaxime, ceftriaxone, and ceferazone have been used successfully to treat typhoid with as short as 3 days courses showing similar efficacy to the usual 10-14 days regimens. Excellent response rates have been reported with ceftriaxone when administered for 5-7 days but the relapse rate remains incompletely defined. These drugs should be reserved for quinolone resistant cases.

Azetreonam and azithromycin, through several small studies have been reported successful in treating typhoid fever comparing with chloramphenicol. But some clinical trials among children in Malaysia showed a high failure rate. Azithromycin may be administered in a dose of 1 gram once daily for 5 days although the disease takes longer to defervesce. The main advantage of azetreonam and azithromycin is that they can be used in children and in pregnant or nursing females.

Corticosteroids are administered for severe toxemia and fever and may produce a dramatic response in the patient with profound sepsis. Infants and children with underlying malnutrition and those infected with multi drug resistant isolates are at higher risk of adverse outcomes. That is why additional treatment with dexamethasone (3 mg/kg initially followed by 1 mg/kg every 6 hours for 48 hours) has been recommended among severely ill patients with shock, stupor or coma but only under strictly controlled conditions and supervision. Proper nursing care also plays a major role in the recovery from typhoid fever. The pyrexia can be managed with tepid baths and sponging. It is better to avoid salicylates and antipyretics as they cause severe sweating ultimately lowering the blood pressure.

**Typhoid Vaccines**

An effective typhoid vaccine could have substantial effect during outbreaks in places where water and sewage-disposal systems are inadequate. Three types of typhoid vaccines are currently available: Phenol-inactivated vaccine; Live, attenuated S. typhi strain, Ty21a; and Purified Vi capsular polysaccharide. Each of these vaccines offers 55% to 85% protection for 3 to 5 years. The main differences relate to their side effects. The purified Vi capsular polysaccharide has significantly fewer adverse effects and commonly used as an alternative to oral typhoid vaccine. Its efficacy has been reported to be >90% when conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (Vi-rEPA). Two injections of this vaccine, given 6 weeks apart, prevented typhoid fever within 27 months in 5525 children of 2-5 years in an endemic country- Vietnam. The vaccination proved to be a successful intervention during an epidemic in Thiland in 70’s. Thus, an effective well-tolerated typhoid vaccine could help control both endemic and epidemic disease.

**Conclusion**

Management of typhoid fever continues to pose a challenge, even after one hundred years the microorganism was first isolated. The absence of reliable rapid diagnostic test constantly challenges the diagnostic skills of the physicians. A concerted effort involving clean water supply, sewage disposal, effective vaccination, early diagnosis and treatment of cases and carriers will be required to control the disease. Therapeutic strategies will have to take into account the local antibiotic sensitivity patterns of *S. typhi* while defining treatment. Also the indiscriminate use of drugs should be discouraged. Adaptation of these strategies will facilitate the success in combating the new resistant patterns of typhoid fever and overcome this global crisis by saving millions of lives.

**References:**

2. *Indian Journal of Medicine* Res. 120, August 2004
6. *World Health Organization*
Over twenty-five percent of abnormalities found at birth involve the genitalia or urinary tract. While not life threatening, common urologic problems greatly impact the physical and psychological health of millions of young children. These conditions include phimosis, undescended or retractile testis, vesicoureteric junction reflux, hypospadias, neonatal hydronephrosis, pelvesuretic junction obstruction and some tumors. Fortunately, many of these problems can be resolved with proper medical and surgical treatment as well as careful follow-up while some are resolved spontaneously over time. That is why having an appropriate view of these disease conditions is very much important in general clinical practice.

**Phimosis**

Phimosis is the commonest reason for circumcision although recurrent balanitis and religious or social reasons are among the other indications. At birth, adhesions are present between the glans penis and foreskin, separation of which occurs immediately and continues thereafter. The prepuce normally becomes retractile after the age of two, but many retain some adhesions. These sustained adhesions are the common reason for consulting a doctor although non-retractile foreskin is symptom free and self-limiting and doesn’t require circumcision. They should be treated only if physiological phimosis persists into adolescence and hampers the normal sexual functions. The complaint that the prepuce balloons during urination is a sign of non-retractile foreskin rather than phimosis. Careful examination shows visible urethral meatus through the narrowed peuperal opening. With time, this opening widens allowing the foreskin to retract normally. True or pathological phimosis is rare but may cause considerable problems during childhood or adolescence. Treatment is usually circumcision, whereas alternative treatments are preputioplasty or application of steroid cream.

**Undescended Testis**

The incidence of undescended testis ranges from 3.4% to 5.8% in full term baby boys and it decreases to 0.8% within one year. In 80% of cases, the undescended testis will be palpable in inguinal canal. Patients with such problem have two major concerns. These are the increased incidence of testicular cancer and heightened risk of subfertility. Treatment mostly depends upon the location and palpability of the testis. Ultrasound, computed tomography and magnetic resonance imaging are common investigations but laparoscopy is the current investigation of choice. If the testis is palpable in the inguinal canal, an orchiopexy should be carried out and it should be done as soon as possible if testis is found intra-abdominally in prepubertal child. After puberty orchidectomy is needed to treat intra-abdominal testes as it become incapable of spermatogenesis and the risk of malignancy rises 10 times higher than normal testis. If blind ending spermatic vessels are detected, patient and parents should be counseled and hormonal replacement and also a testicular prosthesis may be effective. In cases of bilateral undescended testis where neither of the testis is palpable, chromosomal and endocrine evaluation is needed.

**Retractile Testis**

As this is a common finding in general practice and is often confused with undescended testis, a proper

<table>
<thead>
<tr>
<th>Indications for circumcision in patients with phimosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recurrent infection under foreskin</td>
</tr>
<tr>
<td>• Appreciable restriction of urinary flow</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sites of undescended testis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inguinal canal (80%)</td>
</tr>
<tr>
<td>• Intra-abdominal (19%)</td>
</tr>
<tr>
<td>• Other (1%) Suprapubic, Femoral, Perineal etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laparoscopic findings of impalpable testis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blind ending spermatic vessels above internal inguinal ring but no testis</td>
</tr>
<tr>
<td>• Intra-abdominal testis</td>
</tr>
<tr>
<td>• Cord structures that enter internal ring</td>
</tr>
</tbody>
</table>
diagnosis is very important. The key distinguishable feature between these two is that the retractile testis will stay in the scrotum after the cremaster muscle has been overstretched, whereas a low undescended testis will immediately pop back to its undescended position after being released. Further doubt should be evaluated by a follow up study and repeated examination.

**Vesicoureteric Junction Reflux**

In the neonatal period, reflux is likely to be due to anatomical abnormalities. The incidence of reflux is equal in the sexes. In later childhood the condition predominantly occurs in girls with voiding disturbances. A vicious cycle of symptoms may exist as reflux may lead to infection leading to bladder instability, dysfunctional voiding and further reflux. These three elements should therefore be considered with equal importance while treating this condition.

Reflux stops spontaneously in a large proportion of patients although the degree of resolution is inversely proportional to the severity of the reflux. For children with reflux of grades 1-2, antibiotic prophylaxis is the recommended initial treatment. In all children with reflux of grade 3-5 surgical correction is recommended. This is also applicable for those with persistent reflux despite a trial of observation on prophylactic antibiotics. Dysfunctional voiding as a result of bladder instability may be treated with anticholinergic agents. Recent findings have proved that reflux alone does not lead to renal damage, infection must also be present.

**Hypospadias**

Hypospadias is a congenital condition affecting 3 in 1000 male infants resulting in underdevelopment of the urethra. The penis may be deviated by chordee, and the urethral opening may be situated anywhere from the perineum to the glans on the ventral surface. The affected child should be referred for urological assessment and surgical treatment. The ideal age for surgery is 6-12 months.

**Neonatal Hydronephrosis**

Fetal urinary tract anomalies are common. They occur in 0.2-0.9% of all pregnancies. Hydronephrosis accounts for more than 50% of these anomalies. Antenatal hydronephrosis may be caused by ureteropelvic junction obstruction, ureterovesical junction obstruction, multicystic kidney, primary obstructive megaureter, vesicoureteric reflux or posterior urethral valves.

In cases of mild unilateral hydronephrosis (<15 mm in diameter) with normal appearing renal parenchyma, further prenatal follow-up is useful than surgery. A postnatal check-up is important to confirm the hydronephrosis has resolved. In cases of moderate unilateral hydronephrosis (15-19 mm), ultrasound and a micturating cystogram should be performed at two months and subsequently at intervals of six months.
Surgery is unlikely to be needed in these cases. In cases of severe unilateral hydronephrosis (20 mm), ultrasound, a micturating cystogram and an isotopic renal scan should be performed at one month. Severe unilateral hydrohephrosis is eventually most likely to need surgery.

**Obstruction of Pelviureteric Junction**

The essential defect here seems to be an aperistaltic segment of ureter from which the normal musculature is congenitally absent. The role of aberrant vessels causing obstruction has recently been questioned. These vessels are normally variants, often pass behind the ureter, and generally do not to cause obstruction.

The condition is usually diagnosed by intravenous urography, which shows delay in appearance of contrast on the affected side and dilated renal pelvis and calices. The ureter, is usually not dilated. Surgery is indicated for obstruction symptoms, stone formation, recurrent urinary infection, or progressive renal impairment. Pyloplasty is the treatment of choice. But if the affected kidney possesses less than 10% of total renal function, a nephrectomy should be performed.

**Common Pediatric Tumors**

*Wilms’ Tumor* or nephroblastoma is the most common primary malignant renal tumor of childhood typically affecting young children. More than 80% of the patients are identified before the age of five years. The most common presentation is an abdominal mass although hematuria is the presenting feature in up to 15% of cases. The diagnosis is initially made by renal ultrasonography, intravenous urography, computed tomography or magnetic resonance imaging. Treatment is usually done by radical nephrectomy, chemotherapy usually given after surgery. Radiotherapy is needed only if residual tumor has been left behind at surgery and for patients with lymphatic and pulmonary metastases. Neoadjuvant chemotherapy is beneficial for patients with bilateral involvement.

**Renal Cell Carcinoma** is rare and is not usually diagnosed until confirmed by histological examination of a presumed Wilms’ tumor. Some tumors are chemosensitive, and radiotherapy may be needed for microscopic residual disease, but radical nephrectomy remains the mainstay of treatment.

*Rhabdomyosarcoma* commonly presents with lower urinary tract symptoms, particularly hematuria or urinary retention. Tumors of vagina may cause foul vaginal discharge and pelvic tumors may present a large mass. Rhabdomyosarcoma is treated effectively with chemotherapy. The role of radical surgery is currently reserved for children who fail to respond to chemotherapy or develop pelvic relapse.

**Conclusion**

In every walks of general practice, the common childhood urological problems continue to question a physician’s knowledge of appropriate diagnosis and management. A guideline with recent concepts and incentives aimed at early case detection and differentiation is therefore considered as one of the gospels in such context. Thus, the combination of medical knowledge and recent clinical guidelines may be able to provide the proper management of these disease conditions ensuring the children a healthier life for today as well as for tomorrow.

**References**

New Strategies for Polio Eradication

South-East Asia, home to three of the world’s four remaining polio endemic countries, is addressing the lingering challenges of polio eradication through revamped strategies, including stepped-up immunization activities. India, which has the highest incidence of indigenous polio in the region, is responding to an outbreak that has caused 373 cases of polio in 2006, 328 of them coming from just one state, Uttar Pradesh. Bangladesh had been unofficially polio-free since 2000, but several new cases have been reported this year, prompting authorities to launch the vaccination drive. However, World Health Organization (WHO) could not declare Bangladesh polio-free because of its proximity to neighbouring India, where there are still polio hot spots.

Health officials said India’s success in combating the virus was vital to polio eradication in Bangladesh. That is why India is conducting a special vaccination drive along the Bangladesh border on request. At the same time Health workers have begun a drive across Bangladesh to immunize 24 million children under-five against polio to combat the crippling virus that has staged a comeback in the South Asian nation. They have planned to repeat the process at least nine times over the next 12 months. Administering oral drops to each child again, to ensure no-one was left out.

Parents were being asked to take their children to various health care centers including mobile units at bus and train stations. In addition, Bangladesh also planned another polio vaccination drive in 2008 if India fails to achieve its goal of eliminating the virus by 2007. Meanwhile WHO is to change its polio eradication program in India, adding a monovalent oral vaccine to the existing regime. It is hoped that this addition will finally rid the country of the disease and enhance its neighbouring countries the privilege of becoming a polio-free nation.

Source: World Health Organization

Long Needles for Immunizing Children

Until recently, little was known about the effect of needle size on vaccine efficacy and side effects. To evaluate that long needles are best for immunizing children, a randomized clinical trial was conducted in the United Kingdom. Here, 696 healthy infants were vaccinated at the age of 2, 3 and 4 months. Each were vaccinated by using the standard 25-mm-long needle, a slightly thicker one (23 gauge, 25 mm long) or slightly shorter one (25 gauge, 16 mm long). The infants received a combined diptheria, tetanus, whole cell pertussis and Haemophilus influenzae type B vaccine in one leg and a serogroup C meningococcal glycoconjugate vaccine in other leg. Patents were advised to maintain a diary record of reactions following immunization.

The end-result of the study showed that infants vaccinated with standard-length needles of both gauges experienced significantly fewer local reactions (like swelling, redness, hardness or tenderness) than infants vaccinated with shorter needles. Longer needles appear to elicit fewer local reactions. The reason may be that they ensure that vaccines are injected into muscle rather than into subcutaneous. The study supports the recommendation of American Academy of Pediatrics’ that infants from 2-12 months should be vaccinated with 22.5-25.4 mm long needles.

Source: British medical Journal 2006:333
Hypertension in Pregnancy Leads to High Future Risk of High Blood Pressure, Stroke

The risk of a woman developing high blood pressure relatively early in life may be increased if that woman was hypertensive during pregnancy, according to the researchers. Doctors report that they have found a link between high blood pressure including preeclampsia during pregnancy not only with raised blood pressure in the early 50s, but a greater risk of stroke and cardiovascular events than occurs in women who do not have hypertension during pregnancy. For many years it has been assumed that hypertension associated with pregnancy went away at childbirth and did not have a lot of long-term consequences. The researchers have found that 50% of women who have hypertension during pregnancy will develop high blood pressure by the time they are age 52. In contrast, generally, women who were not hypertensive in pregnancy do not develop hypertension until age 60. The researchers identified 4,782 women from individuals who participated in the Family Blood Pressure Program (2000-2005). In this group of women with a family history of hypertension, 643 (13.5%) were hypertensive during their pregnancies. The researchers believe that in general about 10% of women become hypertensive when they are pregnant. At other health statistics it was found that the risk of having stroke, coronary heart disease and hypertension later in life were 2.7% vs. 5.2% ($P = 0.003$), 5.4% vs. 6.8% ($P = 0.049$) and 56.9% vs. 60.6% ($P < 0.001$) respectively for the normotensive and hypertensive patients during pregnancy.

Arm Aerobics Relieve Leg Pain

Arm ergometry can improve maximal walking distance in-patients with peripheral artery disease (PAD), according to a randomized controlled study. The researchers said that particularly for PAD patients who are quite disabled, walking on a treadmill could be difficult. Arm aerobics may offer a better option than traditional workouts on a treadmill. Earlier studies have shown that treadmill training improve onset of claudication distance and maximal walking distance in-patients with PAD. But the researchers thought that it was a local effect, with local adaptation of skeletal muscle helping them use oxygen more efficiently. The new study, the first to pit treadmill training against arm ergometry, suggests that exercise has a systemic effect, improving overall cardiovascular function and fitness. The researchers randomly assigned 35 patients with PAD and lifestyle-limiting claudication to 1 of 4 treatment groups: no exercise; treadmill exercise; arm ergometry; or both treatments. Participants in the exercise groups worked out in a supervised setting for 1 hour, 3 times a week for 12 weeks. After 12 weeks of training, maximal walking distance increased from 486.15 m to 778.52 m in the treadmill group ($P < 0.001$ vs. control), from 441.26 m to 593.40 m in the ergometry group ($P = 0.01$ vs. control), and from 441.28 m to 664.37 m in the combination arm ($P < 0.001$ vs. control). The researchers found that there was no significant difference in the degree of improvement between the 3 exercise groups. From this study it is evident that for patients with PAD who are frail, clinicians may want to consider arm ergometry.

Amniotic Fluid Provides Cells to Grow Living Heart Valves for Potential Neonatal Use

Approximately 1% of infants are born with congenital defects of the heart valves; in one third of these cases, the defect is repaired by insertion of a new valve. The nonliving valves currently in use, however, cannot grow with the patient. Thus, new, larger valves must be inserted at intervals, with accompanying surgical risks. A living valve, by contrast, can grow as the patient grows and thus should constitute a permanent repair. Previously researchers have grown living heart valves from differentiated cells derived from blood vessels, from mesenchymal progenitor cells derived from bone marrow, from progenitor cells derived from umbilical cord blood, and from progenitor cells derived from chorionic villi obtained prenatally. Amniotic fluid, however, represents a source from which the patient’s own cells can be obtained with relative safety far enough in advance to allow the valve to be available at birth. Some types of congenital defects can cause permanent secondary damage if not repaired within days. The researchers obtain amniotic fluid by standard amniocentesis. Cells carrying the CD133 markers that indicate potential for mesenchymal differentiation are separated out, are expanded, differentiated, and characterized, then are seeded onto a biodegradable scaffolding. At the end of 4 to 6 weeks of maturation in vitro, the researchers obtain a living heart valve. They showed that the valves are not only anatomically normal but are functionally normal, responding to pulsatile pressures as a normal heart valve would. The researchers suggest that these living replacements with the potential of growth, remodeling, and regeneration may realize the early repair of congenital malformations.
Pictures used in cover page:
A sample of salmonellosis in a petri-dish
Human kidney
A child is being immunized

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