HEMOLYTIC UREMIC SYNDROME:
RECENT DEVELOPMENTS

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The hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal insufficiency. The disorder has emerged as the most common cause of acute renal failure (ARF) in many countries from different parts of the world. HUS was first reported by Gasser in 1955. Subsequently, a large number of cases have been reported from Argentina(1), South Africa(2), some parts of North America(3-5) and Europe(6,7). The dysentery-associated form of HUS has been chiefly observed in the Indian subcontinent and Thailand(8-12). During the initial years the condition was associated with a high mortality rate. The outcome has greatly improved with better supportive management despite the lack of any specific treatment. The etiopathogenesis of HUS was totally unknown until a few years ago when its association with cytotoxin producing bacterial enteropathogens was found.

This review will present important recent developments in the understanding of HUS. Information available in standard texts(13,14) will not be repeated. A comprehensive discussion and an exhaustive bibliography is not included; these can be found in some of the recent reviews(15-18).

What is HUS?

The basic underlying abnormality in HUS is an angiopathy, predominantly in the renal microvasculature. Vascular endothelial injury is followed by localized coagulation. Mechanical trauma to red cells and platelets during their passage through these abnormal vessels leads to their destruction and eventual removal by the reticuloendothelial cells. The picture of HUS may be mimicked by sepsis when complicated by consumption coagulopathy, especially in neonates; such cases should be distinguished from HUS. Rarely, HUS may resemble thrombotic thrombocytopenic purpura (TTP). Whereas thrombotic microangiopathy and the resulting hemolytic anemia and thrombocytopenia are common to both of these disorders(15), their typical profiles are very different(19). TTP mostly occurs in adults and is dominated by serious neurological manifestations. Mild renal involvement is often associated but oliguria and acute renal failure are uncommon.

Secondary HUS

The triad of features constituting HUS...
occasionally may be seen in association with a wide variety of conditions. Some of these are listed in Table I. It is obvious that most are rarely seen during childhood. In adults HUS is very uncommon and heterogeneous(20). An outbreak of hemorrhagic colitis due to E. coli 0157:H7 was recently reported in a nursing home for the elderly, and was complicated by the development of HUS in a large proportion of cases with considerable mortality(21). It is of interest that HUS rarely has been reported in animals(22).

Terminology and Subgroups of HUS

Attempts have been made to classify HUS into “epidemic” and “sporadic” forms and “typical” (diarrhea-related) and “atypical” (without a diarrheal prodrome) groups(16). Epidemic and typical forms were considered to have a better prognosis. Terms such as “classical” and “prototype” have also been used by different authors to describe diarrhea-related HUS(17). Dysentery associated HUS also has been called “secondary”. The use of such labels does not serve a useful purpose(23). If one were to consider various forms of HUS (Table I) the disorder would truly emerge as a syndrome. A scrutiny of the reports of HUS in children from different countries, however, discloses that in a large majority of cases it has a relatively homogeneous profile. A review of 1924 cases in 21 series by Havens et al. in 1989(24) showed that 81% had a prodrome of enteritis; 38% of these cases were from Argentina. This review did not include reports from the Indian subcontinent.

It is suggested that HUS may be grouped into enteritis-related cases (E+) and those without such an association (E−). The latter group would be further qualified and include familial and recurrent forms.

Clinical Features

The condition has been well documented and excellent reviews are available(13-16). HUS is mostly observed in infants and preschool children. In a majority of cases there is a prodrome of diarrhea that is often bloody. The diarrhea may be mild or severe and may be subsiding by the time HUS develops. HUS usually manifests with rapid appearance of pallor, lassitude, drowsiness and oliguria. Hyper-

<table>
<thead>
<tr>
<th>TABLE I—Forms of Hemolytic Uremic Syndrome*</th>
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<tbody>
<tr>
<td>1. Classic (verotoxin producing E. coli)</td>
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<tr>
<td>2. Post infectious: S. dysenteriae 1, Salmonella, Clostridia, Campylobacter, Yersinia, Streptococcus pneumoniae, Coxsackie, Echoviruses, Influenza virus, Infectious mononucleosis, Measles, Mumps, Polio, DPT vaccines.</td>
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<td>3. Familial (marked hypertension, relapsing, outcome poor)</td>
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<td>4. Drugs: Mitomycin, cyclosporine A</td>
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<td>5. Pregnancy, oral contraceptives</td>
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<td>6. Malignant hypertension, radiation to kidneys</td>
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<td>7. Bone marrow, renal transplantation</td>
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<tr>
<td>8. Collagen diseases: Systemic lupus, scleroderma</td>
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<td>9. Complement deficiency (familial, glomerular C3 deposits)</td>
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*References to the conditions listed may be found in 15, 16, 20.
tension is usually present. Uncommon features, except in dysentery-associated form, include gross hematuria, petechiae and purpura, jaundice and convulsions. Renal involvement may be mild but is usually severe; in the latter case clinical features related to complications of ARF may be prominent. In early reports on HUS the mortality rate was very high. With better supportive management and aggressive treatment of renal failure the outcome has greatly improved and a recovery rate of over 90% can be expected. In postdysenteric HUS in India, however, the mortality remains high.

Pathology

The renal pathological findings have been reviewed(13,14,25-27). The early glomerular abnormalities are best demonstrated by electron microscopy and include swelling of the endothelial cells and their separation from the basement membrane and accumulation of PAS-positive material in the subendothelial space. Capillary lumen is narrowed by swollen cells, blood cells and fibrin deposition. Arterioles and small arteries are involved in some cases, when severe hypertension may be prominent. In more severe cases patchy or extensive renal cortical necrosis is present; the incidence is higher in postdysenteric cases(25-27).

HUS in the Indian Subcontinent

The initial reports of HUS appeared from Dacca, Bangladesh(8) and Vellore, India(9). Thereafter the condition has been reported from different parts of India (10-12,28). The description of HUS is very similar in these reports. Most patients have a severe dysenteric illness for varying periods of time before the development of HUS. Renal involvement is severe with a high incidence of oligoanuria. A prominent neutrophilic leucocytosis is usually present. Abnormalities of coagulation suggestive of disseminated intravascular coagulation (DIC) have been detected in a large proportion of cases(29). Renal cortical necrosis is seen in 30-40% cases. The mortality is about 60%, being related to a more profound renal involvement with prolonged oligoanuria and often a persistent colitis that complicates nutritional management. The clinical and laboratory features of dysentery suggest shigellosis, but Shigella spp have been detected in only about a third of cases. In a small proportion of cases, several other organisms such as non-typhoid Salmonella have been isolated from the stools(12). The significance of these bacteria in the pathogenesis of HUS is not clear.

The observation that cases of HUS were rarely seen in the Indian subcontinent until early 1970's has been a subject of much speculation. However, it now seems that a large increase in the incidence of such cases followed epidemics of dysentery due to Shigella dysenteriae type 1, which started in Bangladesh in 1972 and later occurred in south India and thereafter in eastern and northern India and neighboring countries(30). The organisms were often resistant to commonly used antimicrobials such as ampicillin, chloramphenicol and cotrimoxazole. Shigella dysentery has been endemic in the Indian subcontinent, but before the severe epidemic forms encountered in 1970's, the causative type was usually Shigella flexneri. It therefore appears very likely that majority of cases of postdysenteric HUS are related to shigellosis, although the likelihood of the involvement of other pathogens cannot be excluded.
Is Postdysenteric HUS an “Atypical” Form?

HUS following dysentery (presumed to be shigellosis) has been considered “atypical”(17) or to represent a distinct subset(16). A comparison of the salient features of the postdysenteric HUS and the diarrhea-associated HUS is given in Table II. These observations suggest that the former condition is more severe. The high mortality rate could be due to difficulty in providing optimal management of prolonged renal failure and adequate nutritional support (e.g., parenteral nutrition). The likelihood that tertiary centers see the most severe forms and that milder cases may be treated elsewhere and not reported, cannot be excluded. It is of interest that in early reports of HUS from Argentina(1), U.S.A.(31) and Australia(32), a high mortality rate was observed. Coagulation abnormalities were detected in these cases and a pathogenic role for DIC was suggested.

Pathogenesis of HUS

Significant advances have taken place during the last decade in understanding the pathogenesis of HUS.

1. Coagulation abnormalities: Although initial reports had strongly suggested that DIC was important in the pathogenesis of HUS, subsequent studies did not confirm the presence of DIC(33). Abnormalities of coagulation and increased blood levels of fibrin degradation products, suggesting DIC, have been reported in postdysenteric HUS, but additional confirmatory evidence (decreased levels of factors V, VIII and fibrinogen; reduced AT III levels and increased fibrinopeptide A) needs to be presented. It is, however, clear that localized coagulation occurs in the capillaries(15), evidenced by the presence of thrombi in renal microvasculature (and occasionally in other organs), fibrin in the glomeruli and platelets and platelet antigens in the glomeruli in some cases(34).

2. Abnormalities in prostacyclin metabolism: The report by Remuzzi et al.(35) in 1978 that patients with HUS lacked a factor in plasma required to stimulate prostacyclin (PGI₂) synthesis, aroused a great deal of interest. It was proposed that failure of the endothelial cells to produce

| TABLE II–Comparison of the Profiles of Postdysenteric and Diarrhea-associated Cases of HUS |
|---------------------------------------------|---------------------------------------------|
| Features | Postdysenteric HUS | Diarrhea-associated HUS |
| Enteric illness | Severe, may persist for several days after onset of HUS | Mild, stools are often grossly bloody |
| Intestinal complications | Not uncommon | Rare |
| Stool pathogens | Shigella in a variable proportion | VTEC/SLT-producing organisms in majority |
| Leukocytosis | Severe | Less striking |
| Coagulation abnormalities | Often present | Rare |
| Renal involvement | Severe, oligoanuria frequent | Less severe |
| Incidence of renal cortical necrosis | High | Low |
| Geographical location | Indian subcontinent | Argentina, North America, Europe. |
prostacyclin may lead to an imbalance between the vasodilator and antiaggregant effects of PGI₂ and the opposing actions of thromboxane A₂ produced by the platelets, and eventually result in localized coagulation in the capillaries. Diminished synthesis of PGI₂ by endothelial cells on incubation with plasma from HUS patients has been reported(36). However, further studies of the levels of prostacyclin and its metabolites in HUS have shown conflicting results(17). It is more likely that prostacyclin abnormalities reported in the diarrhea-related HUS result from a primary injury to the vascular endothelium. It has been suggested that prostacyclin deficiency may have a pathogenic role in the rare, inherited form of HUS(17).

3. Shiga toxins and Shiga-like toxins: The association of shigellosis with HUS is well-established. The glycolipid globotriosyl ceramide (Gb₃) is the cell surface receptor for Shiga toxin and Shiga-like toxins. Human kidney contains this receptor, and higher concentrations in the cortex than in medulla have been demonstrated(37). After the entry of Shiga toxin inside the cell, protein synthesis is inhibited(17). Besides actual internalization, the toxin could also act through signal transduction mechanism to alter endothelial cell function, leading to an increase in procoagulant activity. Shigella dysenteriae 1 is the most potent toxin producer; smaller amounts are produced by other species.

Verotoxins

Cytotoxins produced by some E. coli and certain other bacteria that kill Vero cells in vitro are called verotoxins. Two distinct types of verotoxins (VT), VT-1 and VT-2 are produced by enterohemorrhagic E. coli and are similar to Shiga-like toxin 1 (SLT-1) and Shiga-like toxin 2 (SLT-2) respectively(37). VT-1 appears to be structurally and immunologically identical to Shiga toxin(37). VT-1, but not VT-2, is neutralized by antibody to Shiga toxin. It is of interest that human isolates of Vibrio, some isolates of Salmonella and Campylobacter jejuni also produce verotoxin(16,37). Verotoxin producing E. coli (VTEC) infection may be asymptomatic, cause watery diarrhea, hemorrhagic colitis, pseudomembranous colitis, TTP and HUS(17).

Cytotoxin-producing Organisms and HUS

A breakthrough in understanding the pathogenesis of HUS came when Karmali et al. in 1983 reported isolation of cytoxin-producing E. coli in stools from patients with HUS(38). Before that, pathogens were rarely detected in stools from such patients, except for Shigella spp in a proportion of dysentery-related HUS in the Indian subcontinent. In recent years VTEC have been isolated from the stools in a large proportion of patients from U.S.A.(39,40), Canada(41) and England(42,43). E. coli 0157:H7 has been the predominant serotype, but others such as 026:H11 have also been found. The criteria for the diagnosis of infection with VTEC have been tested by Kaplan et al.(17) and include production of SLT by isolated colonies of E. coli from stools, SLT in fecal extracts with neutralization by specific antibody, and a 4-fold titer change in serum antibodies to SLT-1 and/or SLT-2.

Considerable evidence suggests that in most cases of enteritis-related HUS in North America and Europe VTEC may have a pathogenic role(44). Other SLT-producing organisms may be involved in different geographic regions. In Argentina
a majority of children with HUS had evidence of infection with SLT-producing organisms (which were also a frequent cause of spring summer diarrhea without HUS), but E. coli 0157:H7 were rarely isolated in these cases(45). Definitive microbiological studies from other countries in patients with HUS would be of great interest and importance.

Hematological Abnormalities

1. Hemolytic anemia: It has been believed that fragmentation of the red cells resulted from mechanical damage as these cells traversed the abnormal microvasculature through a meshwork of fibrin strands. This mechanism may not be the whole explanation(18,46). Increased oxidant damage to RBC membrane may be an additional factor(18). Endotoxin or some other bacterial product such as phospholipase C may have a direct injurious effect on the erythrocyte membrane. The ultrastructural abnormalities of red cells similar to those seen in patients with HUS can be experimentally produced by exposure of normal red cells to clostridial phospholipase(47). The same changes were observed on infusion of this toxin into rats; the infusion induced hemolytic anemia and thrombocytopenia but no microangiopathy or DIC(46). The glycolipid receptor for verotoxin is also present on red cells; the density of receptor expression may explain variable degree of hemolysis of HUS.

The verotoxin receptor has a similar specificity to the red cell antibody anti-Pk. It has been suggested that verotoxin will bind with a strong avidity to Pk positive cells and to a lesser extent to P1 positive cells. The expression of P1 antigen may be protective with absorption of toxin on to red cells and thus prevent toxin attachment to the endothelium in the renal microvasculature(18). Further studies are needed to clarify these relationships and the expression of P1 antigen in different geographical areas where HUS is common.

2. Thrombocytopenia: Platelet counts are almost invariably decreased, returning to normal in 2-3 weeks. There is evidence of enhanced platelet consumption. The number of megakaryocytes is increased in the bone marrow and platelet survival is shortened. Intravascular aggregation of platelets and a decrease in their serotonin content have been detected initially, and persist for several weeks after the recovery of platelet count(47). Platelets show a reduced response to aggregation agonists, since the active aggregation of normal platelets leaves only unresponsive platelets(47). It is likely that platelet destruction is chiefly related to contact with damaged endothelium in renal (and possibly other visceral) microvasculature. A role for platelet aggregating factor and von Willebrand's factor multimers has also been suggested(18,47).

3. Leukocytosis: A neutrophilic leukocytosis is a very common finding in HUS, especially in the postdysenteric form(12). A role for neutrophils has been suggested in the pathogenesis of HUS(48). Activated neutrophils release lysosomal enzymes and reactive oxygen radicals that can cause or aggravate endothelial cell damage. Such effects have been demonstrated in experimental conditions(49,50). Butler et al. showed that leukocyte-mediated renal injury in an experimental mode of HUS could be prevented by prior neutrophil depletion with busulphan(51). Evidence of lipid peroxidation, presumably caused by reactive oxygen radicals, has been found in an experimental model of HUS, indicated by increase in renal cortical malonyldialde-
hyde(52), as well in patients with HUS, indicated by increase in levels of conjugated dienes in the blood(53). Walters et al.(54) observed that the polynuclear cell count was significantly higher in their diarrheaa-associated HUS patients who had a poor outcome. In our patients with HUS no relationship was found between leukocyte counts and the peak blood urea levels(12). The neutrophilic response may be an early manifestation of endothelial injury caused by SLT, perhaps mediated through the release of cytokines.

Endothelial Cell Damage

It is presently believed that endothelial cell injury, chiefly in the renal microvasculature, is the primary event in the pathogenesis of HUS. The vascular endothelial lining presents a nonreactive surface to circulating blood cells to prevent intravascular activation of platelets or the coagulation pathway(55). This property is related to the negative charge on the endothelial cell surface, which repels negatively-charged platelets and red cells, and also to their synthesis of platelet and coagulation-inhibiting factors (such as prostacyclin, plasminogen activator, heparin sulfate). A perturbation in the coagulant-anticoagulant status following cytotoxin-mediated injury may result in coagulation in the capillaries. Platelets are highly reactive cells and can be activated by a variety of stimuli such as contact with damaged endothelium, immune complexes, endotoxin, fibrin, platelet activating factor and other vasoactive agents(44). A direct cytopathic effect of Shiga toxin on cultured human umbilical vein endothelial cells has been demonstrated(56). Release of von Willebrand's factor antigen from endothelial cells by a cytopathic effect might explain the abnormalities of this factor in the plasma of HUS patients, and may be related to platelet agglutination and thrombocytopenia(16,17).

Involvement of Other Organs in HUS

The brunt of the vascular injury falls on the kidney. However, involvement of other organs especially the CNS and the intestine has been emphasized in some reports(57-60). Symptoms related to CNS dysfunction are very frequent and include drowsiness, irritability, coma, convulsions and rarely focal neurological deficits. Complications of acute renal failure particularly electrolyte disturbances and overhydration usually account for these abnormalities, but occlusion of major intracranial vessels and cerebral infarction have also been found(61). Besides intestinal complications (pseudomembranous colitis, perforation, intussusception) that are more common in post-dysenteric HUS, involvement of the liver, heart, endocrine and exocrine pancreas and muscles has also been occasionally reported(16). The incidence, extent and the severity of microangiopathy in different organs in HUS is not known. Most patients who recover do not appear to have residual functional impairment of organs other than the kidney.

Management

The management of HUS has been recently reviewed(62). In enteritis-related cases no specific therapy has been beneficial. Thus anticoagulation, use of antiplatelet and fibrinolytic agents, infusion of fresh frozen plasma and plasma exchange (presumably to provide the "factor" necessary for prostacyclin production), infusion of prostacyclin and administration of vitamin E (for its antioxidant action) have
not been found to be useful. The supportive care includes early and repeated institution of dialysis to prevent and treat complications of renal failure, particularly fluid and electrolyte disturbances, correction of anemia with red cells, strict control of hypertension, prevention and treatment of infections and nutritional support(63). CNS dysfunction and hypertension may result from increased intracranial pressure and also from cerebral microangiopathy with normal intracranial pressure. A careful evaluation is necessary with CT scanning. The need for drugs, especially nephrotoxic agents, should be critically examined and their doses appropriately modified(64). In post-dysenteric cases prolonged dysentery and occasionally its surgical complications interfere with oral feeding and lead to severe malnutrition. Total parenteral nutrition, modified to the requirements of acute renal failure, must be instituted.

**Immunologic Therapy**

In enteritis-related and postdysenteric HUS neutralization of circulating cytotoxin could be beneficial, although by the time the diagnosis is made most of the target damage may already have occurred. Intravenous administration of immune globulins (IVIG) has been reported to be useful in a few children with HUS(65). Commercially available preparations of immune globulins have been shown to contain cytotoxin-neutralizing antibodies that neutralized Shiga toxin (produced by *S. dysenteriae* 1) and SLT-1 (produced by *E. coli* 026:H11) but not SLT-2(66). A carefully controlled trial fo IVIG therapy in postdysenteric HUS would be of particular interest. To be of any possible use the preparation would need to be administered early in the course of the disease.

Milford *et al.*(67) have suggested that early infusion of strongly P1 positive red cells in HUS may bind and effectively neutralize circulating antitoxin, and may favorably influence the disease process. These interesting therapeutic approaches need further investigation.

**Outcome**

With optimal management most patients should recover. The death rate in the acute stage is about 5-10%, from infections and serious complications especially of the CNS. Significant return of renal function seldom occurs in patients with extensive renal cortical necrosis.

There is some uncertainty about the long-term prognosis of the patients. A variable proportion of patients who recover from the acute illness are left with impaired renal function or persistent urinary abnormalities. In 3 large series from Europe(15) including a total of 180 cases, 6% died in the acute stage, 64% had complete recovery, 16% had mild late sequence and 14% had chronic renal failure or end-stage kidney disease. Thus 80% patients recovered or had only mild sequence. The long-term follow-up of patients who seem to completely recover reveals that a variable proportion have proteinuria, hypertension or reduced renal function(68-70). The long-term outcome in postdysenteric HUS has been reported to be satisfactory(71). Renal transplantation has been successfully carried out in patients with end-stage renal disease due to HUS(72), although there may be a risk of recurrence of HUS in the transplanted kidney(73).

**Risk Factors for the Development and Outcome of HUS**

The prevalence of VTEC-related
Enteric illness and shigellosis varies in different parts of the world. In North America a comparatively high proportion (9-30%) of patients with diarrhea due to *E. coli* 0157:H7 have been reported to develop HUS(39,74). *Shigella* dysentery is widely prevalent in the Indian subcontinent, but the proportion of patients who develop HUS is probably very small(75). Similarly in Argentina the prevalence of spring-summer diarrhea due to SLT-1 or SLT-2 producing organisms is very high, but most of these illnesses are not complicated by HUS(45).

Antibiotic Therapy

The use of antibiotics to treat diarrhea(21,39) or dysentery(76) especially if the causative organisms were resistant to the drugs employed, has been considered a risk factor for the development of HUS. Antibiotics could alter the intestinal bacterial flora and promote the growth of virulent organisms or increase the release of cytotoxin from dying bacteria.

Use of Antimotility Drugs

The use of antimotility agents was found to be a risk factor in the progression of *E. coli* enteritis to HUS by Cimolai et al.(77); a relationship with the use of antibiotics was, however, not detected.

Neutrophilic Leukocytosis

A polymorphonuclear leukocytosis has been suggested as a risk factor for the development of HUS in *Shigella* dysentery(76), as well as in VTEC diarrhea(77). In diarrhea-related HUS a worse outcome was observed for patients who had higher polymorphonuclear cell counts(49). Evidence for lipid peroxidation has been found in patients with enteritis-related HUS(53). This phenomenon could reflect cell membrane injury caused by reactive oxygen species produced by activated neutrophils. In postdysenteric HUS, however, no correlation was found between leukocyte counts and the severity of renal injury as reflected by peak blood urea levels(12). A neutrophilic leukocytosis, occasionally in the leukemoid range, is a well recognized feature of Shigellosis(78). The present studies fail to establish a role for one or more clinical or laboratory features as predisposing factor for the development of HUS. Careful, prospective case control studies will need to be carried out in the hospital as well as in the community to identify risk factors for the development of HUS and its outcome.

Areas of Research

The role of *Shigella* toxin and Shigellalike toxins (SLT-1, SLT-2) produced by some strains of *E. coli*, in the pathogenesis of HUS appears very likely. The exact mechanism by which these toxins produce endothelial injury in the vasculature remains to be defined. The role of neutrophils and the mediators of their injury such as lysosomal enzymes and reactive oxygen species needs to be examined.

There is little published information on the epidemiological and the microbiological aspects of postdysenteric or other forms of HUS from developing countries. Despite similar sanitary and hygienic conditions and a high prevalence of diarrheal diseases, HUS appears to be rare in many of these countries. It is unlikely that mild renal involvement does not occur in postdysenteric HUS. Such cases may not be seen at tertiary referral centers.
Prospective investigations are needed to study the renal involvement in dysentery. Long-term follow-up studies of postdysenteric HUS also need to be carried out.

Control Measures

Since a large majority of cases of HUS in children are related to enteritis due to VTEC, *Shigella* species or SLT-producing organisms, the control of such infections in the community should result in a decline of HUS. Antibiotic treatment of *E. coli* 0157:H7 diarrhea does not appear to affect the course of enteric illness (39,79); treatment with cotrimoxazole has been suggested to be a risk factor for the development of HUS (39). Standard methods of control of diarrheal diseases would be needed to prevent VTEC enteritis. It is of interest that in postdysenteric HUS, dysentery has mostly been severe and the organisms often resistant to various antimicrobial agents. Prompt and effective treatment of dysentery with drugs to which the organisms are sensitive (which property may vary in different communities and on different occasions) should shorten the course of the illness and possibly prevent renal complications.

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NOTES AND NEWS

TUBERCULOSIS IN CHILDREN

Guest Editor: Dr. Vimlesh Seth

Publication of Indian Pediatrics

Tuberculosis remains a major health problem in the less developed nations. In contrast to adults, tuberculosis in children presents unique problems which may pose diagnostic and therapeutic challenges. Further, the past two decades have witnessed rapid advances in the diagnosis and management of this disease.

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