OPPORTUNISTIC INFECTIONS/CLINICAL COMPLICATIONS IN ADULTS Management of Opportunistic Infections and Clinical Complications

Resources for Opportunistic Infections pages unless otherwise stated:

Standard Treatment Guidelines and Essential Medicines List: Hospital Level Adults. National Department of Health, South Africa. 2012.

Primary Care 101. National Department of Health, South Africa. 2013/14.

Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents. National Department of Health, South Africa. 2010.

PAGE 82

Clinical Presentation: Classic presentation includes headache with stiff neck, mental status changes and high fever. Petechial rash may present with Meningococcal Meningitis. Signs include stiff neck and positive Kernig's sign.

Causative Agents: *Streptococcus pneumoniae, Haemophilus influenzae,* meningococci.

Diagnosis: Lumbar Puncture with CSF sent for gram stain and culture. Bacterial organisms present on gram stain with culture yielding bacterial pathogen. Blood cultures x 2 sent, will likely result bacteremic.

Treatment: Broad spectrum antibiotics should be initiated without delay. Usual initial treatment is Ampicillin 150-200mg/kg/day IV divided every 3-4 hours.

Once culture results available, tailor treatment based on organism.

Follow-up: Prognosis for bacterial meningitis is dependant on how quickly the empiric diagnosis is made and antibiotics are administered. Delays in diagnosis and can result in poorer outcomes than patients who are treated promptly. **Clinical Presentation:** Typically a sudden onset of fever, chills, cough with sputum production, dyspnoea, and pleuritic chest pain

Causative Agent: Streptococcus pneumoniae, Haemophilus influenzae and Staphylococcus Aureus. Other frequent bacterial pathogens include Moraxella cattharalis, Klebsiella pneumoniae, P. aeruginosa and Mycoplasma pneumoniae.

Diagnosis: Clinical evaluation followed by chest radiograph with or without microbiologic testing.

Laboratory Findings: High white blood cell count. Gram stain of sputum and culture yields the diagnosis in 75% of cases

Radiographic Presentation: The classic presentation shows segmental or lobar consolidations. Infiltrates are localised in one lobe but may be more diffuse in immunosuppressed individuals.

Treatment:

Options for uncomplicated non-severe bacterial pneumonia include amoxicillin 500mg orally three times daily for 5-10 days. Or amoxicillin/clavulanic acid 250/125 (375), orally three times daily for 5-10 days.

Treatment for severe life-threatening pneumonia is ceftriaxone 1 gram IV once at outpatient facility with referral to inpatient facility where IV antibiotics could be administered.

Follow-up: Chest x-ray findings usually clear more slowly than clinical manifestations. Slow or incomplete resolution of pneumonia despite treatment is a common clinical problem (15%). Referral to specialized services is required.

Patient Education: Smoking cessation, Pneumococcal vaccination (if available).

Clinical Presentation: Gradually increasing headache with low grade fever. Additional symptoms may include nausea and vomiting, neck stiffness, confusion, seizures, focal neurologic signs with cranial nerve abnormalities, abnormal behaviour, new-onset psychiatric problems, diplopia, and unexplained blindness. Cutaneous lesions and pulmonary involvement may also be observed.

Causative agent: *Cryptococcus neoformans.* Cryptococcosis is the cause of the most common life-threatening meningitis in AIDS.

Screening: If CD4 cell count ≤ 100 send serum for cryptococcal antigen. If positive, a lumbar puncture (LP) is needed to assess whether meningitis is present and determine what course of anti-fungal treatment is needed. Start ART once induction phase completed and evidence of clinical response (after 2-6 weeks therapy). Patients with a prior diagnosis of cryptococcal meningitis do not need to be screened. (National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults. December 2014)

Diagnosis: Perform lumbar puncture (LP) and measure opening pressure (a high opening pressure >200mm H₂0 presents in 70% of patients). Send CSF for india ink staining, cryptococcal antigen (CRAG), bacterial gram stain and culture. Send serum for CRAG. The definitive diagnosis can be made by culture or presumptively by india ink or CSF cryptococcal antigen. A CT scan is recommended in patients with focal neurologic signs to ensure LP is safe.

Treatment:

 Initial treatment: Induction phase – Amphotericin B 1mg/kg/ dose IV PLUS Fluconazole 800mg daily for 2 weeks. Consolidation phase – Fluconazole 400mg orally daily for 8 weeks. Maintenance

Continued

phase – Subsequent episode: Induction phase – Amphotericin B 1mg/kg/dose IV for 2-4 weeks or until CSF is sterile. Consolidation phase – Fluconazole 800mg orally daily for 8 weeks with or without weekly amphotericin B 1mg/kg. Maintenance phase – Fluconazole 400mg orally daily OR weekly Amphotericin B 1 mg/kg/dose with or without Fluconazole 400mg orally daily for life or until CD4 > 250 cells/mm³ for > 6 months, following at least 12 months of fluconazole therapy.

- Consider alleviating raised intracranial pressure by draining not more than 20-30 ml of CSF.
- In areas where Amphotericin B is not available high doses of fluconazole are typically used for the Induction phase.

Follow-up: Re-assess daily for signs and symptoms of increased intracranial pressure. If present, repeat lumbar puncture for CSF removal.

Clinical Presentation: Cryptosporidium can cause an asymptomatic infection, a mild diarrhoeal illness, or severe enteritis. HIV patients often report an explosive, profuse watery diarrhoea associated with malaise, nausea and anorexia and crampy abdominal pain. Malabsorption, malnutrition, dehydration, and cachexia are also observed. Chronic cryptosporidiosis confers a WHO Stage IV diagnosis.

Causative Agent: Cryptosporidium parvum.

Diagnosis: Microscopic identification of the oocysts in stool or tissue.

Treatment: Initiating ART is the most effective treatment. Provide supportive care including oral rehydration, nutritional supplements and loperamide or codeine.

Follow-up: As needed

Patient Education: Good hygiene, such as handwashing and proper disposal of contaminated material, and boiling or filtering water may decrease the risk of infection in immunosuppressed patients. Prophylaxis for Cryptosporidium is not routinely recommended.

Clinical Presentation: Most often presents with ocular and gastrointestinal signs and symptoms. Retinitis may be asymptomatic or present with rapidly progressing visual loss. Additional symptoms may be floaters, blind spots, distortion, no pain, redness and photophobia. Unilateral retinal signs with contralateral involvement developing within six months. CMV can appear on any part of the GI tract, where it produces ulcerating lesions. The oesophagus and colon are the most common sites of GI involvement. Oesophageal infection usually presents with fever and odynophagia. Lesions on the colon produce an acute colitis presenting with diarrhoea that may be bloody, often with severe abdominal pain.

Causative Agent: Cytomegalovirus, a member of the Herpes virus family.

Diagnosis: CMV retinitis visible via direct opthalmoscopy. Endoscopy shows large shallow ulcerations. Sigmoidoscopy or colonoscopy shows colitis with friable edematous mucosa and scattered ulcerations. Diagnosis is made by CMV PCR or culture directly from biopsy specimen. Systemic infection can be confirmed by viral PCR or culture of white blood cells from the buffy coat of a centrifuged specimen of blood.

Treatment: Ganciclovir is the treatment of choice, but this agent is toxic and expensive and can only be used by a specialist familiar with its use. To prevent recurrent disease commence patients on ART as soon as possible after initiating ganciclovir.

- CMV Retinitis: Ganciclovir intravitreal, 2mg once weekly (by opthalmologist)
- Initial treatment: Ganciclovir IV, 5mg/kg 12 hourly for 14 days. Specialist initiated.

Continued

 Maintenance treatment: Ganciclovir IV, 5mg/kg daily until CD4 rises to >100 cells/mm³ on ART.

Note: Only patients with good clinical response should be considered for maintenance, as the cost is currently very high.

Follow-up: Side effects of most of the antiviral drugs lead to bone marrow suppression.

Patient Education: Hygienic precautions are efficient in preventing CMV infection during pregnancy.

Clinical Presentation: Giardia lamblia is an intestinal parasitic infection in which transmission occurs via the oral-faecal route. Infects the small bowel mucosa where it may be asymptomatic but usually causes diarrhoea with abdominal cramping, bloating and nausea. In severe cases it may produce malabsorption and steatorrhoea.

Causative Agent: Giardia lamblia

Diagnosis: Stool microscopy demonstrates Giardia ova and cysts.

Treatment: Metronidazole 400mg orally 8 hourly for 5 days. If pregnant, avoid use of metronidazole and use paromomycin 500mg orally four times daily for 7 days.

Follow-up: Relapse is common.

Patient Education: Handwashing and proper disposal of contaminated material, boiling or filtering water, and properly cooking food may decrease the risk of infection in immunosuppressed patients.

Clinical Presentation: Recurrent herpes labialis occurs on the border of the lips. Usually starts with itching or pain followed by appearance of small vesicles. Vesicles rupture and form crusts.

Recurrent intra oral herpes usually occurs on the keratinized mucosa such as hard palate and gingival and appears as clusters of painful small vesicles that rupture and ulcerate and usually heal within a few weeks.

Clinically herpetic oesophagitis presents with extreme pain and difficulties in swallowing. Most commonly infects the oesophagus to produce multiple oesophageal ulcerations.

Genital herpes simplex presents as grouped blisters that rupture, crust and heal in a few weeks. Painful and extensive lesions usually localise in the ano-genital area, although oro-labial lesions can be seen.

HIV-infected individuals with low CD4 counts may experience chronic or extensive outbreaks.

Causative Agent: Herpes simplex virus type 1 and 2 (HSV 1 & HSV 2). The virus is transmitted by close contact.

Diagnosis: Clinical observation. Viral culture positive for HSV. Endoscopy of herpetic oesophagitis: ulcers usually multiple and small. Biopsy will show multinucleated giant cells.

Treatment: Treatment only shortens the healing time of individual episodes.

Oral Acyclovir 400mg 8 hourly for 7 days. Paracetamol as needed for pain.

For recurrent HSV - Acyclovir 400mg orally 8 hourly for 7 days or 800mg orally twice daily for 5 days.

For severe or refractory HSV – Acyclovir 5-10mg/kg IV 8 hourly infused over 1 hour for 5-7 days or Acyclovir 400-800mg orally 5 times a day for 7-14 days.

For disseminated HSV – Acyclovir 30mg/kg/day IV and test sensitivity of isolate to Acyclovir.

Patient Education: Recurrences may occur frequently. Condom use and partner notification should be recommended. When possible, treatment at initial symptoms of lesions is most efficient.

Clinical Presentation: Painful prodrome followed by erythematous papules, which quickly evolve into grouped vesicles or bullae. The skin lesions form crusts while oral lesions join together to form large ulcers. Zoster is generally limited to one dermatome, but can occasionally affect two or three neighboring dermatomes. The thoracic and lumbar dermatomes are the most commonly involved sites of herpes.

Causative Agent: Caused by reactivation of the Varicella Zoster Virus (VZV).

Diagnosis: Clinical evaluation.

Treatment:

Acyclovir limits the duration of the lesions.

Acyclovir oral 800 mg five times daily for 7 days.

Flucloxacillin oral, 500mg 6 hourly for 5 days if secondary infection.

Amitriptyline can be used for pain management. Carbamezapine is not recommended for pain management due to drug interactions with antiretrovirals.

If Zoster involves eye or nose (ophthalmic nerve) urgent ophthalmologic referral is indicated for possible IV antibiotics to prevent blindness.

Patient Education: Treatment is more efficient before the appearance of the lesions. Patients who are able to identify a prodrome should be encouraged to seek treatment.

Clinical Presentation: Colitis with bloody diarrhoea and abdominal cramps. Asymptomatic carriers are more frequent among PLWHAs. Dissemination might be seen more in HIV-infected patients.

Causative Agent: Entamoeba histolytica.

Diagnosis: Microscopy of fresh stool specimen demonstrates cysts and parasites. Sigmoidoscopy may show evidence of colitis, and typical punched-out "flask-shaped" ulcers.

Treatment:

Metronidazole oral, 800mg 8 hourly for 10 days.

Followed by Paromomycin 25-35mg/kg/day orally divided in three daily doses for 7 days.

Avoid use of metronidazole in pregnancy. Loperamide is contraindicated as it may cause toxic megacolon.

Patient Education: Avoid drinking unboiled water in endemic areas. Caution consuming uncooked foods, such as fruit and vegetables that may have been washed in infected water.

Clinical Presentation: Lesions are multiple and can involve the skin and the mucous membranes. Cutaneous lesions occur most commonly on the trunk, the extremities and the face. Initial lesions are papular. Later the papules become nodules and plaques, and the colour changes from dark brown to violet. May affect mucous membranes, including oral palate and intestines.

Causative Agent: A cancer of the skin and the blood vessels associated with a sexually transmitted Human Herpes Virus (HHV8).

Diagnosis: Generally, lesions are recognised clinically and the diagnosis can be confirmed by biopsy.

Treatment: ART may improve localised disease. Extensive cutaneous or organ involvement will require cytotoxic chemotherapy to assist in resolving extensive disease. Referral to oncology is critical. Intralesional chemotherapy (vinblastine), local radiotherapy, liquid nitrogen cryotherapy or topical aliretinoin 0.1% gel may be effective for small skin and oral lesions.

Patient Education: Importance of starting lifelong ART. Importance of adherence to care and treatment. **Clinical Presentation:** Molluscum contagiosum presents as pearly, umbilicated papules. Extensive molluscum contagiosum is a marker of advanced HIV disease. May be extensive and involve the face, axillae and groin. The most common location is the eyelids.

Causative Agent: Molluscum Contagiosum Virus.

Diagnosis: Clinical. Consider biopsy to rule out cryptococcal skin rash or cutaneous lymphoma if clinical picture is unclear.

Treatment: Antiretroviral therapy may improve success of topical treatments. Apply tincture of iodine or 1% phenol to individual lesions. Other options include cryotherapy with liquid nitrogen, surgical excision/curettage, or electrosurgery.

Follow-up: ART Initiation

Patient Education: Do not touch molluscum bumps on other people. Treatment of the genital areas can help to prevent the spread of infection during sex. Partner notification and treatment. Counsel regarding condom use.

Oral and Oesophageal Candidiasis

Clinical presentation: Presentation varies. Oral candidiasis may present with lesions or burning of the mouth, changes in taste, and difficulty eating spicy foods. Trouble swallowing and presentation on the posterior pharynx may indicate oesophageal candidiasis.

Causative agent: Candida Albicans

Candida Albicans is frequently part of the normal oral flora. Candidiasis occurs mostly in patients with a falling CD4+ count.

Diagnosis: Clinical presentation and by detection of organisms by microscopy.

Treatment: Oral candidiasis can be treated topically or systemically.

Topical Treatment for Oral Candidiasis:

- Nystatin suspension oral 100,000 iu/ml 1-2mL 4 times daily, or oral lozenges sucked 6 hourly for 10 days.
- Miconazole 2% oral gel applied twice daily for 10 days.

If no improvement, Amphotericin B lozenges 10mg 1 slowly 4 times daily, up to 8 lozenges in severe cases.

Oral Treatment for Oesophageal Candidiasis:

 Fluconazole 200mg orally daily for 14 days. The usual route is oral, but may be given IV if patient unable to swallow or is vomiting.

Follow-up: Short courses of topical therapy rarely result in adverse effects.

Patient Education: ART plays an important role in preventing recurrent disease. Discuss ART initiation.

Clinical Presentation:

 Lesions occur commonly on the lateral margins of the tongue and may be bilateral or unilateral. They appear as whitish-grey corrugations which cannot be removed. Hairy Leukoplakia lesions may also occur on the buccal mucosa as flat lesions. It has no associated symptoms.

Causative Agent: Associated with Epstein Barr Virus but actual cause is still unknown.

Diagnosis: Mainly clinical though definitive diagnosis can be made by biopsy.

Treatment:

- Hairy leukoplakia is asymptomatic and does not require treatment. It is almost always a manifestation of HIV infection and/or immunosuppression.
- Improvement in immune status with ART may resolve symptoms.

Follow-up: N/A

Patient Education: N/A

Pneumocystis Jirovecii Pneumonia (PCP)

Clinical Presentation: A history of several weeks of fever and cough. Tachypnoea may be pronounced, and patients may be severely dyspnoeic. On physical exam, chest findings may be minimal. More likely to occur with CD4 count < 200 cells/mm³.

Causative Agent: Pneumocystis jirovecii

Diagnosis: Mainly clinical. Lab and Chest X-ray are beneficial to rule out differential diagnosis.

Laboratory Findings:

CBC and ESR show no characteristic pattern.

Radiographic Presentation:

The classic presentation is a diffuse interstitial infiltrate, although the following presentations can be observed: abscesses, cavitations or cystic lesions, lobar consolidation, nodular lesions, effusions, pneumothorax, pneumo-mediastinum and a normal chest radiograph.

Treatment

- Cotrimoxazole 80/400mg orally 6 hourly for 21 days <60kg: 3 tablets
 >60kg: 4 tablets
- If vomiting, Cotrimoxazole IV, 6 hourly:
 <60kg: 240/1200mg
 >60kg: 320/1600mg
- Monitor FBC and potassium when on high dose therapy
- A corticosteroid taper should accompany initial treatment. One option is Prednisone 80mg orally twice daily x 5 days, then 40mg orally daily x 5 days, then 20mg orally daily x 5 days.

Pneumocystis Jirovecii Pneumonia (PCP)

Continued

 Maintenance therapy is Cotrimoxazole 160/800 mg (2 single strength) orally daily until CD4 > 350 cells/mm³ on 2 separate occasions.

Follow-up: Cotrimoxazole markedly reduces hospitalisation and mortality and provides protection. Prescribe 160/800 mg (2 single strength tablets) orally once daily to patients with CD4 \leq 350 cells/mm³ or stage 2, 3 or 4 HIV disease (including TB). Evaluate HIV and initiate ART.

In patients with a severe sulfa allergy, rapid desensitisation to TMP/SMX or Cotrimoxazole is the preferred treatment of choice, but should occur in a closely monitored setting (as an inpatient). If this is not possible, then alternative regimens for the treatment of PCP pneumonia are clindamycin 600mg orally every eight hours plus dapsone 100 mg orally daily or clindamycin 600mg orally every eight hours plus primaquine 15 mg orally daily (exclude G6PD deficiency when giving primaquine).

Patient Education: Adherence to Cotrimoxazole prophylaxis and to ART drugs once initiated.

Clinical Presentation: An initial phase lasting two to three weeks characterised by malaise, confusion, headache, low grade fever and personality change. The menningitic phase follows with more pronounced neurologic symptoms such as meningismus, lingering headache and confusion, and varying degrees of cranial nerve. During the paralytic phase the pace of illness may accelerate rapidly. Confusion gives way to stupor and coma, seizures and at times hemiparesis.

• On exam neck stiffness and positive Kernig's sign.

Causative Agent: Mycobacterium tuberculosis

Diagnosis: Diagnosis can be difficult. Maintaining a high degree of suspicion is vital to initiate therapy.

- CSF examination: Clear CSF, elevated protein, elevated pressure, high lymphocyte count, low glucose. AFB stain or GeneXpert, and culture.
- Negative cryptococcal Antigen test.
- CT scan can show lesions like basilar arachinoditis, cerebral oedema and infarction, and presence and cause of hydrocephalus.

Treatment: The treatment is in two phases.

If New Case

Intensive Phase: 2 months with daily Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. Adjuvant therapy Corticosteroids e.g. Dexamethasone IV, 12mg 12 hourly, followed by Prednisone oral, 120mg daily; after 1 week, taper dose gradually over next 6 weeks.

Continuation Phase: Daily course of Rifampicin and Isoniazid. Discuss length of treatment with a specialist.

If retreatment case or MDR/XDR-TB refer to a specialist.

Follow-up: Assessment for pulmonary and other extrapulmonary forms of TB should take place. A social evaluation should be undertaken to assess eligibility for support grants. Within one week of hospitalisation, a plan for DOT management on discharge should be developed.

Patient Education: A health education plan should be implemented to counsel the client about TB and to develop an adherence plan to ensure treatment completion.

Clinical Presentation: Recognised major cause of neurologic morbidity and mortality among patients with advanced HIV disease. Transmission to humans usually occurs by eating food contaminated with cysts and oocysts, and by vertical transmission

- Toxoplasmosis causes a multifocal cerebritis and the initial symptoms are often both diffuse and focal. The symptoms are often vague and nonspecific.
- Headaches, usually dull and constant, are present in 50% of patients presenting with toxoplasma encephalitis (TE).
- Fevers occur in 40-50% of cases.
- Confusion and lethargy are common.
- Generalised or focal seizures occur in 15 to 30% of patients. Among all HIV related Ols, toxoplasmosis is the most common cause of seizures.
- Hemiparesis, hemisensory loss or other focal neurological deficits also occur.

Causative Agent: Toxoplasma gondii

Diagnosis:

- CT scan and MRI may display mass lesions with ring enhancement.
- Lumbar Puncture (LP) excludes other OIs. CSF usually reveals normal glucose content, mildly raised protein, mild mononuclear pleocytosis.
- Positive antibody helps define risk but is not diagnostic.

Treatment:

- Cotrimoxazole 320/1600mg every 12 hours for four weeks, followed by cotrimoxazole 160/800mg every 12 hours for 12 weeks. Consider corticosteroid use if significant mass effect or midline shift on CT scan.
- Continue on cotrimoxazole 160/800mg daily until CD4 count > 250 cells/mm³ for at least 6 months.

Follow-up: Clinical improvement precedes radiographic improvement – Neuro exam is more important than Xrays in assessing the response to therapy. Monitoring of patients includes clinical evaluations, brain CT scan, and assessment of any adverse events.

Patient Education: Patients seropositive for *T. gondii* should receive prophylaxis with cotrimoxazole.

Clinical Presentation/Features: Acute inflammatory disorder of the brain due to direct viral invasion or hypersensitivity initiated by a virus or other foreign protein.

Causative Agents: The herpes viruses: herpes simplex 1 and 2 (HSV-1 and -2), herpes zoster (HZV), and cytomegalovirus (CMV). Each can cause a meningoencephalitis with mental status changes and focal neurologic findings.

Diagnosis: Can be difficult, especially because of the lack of availability and low yield of CSF viral cultures in this setting. Sensitive CSF PCR assays, such as HSV, have been developed. Where available, can greatly aid diagnosis.

Treatment: Acyclovir 10mg/kg IV every 8 hours for 10 days. Due to high mortality rate associated with HSV encephalitis rapid initiation is essential.

Follow-up: The prognosis for encephalitis varies. Some cases are mild and patients have full recovery. Other cases are severe, full recovery might take months, and permanent impairment or death is possible.

Clinical Presentation: In most cases they appear as regular or flat warts. Rarely, they may be very extensive lesions. They are commonly found in the anogenital area, but can be found anywhere on the body, including orally.

Causative Agents: Human papilloma virus (HPV).

Diagnosis: Clinical observation biopsy.

Treatment: The goal is to eradicate all warts.

- Podophyllin resin (10-25%) in compound tincture with benzoin apply a small amount once weekly for 6-10 weeks. Limit to < 0.5mL of podophyllin or < 10 cm² to avoid problems with systemic absorption or toxicity. Do not use in pregnancy.
- Salicylic acid 25% ointment under a plaster at night is another option for application at base of warts.
- Other methods include: Surgical removal via tangential scissor excision, tangential shave excision, curettage, or electrosurgery or cryotherapy with liquid nitrogen or cryoprobe.
- Refer to a specialist for removal of extensive warts.

Other Methods Include: Cryotherapy, excision or injections with alpha interferon in the lesion.

Follow-up: Female patients must have regular gynaecological examinations and pap smears. Individuals who have had anal warts, should have regular rectal examinations.

Patient Education: HPV spreads by skin-to-skin contact and other close contact. Recurrence of warts may occur. Papanicolau smears are recommended for cervical cancer screening in all patients with a history of diagnosed genital HPV, which may present as viral genital warts.

Clinical Presentation: The involuntary weight loss of 10% of baseline body weight plus either chronic diarrhoea (two loose stools per day for more than 30 days) or chronic weakness and documented fever (for 30 days or more, intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that would explain the findings.

Causative Agent: The cause is not well understood. Hypermetabolic state and gradual weight loss due to gastrointestinal disease with diarrhoea are likely associated.

Diagnosis: Clinical signs and symptoms.

Treatment: Opportunistic infections should be treated if possible. Caloric intake should be optimized; dietitians can help patients maximize caloric intake.

Follow-up: ART initiation according to guidelines.

Patient Education: Monitor weight. Maintain intake of nutritious foods. Immediately seek treatment for serious diarrhoea.