Kandahar Medical Faculty

Amirzada's
Short Textbook of
Infectious Diseases

(In English)

First edition
Dr M. Zakarya Amirzada
2012

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Message from the Ministry of Higher Education

In the history, book has played a very important role in gaining knowledge and science and it is the fundamental unit of educational curriculum which can also play an effective role in improving the quality of Higher Education. Therefore, keeping in mind the needs of the society and based on educational standards,new learning materials and textbooks should be published for the students.

I appreciate the efforts of the lecturers of Higher Education Institutions and I am very thankful to them who have worked for many years and have written or translated textbooks.

I also warmly welcome more lecturers to prepare textbooks in their respective fields. So, that they should be published and distributed among the students to take full advantage of them.

The Ministry of Higher Education has the responsibility to make available new and updated learning materials in order to better educate our students.

At the end, I am very grateful to the German Federal Foreign Office, the German Academic Exchange Service (DAAD) and all those institutions and people who have provided opportunities for publishing medical textbooks.

I am hopeful that this project should be continued and publish textbooks in other subjects too.

Sincerely,

Prof. Dr. Obaidullah Obaid

Minister of Higher Education

Kabul, 2012

Publishing of textbooks & support of medical colleges in Afghanistan

Honorable lecturers and dear students,

The lack of quality text books in the universities of Afghanistan is a serious issue, which is repeatedly challenging the students and teachers alike. To tackle this issue we have initiated the process of providing textbooks to the students of medicine. In the past two years we have successfully published and delivered copies of 60 different books to the medical colleges across the country.

The Afghan National Higher Education Strategy (2010-1014) states:

"Funds will be made ensured to encourage the writing and publication of text books in Dari and Pashto, especially in priority areas, to improve the quality of teaching and learning and give students access to state-of- the-art information. In the meantime, translation of English language textbooks and journals into Dari and Pashto is a major challenge for curriculum reform. Without this, it would not be possible for university students and faculty to acquire updated and accurate knowledge"

The medical colleges' students and lecturers in Afghanistan are facing multiple challenges. The out-dated method of lecture and no accessibility to update and new teaching materials are main problems. The students use low quality and cheap study materials (copied notes & papers), hence the Afghan students are deprived of modern knowledge and developments in their respective subjects. It is vital to compose and print the books that have been written by lecturers. Taking the critical situation of this war torn country into consideration, we need desperately capable and professional medical experts. Those, who can contribute in improving standard of medical education and public health throughout Afghanistan, thus enough attention, should be given to the medical colleges.

For this reason, we have published 60 different medical textbooks from Nangarhar, Khost, Kandahar, Herat, Balkh & Kabul medical colleges. Currently we are working on to publish 60 more different medical textbooks, a sample of which is in your hand. It is to mention that all these books have been distributed among the medical colleges of the country free of cost.

As requested by the Ministry of Higher Education, the Afghan universities, lecturers & students they want to extend this project to non-medical subjects like (Science, Engineering, Agriculture, Economics & Literature) and it is reminded that we publish textbooks for different colleges of the country who are in need.

As stated that publishing medical textbooks is part of our program, we would like to focus on some other activities as following:

1.Publishing Medical Textbooks

This book in your hand is a sample of printed textbook. We would like to continue this project and to end the method of manual notes and papers. Based on the request of Higher Education Institutions, there is need to publish about 100 different textbooks each year.

2.Interactive and Multimedia Teaching

In the beginning of 2010, we were able to allocate multimedia projectors in the medical colleges of Balkh, Herat, Nangarhar, Khost & Kandahar. To improve learning environment the classrooms, conference rooms & laboratories should also be equipped with multimedia projectors.

3.Situational Analysis and Needs Assessment

A comprehensive need assessment and situation analysis is needed of the colleges to find out and evaluate the problems and future challenges. This would facilitate making a better academic environment and it would be a useful guide for administration and other developing projects.

4.College Libraries

New updated and standard textbooks in English language, journals and related materials for all important subjects based on international standards should be made available in the libraries of the colleges.

5.Laboratories

Each medical college should have well-equipped, well managed and fully functional laboratories for different fields.

6.Teaching Hospitals (University Hospitals)

Each medical college should have its own teaching hospital (University Hospital) or opportunities should be provided for medical students in other hospitals for practical sessions.

7.Strategic Plan

It would be very nice if each medical college has its own strategic plan according to the strategic plan of their related universities.

I would like to ask all the lecturers to write new textbooks, translate or revise their lecture notes or written books and share them with us to be published. We assure them quality composition, printing and free of cost distribution to the medical colleges.

I would like the students to encourage and assist their lecturers in this regard. We welcome any recommendations and suggestions for improvement.

We are very thankful to the German Federal Foreign Office & German Academic Exchange Service (DAAD) for providing funds for 90 different medical textbooks and the printing process for 50 of them are ongoing. I am also thankful to Dr. Salmaj Turial from J. Gutenberg University Mainz/Germany, Dieter Hampel member of Afghanic/Germany and Afghanic organization for their support in administrative & technical affairs.

I am especially grateful to GIZ (German Society for International Cooperation) and CIM (Centre for International Migration & Development) for providing working opportunities for me during the past two years in Afghanistan.

In Afghanistan, I would like cordially to thank His Excellency the Minister of Higher Education, Prof. Dr. Obaidullah Obaid, Academic Deputy Minister Prof. Mohammad Osman Babury and Deputy Minister for Administrative & Financial Affairs Associate Prof. Dr. Gul Hassan Walizai, the universities' chancellors and deans of the medical colleges for their cooperation and support for this project. I am also thankful to all those lecturers that encouraged us and gave all these books to be published.

At the end I appreciate the efforts of my colleagues Dr. M. Yousuf Mubarak, Abdul Munir Rahmanzai, Ahmad Fahim Habibi, Subhanullah and Hematullah in publishing books.

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In the name of Allah, Most Gracious, Most Merciful.

Dedication

My this try is dedicated to Momin, courageous (oppressed) and poor people of Afghanistan

Preface

The *Amirzada's short text of Infectious diseases,* First edition has updated topics reflecting the most current definition, etiology, epidemiology, pathology/pathogenesis, clinical features, investigations, treatment recommendations, prevention and prognosis of infectious diseases.
This book is the result of my 12 years practice and studies in infectious diseases ward (IDW) of Merwais hospital.
I have written this book to solve the problems of infectious diseases in advance and short fashion.
At the end of more paragraphs, sentences or phrase of this book there are abbreviations for reference. (See the abbreviations)
This book is a very simple try and requires a lot of improvements. I, with the help of my colleagues will continue to update and improve it.

Dr M. Zakarya Amirzada

Abbreviations

1. NB: Note be remember
2. ê: With
3. ei: That is (L. *id est*)
4. etc: (etcetera) And so further
5. CNS: Central Nervous System
6. DIC: Disseminated Intravascular Coagulation
7. e.g.: For example (L. *exampli gratia*)
8. OD: Abbreviation for L. Omni di'e (once a day)
9. BID: Abbreviation for L. Bis di'e (twice a day)
10. TID: Ab. for L. Ter in di'e (three times a day)
11. QID: Ab. for L. Quarter in di'e (four times a day)
12. HIV: Human immunodeficiency virus
13. AIDS: Acquired Immunodeficiency Syndrome
14. C/F: Clinical features
15. DDx: Defferntial Diagnosis
16. Dx: Diagnosis
17. Ix: Investigation
18. Rx: Treatment
19. FUO: Fever of unknown origin

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- *Human immunodeficiency virus (HIV) and AIDS*

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Infectious diseases

Despite of dramatic progress in the treatment and prevention of infectious diseases, they remain major causes of:

- Diseases
- Debility
- Death. [1] (3)

The term of infectious diseases is commonly used for those infections which are contagious or communicable ie (that is) transmissible from man to man. (2)

Definition:

Infection may be defined as multiplication of microbes (e.g., from viruses to multicellular parasites) in the tissues of the host. [2] (4)

Difference to other diseases:

The infectious diseases differ from other diseases as following:

1. Known etiology
2. Transmissibility
3. Curability

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[1] Infections are a major cause of morbidity and mortality in the world. Of the approximately 53 million deaths worldwide in 2002, at least a third were due to infectious diseases. In the United States, pneumonia is the fifth leading cause of death overall and the most common cause of death related to infection. In addition, invasive disease caused by *Streptococcus pneumoniae* and community-acquired pneumonia overall have increased in incidence over the past decade. Acquired immunodeficiency syndrome (AIDS) threatens to disrupt the social fabric in many countries of Africa and is severely distressing the health care system in the United States and other parts of the world. (4)

[2] The host may or may not be symptomatic. For example, HIV infection may cause no overt signs or symptoms of illness for years. The definition of infection should also include instances of multiplication of microbes on the surface or in the lumen of the host that cause signs and symptoms of illness or disease. For example, toxin-producing strains of *Escherichia coli* may multiply in the gut and cause a diarrheal illness without invading tissues. (4)

4. Preventability [2]

Infection can involve any organ or system of the body and is discussed in every system and in this part general aspect of infections is described. [2]

Headings:

We discuss an infectious disease as follow:

1. Definition
2. Etiology
3. Epidemiology:
   - Prevalence/Incidence
   - Geographical variation
   - Age group
   - Seasonal variation
   - Rout of Transmission
   - Reservoir of infection
   - Incubation Period
   - Infectivity Period
4. Pathogenesis/Pathology
5. Clinical features (C/F)
   - Symptoms
   - Signs
6. Complications
7. Investigation(Ix)
8. Treatment(Rx)
   - General Rx
   - Specific Rx
9. Prevention
10. Prognosis

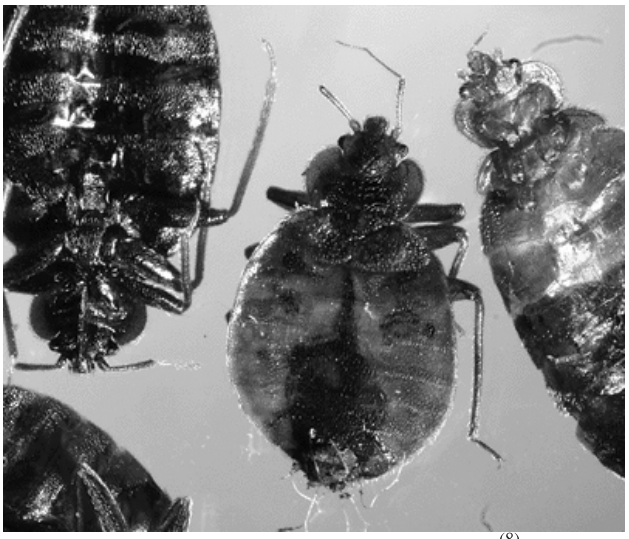
Definition:

The definition of infectious diseases may be on the base of causes, clinical features or incidence of the disease.

Etiology:

The etiology is the description about agent and vector of a disease. The common vectors of diseases are:

1. Mosquito
2. Mite
3. Louse
4. Tick
5. Bug
6. Sand fly
7. Tsetse fly
8. Flea



(Fig. 1) Bedbugs, Cimex lectularius. [8]

(Fig. 2) Catflea, Ctenocephalides felis : a common cause of flea bites in humans. [8]

(Fig. 3) Underside of hedgehog tick, Ixodes hexagonus to show sucking mouthparts (hypostome). [8]

(Fig. 4) Louse, Pediculus humanus : head lice and body lice are morphologically similar. [8]

(Fig. 5) Adult female (right) and nymphal (left) - ticks of the Ixodes scapularis species. [8]

Epidemiology:

The epidemiology is the study of host, agent and environment relationship.

The description of epidemiology consists of:

1. Incidence
2. Geographical variation
3. Age group
4. Seasonal variation
5. Rout of Transmission
6. Reservoir/source of infection
7. Incubation Period
8. Infectivity Period

Prevalence/Incidence:

The incidence is the numbers of new cases of a disease in a population over period of time.

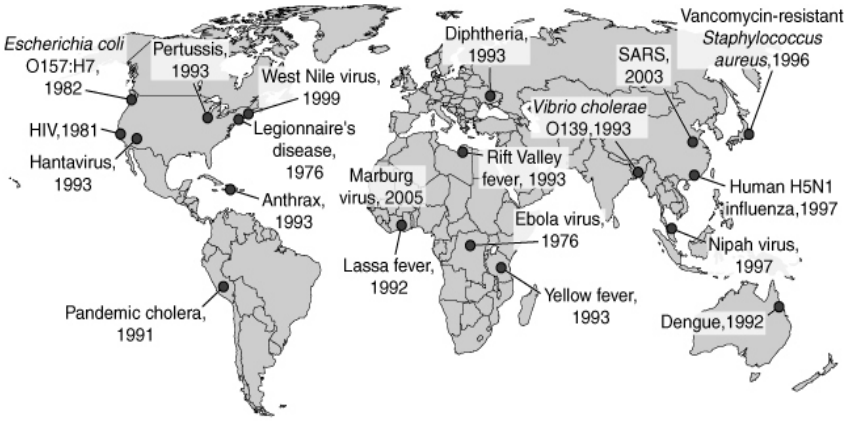
The prevalence measures the burden of disease in a population inclusive of old and new cases.

The occurrence of a disease may be:

- Sporadic: Occurring singly widely scattered.
- Endemic: Present in a community at all time or occurring in an area.
- Epidemic: Attacking many people in a region, widely & rapidly spreading.
- Pandemic: More widely& rapidly spreading disease occurring in certain regions.

Geographical variation:

The geographical variation is the occurrence of a disease in different geographical site.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

(Fig. 6) Map of the world showing examples of geographic locales where infectious diseases were noted to have emerged or resurged. [3]

Age group:

The age group is that period of age in which the occurrence of disease is common.

The age group may be:

- Neonate: The first 4 weeks of the life.
- Infant: The first tow years.
- Preschool
- School age
- Adolescent
- Adult
- Aged people
- Specific years
- Specific sex
- Male female ratio

Seasonal variation:

The seasonal variation is the occurrence of the disease in different season or weather of year.

The seasonal variation may be:

- Rainy weather
- Dry weather
- Summer or hot weather
- Winter or cold weather
- Spring
- Autumn

Route of transmission:

The route of transmission is the way of entry of microorganism to the body.

The route of transmission may be:

- Faeco-oral
- Droplets or dust
- Contact, person to person
- Zoonosis
- Arthropods
- Inoculation
- Sexual route
- Animal bite
- Transplacental
- Transfusion
- Organ transplantation

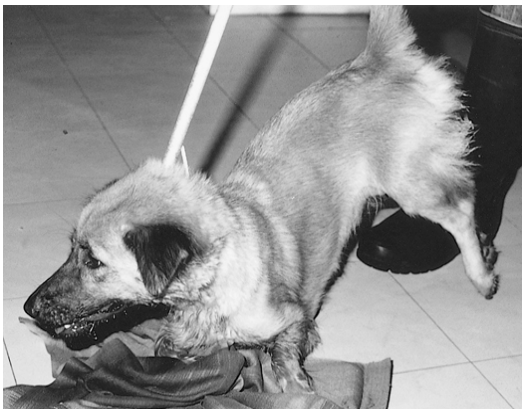
Reservoir/Source of infection:

The reservoir of infection is a host or passive carrier of a pathogenic microorganism.

The reservoir of infection may be:

- Human

- Animals
- Birds
- Fish
- Rodent



(Fig. 7) Dog with paralytic rabies showing paralysis of the limbs and hypersalivation. [8]

The source of infection is that material which contain microorganism & may be:

- Water
- Meat
- Milk
- Fruit
- Wool

Incubation period:

The incubation period is the period of time from entry of microorganism to the appearance of symptoms.

Infectivity period:

The infectivity period is period of time in which the patient is infectious to others.

Pathogenesis:

The pathogenesis of infection cosist of:

1. Microbial entry
2. Microbial adherence
   - Adenovirus with fibro protein
   - Escherichia coli with pili
   - Entamoeba histolytica with surface lectin
   - Pseudomonas aerogenosa with pili& flagella
3. Microbial growth after entry
4. Avoidance of innate host defenses
   - Epithelial cells
   - Phagocytosis
5. Tissue tropism
6. Tissue invasion
7. Tissue damage and disease (Table 1)
8. Host response
9. Transmission for new host. [3]

	Microbe mediated	Host mediated
Direct	Cell distraction eg. Poliomyelitis Rabies Hepatitis Malaria	Neutrophils Macrophages by production of tumor necrosis factor (TNF)
Exotoxin	Tetanus Cholera Botulism Diphtheria	Complement activation Clotting process activation

Endotoxin	Typhoid fever Meningococcal infection Plague Brucellosis	Immune mechanism Secondary autoimmune mechanism

(Table 1) The mechanism of tissue damage and disease [2]

Clinical features (C/F):

The clinical features are symptoms and signs (S/S)

The common symptoms of infectious diseases are:

1. Fever
2. Headache
3. Malaise
4. Prostration
5. Anorexia
6. Body ache
7. Abdominal pain
8. Diarrhea
9. Nausea
10. Vomiting
11. Constipation
12. Cough
13. Sneezing
14. Convulsion
15. Nasal bleeding
16. Weight loss

The common signs of infectious diseases are:

1. Fever
2. Tachycardia
3. Lymphadenopathy
4. Hepatomegaly
5. Splenomegaly

6. Nick stiffness
7. Skin rash
8. Abdominal tenderness
9. Coated tongue
10. Signs of dehydration
11. Coma

Investigation (Ix):

The common investigations to diagnose infectious diseases are:

1. Blood exam:
   - TLC
   - DLC
   - Hb
   - ESR
   - Platelet count
2. Urine exam
3. Stool exam
4. Culture of:
   - Blood
   - Stool
   - Urine
   - Sputum
   - CSF
   - Throat swab
5. Imaging:
   - Ultrasound
   - CT Scan
   - MRI
6. X ray
7. Serologic tests
8. Biochemistry:
   - Urea

- Creatinine
- Electrolytes
- LFT

9. Bronchoscopy

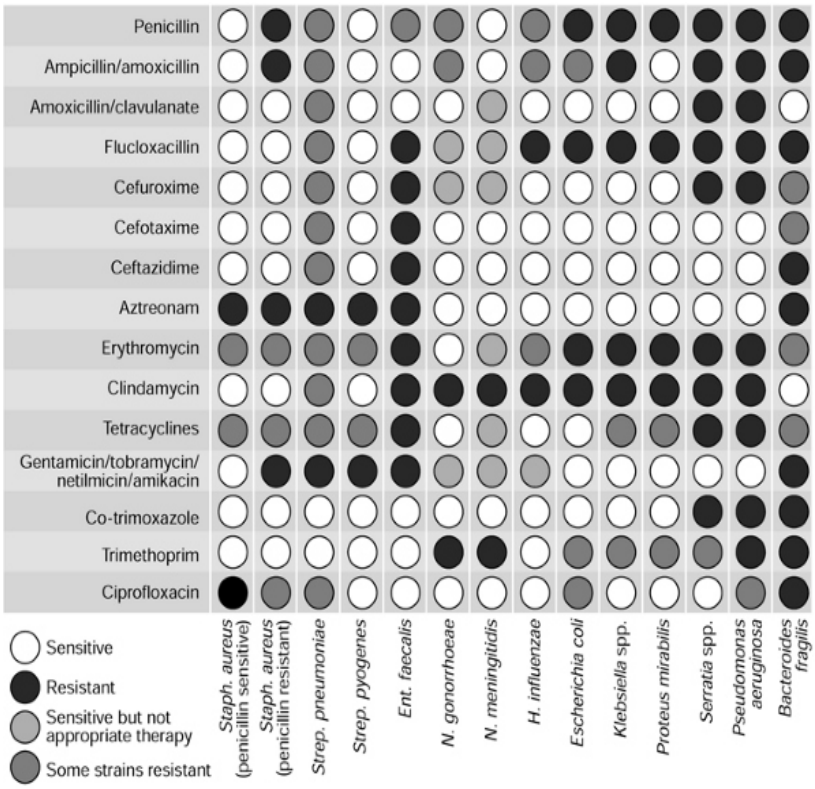
Treatment (Rx):

General Rx:

1. Admission
2. Feeding
3. Hydration
4. Nursing care of the patient
5. Symptomatic treatment

Specific Rx:

1. Antimicrobial Treatment
2. Antitoxin prescription



(Fig. 8) Sensitivity of selected pathogenic bacteria to some common antibacterial agents. [8]

Table 2 Mechanisms of action of antibacterial agents

Agent	Site of Action	Effect	Cidal	Static
β-Lactams (penicillins, cephalosporins, carbapenems, and aztreonam)	Cell wall: penicillin-binding proteins	Inhibit cross-linking of peptidoglycan (transpeptidation), impair cell wall synthesis	+	Occasionally (enterococci)
Vancomycin, teicoplanin,	Cell wall: terminal D-	Inhibit polymerization of	+	Occasionally (enterococci)

Agent	Site of Action	Effect	Cidal	Static
dalbavancin, and telavancin	alanyl-D-alanine of pentapeptide peptidoglycan precursor	disaccharide precursors to peptidoglycan (transglycosylation), impair cell wall synthesis		
Daptomycin	Cell membrane	Rapid depolarization of membrane potential	+	Occasionally (enterococci)
Aminoglycosides	Protein synthesis: 30S ribosome subunit	Inhibit peptide elongation, cause misreading of genetic code, inhibit protein synthesis	+	
Tetracyclines and glycylcyclines	Protein synthesis: 30S ribosome subunit	Inhibit binding of transfer RNA, inhibit protein synthesis	Occasionally	+
Chloramphenicol	Protein synthesis: 50S ribosome subunit	Block attachment of aminoacyl transfer RNA, inhibit protein synthesis	Occasionally	+
Macrolides, azalides, and ketolides	Protein synthesis: 50S ribosome subunit	Block transfer of amino acids to peptide chain, inhibit protein synthesis	Occasionally	+
Clindamycin	Protein synthesis: 50S ribosome subunit	Blocks transfer of amino acids to peptide chain, inhibits protein synthesis	Occasionally	+
Quinupristin-dalfopristin	Protein synthesis: 50S ribosome subunit	Blocks extrusion of peptide chains, inhibits protein synthesis	+	+ (with quinupristin resistance)

Agent	Site of Action	Effect	Cidal	Static
Linezolid	Protein synthesis: 50S ribosome subunit	Blocks formation of the 70S initiation complex, inhibits protein synthesis	Occasionally	+
Rifampin	Nucleic acid synthesis: B subunit of DNA-dependent RNA polymerase	Inhibits RNA synthesis	+	
Metronidazole	Nucleic acid synthesis	Damages nucleic acids, inhibits DNA synthesis	+	
Quinolones	Nucleic acid synthesis: DNA gyrase and topoisomerase IV	Impair supercoiling of DNA, prevent decatenation of DNA molecules after replication, inhibit DNA synthesis	+	
Sulfonamides	Folic acid synthesis: dihydropteroate synthetase	Competitive inhibition of synthesis of dihydrofolate from *p*-aminobenzoic acid, pteroate, and glutamic acid	Occasionally (when used with trimethoprim)	+
Trimethoprim	Folic acid synthesis: dihydrofolate reductase	Inhibits reduction of dihydrofolate to tetrahydrofolic acid	Occasionally (when used with sulfonamide)	+

Antibacterials that only inhibit bacterial growth are called *bacteriostatic,* whereas those that kill bacteria over an 18- to 24-hour period are called *bactericidal.* Occasionally, the mechanism of bacterial killing is different from the mechanism of bacterial inhibition for some antibacterials. For most bacteria, inhibition of cell wall synthesis by the penicillins

indirectly activates bacterial enzymes (murein hydrolases) that cause killing by cell lysis. Combinations of drugs can produce antibacterial effects that are greater than the sum of the individual antimicrobial activities, a relationship called *synergism.* For example, penicillin, ampicillin, and vancomycin can enhance bacterial uptake of aminoglycosides, thereby resulting in bactericidal synergism against enterococci. The sequential inhibition of multiple steps in a biosynthetic pathway, such as inhibition of folic acid synthesis by a sulfonamide and trimethoprim, can also result in synergism. [(4)]

Prevention:

The prevention of infectious diseases consists of:

1. Notification
2. Isolation
3. Disinfection
4. Treatment and chemoprophylaxis
5. Environmental sanitation
6. Immunization
7. Health education

Catch-up Immunization Schedule **UNITED STATES • 2007**

for Persons Aged 4 Months–18 Years Who Start Late or Who Are More Than One Month Behind

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS–6 YEARS					
Hepatitis B[1]	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Rotavirus[2]	6 wks	4 weeks	4 weeks		
Diphtheria, Tetanus, Pertussis[3]	6 wks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 wks	4 weeks if first dose administered at age < 12 months 8 weeks (as final dose) if first dose administered at age 12-14 months No further doses needed if first dose administered at age ≥ 15 months	4 weeks[4] if current age < 12 months 8 weeks (as final dose)[4] if current age ≥ 12 months and second dose administered at age < 15 months No further doses needed if previous dose administered at age ≥ 15 months	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	
Pneumococcal[5]	6 wks	4 weeks if first dose administered at age < 12 months and current age < 24 months 8 weeks (as final dose) if first dose administered at age ≥ 12 months or current age 24–59 months No further doses needed for healthy children if first dose administered at age ≥ 24 months	4 weeks if current age < 12 months 8 weeks (as final dose) if current age ≥ 12 months No further doses needed for healthy children if previous dose administered at age ≥ 24 months	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months	
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	3 months			
Hepatitis A[9]	12 mos	6 months			
CATCH-UP SCHEDULE FOR PERSONS AGED 7–18 YEARS					
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis[10]	7 yrs[10]	4 weeks	8 weeks if first dose administered at age < 12 months 6 months if first dose administered at age ≥ 12 months	6 months if first dose administered at age < 12 months	
Human Papillomavirus[11]	9 yrs	4 weeks	12 weeks		
Hepatitis A[9]	12 mos	6 months			
Hepatitis B[1]	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Inactivated Poliovirus[6]	6 wks	4 weeks	4 weeks	4 weeks[6]	
Measles, Mumps, Rubella[7]	12 mos	4 weeks			
Varicella[8]	12 mos	4 weeks if first dose administered at age ≥ 13 years 3 months if first dose administered at age < 13 years			

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Table **3 Catch-up immunization schedule for persons aged 4 months–18 years who start late or who are more than 1 month behind. 1. Hepatitis B vaccine (HepB).** *(Minimum age: birth)* Administer the 3-dose series to those who were not previously vaccinated. A 2-dose series of Recombivax HB is licensed for children aged 11–15 years. **2. Rotavirus vaccine (Rota).** *(Minimum age: 6 weeks)* Do not start the series later than age 12 weeks. Administer the final dose in the series by age 32 weeks. Do not administer a dose later than age 32 weeks. Data on safety and efficacy outside of these age ranges are insufficient. **3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).** *(Minimum age: 6 weeks)* The fifth dose is not necessary if the fourth dose was administered at age 4 years. DTaP is not indicated for persons aged 7 years. **4. Haemophilus influenzae type b conjugate vaccine (Hib).** *(Minimum age: 6 weeks)* Vaccine is not generally recommended for children aged 5 years. If current age <12 months and the first 2 doses were PRP-OMP (PedvaxHIB or ComVax [Merck]), the third (and final) dose should be administered at age 12–15 months and at least 8 weeks after the second dose. If first dose was administered at age 7–11 months, administer 2 doses separated by 4 weeks plus a

booster at age 12–15 months. **5. Pneumococcal conjugate vaccine (PCV).** *(Minimum age: 6 weeks)* Vaccine is not generally recommended for children aged 5 years. **6. Inactivated poliovirus vaccine (IPV).** *(Minimum age: 6 weeks)* For children who received an all-IPV or all-oral poliovirus (OPV) series, a fourth dose is not necessary if third dose was administered at age 4 years. If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. **7. Measles, mumps, and rubella vaccine (MMR).** *(Minimum age: 12 months)* The second dose of MMR is recommended routinely at age 4–6 years but may be administered earlier if desired. If not previously vaccinated, administer 2 doses of MMR during any visit with 4 weeks between the doses. **8. Varicella vaccine.** *(Minimum age: 12 months)* The second dose of varicella vaccine is recommended routinely at age 4–6 years but may be administered earlier if desired. Do not repeat the second dose in persons aged <13 years if administered 28 days after the first dose. **9. Hepatitis A vaccine (HepA).** *(Minimum age: 12 months)* HepA is recommended for certain groups of children, including in areas where vaccination programs target older children. See MMWR 2006;55(No. RR-7):1–23. **10. Tetanus and diphtheria toxoids vaccine (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).** *(Minimum ages: 7 years for Td, 10 years for BOOSTRIX, and 11 years for ADACEL)* Tdap should be substituted for a single dose of Td in the primary catch-up series or as a booster if age appropriate; use Td for other doses. A 5-year interval from the last Td dose is encouraged when Tdap is used as a booster dose. A booster (fourth) dose is needed if any of the previous doses were administered at age <12 months. Refer to ACIP recommendations for further information. See MMWR 2006;55(No. RR-3). **11. Human papillomavirus vaccine (HPV).** *(Minimum age: 9 years)* Administer the HPV vaccine series to females at age 13–18 years if not previously vaccinated. [3]

Table 4 Isolation for Specific Infections and Duration of Isolation

Isolation type and diseases	Duration of isolation
Airborne	
Tuberculosis (TB)	Until TB is ruled out with three negative acid-fast bacilli smears on consecutive days. (If patient has documented or strongly suspected TB, isolation for hospitalized patients should continue for at least 2 wk of therapy with a good clinical response; however, patients can be discharged during this time if proper follow-up has been arranged with the local health department.)
Measles	4 days after start of rash or for duration of illness if patient is immunocompromised
Chickenpox[a]/disseminated zoster[a]	Until all lesions are crusted. (Note: Nonimmune persons are potentially contagious days 8â “21 after exposure to

	varicella-zoster virus.)
Severe acute respiratory syndrome (strict isolation: airborne, contact, and eye/nose protection)	Duration of illness
Avian influenza	Duration of illness
Droplet	
Adenovirus (pneumonia)	Duration of illness
Diphtheria (pharyngeal)	Until cultures are negative (at least 24 hr after stopping antibiotics)
Influenza	Duration of illness
Meningitis	24 hr after start of therapy for known or suspected *Neisseria meningitidis* or *Haemophilus influenzae*; this is prudent for all meningitis initially
Mumps[a]	9 days after onset of swelling
Mycoplasma	Duration of illness
Parvovirus B19[b]	7 days for aplastic crisis or for duration of illness if patient is immunosuppressed
Pertussis	5 days after start of therapy
Plague (pneumonic)	72 hr after start of therapy
Rubella[b]	7 days after onset of rash; for congenital rubella place infant on contact precautions during any admission until 1 yr of age unless nasopharyngeal and urine cultures are negative after age 3 mo
Streptococcal pharyngitis, pneumonia, or scarlet fever in infants and young children	24 hr after start of therapy
Contact	
Acute infectious diarrhea	Duration of illness
Abscess/draining wound	Duration of illness
Clostridium difficile	Until diarrhea resolves or treatment is completed
Enterovirus	Duration of illness
Herpes simplex (neonatal, primary or disseminated mucocutaneous, severe)	Duration of illness

Hepatitis A	Until 1 wk after onset of symptoms
Parainfluenza	Duration of illness
Respiratory syncytial virus (infants, young children, and immunocompromised adults)	Duration of illness
Scabies	24 hr after start of therapy
Viral conjunctivitis (â œpink eyeâ)	Duration of illness
Oxacillin-resistant *Staphylococcus aureus*	Duration of hospitalization and future hospitalizations[c]
Vancomycin-resistant or intermediate-sensitive *S. aureus*	Duration of hospitalization and future hospitalizations[c]
Vancomycin-resistant enterococci	Duration of hospitalization and future hospitalizations[c]
Multidrug-resistant gram-negative bacteria	Duration of hospitalization and future hospitalizations[c]

[a]Nonimmune persons should stay out of room if possible.
[b]Nonimmune pregnant women should stay out of room (Barnes-Jewish Hospital policy, not an official Centers for Disease Control and Prevention recommendation).
[c]Unless criteria for discontinuing isolation have been met; consult hospital infection control specialists for specific criteria. (1)

Table 5 Isolation for Centers for Disease Control and Prevention Class A[a] Agents of Bioterrorism

Isolation type and agent	Duration of isolation
Airborne	
Smallpox[b]	Duration of hospitalization or until scabs fall off
Viral hemorrhagic fevers[c]	Duration of hospitalization
Droplet	
Pneumonic plague (*Yersinia pestis*)	Until 72 hr after start of antimicrobial therapy
Contact	

Cutaneous anthrax	Until lesions resolve
Standard precautions	
Inhalational anthrax	Duration of hospitalization
Botulism	Duration of hospitalization
Tularemia	Duration of hospitalization

[a]Six class A agents have been identified by the Centers for Disease Control and Prevention. Criteria for inclusion in class A are easily disseminated or transmitted person to person, high mortality, potential for major public health impact, potential for public panic and social disruption, and requirement for special action for public health preparedness.
[b]Contact precautions should be used in handling items potentially contaminated by infectious lesions.
[c]Lassa, Marburg, Ebola, Congo-Crimean. Droplet isolation can be used if the patient does not have prominent coughing, vomiting, diarrhea, or ` hemorrhaging. Private rooms with potential for conversion of air flow to negative pressure are recommended at admission to avoid later patient transport to negative-pressure isolation. (1)

Fever of unknown origin (FUO)

Definition:

Fever of unknown origin (FUO) was defined as:

- Temperatures of >38.3°C (>101°F) on several occasions
- A duration of fever of >3 weeks
- Failure to reach a diagnosis despite 1 week of inpatient investigation [3]

Classification:

- Classic FUO
- Nosocomial FUO
- Neutropenic FUO
- FUO associated with HIV infection. [3]

Etiology:

The etiology of FUO is summarized in table 6.

Table 6 Various causes of FUO

Leading causes of FUO (by category and approximate frequency)	**Uncommon or rare causes of FUO (in alphabetical order)**
Infection (30â “50%)	Alcoholic hepatitis
Bacterial abscesses (especially intra-abdominal)	Aortic dissection
Mycobacterial infections (human and atypical)	Atrial myxoma
Urinary tract infections	Beh¡et's syndrome
Infective endocarditis	Castleman disease
Viral infections (HIV, CMV, EBV)	Chronic meningitis
Amoebic abscess	Carcinomatous meningitis
Leishmaniasis	Cyclic neutropenia
Brucellosis	Drug fever and other hypersensitivities

Schistosomiasis

Malignancy (15â “20%)
Lymphoma
Leukaemia
Other haematological malignancies
Solid tumours

Connective tissue diseases (10â “20%)
Temporal arteritis/polymyalgia rheumatica
Still's disease
Systemic lupus erythematosis
Polyarteritis nodosa
Rheumatic fever (including recurrences)

Miscellaneous (see right-hand column) (10â “15%)

Undiagnosed (10â “25%)

Erythema multiforme
Fabry's disease
Familial Mediterranean fever
Granulomatous hepatitis
Granulomatous peritonitis
Haemoglobinopathies
Haemolytic anaemias
Histiocytosis X
Inflammatory bowel disease
Lymphomatoid granulomatosis
Pancreatitis
Paroxysmal haemoglobinurias
Pericarditis
Periodic fever
Phaeochromocytoma
Pulmonary emboli

Postpericardiotomy syndrome
Retroperitoneal fibrosis
Sarcoidosis
Serum sickness
Sj¶gren's syndrome
Thrombophlebitis
Thrombotic thrombocytopenic Purpura
Thyroiditis and Thyrotoxicosis
Vogtâ “Koyanagiâ “Harada syndrome
Wegener's granulomatosis
Whipple's disease

FUO, fever of unknown origin; HIV, human immunodeficiency virus; CMV, cytomegalovirus; EBV, Epsteinâ “Barr virus. (8)

Clinical features (C/F):

Major features of four types of FUO are summarized in table 7. (8)

Table 7 Summary of definitions and major features of four types of FUO

	Classical FUO	Nosocomial FUO	Neutropenic FUO	HIV-related FUO
Definition	>38.0°C, >3 weeks, >2 physician visits or 3 days in hospital	>38.0°C, >72 h, not present or incubating on admission	>38.0°C, >72 h, <1000 PMNs/mm^3, negative cultures	>38.0°C, >3 weeks for outpatients, >3 days for inpatients, HIV infection

			after 48 h	confirmed
Patient location	Community, clinic, or hospital	Acute-care hospital	Hospital or clinic	Community, clinic, or hospital
Leading aetiologies	Malignancies, infections, inflammatory conditions, undiagnosed cases, habitual hyperthermia	Nosocomial infections, postoperative complications, drug fevers	Majority due to infections, but aetiology documented in only 40â “60%	HIV, typical and atypical *Mycobacteria* spp., CMV, lymphomas, toxoplasmosis
History emphasis	Travel, contacts, animal and insect exposure, immunizations, family history	Operations and procedures, devices, anatomical considerations, drug treatment	Stage of chemotherapy, drugs administered	Drugs, exposures, risk factors, travel, contacts, staging of HIV infection
Examination emphasis	Abdomen, lymph nodes, spleen, joints, muscles, arteries	Wounds, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, ESR, tuberculin skin test	Imaging, bacterial cultures	Chest radiograph, bacterial cultures	Blood and lymphocyte count; serologies; chest radiograph; stool examination; biopsies of lung, bone marrow, liver; cultures and cytologies; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoid empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	HAART, antimicrobial treatment protocols, revision of treatment regimens, nutrition
Time course of Disease	Months	Weeks	Days	Weeks to months
Tempo of Investigation	Weeks	Days	Hours	Days to weeks
Mortality (attributable to the cause of FUO) [8]	Moderate	Moderate	Low	High

Treatment (Rx):

An empiric course of antimicrobials should be considered if a diagnosis is strongly suspected. However, if there is no clinical response in several weeks, it is imperative to stop therapy and reevaluate the patient.[1] (4)

[1] In the seriously ill or rapidly deteriorating patient, empiric therapy is often given. Once definitive culture results return, streamlining therapy to the most narrow spectrum antimicrobial should take place. Antituberculosis medications (particularly in the elderly or foreign-born) and broad-spectrum antibiotics are reasonable in this setting. Empiric administration of corticosteroids should be discouraged; they can suppress fever if given in high enough doses, but they can also exacerbate many infections, and infection remains a leading cause of FUO. (4)

Measles (Rubeola)

Definition:

Measles is a highly contagious viral disease that is characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by the appearance of [1]a generalized maculopapular rash. (3)

Etiology:

1. The causative agent: Measles virus is a *Paramyxovirus*
2. The characteristics of agent:
   - Spherical
   - Nonsegmented
   - Single-stranded RNA virus. (2 & 3)

Epidemiology:

1. Prevalence/Incidence: Epidemic occurs 2-5 years in USA.
2. Geographical variation: Worldwide but common in poor vaccinated country.
3. Age group: Childhood disease. (3)
4. Seasonal variation: Common in winter and spring. (3)
5. Route of transmission: Droplets infection
6. Reservoir of infection: Human
7. Incubation period: 14 days (3)
8. Infectivity period: 1-2 days before of on[2]set of symptoms until 4 days of rash appearance. (3)

---

[1] Pathogonomic enanthem (Kopliks spots). (3)

[2] The incubation period for measles is 10 days to fever onset and 14 days to rash onset. This period may be shorter in infants and longer (up to 3 weeks) in adults. (3)

Pathogenesis/Pathology:

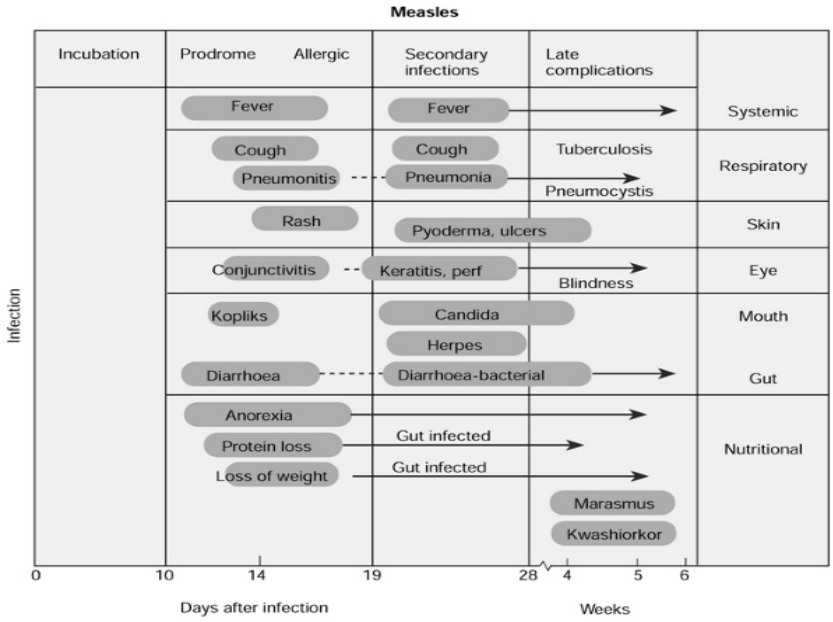
1. Respiratory epithelium invasion
2. Blood stream entry
3. Reticuloendothelial system infection
4. Infect all type of WBC
5. Viremia and virurea
6. Inter endothelial cells of skin and mucus membrane capillary.
7. Immunologic reaction to virus (maculopapular eruption). [3]

Clinical features (C/F):

Symptoms:

a. Catarrhal stage:

1. Malaise [3]
2. Persistent fever
3. Rhinorrhea
4. Sneezing
5. Nasal obstruction
6. Red eyes
7. Lacrimation
8. Cough
9. Hoarseness
10. Photophobia
11. Irritability [2 & 7]

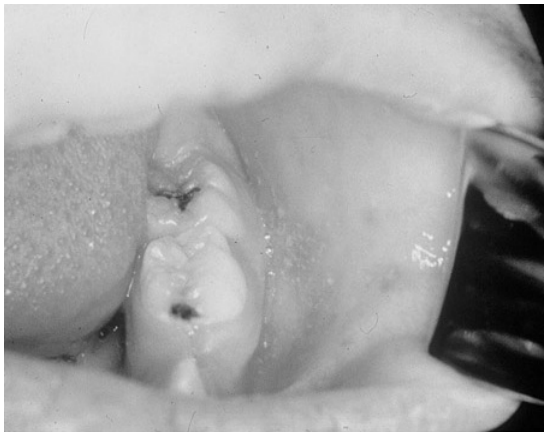


(Fig. 9) Clinical features of measles and some of its complications. (Reproduced with permission from Parry EHOP (1984). Principles of medicine in Africa, 2nd edn, Oxford University Press, Oxford.) [8]

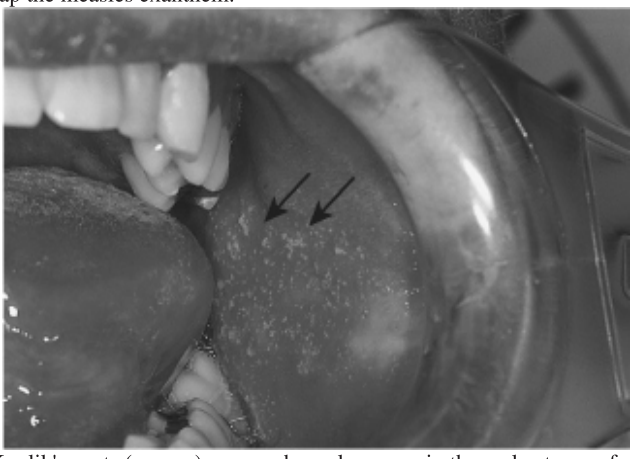
b. Exanthematus stage:

1. After 3-4 days Kopliks spots[3] disappear (Fig. 10 & 11)
2. Red dark macular or maculopapular rash appear (Fig. 12 & 13)
3. First on back of ears and forehead.
4. After 3-4 days of full eruption will give brown desquamation (Fig. 14).

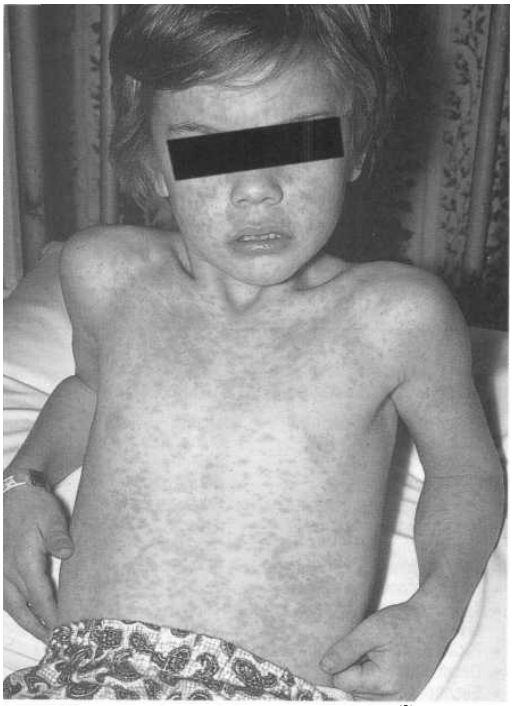
[3] Kopliks spots are 1-2 mm Blue-white spots on a red background [3]



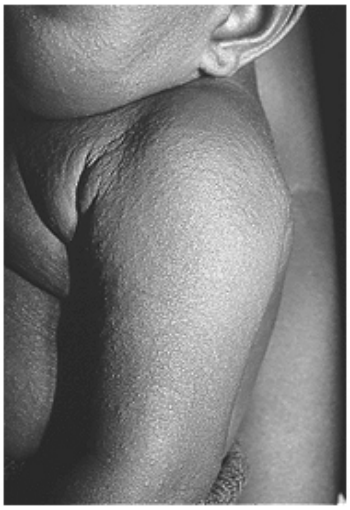
(Fig 10) **Koplik's spots,** which manifest as white or bluish lesions with an erythematous halo on the buccal mucosa, usually occur in the first 2 days of measles symptoms and may briefly overlap the measles exanthem. [3]



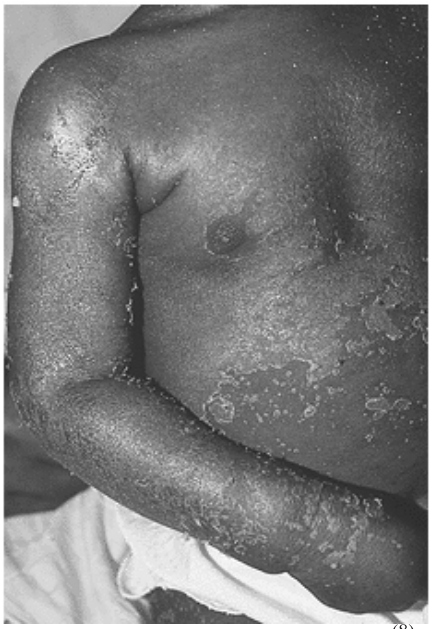
(Fig 11) Koplik's spots (arrows) seen on buccal mucosa in the early stages of measles. [2]



(Fig 12) Typical measles rash. [2]



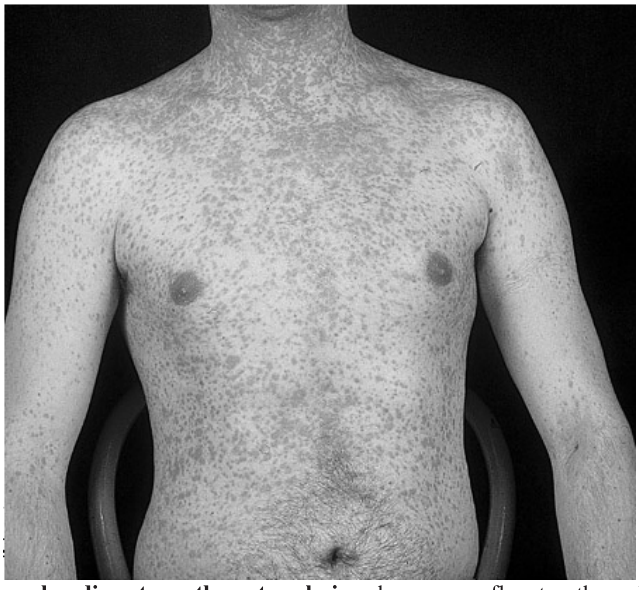
(Fig. 13) Measles rash (African). [8]



(Fig. 14) Measles rash (African). [8]

Signs:

1. Fever (40-40,6 C)
2. Kopliks spots
3. Maculopapular eruption (Fig. 15)
4. Red eyes
5. Pharyngeal erythema
6. Yellowish exudates on tonsils
7. Coating of tongue
8. Moderate generalized lymphadenopathy
9. Splenomegaly (occasionally)
10. Respiratory signs:
    - Crepitation
    - Rhonchi
11. Copper brow desquamation (Fig. 14) [7]



(Fig 15) **In measles, discrete erythematous lesions** become confluent as the rash spreads downward. [3]

Complications:

1. Effects of measles virus:
   - STomtits
   - Enteritis
   - Pneumonia
   - Keratitis
   - Bronchitis
2. Secondary bacterial infection:
   - Otitis media
   - Bronchopneumonia
   - Conjunctivitis
   - Cervical adenitis
3. Neurological complication:
   - Post viral encephalitis
   - Sub acute sclerosing pan encephalitis
4. Nutritional complications:
   - Sever weight loss
   - Kwashiorkor (tropics)
   - Corneal ulceration (tropics Vit-A deficiency)
2. Tuberculosis: May exacerbate tuberculosis [2 & 7]

Investigations (Ix):

1. TLC:
   - Leucopenia
   - Leukocytosis(may be in secondary infection)
2. DLC:
   - Lymphocytosis
   - Neutropenia
3. Tissues culture of:
   - Respiratory secretion
   - Urine

4. Urine exam: Proteinuria (often)

Treatment (Rx):

General Rx:

1. Admission
2. Nutrition: Vit-A[4] with good nutrition
3. Paracetamol for fever
4. Tetracycline eye ointment for eyes

Specific Rx:

1. Antiviral:
   - Ribavirin [(3)]
   - Interferon
2. Antibiotics for secondary infection (pneumonia):
   - Ampicillin 1gr QID
   - Gentamicin 80mg TID

Prevention:

1. Isolation
2. Immunization with MMR (Licensed in 1963)
3. Health education

Prognosis:

1. Between 1999-2005, measles mortality rate was reduced an estimated 60%
2. In US fatality rate is 3 per 1000 reported cases
3. The mortality for encephalitis is 15%.
4. Case-fatality proportions for refugee camps have been as high as 20–30%. [(3)]

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[4] The dose for Vit A:
- For 1-6 months old 50000IU
- For 7-12 months old 100000IU
- For >1 years old 200000IU [(3)]

Rubella
(German measles)

Definition:

Rubella was historically viewed as a variant of measles or scarlet fever.Rubella is an acute viral infection of children and adult with rash, fever & lymphadenopathy, rubella during pregnancy can lead to fetal infection & malformation. [3]

Etiology:

1. The causative agent: *Toga virus*
2. The characteristics of agent:
   - RNA virus
   - 60 nm in size. [3]

Epidemiology:

1. Prevalence/Incidence: Has an epidemic in 6-9 years. [3]
2. Geographical variation: Worldwide [6]
3. Age group: Common in school age
4. Seasonal variation: Common in spring
5. Route of Transmission: Droplets infection
6. Reservoir of infection: Human
7. Incubation Period: 14 days (range, 12–23 days) [3]
8. Infectivity Period (Maximums): Before & during the time of rash [6]

Pathogenesis/Pathology:

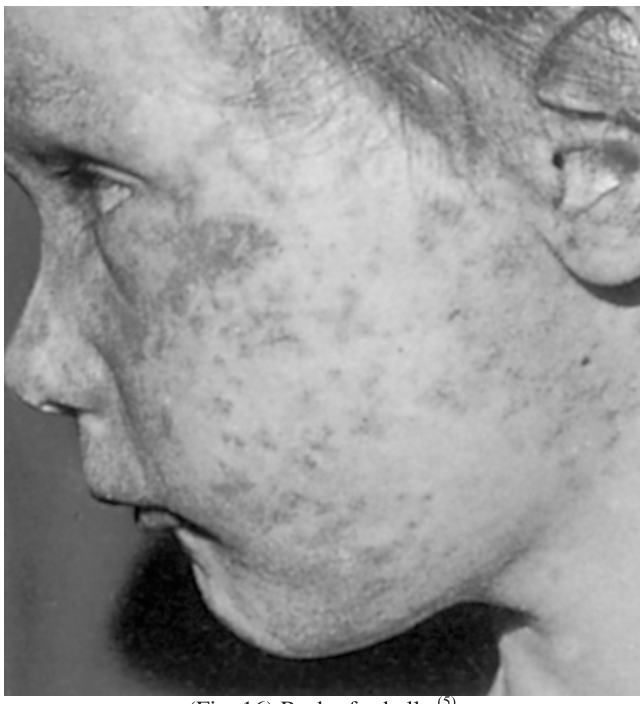
1. Like that of measles
2. Immune reaction to virus cause skin rash. [3]
3. Theories for congenital anomalies:

- Cells necrosis without inflammation
- Mitotic arrest of cell division
- Genetic changes [3]

Clinical features:

a. **In children:**

1. Mild features
2. Pink macular rash (Fig. 16)
3. First appear behind ears & forehead
4. Tender lymphadenopathy



(Fig. 16) Rash of rubella [5]

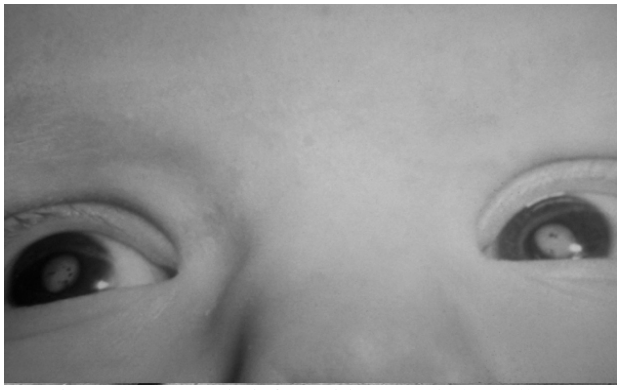
b. **In adult**:

1. Acute onset
2. General aching [2]
3. Malaise
4. Fever
5. Anorexia [3]
6. Mild conjunctivitis
7. Forchheimer spots (Petechial lesion on soft palate)
8. Splenomegaly [6]

c. **Congenital abnormalities**:

1. Congenital rubella syndrome (CRS):
   - Heart (septal defect & patent ductus arteriosis)
   - Eye (cataract) (Fig. 17)
   - Brain (mental retardation & microcephaly)
2. Expanded rubella syndrome (ERS): The ERS is CRS with:
   - Hepatosplenomegaly
   - Myocarditis
   - Interstitial pneumonia
   - Metaphyseal bone lesion [6]

NB: The risk of congenital abnormalities:
In 1st four week of pregnancy 80 %
After 16th week of pregnancy < 5 % [2]



(Fig. 17) Bilateral cataracts in infant with congenital rubella syndrome [5]

Complications:

1. Polyarthritis
2. Encephalitis
3. Thrombocytopenic purpura
4. Secondary pulmonary infection [6]
5. Hepatitis [3]

Investigations:

1. TLC: Leucopenia
2. DLC: Typical Lymphocytes (Positive)
3. Serological test [3]
4. Culture of throat swab & urine [6]

Treatment:

General Rx:

1. Antipyretics for fever
2. Analgesics for joint pain [3]

Specific Rx:

1. No specific therapy
2. Immunoglobulin for pregnant women [3]

Prevention:

1. Isolation
2. Immunization with:
   - MMR (Licensed in 1969) [3]
   - A tetravalent measles, mumps, rubella, and varicella (MMRV) vaccine is available but is not widely used. [3]
3. Health education

Prognosis:

1. In children most cases are sub clinical.
2. Encephalitis occurs about 1/5000 with 20-50% mortality [2]
3. Congenital rubella has a high mortality rate [7]

Mumps

Definition:

Mumps is an acute, systemic viral infection classically associated with swelling of one or both parotid glands and involvement of other salivary glands, meninges, pancreas & gonads. (3)

Etiology:

1. The causative agent: The mumps virus is a *Paramyxovirus*
2. The characteristics of agent:
   - RNA virus
   - 100-300nm in size (3)

Epidemiology:

1. Prevalence/Incidence:
   - Has epidemic[1]
   - Endemic disease (3)
   - Has sporadic cases
   - In 2006, an outbreak in US occurred with 6000 cases (7)
2. Geographical variation: Worldwide
3. Age group: School age
4. Seasonal variation: Common in winter and spring.
5. Route of Transmission: Droplets infection
6. Reservoir of infection: Human
7. Incubation Period: 18 days (7)
8. Infectivity Period: 2-3 days before onset of C/F and for 3 days(6)

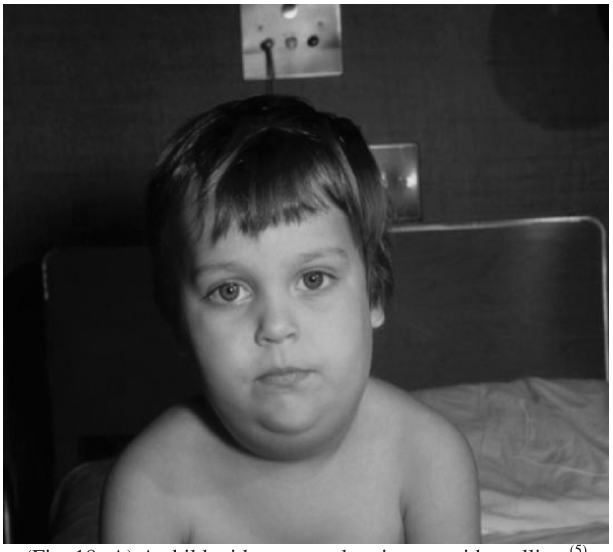
[1] Mumps is endemic worldwide, with epidemics occurring every 3–5 years in unvaccinated populations. (3)

Pathogenesis/pathology:

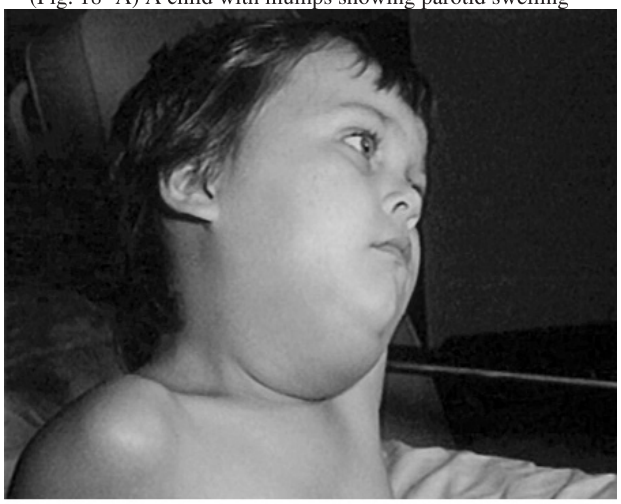
1. Respiratory epithelium entry
2. Replication in epithelial cells
3. Entry into circulation
4. Viremia
5. Parotid gland inflammation and necrosis
6. Gonadal tissue and CNS infection [3]

Clinical features:

1. Prodromal:
   - Malaise
   - Fever
   - Myalgia
   - Anorexia [3]
2. Local:
   - Pain near jaws angle
   - Tender swelling of parotid gland (Fig.18)
   - Tresmus
   - Submandibular gland may involve [2]



(Fig. 18- A) A child with mumps showing parotid swelling [5]



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

(Fig. 18- B)**Child with mumps.** Note the classic submandibular and preauricular enlargement of the parotid gland. *(From the Centers for Disease Control and Prevention.)* [3]

3. Complications and thier C/F:
   - Orchitis: Testicular pain
   - Pancreatitis: Abdominal Pain
   - Oophoritis: Abdominal Pain
   - Acute lymphocytic meningitis: [2]

     Neck stiffness
     Headache
     Drowsiness [3]
4. Rare complications:
   - Encephalomyelitis [2]
   - Guillain- barre syndrome
   - Neuritis (deafness)
   - Transverse myelitis
   - Cerebral ataxia
   - Thrombocytopenic purpura [7]
   - Myocarditis
   - Mastitis
   - Thyroiditis
   - Nephritis
   - Arthritis [3]
   - Abortion(in pregnancy)

Investigation:

1. No blood exam is characteristic
2. CFS exam
3. Culture of saliva & CFS
4. Serologic test
5. Skin test for immunity assessment

Treatment (Rx):

1. General Rx:

- Oral hygiene
- Analgesic for pain
- Cold compression to parotid gland & testis [7]

2. Specific Rx:

- For orchitis: hydrocortisone 100 mg followed by prednisolon 40 mg/day orally for 4 days
- Alpha interferon may be helpful [3 & 7]

Prevention:

1. Notification
2. Isolation
3. Immunization with MMR
4. Health education [3]

Prognosis:

1. Encephalitis occurs 1:6000 cases ê mortality of 1.4 % [3]
2. The entire course of mump rarely exceeds 2 weeks.
3. Rare fatality is usually due to encephalitis [7]

Chickenpox (Varicella)

Definition:

Chickenpox (Varicella) is an extremely contagious acute, usually begin illness of childhood with and exanthematus vesicular rash. [3]

Etiology:

1. The causative agent: Varicella zoster virus
2. The characteristics of agent:
   - A DNA virus
   - Has 180-200 nm size [3]

Epidemiology:

1. Prevalence/Incidence: Sporadic, endemic incidence, has epidemic among susceptible.
2. Geographical variation: Worldwide
3. Age group: Children 5-9 years [3]
4. Seasonal variation: Late winter & early spring
5. Route of transmission: Droplet infection [3]
6. Reservoir of infection: Human
7. Incubation period: 14-17 days [3]
8. Infectivity period: 48h before and during vesicular rash [3]

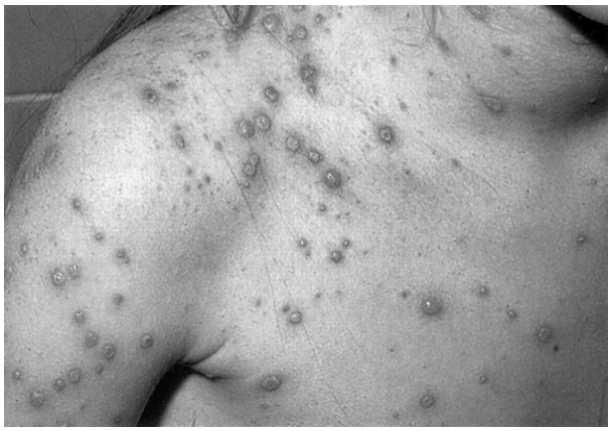
Pathogenesis:

1. Upper respiratory epithelium invasion
2. Localized replication

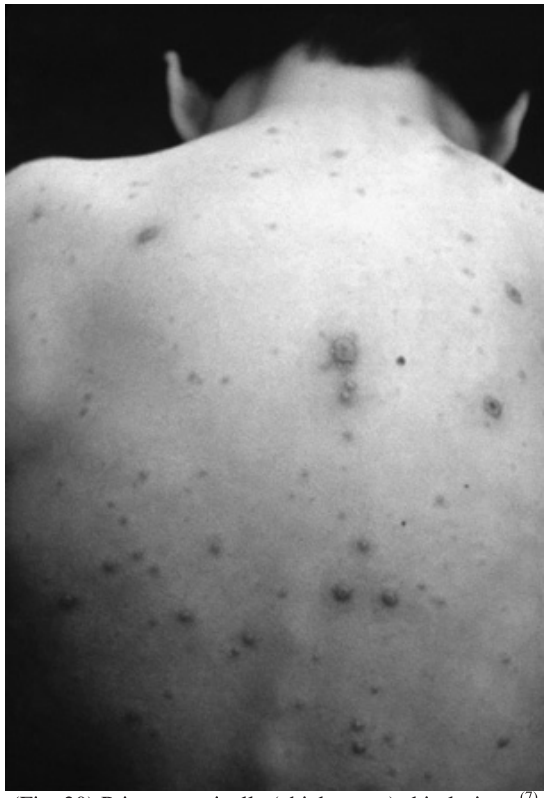
3. Reticuloendothelial system entry
4. Viremia
5. Degenerative change in skin
6. Vesicular rash
7. Necrosis & hemorrhage may occur [3]

Clinical features:

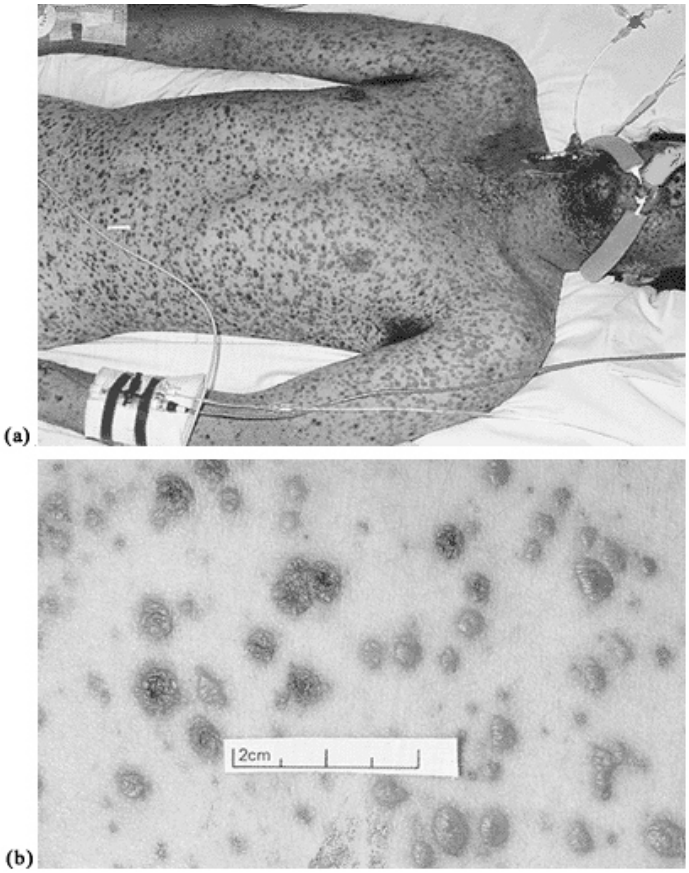
1. Mild fever
2. Malaise
3. Rash: first on palate
   - Than on trunk (Fig. 19& 20)
   - Face
   - Limbs
4. Rash has itching
5. Rash may be as:
   - Macule
   - Papule
   - Vesicle
   - Pustule
   - Scab [2]



(Fig. 19) Varicella-zoster infections. Adolescent with varicella lesions in various stages[5]



(Fig. 20) Primary varicella (chickenpox) skin lesions [7]



(Fig. 21) (a) Severe chickenpox also involving the lungs. (b) Details of the rash. [8]

Complications:

1. Direct viral effects:
   - Pneumonia
   - Myocarditis

2. Post viral:
    - Encephalitis
    - Glomerulonephritis
3. Secondary bacterial infection:
    - Skin infection
    - Septicemia
    - Septic arthritis
    - Osteomyelitis [2]
    - Reye's syndrome (fatty liver ê encephalopathy)
    - Scarlet fever
    - Cellulitis
    - Epiglotitis
    - Meningitis (rare)
    - Erysipelas [7]
4. Intrauterine infection:
    - Congenital limb defect [2]
    - Cicatricial Skin lesion
    - Microcephaly [3]
    - Corneal lesion
    - Myocarditis
    - Hepatitis
    - Growth retardation
    - Microophthalmia
    - Chorioretinitis
    - Cataracts
    - Deafness [7]

Investigation:

1. Culture
2. Leucopenia (often) [7]

Treatment (Rx):

1. **General Rx:**
   - Good hygiene
   - Daily Bathing
   - Antipruritic for itching
2. **Specific Rx:**
   - Acyclovir 800 mg P/O 5 times a day for 5-7 days
   - Valcyclovir for 5-7 days
   - Fimicyclovir for 5-7 days [3]

Prevention:

1. Isolation
2. Immunization: Vaccination ê VZIg.
3. Health education

Prognosis:

1. The total duration of Varicella rarely exceed 2 weeks
2. Fatality are rare except in immunosuppressed patients [3]

Infectious Mononucleosis (Glandular fever)

Definition:

Infectious Mononucleosis is a viral infection ê fever, sore throat, lymphadenopathy & atypical lymphocytosis. (3)

Etiology:

The causative agent: Epstein-Barr virus
The characteristics of agent: A DNA virus (3)

Epidemiology:

1. Prevalence/Incidence:
   - Has sporadic cases
   - Epidemic disease (7)
2. Geographical variation: Worldwide (7)

Age group: Early childhood with a second peak during late adolescence. (3)

3. Seasonal variation: No seasonal variation
4. Route of transmission:
   - Oral contact
   - Blood transfusion

Bone marrow transplantation (3)

   - Sexual route (7)

5. Reservoir of Infection:
   - Patient and
   - Asymptomatic carrier

Incubation period: 7-10 days (3)

6. Infectivity period: Has carrier which is infectious for long time.

Pathogenesis/pathology:

1. Invade oropharyngial epithelium and salivary glands.
2. Infection of B lymphocyte
3. Spread viruses through blood stream
4. Proliferation of infected B cells

Enlargement of lymphoid tissues [3]

Pathogenesis of chronic type:

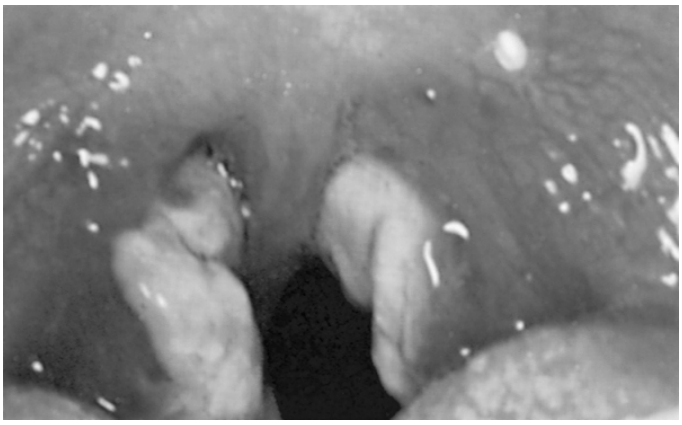
1. Entry to the body
2. Latent infection of tissue (Silent)
3. Slivery gland and bowel
4. If T cells response were decreased,
5. Activation of latent virus

Cause a variety of syndromes [3]

Clinical features:

1. Malaise
2. Tiredness
3. Headache
4. Abdominal Discomfort
5. Anorexia
6. Fever [2]
7. Myalgia
8. Nausea and vomiting
9. Chills [3]
10. Maculopapular rash (in Ampicillin treated patient) [7]
11. Exudative tonsillitis (Fig 22)
12. Petechial rash on palate
13. Lymph gland enlargement
14. Splenomegaly [2]
15. Hepatomegaly (rare)
16. Periorbital edema

17. Jaundice [3]



(Fig. 22) Tonsillitis with membrane formation in infectious mononucleosis [5]

Complications:

1. Chronic fatigue syndrome (common):
   - Debility
   - Confusion
   - Depression
   - Tiredness
   - Low- grade fever [2]
2. Rare complications:
   - Hepatitis
   - Hemolytic anemia
   - Thrombocytopenia
   - Rupture of spleen
   - Meningitis
   - Encephalitis [3]
   - Cholestasis
   - Optic neuritis

- Transverse myelitis
- Guillain-Barre syndrome
- Renal failure
- Pneumonia
- Pleural involvement
- Myocarditis
- Pericarditis
- Airway obstruction from lymph node enlargement
- Mesenteric adenitis [7]

Investigations:

1. Lymphocytosis
2. Atypical lymphocytes
3. Positive monospot test (Paul Bunnell test)
4. A sensitive and easily performed screening test for heterophilic Ab is positive [8]
5. Elevation of liver enzyme
6. Specific virus serologic test
7. TLC: 10000-20000 [3]

Treatment (Rx):

General Rx:

1. Rest
2. Warm Salain throat irrigation or gargales
3. Paracetamol or NSAI drugs for fever
4. 48h course of corticosteroid for sever tonsillar enlargement, to relieve dysphagia and breathlessness [3]

Specific Rx: Acyclovir [3]

Prevention:

1. The isolation of patients with IM is unnecessary
2. Blood screening for EBV.
3. The use of EBV-free blood products

4. Vaccines directed against the major EBV glycoprotein have been effective in animal studies and are undergoing clinical trials. [3]

Prognosis:

1. In cases without complication:
   - Fever disappears in 10 days
   - Lymphadenopathy and Splenomegaly disappear in 4 weeks
2. The debility sometime linger for 2-3 months
3. Death is uncommon and is usually due to splenic rupture [7]

Cytomegalovirus infection

Definition:

It is a congenital infection of fetus ê severe birth defects and wide spectrum of disorders in children and adult ranging from asymptomatic form to mononucleosis like syndrome & disseminated disease in immunocompromized patient. (3)

Etiology:

1. The causative agent: Cytomegalovirus virus
2. The characteristics of agent: DNA virus (3)

Epidemiology:

1. Prevalence/Incidence: Has sporadic cases
2. Geographical variation:
   - Worldwide (3)
   - AIDS patients has 90% opportunistic infection (6)
3. Age group: Perinatal & early childhood infection is common (3)
4. Seasonal variation: No seasonal variation
5. Route of Transmission:
   - Organ transplantation
   - Kissing
   - Sexual intercourse
   - Bone marrow transplantation
   - Blood transfusion
   - Transplacental to the fetus (3)
6. Reservoir of infection: Human
7. Incubation Period: 20-60 days[1] (3)

[1] With incubation periods of 20–60 days, the illness generally lasts for 2–6 weeks. (3)

8. Infectivity Period: For long time [2] [(7)]

Pathogenesis:

1. Cytomegalic infected epithelial cells 3-4 times larger than surrounding cells
2. Inflammatory cells(Owl's eye appearance)
   - Cells:
     a. Plasma cells
     b. Lymphocytes
     c. Monocytes
     d. Macrophages
   - Granulomatus reaction (liver)
   - Owl's eye appearance [(3)]

Clinical features:

1. Congenital infection:
   - Hepatosplenomegaly
   - Purpura
   - Encephalitis
   - Stillborn's [(2)]
   - Jaundice [(3)]
   - Microcephaly
2. Acquired infection:

a. In immunocompetent persons:
   - Symptomatic
   - Mononucleosis like illness
   - Hepatitis (rare)
   - Retinitis (rare) [(2)]

b. In immunosuppressed persons:
   - Retinitis

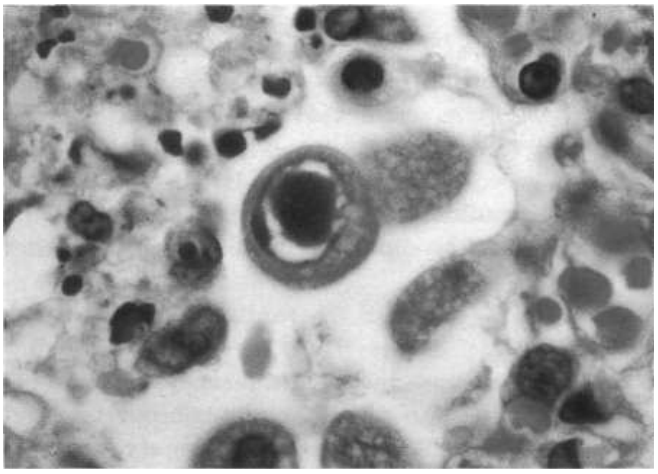
---

[2] Most CMV infections are asymptomatic. After primary infection, the virus remains latent in different cells [(7)]

- Pneumonitis
- Enteritis
- Generalized infection [2]

Investigation (Ix):

1. Urine culture
2. Biopsy of infected tissue (lung. bowel) owl's eye
3. Serology [2]
4. The virus can also be identified in tissues by the presence of characteristic intranuclear 'owl's eye' inclusions (Fig. 23) on histological staining [6]



(Fig. 23) Typical 'owl-eye' inclusion-bearing cell infected with cytomegalovirus. [6]

Treatment (Rx):

General Rx: Hyperimmun globulin [3]

Specific Rx:

- Ganciclovir 5mg/kg BW BID, I/V for 14-21days.
- Valganciclovir 900mg twice daily for 14-21 days [3]

Prevention:

1. The use of CMV-free blood products [5]

2. Prophylaxis:
   - Ganciclovir
   - Valganciclovir [3]
3. Immunization:
   - Has vaccine
   - Passive immunization with IVIG or CMV IVIG for prophylaxis of infection [5]

Prognosis:

1. Patients with CMV mononucleosis usually recover fully
2. Most immunocompromised patients also recover, but many experience severe pneumonitis, with a high fatality rate if hypoxemia develops
3. CMV infection may be fatal in individuals with increased susceptibility to infections such as patients with AIDS [5]

Poliomyelitis

Definition:

The poliomyelitis is an acute viral disease characterized by minor illness ei sore throat, headache, vomiting etc with or without major illness ei CNS involvement & paralysis. [9]

Etiology:

1. The causative agent: Poliovirus type 1, 2 or 3
2. The characteristics of agent: An RNA virus
3. Predisposing factors to the development of paralysis:
   - Male sex
   - Exercise early in the illness.
   - Trauma, surgery or intramuscular injection
   - Recent tonsillectomy [5]

Epidemiology:

1. Prevalence/Incidence:
   - Sporadic disease
   - Endemic in Pakistan, India & Africa.
2. Geographical variation: Rare in developed country (Table 8)
3. Age group: Childhood disease.
4. Seasonal variation:
5. Route of infection: Faeco oral disease

Table 8 Laboratory-Confirmed Cases of Poliomyelitis in 2006		
Country	**Type of Transmission**	**Number of Cases**
Nigeria	Endemic	1123[a]
India	Endemic	676
Pakistan	Endemic	40
Afghanistan	Endemic	31
Somalia	Imported	35
Others[b]	Imported	93
Others[c]	Vaccine-derived	2
Total		2000

[a]Of these cases, 1 were vaccine-derived. [b]Imported cases: Namibia, 19; Bangladesh, 18; Ethiopia, 17; Democratic Republic of the Congo, 13; Niger, 11; Nepal, 5; Angola, 2; Cameroon, 2; Kenya, 2; Indonesia, 2; Chad, 1; Yemen 1.[c]Vaccine-derived cases:Vaccine-derived cases: Myanmar, 1; Cambodia, 1. ***Source:*** World Health Organization. [1] (3)

6. Reservoir of infection: Human
7. Incubation period: 7-14 days
8. Infectivity period: Infectivity is maximal in 1st week but may be for several weeks (7)

[1] Table confirmed cases of poliomyelitis (3)

Country	Confirmed cases in 2001
India	268
Pakistan	119
Nigeria	56
Afghanistan	11
Somalia	7
Niger	6
Egypt	5
Angola, Ethiopia, Sudan and Mauritania	One case each country
Total	

Pathogenesis:

1. Viruses ingestion
2. Gastrointestinal epithelium infection
3. Spread to submucosal lymphoid tissue of the tonsils and Peyer's patches.
4. Spread to spreads to the regional lymph nodes
5. Viremia
6. Replication organs of the reticuloendothelial system
7. A second viremia and further virus replication
8. Viruses enters the CNS via the bloodstream & peripheral nerves
9. Anterior horn cells lesion [3]

Clinical features:

The clinical manifestation varies considerably:

1. Inapparent (asymptomatic) infection:
   - Common form
   - Occurs in 95 % of cases.
2. Abortive poliomyelitis:
   - Occurs in 4-5 % of cases.
   - Fever
   - Sore throat
   - Myalgia
   - Self-limited [6]
   - Headache
   - Vomiting
   - Diarrhea
   - Constipation [7]

3. Non paralytic poliomyelitis:
   - Features of abortive poliomyelitis
   - Signs of meningeal irritation

- Muscles spasm [7]
- Recovery is complete [6]

4. Paralytic poliomyelitis:
   - Occurs in 0,1 % of infected children
   - Features of abortive poliomyelitis
   - May be signs of meningeal irritation
   - Muscle pain [6]
   - Tremor
   - Muscles weakness [7]
   - Asymptomatic paralysis
   - Paralysis of lower limbs (in children under 5 years)
   - Paralysis of upper limbs (in older children)
   - Paraplegia or quadriplegia (in adult) [6]
   - May affect chest muscles [7]

1. Bulbar poliomyelitis:
   - Cranial nerve lesion [6]
   - Diplopia
   - Facial weakness
   - Dysphagia
   - Dysphonia
   - Nasal voice
   - Difficulty in chewing
   - Expel saliva
   - Regurgitation of fluid through nose
   - Respiratory paralysis
   - Lethargy
   - Coma
   - Alteration in BP & heart rate
   - Convulsion (rare) [7]

Complications:

1. Aspiration pneumonia
2. Myocarditis
3. Paralytic ileus
4. Urinary calculi [6]
5. Urinary tract infection
6. Ateletctasis
7. Pulmonary edema
8. Respiratory failure [7]

Investigation:

1. TLC: Normal or increased
2. Lumber puncture: Normal or increased CSF pressure
3. CSF exam:
   - Proteins: Normal or increased
   - Glucose: Normal

4. Culture from:
   - Throat wash (early)
   - Stool (early & late)

5. Complement fixing antibody appear

Treatment:

General Rx:

1. Bed rest (in early stage)
2. Avoid:
   - IM Injection
   - Surgery
3. Physiotherapy
4. Occupational therapy
5. Surgery(occasionally)
6. Respiratory support [6]

Specific Rx: Immunoglobulin

Prevention:

1. Notification of paralysis
2. Isolation of patient
3. Disinfection of faeces
4. Envoirmental sanitation
5. Immunization with oral polio vaccine
6. Health education

Prognosis:

1. During febrile period, paralysis may develop
2. Bulbar poliomyelitis has a mortality rate 50%
3. New muscle weakness & pain may develop after recovery which is called post poliomyelitis syndrome [(7)]

Rabies

Definition:

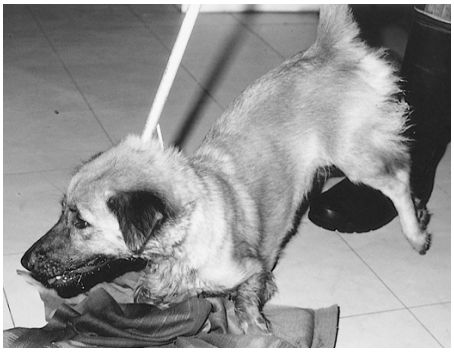
Rabies is a lethal acute viral disease of central nervous system (CNS) that affects all mammals. [3]

Etiology:

1. The causative agent: The causative agent is *Rhabdovirus*
2. The characteristics of agent: An RNA virus [3]

Epidemiology:

1. Prevalence/Incidence:
   - Has 55000 death annually
   - Has sporadic cases
   - Endemic disease, most of these occur in Asia & Africa in rural population [3]
2. Geographical variation: Worldwide
3. Age group: Any age but most frequent children [3]
4. Seasonal variation: All seasons
5. Route of transmission: Through dogs' bites.
6. Reservoir of infection: Domestic dogs and other animals (Fig. 24)

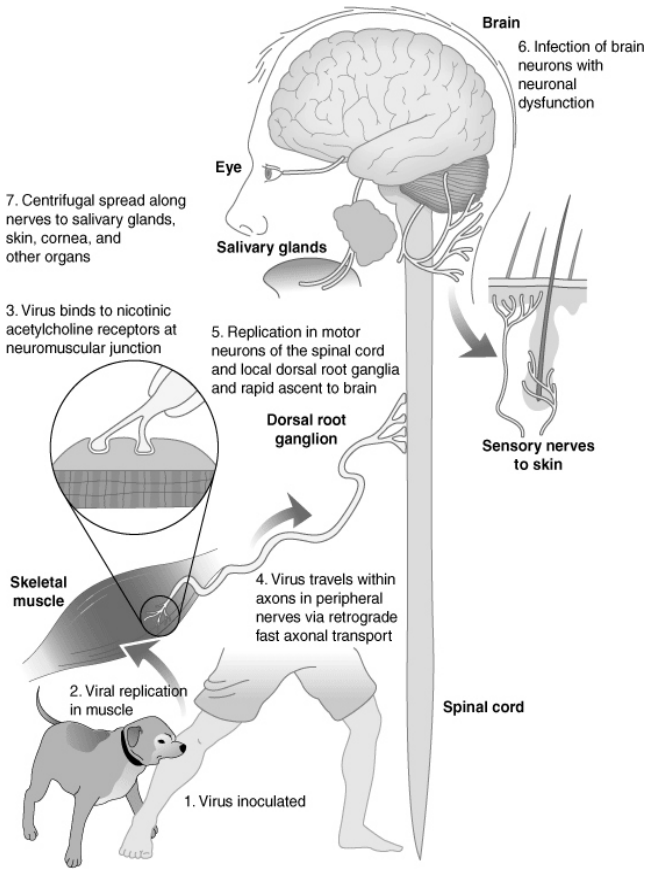


(Fig. 24) Dog with paralytic rabies showing paralysis of the limbs and hypersalivation. [3]

7. Incubation period: From 2 weeks to 1-3 months.
8. Infectivity period: Viruses enter into the salivary glands of dogs 5-7 days before their death, from rabies, thus limiting their period of infectivity [7]

Pathogenesis:

1. Inoculation of viruses (Fig. 11)
2. Replication in muscle cells at the site of inoculation
3. Internalization into the sensory nerve cells endings
4. Spread centripetally up the nerve to the CNS at the rate of 3mm/hours
5. After reaching to CNS replicates within gray matter
6. Passes centrifugally along autonomic nerves to other tissues [3]



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

(Fig. 25) **Schematic representation of the pathogenetic events** following peripheral inoculation of rabies virus [3]

Clinical features:

a. Nonspecific prodrom:

1. Fever
2. Headache

3. Anorexia
4. Nausea
5. Vomiting
6. Malaise
7. Lethargy
8. Focal pain
9. Parasthesia
10. Anxiety
11. Agitation
12. Depression
13. Myalgia
14. Dry cough
15. Fatigue [6]

b. The encephalic phase:

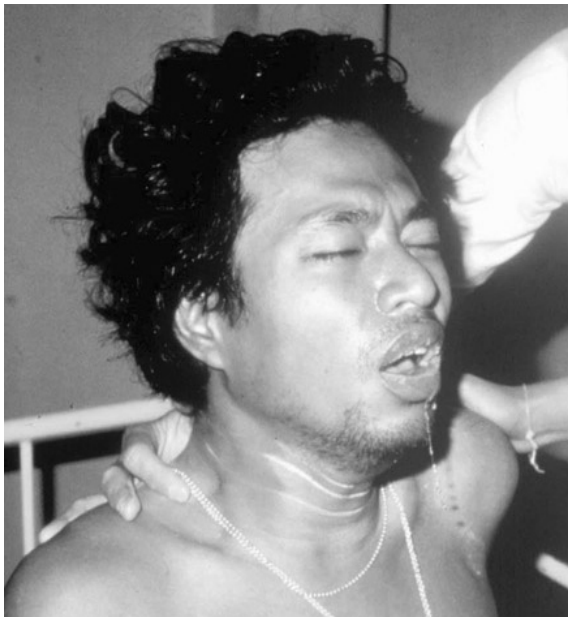
1. Confusion
2. Delirium
3. Hallucination
4. Dysphagia
5. Hypersalivation
6. Aphasia
7. Incoordination
8. Marked hyperactivity
9. Pharyngeal spasm
10. Meningismus
11. Opisthotonic posture
12. Focal paralysis
13. Hydrophobia (Fig. 26)
14. Aerophobia
15. Hyperventilation
16. Hypoxia
17. Seizures [6]

c. Brainstem dysfunction:

1. Diplopia
2. Facial paresis
3. Optic neuritis
4. Difficulty with deglutition
5. Hydrophobia [6]

d. Coma, death or in rare cases recovery:

1. Autonomic instability
2. Hyperventilation
3. Apnea
4. Respiratory arrest
5. Hypo/Hyperthermia
6. Hypotension
7. Pituitary dysfunction
8. Rhabdomyolysis
9. Cardiac arrhythmia
10. Cardiac arrest [6]



(Fig. 26) **Hydrophobic spasm of inspiratory muscles associated with terror** in a patient with encephalitic (furious) rabies who is attempting to swallow water. [3]

Investigation:

1. Blood exam: Show viral disease
2. CSF exam: encephalitis and
3. Serologic test: meningitis

Treatment:

General Rx:

1. Medical management is supportive and palliative [3]
2. Debridment & cleaning of wound [7]

Specific Rx:

1. There is no specific treatment for clinical rabies
2. Post exposure prophylaxis with cell culture vaccine is effective before clinical manifestation [3]

Prevention:

1. Kill rabies animals
2. Pre exposure rabies vaccination [3]

Prognosis:

1. Rabies is an almost fatal disease.
2. Rabies is an almost preventable with postexposur therapy during the incubation period.
3. Their only six cases of survival after symptomatic rabies
4. Death occurs after 7 days of symptoms & usually from respiratory failure [7]

Viral hepatitis

Definition:

The viral hepatitis is a systemic infection affecting the liver predominantly. [3]

Etiology:

1. The causative agent: Hepatitis A virus

The characteristics of agent:

- RNA virus
- Hepatovirus from Picornavirus family
- Nonenveloped
- Heat and acid resistant

2. The causative agent: Hepatitis B virus

The characteristics of agent:

- DNA virus
- Hepadnovirus
- Double shelled

3. The causative agent: Hepatitis C virus

The characteristics of agent:

- RNA virus
- Hepacivirus
- Enveloped

4. The causative agent: Hepatitis D virus

The characteristics of agent:

- Defective RNA virus
- Resembles viroids

- Enveloped

5. The causative agent: Hepatitis E virus

The characteristics of agent:

- RNA virus
- Alphavirus
- Nonenveloped

6. The causative agent: Hepatitis G virus

The characteristics of agent:

- RNA
- Flavivirus [3]

Epidemiology:

1. Prevalence/Incidence:
   - Hepatitis A virus: Epidemic disease with sporadic cases
   - Hepatitis B virus: Sporadic cases
   - Hepatitis C virus: Has sporadic cases
   - Hepatitis D virus: Endemic disease with sporadic cases
   - Hepatitis E virus: Endemic & sporadic disease
   - Hepatitis G virus:
2. Geographical variation:
   - Hepatitis A virus: Common in poor hygiene & overcrowding
   - Hepatitis B virus: Worldwide
   - Hepatitis C virus: Worldwide but common in Egypt
   - Hepatitis D virus: Worldwide
   - Hepatitis E virus: Common in India, Asia, Africa & Central America
   - Hepatitis G virus:
3. Age group:
   - Hepatitis A virus: Children, young adult (5-20 years)

- Hepatitis B virus: Young adult, babies
- Hepatitis C virus: Any age but more common in adults
- Hepatitis D virus: Young adult, babies
- Hepatitis E virus: Young adult (20-40years)
- Hepatitis G virus:

4. Seasonal variation:
   - Hepatitis A virus: Common in late fall & early winter
   - Hepatitis B virus: No seasonal variation
   - Hepatitis C virus: No seasonal variation
   - Hepatitis D virus: No seasonal variation
   - Hepatitis E virus: No seasonal variation
   - Hepatitis G virus:
5. Route of transmission:
   - Hepatitis A virus: Feco oral route (Table 9)
   - Hepatitis B virus: Percutaneous, perinatal & sexual
   - Hepatitis C virus: Percutaneous, perinatal & sexual
   - Hepatitis D virus: Percutaneous, perinatal & sexual
   - Hepatitis E virus: Feco oral route
   - Hepatitis G virus: Percutaneous
6. Reservoir of infection:
   - Hepatitis A virus: Human
   - Hepatitis B virus: Human
   - Hepatitis C virus: Human
   - Hepatitis E virus: Human & swine (in US)
   - Hepatitis G virus: Human
7. Incubation period:
   - Hepatitis A virus: 30 days
   - Hepatitis B virus: 60-90 days
   - Hepatitis C virus: 50 days
   - Hepatitis D virus: 60-90 days

- Hepatitis E virus: 40 days
- Hepatitis G virus:

8. Infectivity period:
    - Hepatitis A virus: No carrier state
    - Hepatitis B virus: Has carrier (0,1-30%)
    - Hepatitis C virus: Has carrier (1,5-3,2%)
    - Hepatitis D virus:
    - Hepatitis E virus: No carrier state
    - Hepatitis G virus: [3]

Pathogenesis:

Ordinarily none of the hepatitis virus is known to be directly cytopathic to hepatocytes.

Liver injury with viral hepatitis is determined by immunologic responses of host. [3]

1. Entry of virus to circulation
2. Entry into hepatocytes
3. Replication in hepatocytes
4. Destruction of hepatocytes by:
    - Immunologic response of host (Cytolytic T cells etc)
    - Viruses
5. Panlobular infiltration of mononuclear cells:
    - Small lymphocytes
    - Plasma cells
    - Eosinophils
6. Hepatocytes necrosis
7. Kupffer cells hyperplasia
8. Variable degree of cholestasis
9. Liver cells regeneration [3]

Table 9 Clinical and Epidemiologic Features of Viral Hepatitis

Feature	**HAV**	**HBV**	**HCV**	**HDV**	**HEV**
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious	Insidious or acute	Acute
Age preference	Children, young adults	Young adults (sexual and percutaneous), babies, toddlers	Any age, but more common in adults	Any age (similar to HBV)	Young adults (20–40 years)
Transmission					
Fecal-oral	+++	–	–	–	+++
Percutaneous	Unusual	+++	+++	+++	–
Perinatal	–	+++	±[a]	+	–
Sexual	±	++	±[a]	++	–
Clinical					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20%[b]	1–2%[e]
Progression to chronicity	None	Occasional (1–10%) (90% of neonates)	Common (85%)	Common[d]	None
Carrier	None	0.1–30%[c]	1.5–3.2%	Variable[f]	None
Cancer	None	+ (neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age, debility	Moderate	Acute, good Chronic, poor	Good
Prophylaxis	IG Inactivated vaccine	HBIG Recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Vaccine

Therapy	None	Interferon Lamivudine Adefovir Pegylated interferon Entecavir Telbivudine	Pegylated interferon plus ribavirin	Interferon ±	None

[a]Primarily with HIV co-infection and high-level viremia in index case; risk 5%.
[b]Up to 5% in acute HBV/HDV co-infection; up to 20% in HDV superinfection of chronic HBV infection.
[c]Varies considerably throughout the world and in subpopulations within countries; see text.
[d]In acute HBV/HDV co-infection, the frequency of chronicity is the same as that for HBV; in HDV superinfection, chronicity is invariable.
[e]10–20% in pregnant women.
[f]Common in Mediterranean countries, rare in North America and western Europe. (3)

Clinical features:

Symptoms:

a. Prodromal phase:

1. Onset may be abrupt or insidious
2. Anorexia
3. Nausea
4. Vomiting
5. Fatigue
6. Malaise
7. Myalgia
8. Arthralgia
9. Headache
10. Photophobia

Upper respiratory symptoms

11. Cough
12. Pharyngitis
13. Coryza
14. Distaste for smoking (Alteration in olfaction & taste)

15. Low grade fever
16. Dark urine
17. Clay colored stools
18. Serum sickness like features [3]
19. Diarrhea or
20. Constipation
21. Abdominal pain (Right upper quadrant pain)
22. Epigastric pain [7]

b. Icteric phase:

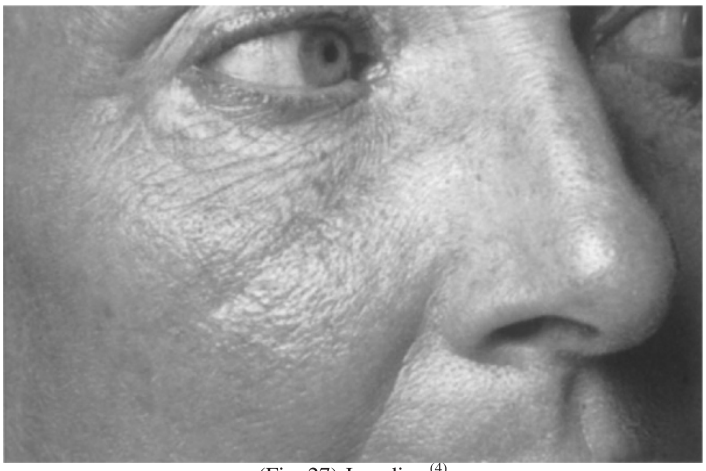
1. Prodromal symptoms diminish (Usually)
2. Mild weight loss
3. Cholestatic picture
4. Right upper quadrant pain and discomfort [3]
5. With the onset of jaundice may worsen the prodromal symptoms [7]

c. Convalescent phase:

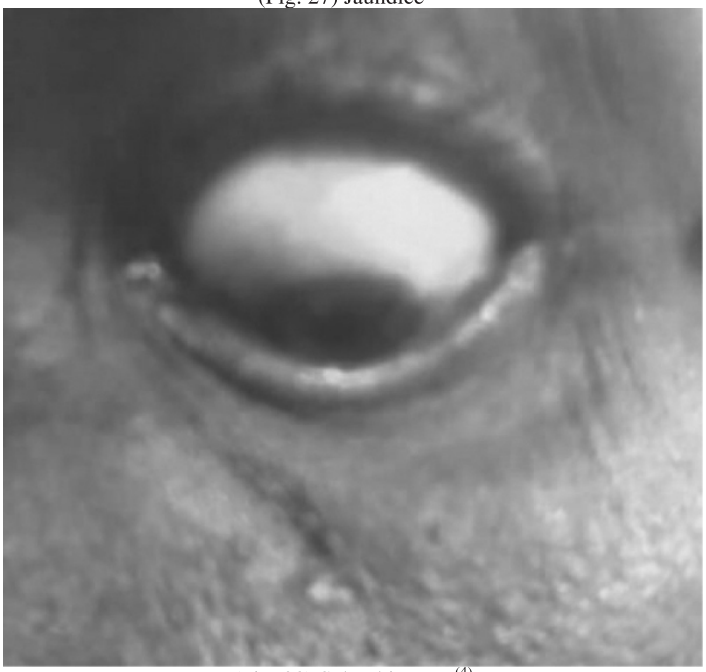
1. Increasing sense of well-being
2. Return of appetite
3. Disappear of:
   - Jaundice
   - Abdominal pain
   - Fatigability

Signs:

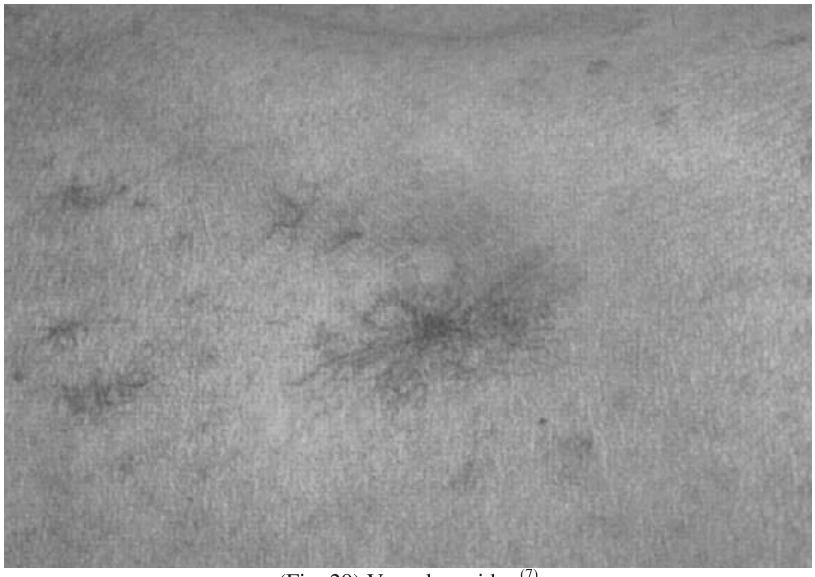
1. Mild fever
2. Jaundice (Fig. 27 & 28)
3. Hepatomegaly
4. Liver tenderness
5. Splenomegaly
6. Cervical lymph nodes enlargement [7]
7. A few spider angiomas (Rarely) (Fig. 29)



(Fig. 27) Jaundice [4]



(Fig. 28) Scleral icterus [4]



(Fig. 29) Vascular spider [7]

Complications and sequelae:

1. Relapsing hepatitis
2. Cholestatic hepatitis
3. Fulminant hepatitis (Massive hepatic necrosis) With:
4. Hepatic failure
5. Hepatic encephalopathy
6. Cerebral edema
7. Brainstem compression
8. Gastrointestinal bleeding
9. Respiratory failure
10. Cardiovascular collapse
11. Renal failure
12. Sepsis

13. Reactive hepatitis (Hepatitis B)
14. Chronic hepatitis

Rare complications:

15. Pancreatitis
16. Myocarditis
17. Atypical pneumonia
18. Aplastic anemia
19. Transverse myelitis

Peripheral neuropathy

20. Liver cirrhosis (Hepatitis B & C)
21. Hepatocellular carcinoma (Hepatitis B & C) [3]

Investigation:

1. TLC: Normal or Low
2. DLC:
   - Neutropenia
   - Lymphopenia [3]
   - Large atypical lymphocytes may be seen
3. Aplastic anemia (Rarely)
4. Urine exam:
   - Mild proteinuria
   - Bilirubinuria
5. Acholic stool
6. ALT or AST elevation
7. Bilirubin
8. Alkaline phosphatase
9. Prothrombin time prolongation
10. Serologic tests [7] (Table 10)

(Table 10) Serologic tests of viral hepatitis [3]

HBsAg	IgM Anti-HAV	IgM Anti-HBc	Anti-HCV	Diagnosis
+		+		Acute hepatitis B
+				Chronic hepatitis B
+	+			Acute hepatitis A superimposed on chr. hepatitis B
+	+	+		Acute hepatitis A and B
	+			Acute hepatitis A
	+	+		Acute hepatitis A&B (HBsAg below detection thr)
		+		Acute hepatitis B (HBsAg below detection thresh)
			+	Acute hepatitis C

Treatment:

General Rx:

1. Bed rest
2. High caloric diet [3]
3. I/V 10% glucose (If nausea & vomiting is present)
4. Small dose of Oxazepam [7]

Specific Rx:

1. Interferon alfa 3 Million S/C 3 times a weeks [3]
2. Ribavirin [1] [1]
3. Lamivudine 100mg/days P/O [2]
4. Adefovir [3]
5. Entecavir [4]
6. Telbivudine [1]

---

[1] Ribavirin 400â "600 mg P/O twice daily is administered for 6â "12 months (For acute and chronic hepatitis C infections). [1]

[2] Lamivudine is a nucleoside analog with antiviral activity. It is administered orally at 100 mg daily (For chronic hepatitis B infections). [1]

[3] Adefovir is a nucleotide analog with antiviral activity. It is administered orally at 10 mg daily (For chronic hepatitis B infections). [1]

[4] Entecavirmg 0.5It is admistered orally at .is a nucleoside analog with antiviral activity [daily in na¯ve nucleoside patients and 1 mg daily in patients with known lamivudine resistance mutations(For chronic hepatitis B infections). [1]

Prevention:

1. The use of hepatitis B, C & D virus-free blood and blood products
2. Disinfection of stool & vomit
3. Immunization:
   - Hepatitis A virus: Passive with Ig & active with vaccine
   - Hepatitis B virus: Passive with Ig & active with vaccine
   - Hepatitis C virus: Passive with Ig & postexposure prophylaxis
   - Hepatitis D virus: Passive with Ig & active with vaccine
   - Hepatitis E virus: Passive with Ig [3]

Prognosis:

1. Previously healthy patients with hepatitis A recover completely.
2. Previously healthy patients with hepatitis B 95-99 % recover completely [3]
3. In most patients, clinical recovery is complete in 3–6 months.
4. Over all mortality rate is less than 1%, but the rate is reportedly higher in older people [7]
5. Chronic hepatitis develops in 1-2% of adult with hepatitis B.
6. Cirrhosis develops in up to 30% of chronic hepatitis C & 40% of chronic hepatitis B [3]

Typhoid Fever (Enteric fever)

Definition:

Typhoid fever is a systemic disease characterized by fever, headache and abdominal pain. Caused by dissemination of *Salmonella Typhi* and *Salmonella Paratyphi* (3 & 6)

NB: Typhoid means similar to Typhus [1] (9)

Etiology:

1. The causative agent: *Salmonella typhi* and *Paratyphi*
2. The characteristics of agent:
   - Gram negative
   - Motile (flagellated)
   - Facultative anaerobic
   - Do not form spores (3)

Epidemiology:

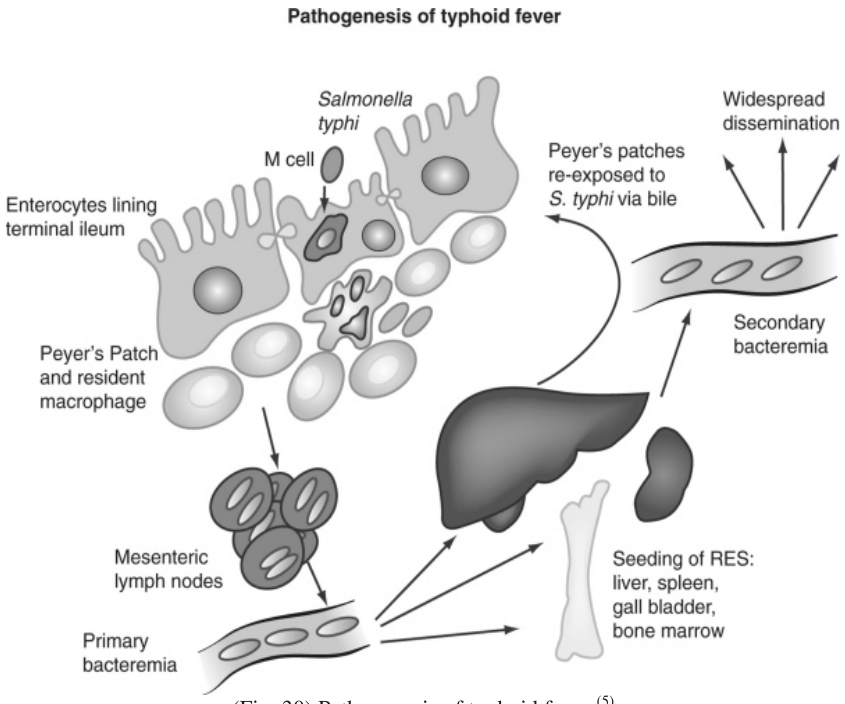
1. Prevalence/Incidence:
   - Has 22 million cases with 200000 death in 2002 (3)
   - Epidemic (has large out break)
   - Endemic
   - Sporadic cases are 80% (3)
2. Geographical variation:
   - Worldwide
   - But common in developing countries

[1] Typhus: Gr. Typhos stupor arising from fever. (9)

3. Age group: Any age but common in young children & adolescent [3]
4. Seasonal variation: Common in summer.
5. Reservoir of infection:
   - Human
   - 1-5%chronic carrier [3]
6. Route of transmission: faeco-oral
7. Incubation period: 10-14 but range from 3-21 days [3]
8. Infectivity period: Has chronic carrier [3]

Pathogenesis:

1. Ingestion of bacteria in food or water
2. Crossing of bacteria from epithelium of small intestine
3. Phagocytosis by macrophages
4. Dissemination of bacteria in macrophage via lymph node
5. Colonization in RE (Reticuloendothelial) tissues (liver, spleen, lymph nodes bone marrow)
6. Enlargement of payers patches (Fig. 30)
7. Septicemia and necrosis [3]



(Fig. 30) Pathogenesis of typhoid fever [5]

Clinical feature:

Symptoms:

1. Insidious onset
2. Malaise
3. Fever > 75%
4. Abdominal pain 30-40% [3]
5. Myalgia
6. Arthralgia
7. Chills
8. Headache
9. Sweating

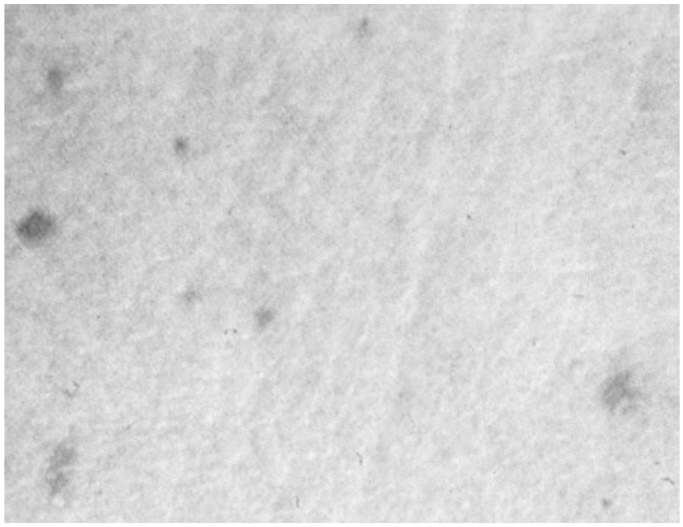
10 Anorexia [3 & 2]

11. Cough
12. Weakness
13. Sore throat
14. Dizziness [7]
15. Drowsiness
16. Limbs aching
17. Epistaxis
18. Constipation
19. Diarrhea in children (Pea soap diarrhea)
20. Nausea
21. Vomiting
22. Delirium [2 & 7]

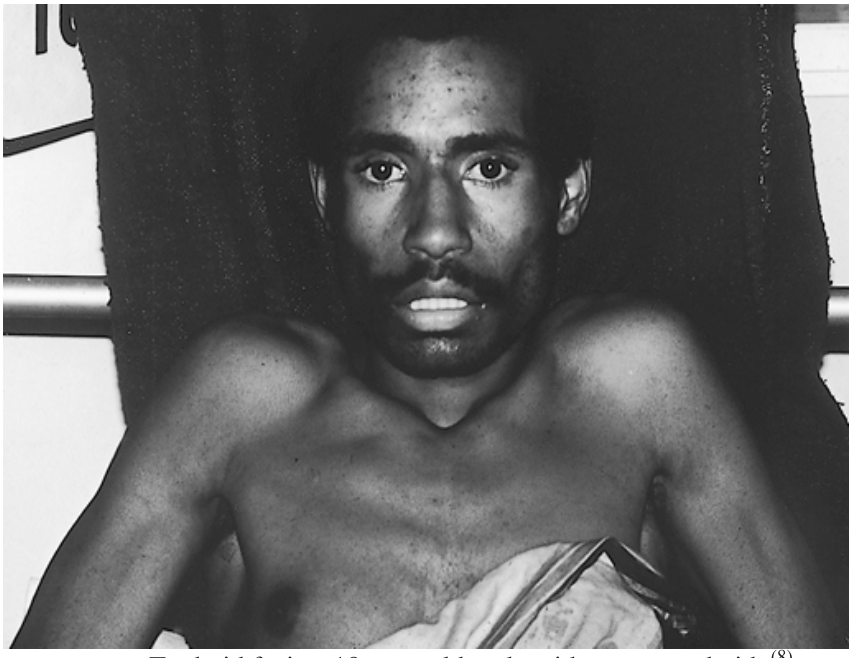
Signs:

1. Fever ascends in stepwise fashion
2. Central coated tongue (51-56%) [3]
3. Pallor (20%)
4. Epistaxis
5. Cervical lymphadenopathy
6. Relative bradycardia
7. Rose red spots in 30% [3 & 5] (Fig. 31)
8. Splenomegaly
9. Hepatomegaly
10. Abdominal tenderness
11. Bloated abdomen (Distension)
12. Meningism [7]
13. Typhoid face[2] [8] (Fig. 32)

[2] Patients with advanced illness may display the â typhoidâ ™ facies (Fig. 2), a thin, flushed face with a staring, apathetic expression. [8]



(Fig. 31) **"Rose spots," the rash of enteric fever** due to *S.* Typhi or *S.* Paratyphi. [3]



(Fig. 32) Typhoid facies: 18-year-old male with severe typhoid. [8]

Complications:

1. Encephalopathy
2. Intestinal perforation
3. Gastrointestinal hemorrhage
4. Pancreatitis
5. Hepatic abscess
6. Splenic abscess
7. Pericarditis
8. Endocarditis
9. Orchitis
10. Osteomyelitis
11. Meningitis
12. Hepatitis
13. Parotitis
14. Nephritis
15. Myocarditis
16. Arthritis
17. Pneumonia [3]
18. Acute cholecystitis
19. Urinary tract infection
20. Hemolytic anemia
21. Polynueropathy [6]
22. Psychosis
23. Thrombophlebitis [7]

Investigations:

1. Blood examination
   - Leucopenia & neutropenia in 15-25%
   - Normal TLC in the majority of cases
   - Leukocytosis in children or in complicated cases e.g. intestinal perforation and secondary infection [(3)]
2. LFT:
   - Aminotransfarases
   - Alkaline phosphatase
   - Lactate dehydrogenase

   Moderately elevated [(3)]
3. ECG: Nonspecific ST &T wave abnormality
4. Culture:
   - Blood culture diagnostic in 1st week 50% positive
   - Stool culture in third week (2-4)
   - Urine in (2^{nd} week)
   - Rose spots fluid
   - Boon marrow (May be positive after 5 days of Rx)
   - Gastric secretion
   - Intestinal secretion [(3)]
5. Serologic tests:
   - Widal test[3]:

   These tests are not clinically useful because of high false positive & false negative results [(3)]

   TO

   TH [4]

---

[3] Widal: G.F.I.Widal French physician (1862-1929) [(9)]

[4] H: (Ger. *Hauch*, breathe because motile bacteria form a spreading film around colonies resembling that produced by breathing on glass).bacterial flagellar antigens important in the serological classification of enteric bacilli especially Salmonella. [(9)]

O: (Ger. *Ohne Hauch* without breathe) the lipopolysaccharid-protein somatic antigens of Gram-negative bacteria, important in the serological classification of enteric bacilli. [(9)]

- Polymerase chain reaction
- DNA probe assay [3]

Treatment:

General Rx:

1. Admission of the patient
2. Good feeding
3. Paracetamol for fever
4. Metoclopramid for vomiting
5. Steroids 1st dose 3mg/kg followed by eight doses of 1mg/kg given every 6/hrs [3]

Steroids are indicated in cases of sever typhoid fever ie:

- delirium
- Stupor
- Coma
- Septic shock [3]

Specific treatment:

1. Ciprofloxacin 750mg BID
2. Ofloxacin 300mg BID
3. Ceftriaxon 2-4 g /day or 90-100mg /kg/day for 10-14 days
4. Cefotaxim 4-6gr/day for 10-14 days
5. Azithromycin 1g p/o daily for 5 days
6. Cefixim 400mg p/o BID for 5 days [3]
7. Chloramphinicol 1g i/v QID
8. Amoxicillin 1g QID
9. Ampicillin 2g QID
10. Cotrimoxazol 960 mg 2 Tab BID [2]

There are some resistances against last four drugs (Table 11)

Table 11 Antibiotic Therapy for Enteric Fever in Adults

Indication	Agent	Dosage (Route)	Duration, Days
Empirical Treatment			
	Ceftriaxone[a]	1–2 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
Fully Susceptible			
	Ciprofloxacin[b] (first line)	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Amoxicillin (second line)	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO or IV)	14–21
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	14
Multidrug-Resistant			
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Ceftriaxone	2–3 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)[c]	5
Nalidixic Acid–Resistant			
	Ceftriaxone	1–2 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
	High-dose ciprofloxacin	750 mg bid (PO) or 400 mg q8h (IV)	10–14

[a]Or another third-generation cephalosporin [e.g., cefotaxime, 2 g q8h (IV), or cefixime, 400 mg bid (PO)]. [b]Or ofloxacin, 400 mg bid (PO) for 2–5 days.
[c]Or 1 g on day 1 followed by 500 mg/d PO for 6 days. [(3)]

Prevention:

1. Disinfection of stool & vomits
2. Environmental sanitation
3. Treatment of cases &carries with Ciprofloxacin
4. Cholcystectomy & Norfloxacin for carriers (6)
5. Immunization: Vaccine for typhoid is available
6. Health education

Prognosis:

1. Mortality rate of typhoid fever is about 2%
2. Elderly or debilitated person has poor prognosis[5]
3. Relapses is in upto 15% (7)

[5] 13-17 millions cases resulting in 600000 deaths per year
Children <1 year are most susceptible to sever disease (16th Edition of Harrison's)

Acute gastroenteritis (AGE)

Definition:

AGE is the passage of 3 or more watery stool in 24 hours for less then 2 weeks.

Etiology:

1. Viruses:
   - Rota virus (RNA)
   - Norwalk virus (RNA)
   - Norwalk like virus (RNA)
   - Cytomegalovirus (DNA)
   - Astrovirus (RNA)
   - Adenovirus (enteric) DNA [3]
2. Chlamydia:
   - Chlamydia psittaci
   - Chlamydia pneumonia
3. Bacteria:

a. Toxin mediated:
   - Staphylococcus aureus
   - Clostridium perfringens
   - Clostridium botulinum
   - Enterotoxigenic Esch. coli
   - Bacillus cereus [7]

b. Direct invasion:
   - Salmonella
   - Campylobacter jejune

- Entero invasive Esch. coli
- Bacillus anthracis
- Listeria monocytogens
- Aeromonase
- Pseudomonas
- Neiseria gonorrhea
- Vibrio paraheamolytica [7]
- Enteropathogenic Esch. coli [6]

4. Protozoa:
    - Giardia lamblia
    - Cryptosporidium
    - Cyclospora [7]
5. Fungi

Epidemiology:

1. Prevalence/Incidence:
    - Commonest disease
    - Epidemic
    - Endemic
    - Sporadic [3]
2. Geographical variation:
    - Worldwide
    - Viral diarrhoea is similar in developing &developed countries.
    - Bacterial diarrhoea is more common in poor hygiene
3. Age group: Any age but common in children
4. Seasonal variation:
    - Viral AGE is common in winter
    - But bacterial AGE is common in summer [3]
5. Route of transmission: Faeco-oral disease
6. Reservoir of infection:

- Viral diarrhoea: Humans
- Bacterial diarrhoea: Human & animal eg campylobacter Esch .coli salmonella

7. Incubation periods:
   - Viral 2-4 days
   - Bacterial 1-7 days [3]
8. Infectivity periods:

Pathogenesis /pathology:

1. Ingestion of micro organism in food
2. Invasion of different part of intestine by different microorganism
3. May induce one or more than one of the following mechanism:
   - Fluid secretion through activation of the enteric nervous system
   - Malabsorption of carbohydrate & fat because of villi broadening and micro villi shortening
   - Toxic may activate adenylate cyclase
   - Accumulation of water & electrolytes in intestinal lumen
5. Water & electrolytes loss (watery diarrhea) [3]

Clinical feature:

Symptoms:

1. Acute onset
2. Watery diarrhea
3. Vomiting
4. Nausea
5. Abdominal cramp
6. Fever
7. Headache
8. Chills
9. Myalgia
10. Anorexia [3]

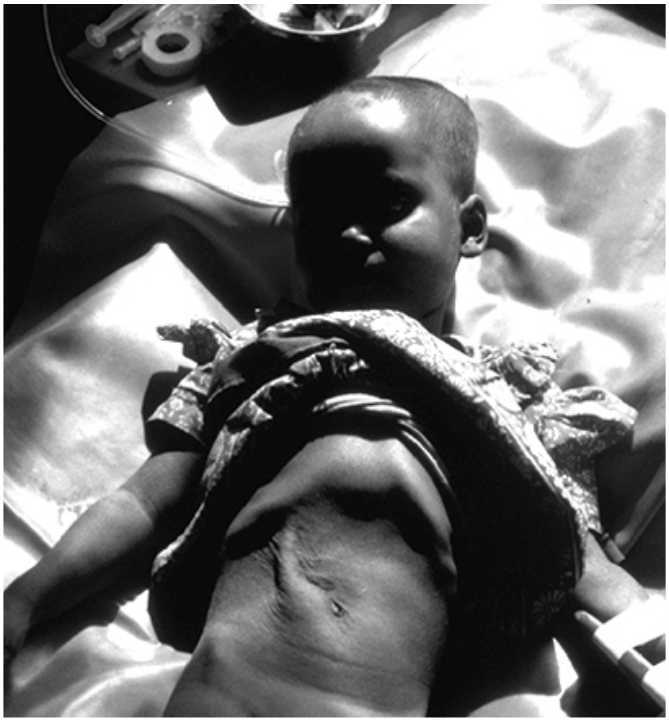
Signs: The signs of dehydration (Fig 33) are summarized in table 12

Table 12 Categorization of dehydration and fluid deficit based on clinical findings

Feature	No or mild dehydration	Moderate or some dehydration	Severe dehydration
Elasticity of subcutaneous tissues as determined by skin pinch*	Normal	Pinch retracts slowly	Tissues remain tented and retract very slowly
Eyes	Normal	Sunken	Dramatically sunken
Respiratory rate and character	Normal	Tachypnoeic	Tachypnoeic, deep, laboured
Heart rate	Normal	Tachycardic	Tachycardic
Radial-pulse character	Normal	Normal	Feeble or non-detectable
Mentation	Alert	Restless or lethargic	Apprehensive, lethargic, stuporous, or comatose
Thirst	Present	Present	Marked
Urine flow	Normal	Scant and dark	Scant or absent
Serum specific gravityâ	<1.027	1.028â “1.034	>1.034
Approximate fluid deficit, mg/kg of body weight	<50	51â “90	> 90
Preferred method of fluid replacement	Oral rehydration therapy	Oral or intravenous, depending on presence of vomiting and rate of continued stool loss	Intravenous

* Sign may be difficulty to distinguish from increased skin elasticity in children with malnutrition and the elderly.

â Patients with malnutrition may have a lower baseline specific gravity; thus the values listed may not be applicable to these patients. (8)



(Fig. 33) Severe dehydration as fluid infusion is begun. In this picture the sunken eyes and lassitude of severe dehydration can be appreciated, as can the abdominal skin tenting following the assertive pinching of the abdominal subcutaneous tissues. [9]

Complication:

1. Severe dehydration & shock
2. Acidosis due to bicarbonate loss in stool
3. Acute renal failure
4. Paralytic ileus

Investigation:

1. Stool exam:
   - Pus cells
   - Protozoa

- Other microorganism by specific methods
- RBC

2. Blood examination:
   - Leukocytes count may be high in bacterial AGE
   - Potassium for hypokalemia
   - Ph for acidosis
3. Stool culture

Treatment:

General Rx:

1. Admission
2. Rehydration

Oral Rehydration Salt (ORS) for mild dehydration & moderate dehydration without vomiting

Ringer lactate (i/v) for moderate dehydration with vomiting or sever dehydration

a. Moderate dehydration (100ml/kg) in 24hrs rehydration:
   - 1st dose 50 % in 4hrs
   - 2nd dose 50% in 20hrs

b. Sever dehydration (100ml/kg):

   If >1year in 3hrs rehydration
   - 30 % in 30 minutes
   - 70 % in 2.5 hrs

   If <1year then in 6hrs rehydration
   - 1st dose 30 % in 1 hr
   - 2nd 70 % in 5 hrs

NB: Sign of over hydration:
   - Respiratory rate increases
   - Pulse rate increases
   - Jugular vein become engorged
   - Increasing edema (puffy eye lids)

3. Paracetamol for fever

4. Metoclopramid for vomiting
5. Vit A:
   - <6 months 50000iu
   - 6 months to 1 year 100000iu
   - >1 year 200000 iu
6. Good feeding
7. Potassium for malnourished patient 0.5 ml/kg
8. Dextrose 50% for malnourished patient 1ml/kg

Specific Rx:

1. Cotrimoxazol p/o
2. Ampicillin i/v
3. Nigram p/o
4. Ciprofloxacin p/o or i/v
5. Cefotaxim i/v
6. Metronidazol for Giardiasis

Prevention:

1. Disinfection of patient stool & vomits
2. Environmental sanitation
3. Health education
4. 6 Fs are important in controlling the disease
   - Fly
   - Fluid
   - Fruit
   - Fingers
   - Faces
   - Food

Prognosis:

1. There are 100million cases of acute diarrhoea per year
2. Have two million deaths annually [3]

Shigellosis (Bacillary dysentery)

Definition:

Shigellosis is an acute bacterial colitis due to shigella genesis a clinical syndrome of fever, intestinal cramps, and frequent passage of small, bloody, mucopurulent stools. (Bacillary dysentery)[1] (3)
Dysentery: Diarrhea with visible blood

Etiology:

1. The causative agent: Shigella is the cause of disease
2. The characteristics of agent:
   - Gram negative bacilli
   - Small size
   - Non motile
   - Aerobic
   - Non capsulated
   - Non spore forming (3)
   - Has 4 sp:
     a. Shigella dysenteria
     b. Shigella Flexner
     c. Shigella sonnies
     d. Shigella boydii

[1] The discovery of *Shigella* as the etiologic agent of dysentery—a clinical syndrome of fever, intestinal cramps, and frequent passage of small, bloody, mucopurulent stools—is attributed to the Japanese microbiologist Kiyoshi Shiga, who isolated the Shiga bacillus (now known as *Shigella dysenteriae* type 1) from patients' stools in 1897 during a large and devastating dysenteryepidemic. *Shigella* cannot be distinguished from *Escherichia coli* by DNA hybridization and remains a separate species only on historical and clinical grounds. (3)

Epidemiology:

1. Prevalence/Incidence:
   - Potential epidemic
   - Has sporadic cases
   - 200 million clinically cases
   - 500000-1,1million deaths annually [3]
2. Geographical variation:
   - Worldwide
   - Common in developing countries
3. Age group: Common in <5 year children
4. Seasonal variation: Common in spring & summer [3]
5. Route of transmission: Faeco-oral disease
6. Reservoir of infection: Human
7. Incubation period: 2days [2] [6]
8. Other: Common in poor environmental sanitation & sever crowding.

Pathogenesis & pathology:

1. Ingestion of bacteria
2. Colonic mucosa attachment
3. Endocytosis by epithelium
4. Intracellular proliferation
5. Cellular death
6. Ulceration and dysentery (blood in diarrhea)
7. Endotoxin in circulation with bacteria [3]

Clinical feature:

1. Acute onset
2. Watery diarrhea initially
3. Bloody diarrhea
4. Malaise

---

[2] 1-4 days [3]

5. Nausea
6. Vomiting
7. Fever
8. Anorexia
9. Abdominal cramps
10. Tenesmus (painful straining with stool) [3]
11. Faecal urgency [6]

Complications:

1. Hemolytic uremic syndrome
2. Encephalopathy
3. Reactive arthritis
4. Reiter's syndrome
5. Pneumonia
6. Meningitis
7. Vaginitis
8. Kertoconjectivitis (rare) [3]
9. Colonic perforation
10. Septicemia
11. Toxic mega colon [6 & 7]

Investigation:

1. Stool exam: Pus cells & RBCs
2. Blood exam:
    - Leukocytosis
    - Neutrophilia
    - Anemia
    - Acidosis
3. Culture of stool
4. Serologic test
5. Endoscopy [3]

Treatment:

General Rx:

1. Admission (sever cases)
2. Rehydration
3. Buscopan for pain
4. Metoclopramid for vomiting
5. Good feeding

Specific Rx:

1. Cotrimoxazol
2. Ampicillin
3. Nigram
4. Ciprofloxacin
5. Azethromycin
6. Ceftriaxon
7. Cefotaxim [3]

Prevention:

1. Isolation
2. Disinfection of stool and vomits
3. Treatment to remove the disease
4. Environmental sanitation

Prognosis:

The prognosis is good, with rare cases not responding to antibiotics or experiencing spontaneous resolution of symptoms.[4]

Cholera

Definition:

Cholera is an acute diarrheal disease that causes severe dehydration in hours [3]

Etiology:

1. The causative agent: *Vibrio cholera*
2. The characteristics of agent:
   - Gram negative rod
   - Comma shaped (,,,,,,,,,,,)
   - Facultative anaerobic
   - Highly motile (flagellated) [3]

Epidemiology:

1. Prevalence/Incidence:
   - Pandemic
   - Epidemic
   - Also endemic
   - Has sporadic cases
2. Geographical variation: Rare in the US until 1991.
3. Age group: Affect adult and children equally
4. Seasonal variation: Common in summer & fall in endemic area
5. Reservoir of infection: Human
   Source is water & food
6. Route of transmission: Faeco oral route
7. Incubation period: 24-48 hrs [3]

8. Infectivity period: Infectious during clinical feature & carrier is infectious for long time.

Pathology:

1. Contaminated food & water ingestion
2. Colonizing small intestine
3. Adhesion to intestinal epithelium with pili
4. Production of exotoxin
5. Toxin binds to toxin receptor (ganglioside)
6. Toxin activate adenylate cyclase
7. High level of cyclic AMP
8. Cyclic AMP inhibits sodium absorption
9. Cyclic AMP activate chorine secretion
10. Accumulation of sodium chloride
11. Water moves passively to lumen
12. Watery diarrhea [3]

Clinical features:

a. Evacuation phase:

1. Abrupt onset
2. Profuse painless watery diarrhea
3. Vomiting
4. Rice water stool: [6]
   - Nonbilious appearance
   - Gray color
   - Slightly cloudy
   - With spots (flecks) or mucus
   - No blood
   - Inoffensive odor [3]

b. Collapse phase:

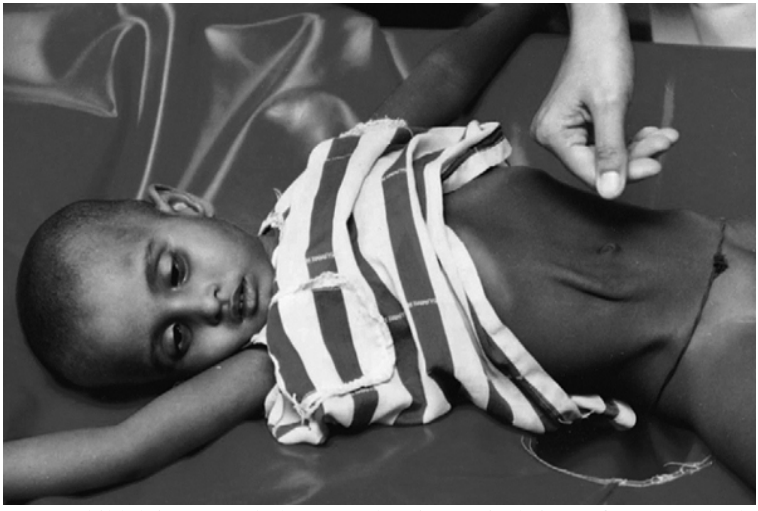
1. Feature of shock:
   - Cold clammy skin
   - Tachycardia

- Hypotension
- Peripheral cyanosis

2. Dehydration: Sunken eyes (Fig 34)
3. Hollow cheeks & decreased urine out put
4. Muscles cramps
5. Apathy
6. Convulsion due to hypoglycemia
7. Aspiration of vomit

c. Recovery phase after treatment

In 1-3 days return to normal



(Fig. 34) A child, lying on a cholera cot, showing typical signs of severe dehydration from cholera. The patient has sunken eyes, lethargic appearance, and poor skin turgor, but within 2 hr was sitting up, alert, and eating normally. [5]

Cholera Sicca; presents with massive collection of fluid & electrolytes into dilated intestinal loops. Without diarrhea & vomiting and mortality rate is high. [6]

Complications:

1. Acute renal failure
2. Metabolic acidosis

In vestigation:

1. Blood:
   - Hematocrit: May be high due to dehydration
   - Mild leukocytosis
   - Neutrophilia
2. Serum:
   - Increased BUN
   - Increase Creatinine
   - Normal sodium
   - Normal chlorine
   - Decreased PH due to bicarbonate loss
   - Decreased HCO3
3. Stool exam:
   - Direct exam is nil
   - Dark field microscope is positive [3]
4. Serologic test: Smart test with filtered stool
5. Stool culture

Treatment:

General Rx:

1. Admission
2. Rehydration with Ringer lactates
3. K for hypokalemia
4. HCO3 for acidosis
5. Metoclopramid for vomiting
6. Soft diet
7. Paracetamol for fever

Specific Rx:

1. Doxycyclin: 300mg single dose or tetracycline 2gr single dose
2. Ciprofloxacin 500 mg Bid

3. Erythrocin 40mg /kg body weight (good choice for children)
4. Azethromycin [7] (Table 13)

Table 13 Options for antimicrobial therapy of patients with cholera [8]

Drug	Adults	Children
Azithromycin	Not evaluated in controlled trials; 1 g as a single dose likely to be effective	20 mg/kg body weight as a single dose; maximum dose 1 g
Ciprofloxacin	1 g as a single dose	Not evaluated; 20 mg/kg body weight as a single dose (maximum 1 g) likely to be effective and safe
Doxycycline	300 mg as a single dose	Not evaluated; 6 mg/kg body weight as a single dose likely to be effective
Erythromycin	500 mg four times daily for 3 days	12.5 mg/kg body weight four times daily for 3 days; maximum individual dose 500 mg
Furazolidone	100 mg four times daily for 4 days	1.25 mg/kg body weight per dose; four doses daily for 3 days; maximum individual dose 100 mg
Tetracycline	1 g as a single dose	12.5 mg/kg body weight four times daily for 3 days; maximum individual dose 500 mg
Cotrimoxazole	320 mg trimethoprim/1600 mg of sulfamethoxazole twice daily for 3 days	4 mg trimethoprim/20 mg of sulfamethoxazole/kg body weight twice daily for 3 days; maximum dose same as adult

Prevention:

1. Notification
2. Isolation
3. Disinfection
4. Environmental sanitation
5. Treatment
6. Health education
7. Immunization with vaccine

Prognosis:

In massive diarrhoea (15L/day) death result from profound hypovolemia [7]

Brucellosis

Definition:

Brucellosis is a bacterial zoonosis transmitted directly or indirectly to human from infected animal & commonly presents as an acute febrile illness [3]

Etiology:

1. The causative agent: *Brucella*
2. The characteristics of agent:
   - Small Gram negative rods (coccobacilli)
   - Unencapsulated
   - Non-sporforming
   - Aerobic [3]
   - Has 8 strains with specific host:
     a. *Brucella melitensis:* Sheep, goats & camels
     b. *Brucella abortus:* Cattle & buffalo
     c. *Brucella suis:* Swine
     d. *Brucella canis:* Dogs
     e. *Brucella ovis:* Birds & sheep
     f. *Brucella neotomae:* Rodents
     g. *Brucella cetaceae:* Marine mammals
     h. *Brucella pinnipediae:* Marine mammals [3]

Epidemiology:

1. Prevalence/Incidence:
   - Endemic
   - Sporadic

2. Geographical variation:
   - B. Abortus: Worldwide [3]
   - B. Melitensis : Mediterranean region
   - B. Suis: Fareast & USA [6]
   - Other types rare
3. Age group: Any age
4. Seasonal variation: All season
5. Reservoir of infection: Animal and human
6. Route of transmission: Feco oral rout & inoculation
7. Incubation period: One week to several months [3]

Pathogenesis:

1. Entry to the body
2. Phagocytosis
3. Lymph node infiltration
4. General septicemia [3]

Clinical feature:

Symptoms:

1. Fever [1]
2. Chills
3. Rigor
4. Sweating at night (91%)
5. Aches
6. Low back pain

---

[1] History:
1. Animal contact (74%)
2. Ingestion of raw milk (71%)
3. Ingestion of raw liver (29%)
4. Infected person contact (36%)

Symptoms:
1. Lack of energy (96%)
2. Fever (93%) (Harrison's Previous editions)

7. Dry cough
8. Sore throat
9. Anorexia
10. Headache
11. Myalgia
12. Arthralgia
13. Fatigue
14. Apathy
15. Abdominal pain
16. Constipation
17. Diarrhea
18. Vomiting
19. Testicular pain [3 & 7]

Signs:

1. Fever
2. Pallor
3. Lymphadenopathy
4. Splenomegaly
5. Hepatomegaly
6. Jaundice (1%)
7. Signs of pneumonia
8. Cardiac murmur (1%)
9. Signs of meningitis
10. Skin rashes (papules, macules) [3]

Complications:

Most common:

1. Spondylitis
2. Suppurative arthritis
3. Endocarditis
4. Meningoencephalitis

Less common:

5. Pneumonitis

6. Pleural effusion
7. Hepatitis
8. Cholecystitis [7]

Investigation:

1. TLC: leukopenia
2. DLC: lymphocytosis & neutropenia
3. ESR & C reactive protein elevated
4. Bilirubin may be elevated
5. Lever enzyme elevated
6. Culture of bacteria from:
   - Blood
   - CSF
   - Bone marrow
   - Joint fluid
   - Tissue aspirate
7. Serologic test:
   - TA for B. Abortus
   - TM for B. Melitensis
8. X-ray for affected joints [3]

Treatments:

General Rx:

1. Symptomatic treatment
2. Feeding
3. Good nursing

Specific treatment:

1. Rifampicin 600mg -900mg/day
2. Doxycyclin 100mg bid
3. Streptomycin 1gr OD
4. Gentamicin 6mg/kg /bw/d
5. Cotrimoxazol 960mg bid
6. Ciprofloxacin 500mg bid

7. Ofloxacin 400mg bid
8. Ceftriaxon [3]

Triple therapy:

- Aminoglycoside
- Tetracycline
- Rifampicin [3]

Prevention:

1. Careful attention for hygiene [6]
2. Pasteurization of milk
3. Immunization with vaccine
4. Treatment of infected person and animals [3]

Prognosis:

1. Has 30% relapse
2. Less than 1% mortality
3. Recovery is slow [3]

Acute bacterial meningitis

Definition:

The bacterial meningitis is an acute purulent infection within the subarachenoid space & may associate with a CNS inflammation (meningoencephalitis) [3]

Etiology:

1. Streptococcus pneumonia
2. Neisseria meningitides
3. Haemophilus influenza
4. Listeria monocytogens
5. Gram negative bacilli
6. Group B streptococci
7. Staphylococcus aureus [3]

Epidemiology:

1. Prevalence/Incidence: Potential epidemic disease with sporadic cases [7]
2. Geographical variation: Worldwide [8]
3. Age group:
   - Meningococcal & pneumococcal meningitis is common in 18-50years.
   - Pneumococcal & listeria meningitis is common over 50years. [7]
4. Seasonal variation: Dry and hot weather
5. Route of transmission: Droplets infection
6. Reservoir of infection: Human
7. Incubation period: 2- 4 days (for meningococcus) [8]
8. Infectivity period: Has carrier [8]

Pathogenesis:

1. Colonization of the nasopharynx
2. Bacteria are transported across epithelial cells
3. Entry to the blood steam
4. Infect choroids plexus epithelial cells
5. Entry of bacteria to CSF
6. Multiply bacteria in CSF
7. Inflammation of meninges [3]
8. Disseminated intravascular coagulation (DIC) may cause ecchymotic skin lesion [7]

Clinical features:

Symptoms:

1. Acute onset in hours or sub acute in several days
2. Fever
3. Headache
4. Nuchal (neck) rigidity
5. Chills
6. Lethargy
7. Coma
8. Nausea
9. Vomiting
10. Photophobia
11. Convulsion [3]
12. Confusion
13. Delirium [7]
14. Constipation

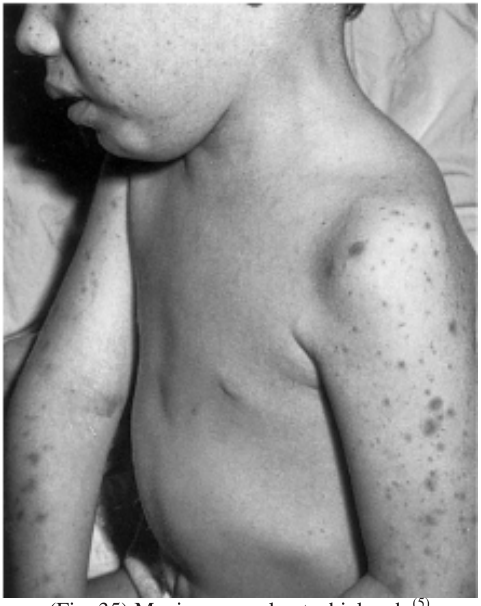
Signs:

1. Fever
2. Neck rigidity
3. Kernig sign
4. Brudzinski sign [3]

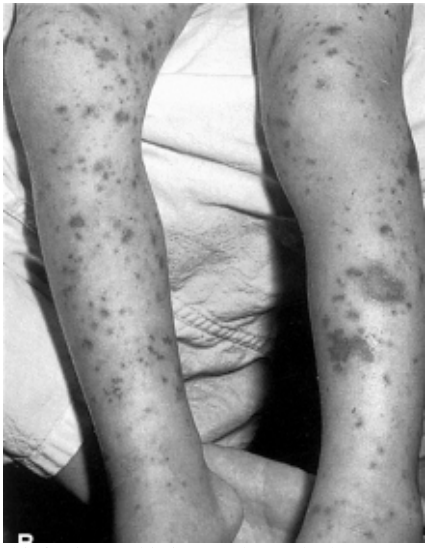
5. Mouth sign
6. Petechial rash (Fig. 35 & 36)

Kernig sign is a pain in the hamstrings upon extension of the knee with the hip at 90 degree flexion. [7]

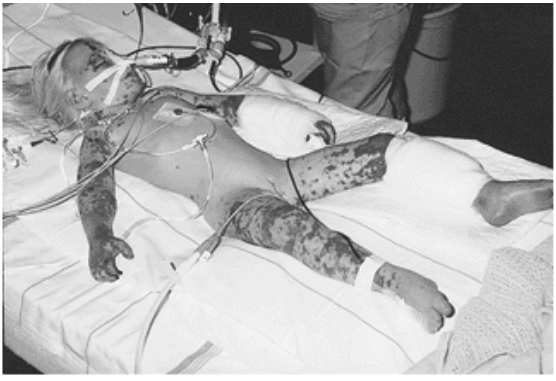
Brudzinski sign is the flexsion of knee in the response of flexsion of the neck. [7]



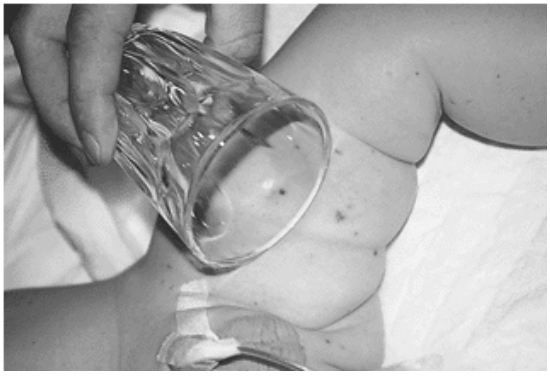
(Fig. 35) Meningococcal petechial rash [5]



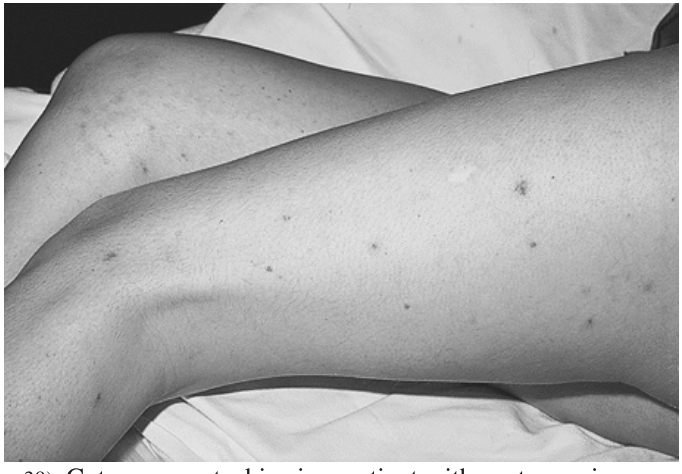
(Fig. 36) Meningococcal infections. This image shows the lower extremities of the patient [5]



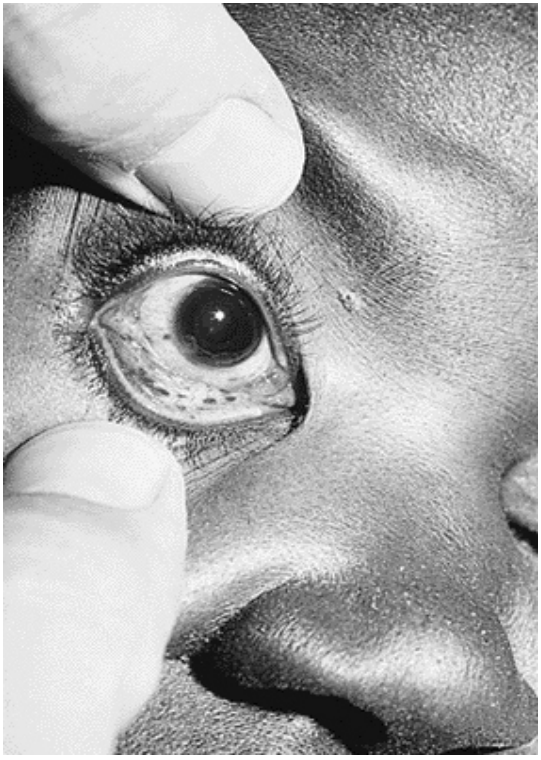
(Fig. 37) Massive skin haemorrhage on the extremities of a 4-year-old girl with fulminant meningococcal septicaemia. The infection was caused by Neisseria meningitidis group B. The left leg had to be amputated below the knee. She needed extensive skin transplantation and several fingers had to be amputated. [8]



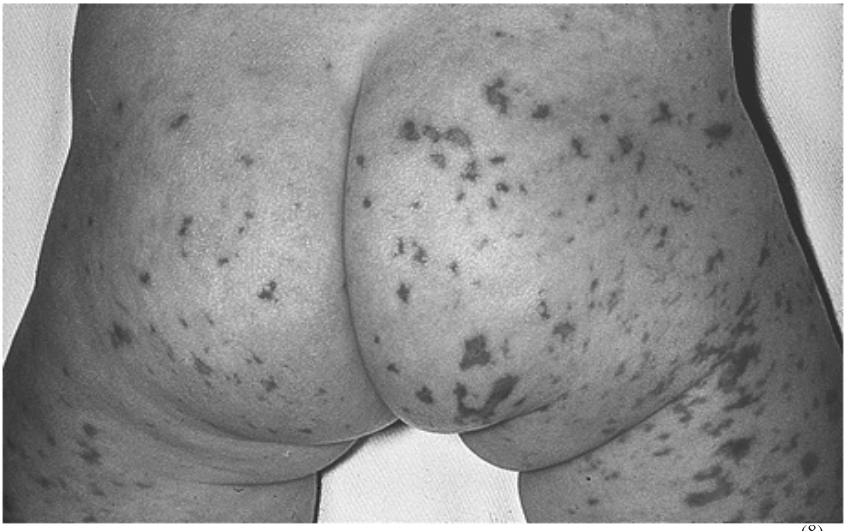
(Fig. 38) The â ےglass testâ ™ used to differentiate haemorrhagic skin lesions from viral or drug rash in an infant with meningococcal meningitis caused by Neisseria meningitidis group B. There was complete recovery after 5 days treatment with benzylpenicillin. [8]



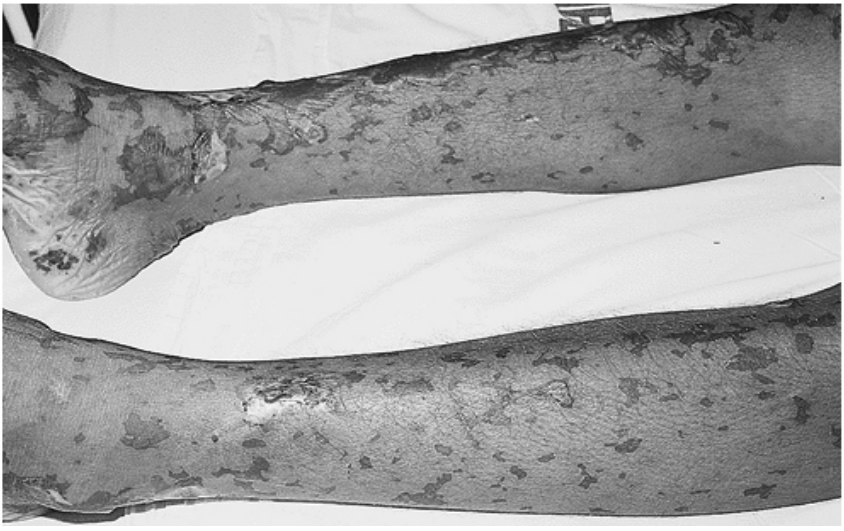
(Fig. 39) Cutaneous petechiae in a patient with acute meningococcal meningitis. (Copyright D.A. Warrell.) [8]



(Fig. 40) Conjunctival petechiae in a Nigerian boy with meningococcal meningitis. (Copyright D.A. Warrell.) [8]



(Fig. 41) The rash of meningococcal septicaemia in an English child. [8]



(Fig. 42) Healing vasculitic rash in a Brazilian boy with meningococcal meningitis and meningococcaemia. (Copyright D.A. Warrell.) [8]

Complications:

1. Seizures
2. Increased ICP
3. Cranial nerve lesion
   - Deafness
   - Blindness
   - Aphasia
4. Stroke
5. Cerebral or cerebellar herniation
6. Thrombosis of the dural venous sinuses.
7. Subdural effusions
8. Anemia may be due to hemolysis or bone marrow suppression.
9. DIC (Disseminated intravascular coagulation)
10. Shock and purpura [5]

Investigation:

1. TLC: Leukocytosis
2. DLC: Neutrophilia
3. Blood culture
4. Lumber puncture
5. CSF exam
6. CSF culture

Treatment:

General Rx:

1. Admission
2. Tube feeding
3. Paracetamol for fever
4. Phenobarbital for convulsion
5. Intravenous dextrose
6. Metoclopramid for vomiting

7. Steroid to reduce the complications

Specific Rx:

1. Ceftriaxon 2gr BID
2. Ceftriaxon 2gr BID plus Ampicillin 3gr QID
3. Cefotaxim 3gr QID
4. Cefotaxim 3gr QID plus Ampicillin 3gr QID
5. Benzyl penicillin 5 million QID to 24 million/day [(3)]
6. Chloramphinicol 1,5gr QID (Table 14)

Table 14 Initial antimicrobial Rx for purulent meningitis of unknown cause.

Population	**Common Microorganisms**	**Standard Therapy**
18–50 years	*Streptococcus pneumoniae, Neisseria meningitidis*	Vancomycin [1] **plus** cefotaxime or ceftriaxone [2]
Over 50 years	*S pneumoniae, N meningitidis, Listeria monocytogenes,* gram-negative bacilli	Vancomycin [1] **plus** ampicillin,[3] **plus** cefotaxime or ceftriaxone [2]
Impaired cellular immunity	*L monocytogenes,* gram-negative bacilli, *S pneumoniae*	Vancomycin [1] **plus** ampicillin[3] **plus** ceftazidime[4]
Postsurgical or posttraumatic	*Staphylococcus aureus, S pneumoniae,* gram-negative bacilli	Vancomycin [1] **plus** ceftazidime[4]

[1]The dose of vancomycin is 10–15 mg/kg/dose IV every 6 hours. [2]The usual dose of cefotaxime is 2 g IV every 6 hours and that of ceftriaxone is 2 g IV every 12 hours. If the organism is sensitive to penicillin, 3–4 million units IV every 4 hours is given. [3]The dose of ampicillin is usually 2 g IV every 4 hours. [4] Ceftazidime is given in a dose of 50–100 mg/kg IV every 8 hours. [(7)]

Prevention:

1. Vaccination against meningococcus & Haemophilus influenza are present.
2. Chemoprophylaxis:
   - Refampin 600mg p/o BID for 2 days
   - Ciprofloxacin 500mg p/o BID for 2 days
   - Ceftriaxon250mg i/m single dose [7]

Prognosis:

Mortality is:

- 3-7 % for H.influenza, N.meningitidus or group B streptococci.
- 15 % for Listeria monocytogens
- 20 % for Streptococcus pneumonia

Plague

Definition:

Plague is an acute febrile zoonotic disease caused by yersinia pestis infection; it is one of the lethal but curable bacterial diseases. [3]

Etiology:

1. The causative agent: *Yersinia pestis*
2. The characteristics of agent:
   - Gram negative
   - Coccobacillus
   - Microarophilic
   - Non motile
   - Non spore forming [3]
3. The victor of plague is flea

Epidemiology:

1. Prevalence/Incidence:
   - Pandemic
   - Epidemic (Black death)
   - Endemic in California, Arizona, Nevada & New Mexico [7]
   - Sporadic
   - There was an out break of plague in India in 1994 [3]
2. Geographical variation:
   - Worldwide [2]
   - During 1989-2003 total cases are 38359 human cases, reported to WHO

- The above cases are (80% from Africa, 14% from Asia & the rest from America) [3]

3. Age groups: Any age
4. Seasonal variation: Any season
5. Route of transmission:
   - Inoculation (Flea bite)
   - Droplets (Inter human)
   - Contact to animals [7]
6. Reservoir of infection:
   - Wild rodents
   - Rats
   - Human
   - Other animals [3]
7. Incubation period: 2-10 days [7]

Pathogenesis:

1. Inoculation
2. Phagocytosis
3. Drainage to lymph nodes
4. Sever inflammatory reaction of lymph node (Bubo)
5. Necrotic purulent lesion of lymph nodes & other organs
6. Hemorrhage
7. Septicemia
8. DIC (Disseminated intravascular coagulation)
9. Shock [3]
10. Septicemic type consist of sepsis without Bubo
11. Pneumonic plague:
    - After inhalation
    - Sever exudation in lungs [3]

Clinical features:

The clinical features are the rapid onset of fever with systemic manifestation (shock & multiple organs failure)

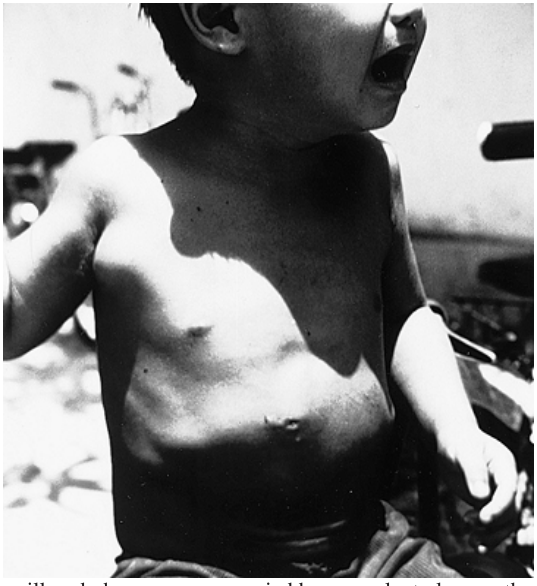
Three principal forms of plague are bubonic plague, septicemic plague and pneumonic plague.

Bubonic plague:

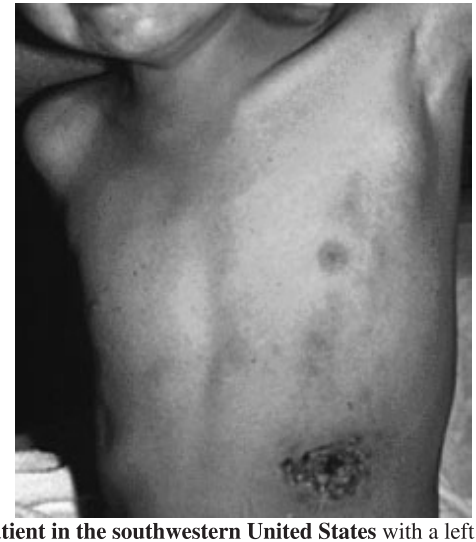
1. Commonest form
2. Sudden onset
3. Chills
4. Fever
5. Malaise
6. Myalgia
7. Arthralgia
8. Headache
9. Feeling of weakness [3 & 7]
10. Aching & swelling of affected lymph node (Fig. 43 & 44)
11. Dry skin [2]

Without treatment:

12. Tachycardia
13. Lethargy
14. Prostration
15. Agitation
16. Confusion
17. Convulsion
18. Delirium [3]



(Fig. 43) A right axillary bubo was accompanied by a purulent ulcer on the abdomen, which was the presumed site of the flea bite. [8]



(Fig. 44) **Plague patient in the southwestern United States** with a left axillary bubo and an unusual plague ulcer and eschar at the site of the infective flea bite. [3]

Septicemic plague:

The patient has gastrointestinal symptoms:

1. Nausea
2. Vomiting
3. Diarrhea
4. Abdominal pain
5. Manifestations of DIC:
   - Petechiae
   - Ecchymosis
   - Bleeding from wound
   - Gangrene of limbs [3]

Pneumonic plague:

1. Very sudden onset
2. Most frequently fatal
3. Chills
4. Fever
5. Headache
6. Myalgia
7. Weakness
8. Dizziness
9. Tachypnoea
10. Dyspnoea
11. Cough
12. Sputum production
13. Chest pain
14. Hemoptysis
15. Cyanosis[3]

Unusual form of plague:

1. Plague meningitis
2. Plague endophthalmitis
3. Plague pharyngitis [3]

Investigation:

1. Blood exam:
   - TLC: 10000-25000/m.l.
   - Neutrophilia
   - Lymphocytopenia
   - Thrombocytopenia
2. Direct exam of :
   - Sputum
   - Aspirate from Bubo
3. Culture of:
   - Sputum
   - Aspirate from Bubo
   - Blood

4. Chest X ray: Opacity [3]

Treatment:

General Rx:

1. Paracetamol for fever
2. Feeding
3. Hydration
4. Metoclopramid for vomiting

Specific Rx:

1. Streptomycin 2gr/day or
2. Gentamicin 3-5mg/kg.bw or
3. Tetracycline 2gr/day or
4. Chloramphinicol 50mg/kg.bw [3] (Table 15)

Table 15 Guidelines for the Treatment of Plague			
Drug	**Daily Dosage**	**Interval, h**	**Route(s) of Administration**
Streptomycin			
Adults	2 g	12	IM
Children	30 mg/kg	12	IM
Gentamicin			
Adults	3–5 mg/kg[a]	8	IM or IV
Children	6.0–7.5 mg/kg	8	IM or IV
Infants/neonates	7.5 mg/kg	8	IM or IV
Tetracycline			
Adults	2 g	6	PO or IV
Children ≥8 y	25–50 mg/kg	6	PO or IV
Doxycycline			
Adults	200 mg	12 or 24	PO or IV
Children ≥8 y	4.4 mg/kg	12 or 24	PO or IV
Chloramphenicol			
Adults	50 mg/kg[b]	6	PO or IV
Children ≥1 y	50 mg/kg[b]	6	PO or IV

[a]Dosage should be reduced to 3 mg/kg daily as soon as clinically indicated.
[b]For meningitis, up to 100 (mg/kg)/d initially. [(3)]

Prevention:

1. Notification
2. Isolation
3. Disinfection of sputum
4. Environmental sanitation (Tab Doldrin kills rodent & fleas)
5. Treatment and chemoprophylaxis:
   - Tetracycline
   - Doxycyclin
   - Cotrimoxazol
   - Ciprofloxacin [3]
6. Immunization: Vaccine is present but efficacy is not satispectory [7]
7. Health education

Prognosis:

1. Without treatment mortality is more than 50% in bubonic disease
2. And near all cases of septicemic & pneumonic diseases
3. Mortality for plague cases was 14% since 1950.
4. Now fatility rate is 10% [3]

Whooping cough (Pertussis)

Definition:

Whooping cough is an acute bacterial infection of respiratory tract, the inspiratory sound made at the end of an episode of paroxysmal coughing gives rise to the common name for the illness, "whooping cough."[1] (3)

Etiology:

1. The causative agent: *Bordetella pertusis*
2. The characteristics of agent:
   - A gram negative bacteria
   - Aerobic bacilli
   - Pleomorphic (3)

Epidemiology:

1. Prevalence/Incidence:
   - Epidemic disease, epidemic occur in 3-5 years
   - Sporadic disease
2. Geographical variation: Worldwide
3. Age group:
   - Childhood disease
   - But can affect people of all age
   - Has peak <1year

[1] The name *pertussis* means "violent cough," which aptly describes the most consistent and prominent feature of the illness. (3)

1. Seasonal variation: Has peak in the summer & autumn
2. Route of transmission: Droplets infection
3. Reservoir of infection: Human
4. Incubation period: 7-10 days [3]
5. Infectivity period: 7 days after exposure to 3 weeks after onset of symptoms [2]

Pathogenesis/Pathology:

1. Inhalation of bacteria
2. Attachment to ciliated epithelium
3. Multiplication of bacteria at the site of attachment
4. Production of toxins
5. Local mucosal damage
6. Impairment of host defense by toxin
7. Local cellular invasion without systemic dissemination [3]

Clinical features:

Has 3 phases (stages):

Catarrhal Phase:

1. Coryza
2. Sneezing
3. Lacrimation
4. Redness of eyes
5. Mild coughing
6. Low grade fever
7. Malaise [3]
8. Anorexia [7]

Paroxysmal Phase:

1. Series of short, sharp dry cough
2. End with deep inspiration (Whoop)
3. At the end may vomit
4. Older children & adult may be without cough
5. Fatigue

6. Weight loss [3]

During a spasm:

7. Neck vein distension
8. Bulging eyes
9. Tongue protrusion
10. Cyanosis [3]

Convalescent Phase:

1. Gradual resolution of cough
2. Less tenaciousness of sputum [3]

Complications:

1. Subconjectival hemorrhage
2. Abdominal and inguinal hernia
3. Pneumothorax
4. Facial and truncal petechia
5. Broncheictasis
6. Atelectasis
5. Bronchopneumonia
6. Cough syncope
7. Sever weight loss
8. Rib fracture
9. Carotid artery aneurysm
10. Encephalopathy [3]
11. Rectal prolapse
12. Convulsion
13. Ulceration of frenum [2]

Investigation:

1. Blood
    - TLC: Usually 1500-2500/mcL
    - DLC: Lymphocytosis (60-80%)
2. Direct exam of swab from posterior wall of nasopharynx
3. Culture in Bordet-Gengu agar [7]

4. Serologic test

Treatment:

General Rx:

1. Nutrition
2. Good nursing

Specific treatment:

1. Erythromycin 500mg qid for 7 days
2. Clarithromycin 500 mg bid for 7 days
3. Azithromycin 500mg/day 1st day than 250mg for 4 days
4. Cotrimoxazol 960 mg bid for 7 days [3] (Table 16)

Table 16 Antimicrobial Therapy for Pertussis [3]

Drug	Adult Daily Dose	Frequency	Duration (Days)	Comments
Erythromycin estolate	1–2 g	3 divided doses	7–14	Frequent gastrointestinal side effects
Clarithromycin	500 mg	2 divided doses	7	
Azithromycin	500 mg on day 1, 250 mg subsequently	1 daily dose	5	
Trimethoprim-sulfamethoxazole	160 mg of trimethoprim, 800 mg of sulfamethoxazole	2 divided doses	14	For patients allergic to macrolides; data on effectiveness limited

Prevention:

1. Isolation
2. Treatment and chemoprophylaxis with erythromycin [7]
3. Immunization with DPT
4. Health education

Prognosis:

1. There are 60 million cases of pertussis each year worldwide, resulting in >500,000 deaths.
2. Before vaccination was available, pertussis was the leading cause of death due to communicable disease among children <14 yr of age in the United States, with 10,000 deaths annually[5]

Diphtheria

Definition:

Diphtheria is a localized infection of mucous membrane or skin and may be associated with pseudomembrane at the site of infection; the toxin of diphtheria may cause myocarditis, polynueropathy, and other systemic toxic effects [3]

Etiology:

1. The causative agent: *Cornyebacteruim diphtheria*
2. The characteristics of agent:
   - Gram positive rod
   - Non motile
   - Aerobic
   - Non sporulating
   - Clib shaped
   - Arranged in cluster (Chines letters)
   - Parallel arrays (palisdes) [3]

Epidemiology:

1. Prevalence/Incidence:
   - Sporadic cases
   - Has epidemic
2. Geographical variation: Worldwide [6]
3. Age group: Any age
4. Seasonal variation: Any season and has peak in colder months
5. Route of transmission: Droplets infection & direct contact
6. Reservoir of infection: Human
7. Incubation period: 2-5 days [3]

Pathology/pathogenesis:

1. Respiratory epithelium invasion
2. Local inflammation
3. Liboration of exotoxin which cause:
    - Coagulation of cell debris with other secretion
    - Absorption to blood stream
    - And causes:

      Myocarditis

      Polynueropathy

      Focal necrosis of liver kidney etc [3]

Clinical features:

a. General:

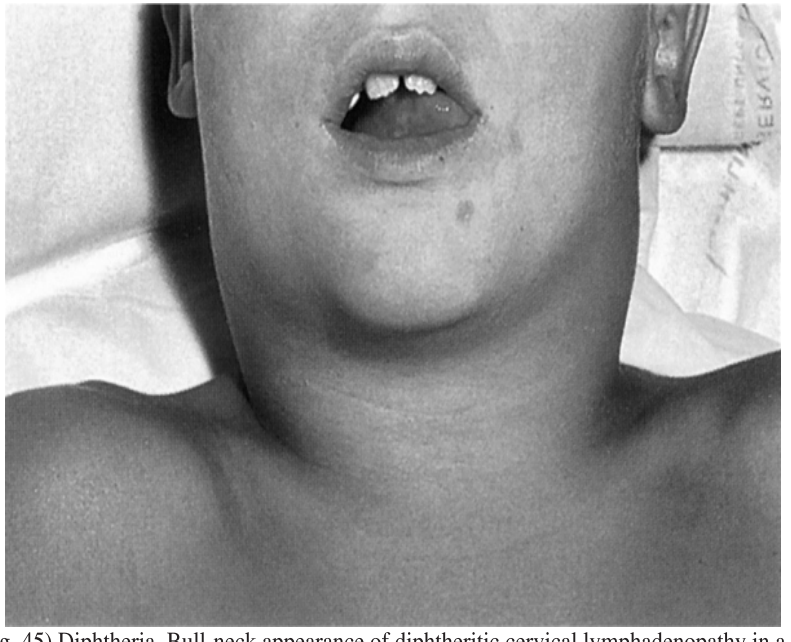
1. Insidious onset
2. Mild fever
3. Anorexia
4. Nausea
5. Sore throat
6. Dysphagia
7. Headache
8. Voice changes [3]

b. Local

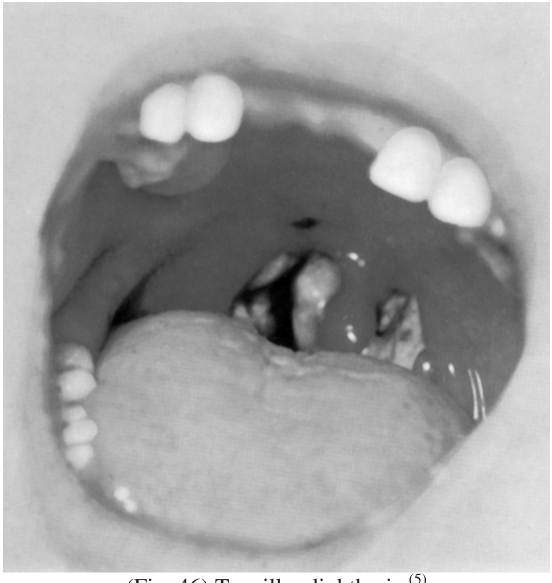
1. Bloody nasal discharge (nasal diphtheria)
2. Respiratory obstruction (nasopharyngeal type)
3. Dry coughs (laryngeal diphtheria)
4. Husky voice
5. Neck swelling (bull neck) (Fig. 45)
6. Pseudomembran:
    - Gray color (Fig. 46 & 47)
    - Wash leather

- Surrounded by red inflammatory area
- Close attached
- Removal causes bleeding

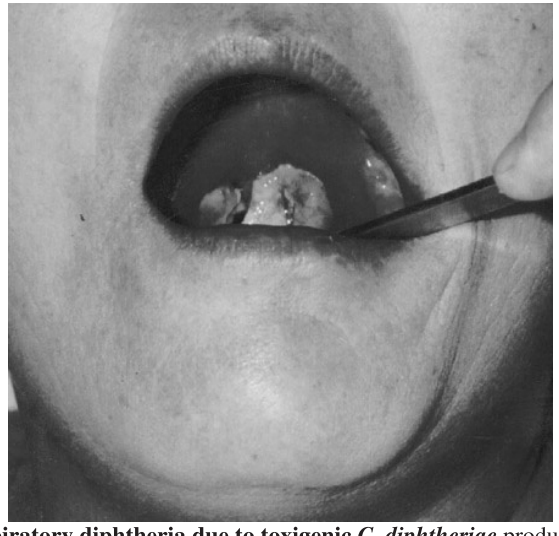
7. Cervical lymphadenopathy
8. Foul breath
9. Conjunctival infection
10. Skin & wound infection [3]



(Fig. 45) Diphtheria. Bull-neck appearance of diphtheritic cervical lymphadenopathy in a 13 yr old boy [5].



(Fig. 46) Tonsillar diphtheria [5]



(Fig. 47) **Respiratory diphtheria due to toxigenic *C. diphtheriae*** producing exudative phsaryngitis in a 47-year-old woman with neck edema and a pseudomembrane extending from the uvula to the pharyngeal wall. [3]

Complication:

1. Myocarditis
2. Heart block
3. Heart failure
4. Arrhythmias
5. Polynueropathy
6. Palate paralysis
7. Paralysis of accommodation
8. Pneumonia
9. Less common complications:
    - Renal failure
    - Encephalitis
    - Cerebral infarction
    - Endocarditis
    - Pulmonary embolism [3]

Investigation:

1. Direct exam of swab
2. Culture from swab [3]

Treatment:

General treatment:

1. Admission
2. Feeding
3. Paracetamol for fever
4. Antitoxin

Specific Rx:

1. Benzyl penicillin 5 million u I/V QID
2. Erythromycin 500mg P/O QID
3. Procaine Penicillin G 600000u I/M BID [3]

Prevention:

1. Notification of disease
2. Isolation of the patient
3. Disinfection of sputum and respiratory secretion
4. Treatment and chemoprophylaxis with erythromycin, benzathin penicillin
5. Immunization DPT [3]
6. Health education

Prognosis:

1. Before the use of antitoxin mortality was 30-55%
2. With anti toxin treatment the mortality is from 5-10 %
3. Mortality increase in:

- Bull neck diphtheria
- Myocarditis
- Alcoholics [3]

Anthrax

Definition:

Anthrax is an acute bacterial infection caused by Bacillus anthracis. [8] The name comes from the Greek word for "coal," a reference to the black eschar that eventually forms in the cutaneous form of anthrax.[1] [4]

Aetiology:

1. The causative agent: *Bacillus anthracis*
2. The characteristics of agent:
   - The bacterium is a gram-positive rod
   - It has a central to subterminal spores
   - Encapsulated[2]
   - Aerobic or facultatively anaerobic [4]
   - Large, non-motile bacillus [8]

Epidemiology:

1. Prevalence/Incidence: Has outbreaks of anthrax in humans [4]
   - From 1900 to 2005, at least 82 cases of inhalation anthrax were reported in detail in the worldwide medical literature, including 18 from the United States [4]

---

[1] Anthrax is primarily a disease of animals, but it has also been developed in past decades by some nations as a biowarfare weapon and was used by one or more unidentified persons as a bioterrorist weapon in 2001 in the United States. Historical names that reflect the zoonotic nature of most human anthrax infections include "woolsorter's disease" and "ragpicker's disease." [4]

[2] Virulent strains of B. anthracis possess two virulence factors: a capsule and a three-component protein exotoxin (anthrax toxin) that is made up of protective antigen (PA), oedema factor (EF), and lethal factor (LF). The capsule, which is composed of D-glutamic acid polypeptide, enhances virulence by making the organism resistant to phagocytosis. [8]

- Etimated 10,000 human infections with cutaneous anthrax occurred in Zimbabwe from 1979 to 1985 (4)

2. Geographical variation: Worldwide (4)
3. Age group: Any age
4. Seasonal variation: No seasonal variation
5. Route of Transmission:
   - Inhalation
   - Direct contact
   - Ingestion

In the United States, bioterrorism via anthrax in mailed letters caused 11 cases of cutaneous anthrax in addition to the 11 inhalational cases. (4)

6. Reservoir of infection:
   - Human
   - Animals[3]
7. Incubation Period: 2-14 days (7)

Pathogenesis

1. Spores of B. anthracis are entering subcutaneously
2. They germinate and multiply
3. The antiphagocytic capsule facilitates local spread
4. The oedema and lethal toxins impair leucocyte function[4]
5. They contribute to tissue necrosis, oedema, and relative absence of leucocytes in the skin lesion.
6. The bacilli spread to the draining lymph node

[3] Human infection with *B. anthracis* is usually linked to a zoonotic source such as goats, sheep, cattle, antelope, kudu, pigs, horses, zebu, and other animals. Animal-related products that can transmit the infection include meat, wool, hides, bones, and hair. Soil contaminated with spores that can persist for many years is also a source of infection. (Cec)

[4] The biological effects of EF include the formation of oedema characteristic of the disease. A mixture of EF and PA, known together as oedema toxin, also inhibits phagocytosis by polymorphonuclear leucocytes. The action of LF, believed to be a metalloproteinase, is less understood. (O)

7. Resulting in the typical findings of haemorrhagic, oedematous, and necrotic lymphadenitis.[5] (8)

Clinical Features:

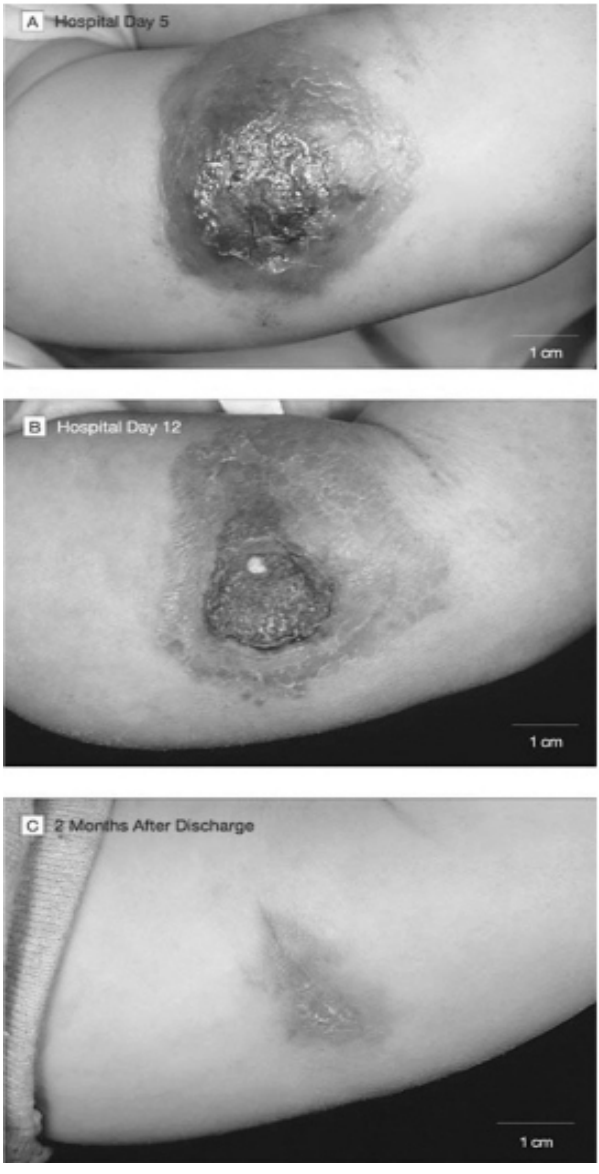
Cutaneous Anthrax

1. This occurs within 2 weeks after exposure to spores [6]
2. The initial lesion is an erythematous papule
3. Often on an exposed area of skin
4. That vesiculates
5. Then ulcerates
6. Undergoes necrosis
7. Ultimately progressing to a purple to black eschar
8. The eschar typically is painless; pain indicates secondary staphylococcal or streptococcal infection. The surrounding area is edematous and vesicular but not purulent
9. Regional adenopathy
10. Fever
11. Malaise
12. Headache
13. Nausea
14. Vomiting may be present
15. The infection is self-limited in most cases, but hematogenous spread with sepsis or meningitis may occur (7)

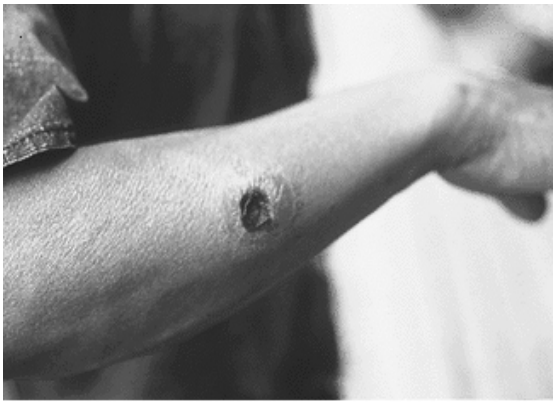
---

[5] Gastrointestinal anthrax follows ingestion of contaminated and undercooked meat. Multiplication of the bacilli in the oropharynx and the draining lymph nodes causes the oropharyngeal ulcer and neck swelling. When the organisms are deposited in the duodenum, ileum, or caecum, they cause mucosal inflammation and ulcers. Transport of the bacteria to the mesenteric lymph nodes results in the development of haemorrhagic adenitis and ascites. Inhalation anthrax follows deposition of spore-bearing particles of 1 to 5 μm into alveolar spaces. They are phagocytosed by alveolar macrophages and transported to the tracheobronchial and mediastinal lymph nodes, where they germinate. Production of toxins leads to haemorrhagic, oedematous, and necrotic lymphadenitis and mediastinitis.
In all primary forms of anthrax, especially inhalation anthrax, the bacilli can spread through the blood causing septicaemia and at times haemorrhagic meningitis. (8)

[6] There is no latency period for cutaneous disease. (7)



(Fig. 48) The lesion of cutaneous anthrax. [4]



(Fig. 49) Cutaneous anthrax lesion on the forearm on day 10 showing an ulcer with a depressed black eschar. (8)

Inhalational Anthrax:

1. Illness occurs in two stages:[7]
2. Initial stage: Nonspecific viral-like symptoms:
   - Fever
   - Malaise
   - Headache
   - Dyspnea
   - Cough
   - Congestion of the nose, throat, and larynx
   - Anterior chest pain is an early symptom of mediastinitis.
3. Fulminant stage[8] of infection occurs in which symptoms or signs of overpowering sepsis predominate.
4. Meningeal irritation:[9]
   - Delirium
   - Obtundation (7)

[7] Beginning on average 10 days after exposure, but may begin up to 6 weeks after exposure.
[8] Within hours to a few days, progression to the fulminant stage of infection occurs in which symptoms or signs of overwhelming sepsis predominate.
[9] Suggest an accompanying hemorrhagic meningitis.

Gastrointestinal Anthrax:

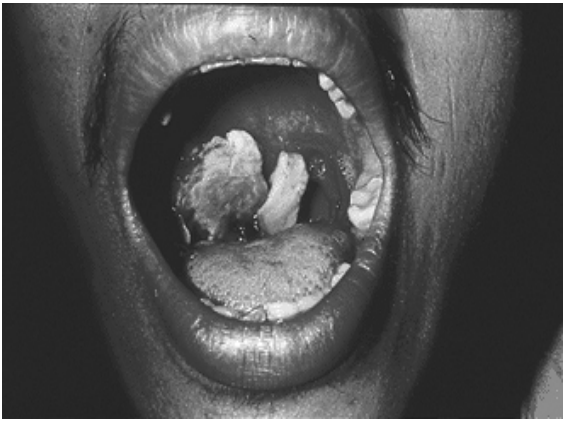
1. This form has not been reported in the United States.
2. Fever
3. Diffuse abdominal pain
4. Rebound abdominal tenderness
5. Vomiting
6. Constipation
7. Diarrhea[10]
8. The primary lesion is ulcerative, producing emesis that may be blood-tinged or coffee-grounds and stool that may be blood-tinged or melenic.
9. Bowel perforation can occur (7)

Oropharyngeal anthrax:

The oropharyngeal form of the disease is characterized by:

1. Local lymphadenopathy
2. Cervical edema (neck swelling)
3. Dysphagia
4. Upper respiratory tract obstruction (7)
5. Fever
6. Sore throat
7. Oropharyngeal ulcer (8)

[10] The above symptoms occur 2–5 days after ingestion of meat contaminated with anthrax spores.



(Fig. 50) Oropharyngeal anthrax on day 9 showing a pseudomembrane covering an ulcer. [8]

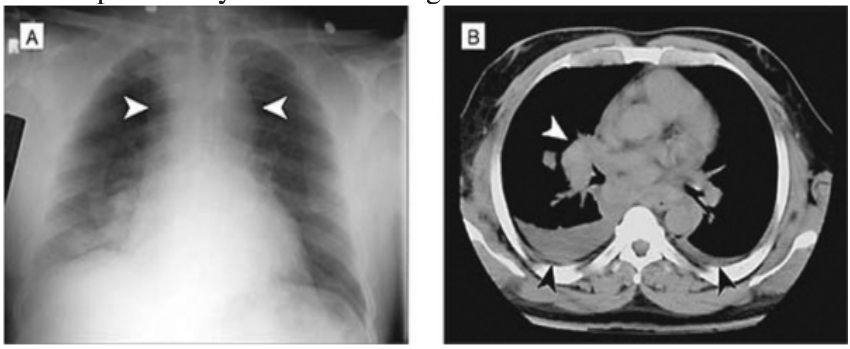
Meningeal anthrax:

1. Sudden onset of confusion
2. Loss of consciousness
3. Focal neurological signs
4. The disease is almost always fatal [8]

Investigations:

1. TLC: Initially may be normal or modestly elevated
2. DLC: Polymorphonuclear predominance
3. Pleural fluid from patients with inhalational anthrax is typically hemorrhagic with few WBC [7]
4. Cerebrospinal fluid from meningitis cases is also hemorrhagic. Gram stain of pleural fluid, cerebrospinal fluid, unspun blood, blood culture, or fluid from a cutaneous lesion may show the characteristic boxcar-shaped encapsulated rods in chains.
5. Cultures are invariably positive [7]
6. If anthrax is suspected on clinical or epidemiologic grounds, immunohistochemical tests (eg, to detect capsular antigen), polymerase chain reaction assays, and serologic tests (useful for documenting past cutaneous infection) [7]

7. Any suspected case of anthrax should be immediately reported to the CDC so that a complete investigation can be conducted.
8. The chest radiograph is the most sensitive test for inhalational disease, being abnormal (though the findings can be subtle) initially in every case of bioterrorism-associated disease. (7)
9. Mediastinal widening due to hemorrhagic lymphadenitis, a hallmark feature of the disease, has been present in 70% of the bioterrorism-related cases. (7)
10. Pleural effusions were present initially or occurred over the course of illness in all cases, and approximately three-fourths had pulmonary infiltrates or signs of consolidation. (7)



(Fig. 51) **Clinical features of anthrax. A,** A portable chest radiograph in a 56-year-old man with inhalational anthrax depicts a widened mediastinum (arrowheads), bilateral hilar fullness, right pleural effusion, and bilateral perihilar air space disease. **B,** A non–contrast-enhanced spiral computed tomography scan depicts an enlarged and hyperdense right hilar lymph node (white arrowhead), bilateral pleural effusions (black arrowheads), and edema of mediastinal fat. (4)

Treatment:

1. Ciprofloxacin is considered the drug of choice[11] (Table 33–2) for treatment and for prophylaxis following exposure to anthrax spores. (7)
2. Other fluoroquinolones with activity against gram-positive bacteria (eg, levofloxacin, moxifloxacin), are likely to be just as effective as ciprofloxacin. (7)
3. Doxycycline is an alternative first-line agent.
4. Combination therapy with at least one additional agent is recommended for inhalational or disseminated disease and in cutaneous infection involving the face, head, and neck[12] Anecdotally, four of the six survivors of the 2001 inhalational cases were treated with combinations that included both a fluoroquinolone and rifampin.
5. Single-drug therapy is recommended for prophylaxis following exposure to spores. (7)

[11] Strains of *B anthracis* (including the strain isolated in the bioterrorism cases) are susceptible in vitro to penicillin, amoxicillin, chloramphenicol, clindamycin, imipenem, doxycycline, ciprofloxacin (as well as other fluoroquinolones), macrolides, rifampin, and vancomycin. Susceptibility to cephalosporins is variable. *B anthracis* may express Beta - lactamases that confer resistance to cephalosporins and penicillins. For this reason, penicillin or amoxicillin is no longer recommended for use as a single agent in treatment of disseminated disease. Based on results of animal experiments and because of concern for engineered drug resistance in strains of *B anthracis* used in bioterrorism or weaponized, ciprofloxacin is considered the drug of choice. (7)

[12] or associated with extensive local edema or systemic signs of infection, eg, fever, tachycardia and elevated white blood cell count.

Table 17. Antimicrobial agents for treatment of anthrax or for prophylaxis against anthrax. [7]
First-line agents and recommended doses
Ciprofloxacin, 500 mg twice daily orally or 400 mg every 12 hours intravenously
Doxycycline, 100 mg every 12 hours orally or intravenously
Second-line agents and recommended doses
Amoxicillin, 500 mg three times daily orally
Penicillin G, 2–4 million U every 4 hours intravenously
Alternative agents with in vitro activity and suggested doses
Rifampin, 10 mg/kg/d orally or intravenously
Clindamycin, 450–600 mg every 8 hours orally or intravenously
Clarithromycin, 500 mg orally twice daily
Erythromycin, 500 mg every 6 hours intravenously
Vancomycin, 1 g every 12 hours intravenously
Imipenem, 500 mg every 6 hours intravenously

The required duration of therapy is poorly defined.[13]

Prevention:

1. Notification
2. Isolation
3. Disinfection
4. Prophylaxis: In 2001, the CDC offered one of two options for postal workers receiving prophylaxis for exposure to

[13] In naturally occurring disease, treatment for 7–10 days for cutaneous disease and for at least 2 weeks following clinical response for disseminated, inhalational, or gastrointestinal infection have been standard recommendations. Because of concern about relapse from latent spores acquired by inhalation of aerosol in bioterrorism-associated cases, the initial recommendation was treatment for 60 days.

contaminated mail: (1) antibiotics for 100 days (fearing that even with 60 days of treatment late relapses might occur) or (2) vaccination with an investigative agent (three doses administered over a 1-month period) in conjunction with 40 days of antibiotic administration to cover the time required for a protective antibody response to develop.

5. Immunization: There is also an FDA-approved vaccine for persons at high risk for exposure to anthrax spores. The vaccine is cell-free antigen prepared from an attenuated strain of *B anthracis.* Multiple injections over 18 months and an annual booster dose are required to achieve and maintain protection. Existing supplies have been reserved for vaccination of military personnel. [7]
6. Health education

Prognosis:

1. The prognosis in cutaneous infection is excellent.
2. Death is unlikely if the infection has remained localized, and lesions heal without complications in most cases. [7]
3. The reported mortality rate for gastrointestinal and inhalational infections is up to 85%. [7]
4. The experience with bioterrorism-associated inhalational cases in which six of eleven victims survived suggests a somewhat better outcome with modern supportive care and antibiotics provided that treatment is initiated before the patient has progressed to the fulminant stage of disease.
5. No cases of anthrax have occurred among the several thousand individuals receiving antimicrobial prophylaxis following exposure to spores. [7]

Tetanus

Definition

Tetanus is a neurologic disorder, characterized by increased muscle tone and spasms. [3]

Etiology:

1. The causative agent: *Clostridium tetani*
2. The characteristics of agent:
   - Anaerobic
   - Motile
   - Gram-positive rod
   - Forms an oval, colorless, terminal spore
   - Shape resembling a tennis racket or drumstick
   - Spores may survive for years in some environments and are resistant to various disinfectants and to boiling for 20 min. [3]

Epidemiology:

1. Incidence:
   - Tetanus occurs sporadically
   - In 2002 the *estimated* number of tetanus-related deaths in all age groups was 213,000, of which 180,000 (85%) were attributable to neonatal tetanus [3]
2. Geographical variation:
   - Worldwide
   - Common in areas where soil is cultivated, in rural areas
3. Age group:
   - Common in neonates
   - Other young children

4. Seasonal variation: Common in
   - Warm climates
   - During summer months, and among males.
5. Route of transmission: Contamination of wounds
6. Reservoir of infection: The organism is found worldwide in soil, in animal feces, and occasionally in human feces.
7. Incubation period: The median time of onset after injury is 7 days; 15% of cases occur within 3 days and 10% after 14 days. (3)

Pathogenesis:

1. Contamination of wounds with spores of *C. tetani*
2. Toxin production occurs only in wound[1]
3. Toxin released in the wound binds to peripheral motor neuron terminals
4. Enters the axon
5. Transport to the nerve-cell body in the brainstem and spinal cord
6. The toxin then migrates across the synapse to presynaptic terminals
7. Blocks release of the inhibitory neurotransmitters glycine and Gamma-aminobutyric acid (GABA) from vesicles
8. With diminished inhibition, the resting firing rate of the alfa motor neuron increases, producing rigidity (3)

Clinical features:

Generalized tetanus:

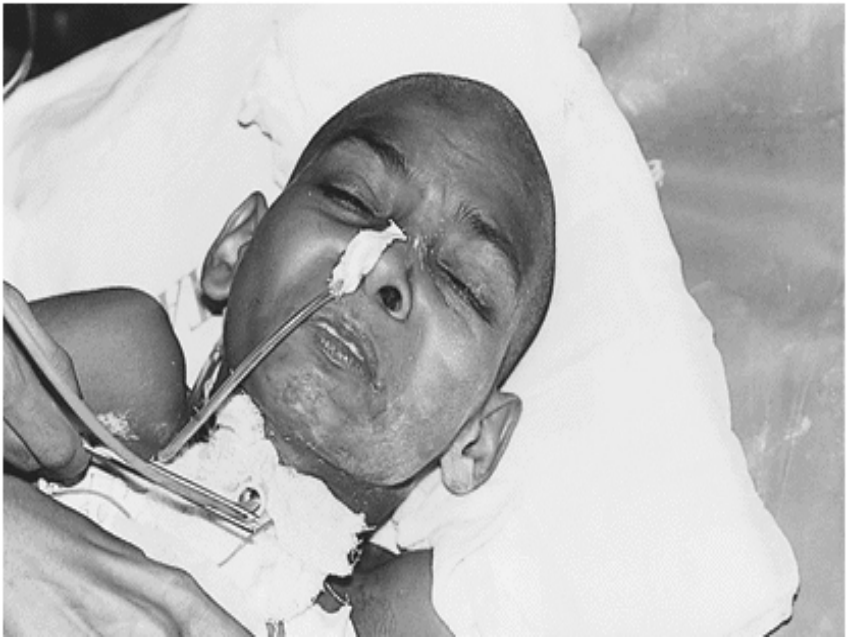
1. Most common form of the disease
2. Increase muscle tone
3. Generalized spasms

[1] Toxin production occurs only in wound with low oxidation-reduction potential, such as those with devitalized tissue, foreign bodies, or active infection.

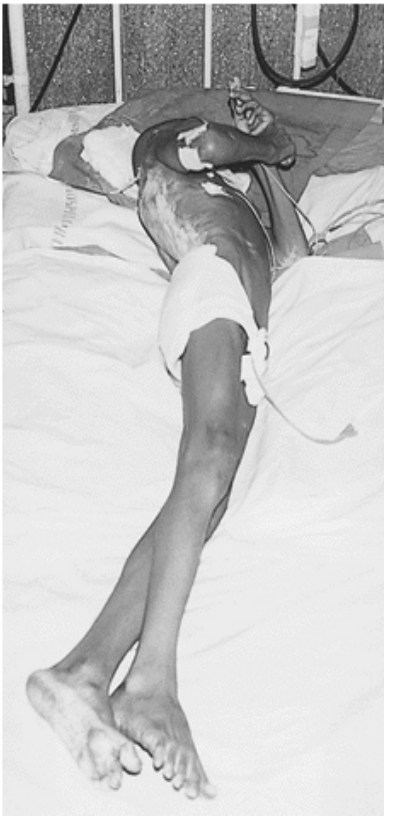
4. Typically, the patient first notices increased tone in the masseter muscles (trismus, or lockjaw).
5. Dysphagia
6. Stiffness
7. Pain in the neck, shoulder, and back muscles appears concurrently or soon thereafter
8. Rigid abdomen
9. Stiff proximal limb muscles[2]
10. Sustained contraction of the facial muscles results in a grimace or sneer (risus sardonicus) (Fig. 52)
11. Back muscles contraction produces an arched back (opisthotonos) (Fig. 53)
12. Cyanosis and threaten ventilation[3]
13. Apnea or laryngospasm
14. The severity of illness may be:
    - Mild (muscle rigidity and few or no spasms)
    - Moderate (trismus, dysphagia, rigidity, and spasms)
    - Severe (frequent explosive paroxysms)
15. The patient may be febrile
16. Deep tendon reflexes may be increased (3)

[2] The hands and feet are relatively spared. (3)

[3] These spasms occur repetitively and may be spontaneous or provoked by even the slightest stimulation. (3)



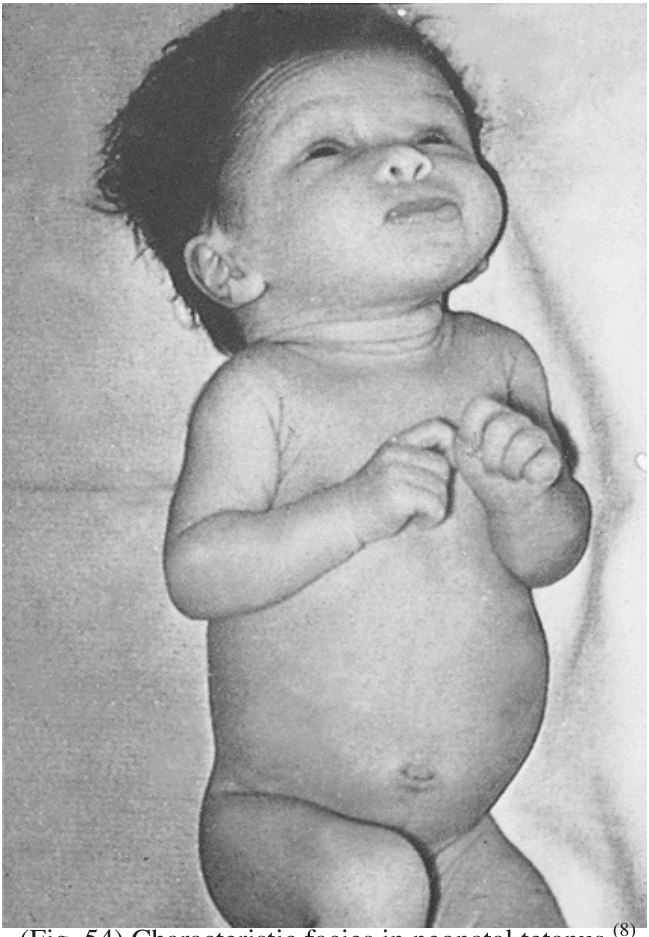
(Fig. 52) Facies in tetanus. (O)



(Fig. 53) Opisthotonos in severe tetanus during seizures. [8]

Neonatal tetanus:

1. Usually occurs as the generalized form (Fig. 54)
2. Usually fatal if left untreated
3. It develops in children born to inadequately immunized mothers
4. Frequently after unsterile treatment of the umbilical cord stump
5. Its onset generally comes during the first 2 weeks of life [3]



(Fig. 54) Characteristic facies in neonatal tetanus [8]

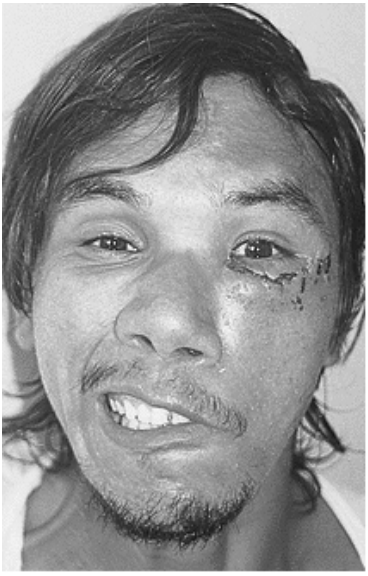
Local tetanus:

1. Uncommon form
2. Manifestations are restricted to muscles near the wound
3. The prognosis is excellent[3]

Cephalic tetanus:

1. Rare form of local tetanus

2. Follows head injury or ear infection
3. Involves one or more facial cranial nerves (Fig. 55)
4. The incubation period is a few days and mortality is high [3]



(Fig. 55) Brazilian patient with local tetanus confined to muscles innervated by the left VIIth cranial nerve and with trismus, showing the wound causing the infection. (By courtesy of Dr Pedro Pardal, Bel©m, Brazil.) [8]

Complications:

Autonomic dysfunction commonly complicates severe cases

1. Hypertension
2. Tachycardia
3. Dysrhythmia
4. Hyperpyrexia
5. Profuse sweating
6. Peripheral vasoconstriction
7. Periods of bradycardia and hypotension
8. Sudden cardiac arrest

9. Aspiration pneumonia (Other complications)
10. Fractures
11. Muscle rupture
12. Deep-vein thrombophlebitis
13. Pulmonary emboli
14. Decubitus ulcer
15. Rhabdomyolysis (3)

Investigations:

1. Wounds should be cultured in suspected cases
2. However, *C. tetani* can be isolated from wounds of patients without tetanus[4]
3. The leukocyte count may be elevated
4. Electromyograms may show continuous discharge of motor units
5. Nonspecific changes may be evident on the electrocardiogram
6. Muscle enzyme levels may be raised
7. Serum antitoxin levels (3)

Differential diagnosis:

1. The differential diagnosis includes conditions also producing trismus, such as:
   - Alveolar abscess
   - Strychnine poisoning
   - Dystonic drug reactions (e.g., phenothiazines and metoclopramide)
   - Hypocalcemic tetany
2. Meningitis/encephalitis
3. Rabies
4. Acute intraabdominal process (because of the rigid abdomen)[5] (3)

[4] frequently cannot be recovered from wounds of those with tetanus (3)

Treatment:

General Rx:

1. Patients should be admitted to a quiet room in an intensive care unit
2. Observation and cardiopulmonary monitoring can be maintained continuously but stimulation can be minimized.
3. Protection of the airway is vital
4. For control of muscles pasms:
   - Diazepam: The large doses (250 mg/d) may be required
   - Lorazepam, with a longer duration of action
   - Midazolam, with a short half-life
   - Barbiturates and chlorpromazine are considered second-line agents
5. Intubation or tracheostomy, with or without mechanical ventilation
6. Verapamil for treatment of cardiovascular instability [(3)]

Specific Rx:

1. Wounds should be explored, carefully cleansed, and thoroughly debrided
2. The use of penicillin (10–12 million units IV, given daily for 10 days)
3. Metronidazole (500 mg every 6 h or 1 g every 12 h)
4. Clindamycin and erythromycin are alternatives for the treatment of penicillin-allergic patients
5. Antitoxin is given to neutralize circulating toxin and unbound toxin in the wound
6. Human tetanus immune globulin (TIG) is the preparation of choice and should be given promptly[6] [(3)]

---

[5] Markedly increased tone in central muscles (face, neck, chest, back, and abdomen), with superimposed generalized spasms and relative sparing of the hands and feet, strongly suggests tetanus [(3)]

[6] The dose is 3000–6000 units IM, usually in divided doses because the volume is large. [(3)]

Prevention:

Active Immunization:

All partially immunized and unimmunized adults should receive vaccine, as should those recovering from tetanus (Tdap or Td). [3]

Wound Management:

Passive immunization with TIG

Active immunization with vaccine (Tdap or Td; Table 18) [3]

Table 18 Guide to Tetanus Prophylaxis and Routine Wound Management

	Clean Minor Wound		**All Other Wounds[a]**	
History of Adsorbed Tetanus Toxoid (Doses)	**Tdap or Td[b]**	**TIG**	**Tdap or Td[b]**	**TIG**
Unknown or <3	Yes	No	Yes	Yes
3	No[c]	No	No[d]	No

[a]Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds from missile or crushing injuries, burns, and frostbite.

[b]Tdap is preferred to Td for adults 19–64 years old who have never received Tdap. Td is preferred for adults who have received Tdap previously and is used when Tdap is not available. Td is also recommended for persons >64 years old. If TT and TIG are both used, TT adsorbed rather than TT for booster use only (fluid vaccine) should be used.

[c]Yes, if 10 years have elapsed since the last TT-containing vaccine dose.

[d]Yes, if 5 years have elapsed since the last TT-containing vaccine dose.

Note: Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed; DT, diphtheria and tetanus vaccine; DTP, diphtheria, tetanus, and pertussis vaccine; Td, tetanus-diphtheria toxoid, adsorbed; TIG, tetanus immune globulin; TT, tetanus toxoid.

Source: Modified from Centers for Disease Control and Prevention, 2006. [3]

Neonatal Tetanus:

1. Preventive measures include maternal vaccination, even during pregnancy
2. Efforts to increase the proportion of births that take place in the hospital
3. Provision of training for nonmedical birth attendants [3]

Prognosis:

1. Methods to monitor and support oxygenation has markedly improved the prognosis in tetanus
2. Mortality rates as low as 10% have been reported
3. In the United States in 2003, there were 20 cases and 2 deaths
4. The outcome is poor in neonates and the elderly and in patients with a short incubation period
5. The course of tetanus extends over 4–6 weeks [3]

Malaria

Definition:

Malaria is a protozoal fibril disease transmitted by the bite of infected anopheles mosquitoes [3]

Etiology:

1. The causative agent: *Plasmodium*
2. The types of agent:
   - Plasmodium flaciparum
   - Plasmodium vivax
   - Plasmodium ovale
   - Plasmodium malaria [2]
3. The victor: Anopheles mosquitoes [3]

Epidemiology:

1. Prevalence/Incidence:

a. Affect > 1 billion people causing 1-3 million deaths annually [3]

b. Has epidemic:

When there are changes in environmental economic and social condition such as heavy rains following droughts migration to a higher area transmission a breakdown in malaria control

c. Endemic disease:

Endemicity defined by parasitemia rates palpable spleen rate in children 2- 9 years may be:

- Hypoendemic <10 %
- Mesoendemic (11-50%)
- Hyperendemic (51-75%)
- Holoendemic >75%

2. Geographical variation:

Occur in most of tropical region of the world (103 countries) [3]
P. falciparum is common in:

- Africa
- New Guinea
- Haiti

P. vivax is more common in Central America Indian subcontinent
The above tow species is equal in South America
East Asia and Oceania
P. ovale is unusual outside of Africa
3. Age groups: Any age but common in children due to poor immunity.
4. Seasonal variation: common in summer and spring
5. Route of transmission: Mosquitoes bite
6. Reservoir of infection: Human [3]
7. Incubation period: 8-30 days (Table 14)
8. Infectivity period:

(Table 19)Relationships between life cycle of parasite and clinical features of malaria

Cycle/feature	***P. vivax*, *P. ovale***	***P. malariae***	***P. falciparum***
Pre-patent period (minimum incubation)	8-25 days	15-30 days	8-25 days
Asexual cycle	48 hrs synchronous	72 hrs synchronous	< 48 hrs asynchronous
Periodicity of fever	'Tertian'	'Quartan'	Aperiodic
Exo-erythrocytic cycle	Persistent as hypnozoites	Pre-erythrocytic only	Pre-erythrocytic only
Delayed onset	Common	Rare	Rare
Relapses	Common up to 2 years	Recrudescence many years later	Recrudescence up to 1 year

P. falciparum and *P. malariae* have no persistent exoerythrocytic phase but recrudescences of fever may result from multiplication in the red cells of parasites which have not been eliminated by treatment and immune processes. [2]

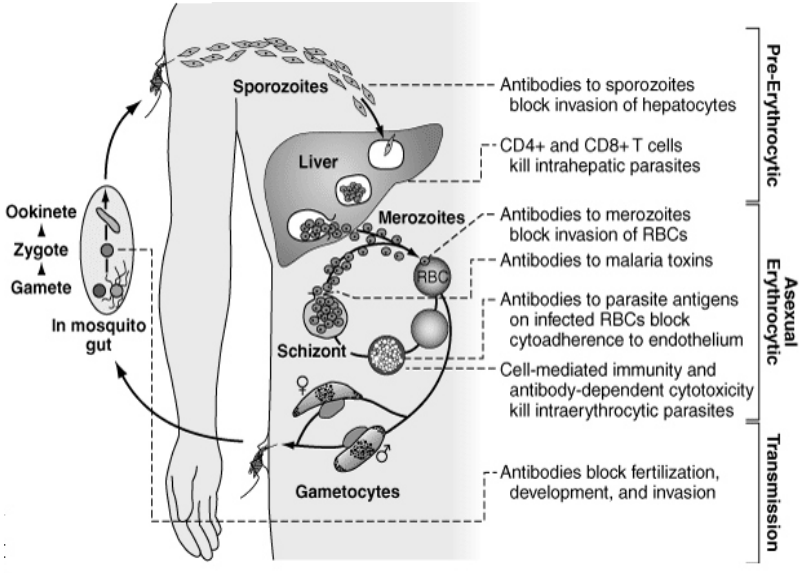
Pathogenesis/life cycle:

a. In human:

1. Entry into the body (sporozoites)
2. Entry into the liver (sporozoites)
3. In the liver cells (hypnozoites)
4. Proliferation in the liver (exo erythrocyte schizont)
5. Entry into the circulation (merozoites)
6. Invasion of RBC (merozoites)
7. In the erythrocytes:
    - Ring form
    - Trophozoites
    - Schizont
8. Release of merozoites and gametocytes from schizont
9. Invasion of other merozoites on RBCs (Fig. 56)

b. In mosquito:

10. Entry of gametocytes into mosquitos' stomach
    - Zygote formation
    - Ookinete
    - Oocyte
    - Sporozoites
11. Migration of sporozoites to salivary gland of mosquitoes.



(Fig. 56) **The malaria transmission cycle** from mosquito to human. RBC, red blood [3]

c. Mechanism of the appearance of symptoms:

The appearances of general symptoms are due to release[1] of:

1. Tissue necrosis factor (TNF)
2. Other cytokines

d. Mechanism of anemia in malaria:

1. Hemolysis of infected erythrocytes
2. Hemolysis of none infected erythrocytes
3. Dyserythrocytosis
4. Splenomegaly
5. Folate depletion [6]

e. Mechanism of organ damage:

1. Adhesion of schizont form of P. flaciparum in the small capillaries.
2. Blockage of capillaries
3. Anoxia and ischemia

[1] From Schizont

4. Organ damage [3]

Clinical features:

Symptoms:

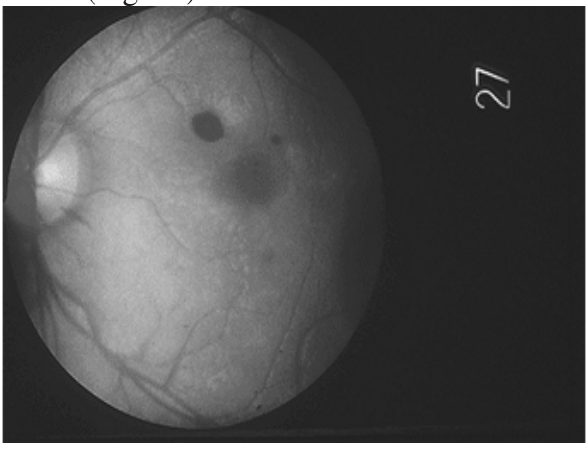
a. Non specific clinical features:
1. Malaise
2. Fatigue
3. Headache
4. Backache
5. Myalgia
6. Arthralgia
7. Dizziness
8. Mild diarrhea
9. Abdominal pain
10. Anorexia
11. Nausea
12. Vomiting
13. Dry cough [7]
14. Chest pain [3]

b. Classical attack:
1. Cold stage (rigors and chills)
2. Hot stage (high fever)
3. Sweating stage (diaphoresis)
4. Between attacks (tiredness)
5. Tertian fever (every second day) in cases of
   - P.Vivax
   - P.Ovale
6. Quartan fever (every third day) in case of P.Malaria
7. Irregular fever in case of P. flaciparum [7]

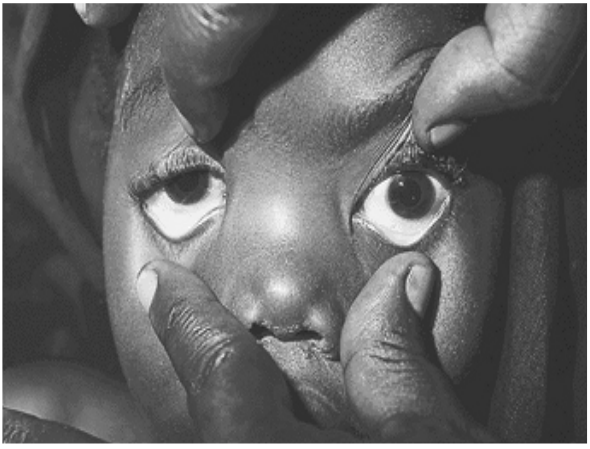
Signs:

1. Fever
2. Pallor (Fig. 58, 59)
3. Splenomegaly

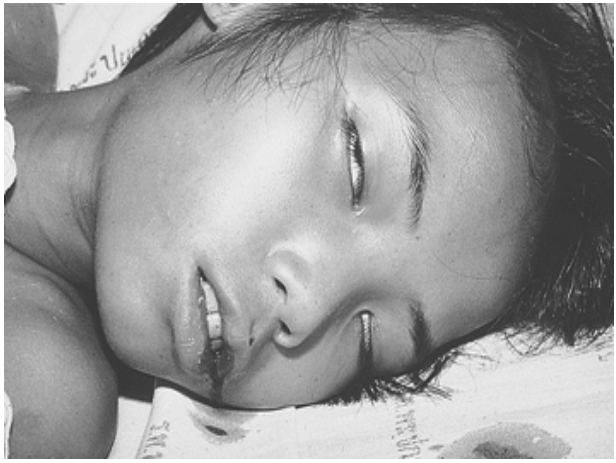
4. Mild hepatomegaly
5. Mild jaundice (Fig. 60) [3]



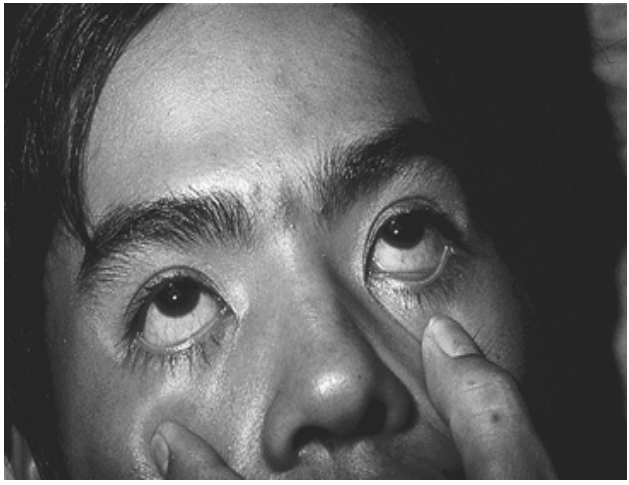
(Fig. 57) Retinal haemorrhages close to the macula in a Thai patient with cerebral malaria. (Copyright D.A. Warrell.) [8]



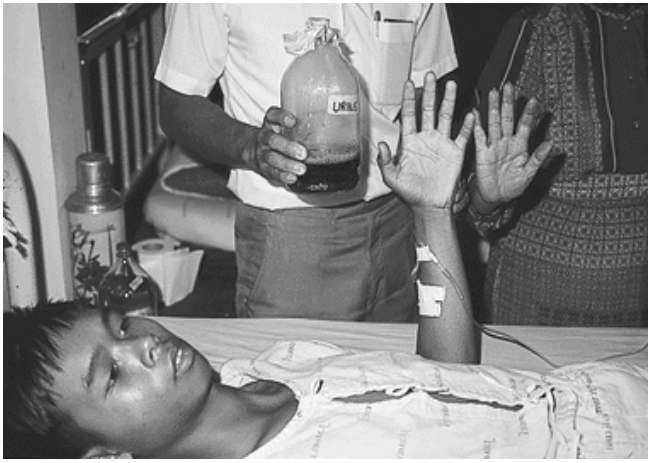
(Fig. 58) Profound anaemia (haemoglobin 1.2 g/dl) in a Kenyan child with P. falciparum parasitaemia. (Copyright D.A. Warrell.) [8]



(Fig. 59) Cerebral malaria. Spontaneous systemic bleeding in a Thai patient with disseminated intravascular coagulation. (Copyright D.A. Warrell.) [8]



(Fig. 60) Deep jaundice in a Vietnamese man with severe falciparum malaria. (Copyright D.A. Warrell.) [8]



(Fig. 61) Intravascular haemolysis in a Karen patient with glucose 6-phosphate dehydrogenase deficiency in whom treatment with an oxidant drug resulted in haemoglobinuria and anaemia (normal hand in comparison). (Copyright D.A. Warrell.) [8]

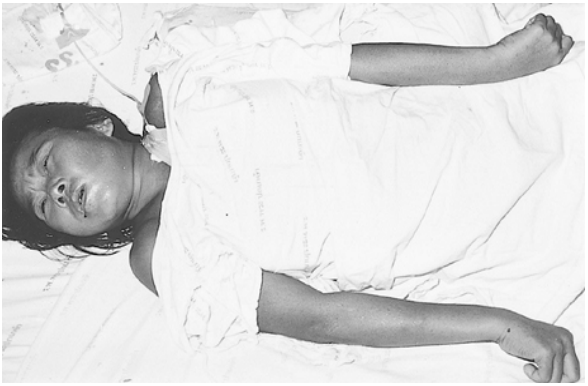
Complications:

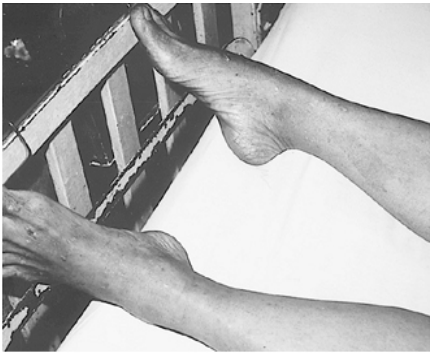
a. Organ damage:

1. Brain:

- Confusion
- Convulsion[2] (Fig. 62)
- Delirium

[2] The global case fatality of falciparum malaria is probably around 1 per cent or 1 to 3 million deaths per year. Cerebral malaria is the most important of the severe manifestations of P. falciparum infection, accounting for 80 per cent of these deaths.





(Fig. 62) Extensor posturing (decerebrate rigidity) in a Thai woman with cerebral malaria and profound hypoglycaemia [8]

2. Heart:
    - Cardiac dysarrhythmia
    - Coma
3. Lungs: Non cardiogenic pulmonary edema
4. Liver:
    - Jaundice
    - Hepatic encephalopathy
5. Kidney:
    - Oliguria
    - Acute tubular necrosis
    - Uremia

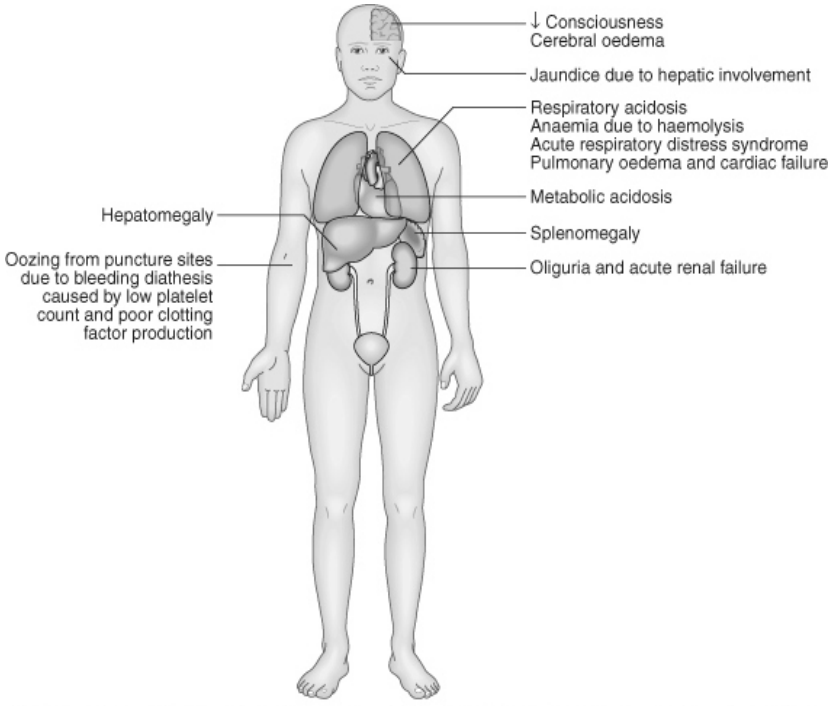
6. Intestine:
    - Diarrhea
    - Dysentery

b. Blood complications:
1. Hemolysis (black water fever)
2. Hemorrhage
3. DIC (disseminated intra vascular coagulation)

c. Metabolic complications:
1. Hypoglycemia
2. Metabolic acidosis (Fig. 63)

d. In pregnant mothers
1. Death of mother
2. Abortion
3. Still birth
4. Low birth weight

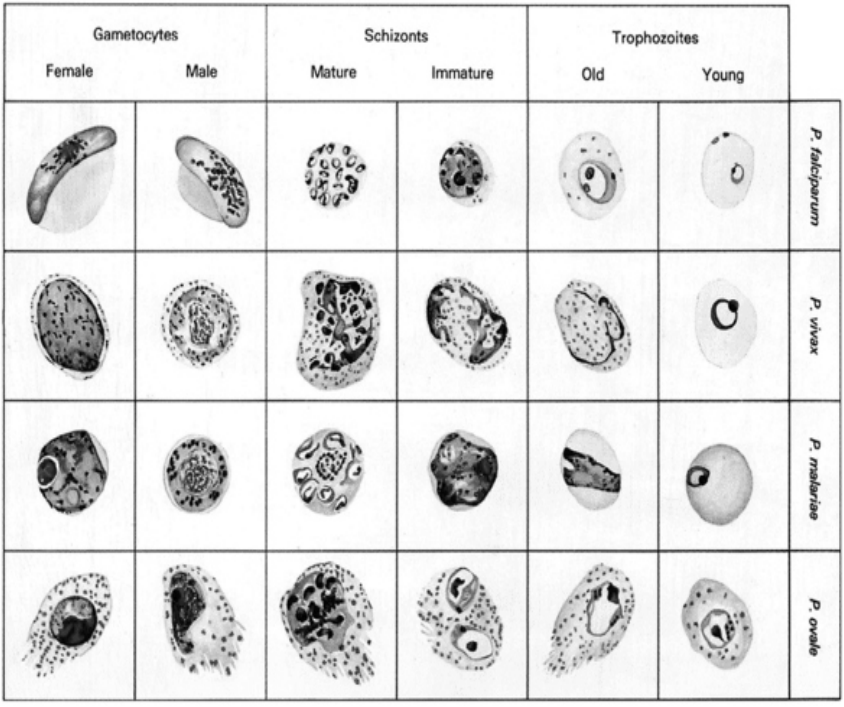
e. Others:
1. Hyperpyrexia
2. Hypovolemic shock
3. Septicemia secondary to shock
4. Electrolytes imbalance [3]



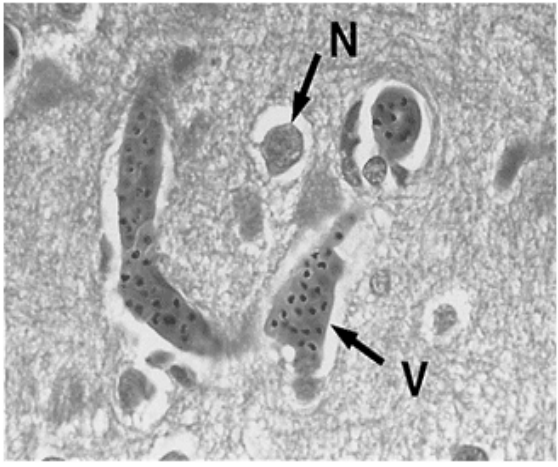
(Fig. 63) Organ involvement in severe malaria . [2]

Investigation:

1. Thick and thin blood film (parasites) (Fig. 64)
2. TLC: Leucopenia
3. Hb: Anemia
4. Platelets: Thrombocytopenia
5. Peripheral smears: Reticulocytosis
6. LFTs: Hemolytic jaundice
7. Serological tests
   - May be positive
   - After 8-10 days of symptoms appearance
   - These tests are not useful for diagnosis of acute attack
   - May be useful when repeated blood films are negative [3]



(Fig. 64) Malaria parasites developing in erythrocytes. (By courtesy of The Wellcome Trust.) [8]



(Fig. 65) Section of frontal cortex from a Vietnamese patient who died of cerebral malaria, showing sequestration of parasitized red blood corpuscles in blood vessels (N=neurone, V=vessel). (By courtesy of Dr Gareth Turner, Oxford.) [8]

Treatment:

General treatment:

1. Paracetamol for fever
2. Metoclopramid for vomiting
3. Admission (in sever cases)
4. Feeding
5. Phenobarbital or diazepam for convulsion
6. Dextrose for hypoglycemia

Specific Rx:

1. Chloroquine
2. Amodiaquine
3. Quinine
4. Quinidine
5. Mefloquine
6. Premaquine
7. Fansidar

8. Halofantrin
9. Artemether
10. Artesunate [7] (Table 15)

Table 20 Treatment of malaria.

Clinical Setting	**Drug Therapy**[1]	**Alternative Drugs**
Chloroquine-sensitive *Plasmodium falciparum* and *Plasmodium malariae* infections	Chloroquine phosphate, 1 g, followed by 500 mg at 6, 24, and 48 hoursor–Chloroquine phosphate, 1 g at 0 and 24 hours, then 0.5 g at 48 hours	
Plasmodium vivax and *Plasmodium ovale* infections	Chloroquine (as above), then (if G6PD normal) primaquine, 30 mg base daily for 14 days	
Uncomplicated infections with chloroquine-resistant *P falciparum*	Quinine sulfate, 650 mg three times daily for 3–7 days+ \ Plus one of the following (when quinine given for < 7 days)– Doxycycline, 100 mg twice daily for 7 days or– Clindamycin, 600 mg twice daily for 7 days	Malarone, 4 tablets (total of 1 g atovaquone, 400 mg proguanil) daily for 3 days or– Mefloquine, 15 mg /kg once or 750 mg, then 500 mg in 6–8 hours or– Coartem[2] (artemether 20 mg, lumefantrine 120 mg), four tablets twice daily for 3 days or– ASAQ[2] (artesunate 100 mg, amodiaquine 270 mg), two tablets daily for 3 days
Severe or complicated infections with *P falciparum* [3]	Artesunate 2.4 mg/kg IV every 12 hours for 1 day, then daily[3,6]	Quinidine gluconate,[4–6] 10 mg/kg IV over 1–2 hours, then 0.02 mg/kg IV/min

		or– Quinidine gluconate,[4–6] 15 mg/kg IV over 4 hours, then 7.5 mg/kg IV over 4 hours every 8 hours or– Quinine dihydrochloride,[2,4–6] 20 mg/kg IV over 4 hours, then 10 mg/kg IV every 8 hours or– Artemether,[2,6] 3.2 mg/kg IM, then 1.6 mg/kg/d IM

[1]All dosages are oral and refer to salts unless otherwise indicated. See text for additional information on all agents, including toxicities and cautions. See Centers for Disease Control and Prevention's guidelines (phone: 877-FYI-TRIP; http://www.cdc.gov) for additional information and pediatric dosing. [2]Not available in the United States. [3]Available in the United States only on an investigational basis through the CDC (phone: 770-488-7788). [4]Cardiac monitoring should be in place during intravenous administration of quinidine or quinine. [5]Avoid loading doses in persons who have received quinine, quinidine, or mefloquine in the prior 24 hours. [6]With all parenteral regimens, change to an oral regimen (most commonly doxycycline in adults or clindamycin in children) as soon as the patient can tolerate it. G6PD, glucose-6-phosphate dehydrogenase. Modified, with permission, from Katzung BG. *Basic & Clinical Pharmacology*. 10th edition. McGraw-Hill, 2007. (7)

Prevention:

1. Insecticide
2. Bed nets
3. Insecticide for spraying
4. Chemoprophylaxis [3] (Table 21)

Table 21 Drugs Used in the Prophylaxis of Malaria

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Atovaquone/proguanil (Malarone)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *Plasmodium falciparum*	1 adult tablet PO[a]	5–8 kg: 1/2 pediatric tablet[b] daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious area and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate <30 mL/min). It is not recommended for children weighing <5 kg, pregnant women, or women breast-feeding infants weighing <5 kg. Atovaquone/proguanil should be taken with food or a milky drink.
			≥ 8–10 kg: 3/4 pediatric tablet daily	
			≥ 10–20 kg: 1 pediatric tablet daily	
			≥20–30 kg: 2 pediatric tablets daily	
			≥30–40 kg: 3 pediatric tablets daily	
			≥40 kg: 1 adult tablet daily	
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with	300 mg of base (500 mg of	5 mg/kg of base (8.3 mg of	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same

	chloroquine-sensitive *P. falciparum*[c]	salt) PO once weekly	salt/kg) PO once weekly, up to a maximum adult dose of 300 mg of base	day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine phosphate may exacerbate psoriasis.
Doxycycline (many brand names and generic)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *P. falciparum*[c]	100 mg PO qd	≥8 years of age: 2 mg/kg, up to adult dose	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children <8 years of age and in pregnant women.
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c]	310 mg of base (400 mg of salt) PO once weekly	5 mg of base/kg (6.5 mg of salt/kg) PO once weekly, up to maximum adult dose of 310 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Hydroxychloroquine may exacerbate psoriasis.
Mefloquine (Lariam and generic)	Prophylaxis in areas with chloroquine-resistant *P. falciparum*	228 mg of base (250 mg of salt) PO once weekly	≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g., quinine and quinidine) and in persons with active or recent depression,
			10–19 kg: 1/4 tablet once weekly	
			20–30 kg:	

			$^1/_2$ tablet once weekly	generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities.
			31–45 kg: $^3/_4$ tablet once weekly	
			≥46 kg: 1 tablet once weekly	
Primaquine	An option for prophylaxis in special circumstances	30 mg of base (52.6 mg of salt) PO qd	0.5 mg of base/kg (0.8 mg of salt/kg) PO qd, up to adult dose; should be taken with food	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine is contraindicated in persons with G6PD1 deficiency. It is also contraindicated during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level. Use in consultation with malaria experts.
Primaquine	Used for presumptive antirelapse therapy (terminal prophylaxis) to decrease risk of relapses of *P. vivax* and *P. ovale*.	30 mg of base (52.6 mg of salt) PO qd for 14 days after departure from the malarious area	0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO qd for 14 days after departure from the malarious area	This therapy is indicated for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*. It is contraindicated in persons with G6PD1 deficiency as well as during pregnancy and in lactation unless the infant being breast-fed has a documented normal G6PD level.

[a]An adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride. [b]A pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloide. [c]Very few areas now have chloroquine-sensitive malaria [(3)]

Prognosis:

1. The mortality of acute vivax, ovale, and malariae malarias is negligible.
2. Cerebral malaria has a mortality of about 10 to 15 per cent when medical facilities are good, and may be less than 5 per cent in Western intensive care units. [3] (8)

[3] Antecedent factors that predispose to severe falciparum malaria include the lack of acquired immunity or lapsed immunity, splenectomy, pregnancy, and immunosuppression. There is a strong correlation between the density of parasitaemia and disease severity. Severe clinical manifestations, such as impaired consciousness, retinal haemorrhages, renal failure, hypoglycaemia, haemoglobinuria, metabolic acidosis, and pulmonary oedema, carry a bad prognosis. The case fatality of pregnant women with cerebral malaria, especially primiparae in the third trimester, is approximately 10 times greater than in non-pregnant patients. The following laboratory findings carry a poor prognosis: peripheral schizontaemia, peripheral leucocytosis exceeding 12 000/$^{-1}$µl, malarial pigment in >5 per cent of circulating neutrophils, high CSF lactate or low glucose, low plasma antithrombin III, serum creatinine exceeding 265 $^{-1}$µmol/l, or a blood urea nitrogen of more than 21.4 mmol/l, haematocrit less than 20 per cent, blood glucose less than 2.2 mmol/l, and elevated serum enzyme concentrations (for example, aspartate and alanine aminotransferases, lactate dehydrogenase). (8)

Amoebiasis

Definition:

Amoebiasis is an infection with intestinal protozoan *Entamoeba histolytica*, 90% infections are asymptomatic, the remaining produce syndromes ranging from dysentery to liver or other abscesses. (3)

Etiology:

The causative agent: An intestinal protozoa *Entamoeba histolytica*

Life cycle:

1. Ingestion of cysts containing contaminated water or food
2. Release of motile trophozoites from cysts in small intestine
3. Trophozoites invade bowel mucosa
4. Watery or bloody diarrhea
5. Enter into circulation
6. Liver, lungs or brain abscesses (3)

Epidemiology:

1. Prevalence/Incidence:
   - About 10 % world's population have infection
   - The 3rd common cause of death from parasitic diseases
2. Geographical variation: Common in:
   - Developing countries in the tropics
   - Mexico
   - India
   - Central & South America
   - Tropic Asia

- Tropic Africa [3]

3. Age group: Any age
4. Seasonal variation: Warm weather
5. Route of transmission: Faeco oral route
6. Reservoir of infection: Human
7. Incubation period: 2-4 weeks[1]
8. Infectivity period: Has carrier[2] [7]

Pathogenesis:

1. Cyst ingestion
2. Release of trophozoites from cysts in small gut
3. Trophozoites attach by lectin to colonic mucosa
4. Micro ulceration in:
   - Cecum
   - Sigmoid colon
   - Rectum
5. Release of:
   - Erythrocytes
   - Inflammatory cells
   - Epithelial cells
6. Submucosal extension of ulceration (Flask-shaped ulcer)
7. Full-thickness necrosis (Occasionally)
8. Intestinal perforation (Occasionally)
9. Rarely may form a mass lesion (Ameboma)
10. After entry to the circulation may cause:
    - Liver abscesses
    - Lung abscesses
    - Brain abscesses [3]

---

[1] Diarrhea may begin within a week of infection, although an incubation period of 2–4 weeks is more common. [7]

[2] In most infected persons, the organism lives as a commensal, and the carrier is without symptoms. [7]

Clinical features:

Intestinal amoebiasis:

a. Asymptomatic:

1. In most infected person the organisms live as a commensal
2. Carrier without symptom

b. Mild to moderate colitis:

Symptoms:

1. Watery diarrhea
2. Abdominal crump
3. Flatulence
4. Fatigue
5. Weight loss
6. Fever (Uncommon)
7. Has period of remission and recurrence
8. During remission may have constipation

Signs:

1. Abdominal distension
2. Hyperperistalsis
3. Abdominal tenderness
4. Colon may be thick & palpable (In chronic case)
5. Mild hepatomegaly (Due to toxin)
6. Low grade enzyme abnormalities without trophozoites in the liver.

c. Sever colitis (Dysenteric colitis):

1. Liquid stool
2. Large numbers of stools (10-20 or more)
3. Little fecal material
4. Blood in stool (Fresh or dark)
5. Bits of necrotic tissue
6. Prostration
7. Patient may be toxic
8. Pyrexia (up to 40,5 C)

9. Colic
10. Tenesmus
11. Vomiting
12. Generalized abdominal pain
13. Abdominal tenderness
14. Non specific hepatic enlargement

Localized ulcerative lesion of colon:

1. Rectal ulcer:
   - Formed stool
   - Bloody exudates
2. Ulcer limited to cecum:
   - Mild diarrhea
   - Simulate appendicitis
3. Amebic appendicitis
   - Appendix is extensively involved
   - No other involvement
   - Rare

Granuloma of colon (Ameboma):

1. Excessive granulation tissues
2. May be due to:
   - Dysentery or
   - Chronic infection
3. May be:
   - Single or multiple
   - Irregular
   - Up to several centimeter in length
4. Clinical findings:
   - Pain
   - Obstructive symptoms
   - Hemorrhage
5. X ray findings may simulate:

- Colonic carcinoma
- Tuberculosis
- Lymphogranuloma venereum

6. Endoscopy:
   - Deep rectal mass
   - Bleeds easily
   - Biopsy show granuloma & E Histolytica

Extraintestinal amoebiasis:

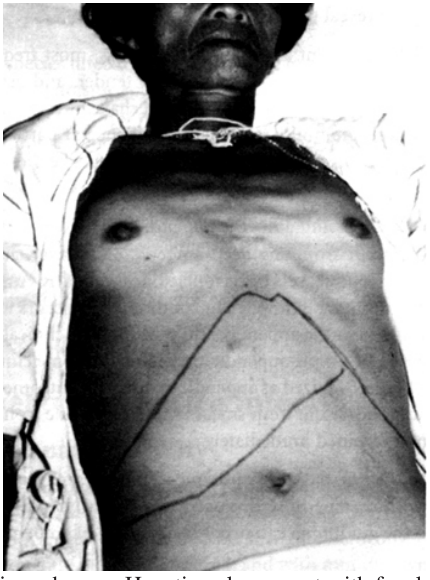
a. Hepatic amoebiasis (Result from 3-9%)

1. Liver abscesses of intestinal amoebiasis
2. Liver abscess may be without intestinal symptoms
3. Sudden or gradual onset
4. Fever (often high)
5. Pain(Continuous, stabbing or pleuritic & sometime sever)
6. Enlarged tender liver (Fig. 66)
7. Malaise
8. Prostration
9. Sweating
10. Chills
11. Anorexia
12. Weight loss
13. May be cough
14. Finding of right lung base
    - Dullness of percussion
    - Rales
    - Decreased breath sound
15. Intercostals tenderness (Over base)
16. Skin edema & tenderness
17. Abscess may rupture into
    - Pleural space
    - Peritoneal space

- Pericardial space
- Other contagious organ
- Death may follow

Other extraintestinal infection

1. Skin infection may develop in perianal area
2. Metastatic infection may occur in:
   - Lungs
   - Brain
   - Genitalia [7]



(Fig. 66) Amoebic liver abscess. Hepatic enlargement with focal tenderness in a Thai woman. [8]

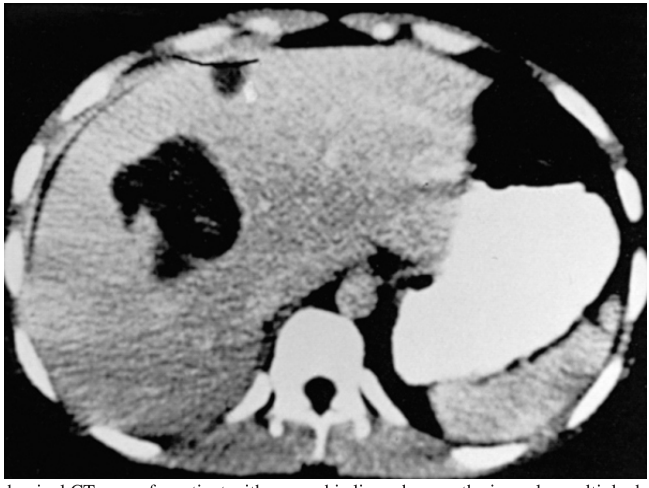
Complications:

1. Appendicitis
2. Bowel perforation
3. Fulminating colitis
4. Massive mucosal sloughing

5. Hemorrhage
6. Death [7]

Investigation:

1. Stool exam:
   - Microscopic (Trophozoites, cyst & leukocytes)
   - Antigen detection
   - Culture
2. Colonoscopy
3. Rectal biopsy (From the edge of the ulcer)
4. Serologic test for antibodies
5. Blood exam: May be Leukocytosis (2000/ml)
6. Ultrasound
7. CT Scan (Fig. 67)
8. MRI
9. Radio Isotope Scanning
10. Gallium Scan



(Fig. 67) Abdominal CT scan of a patient with an amebic liver abscess; the irregular multiple defects present in the right lobe of the liver cannot be differentiated from a pyogenic abscess or hepatocellular carcinoma.

(From Mandell GL, Bennett JE, Dolin R [editors]: Principles and Practice of Infectious Diseases, 6th ed, Vol 2. Philadelphia, Elsevier, 2006, p 3105.) [8]

Treatment:

General Rx:

1. Rehydration
2. Good feeding
3. Buscopan plus for pain & fever
4. Metoclopramid for vomiting

Specific Rx:

a. Mild to moderate colitis

1. Metronidazol 750mg TID for 10days or
2. Tinidazol 800mg TID for 3days Plus
3. Diloxanid furoate 500mg TID for 10days or
4. Iodoqinol 650mg TID for 21days or
5. Paromomycin 25-30mg/kg in 3 divided dose for 7days

b. Sever colitis (Dysentery):

1. Metronidazol 750mg TID for 10days or
2. Tinidazol 800mg TID for 3days Plus
3. Diloxanid furoate 500mg TID for 10days or
4. Iodoqinol 650mg TID for 21days
5. Intravenous (I/V) Therapy:

Metronidazol until oral therapy can be started.
Then give oral Metronidazol Plus
Diloxanid furoate 500mg TID for 10days or
Iodoqinol 650mg TID for 21days

c. Hepatic abscess:

1. Metronidazol 750mg TID for 10days or
2. Tinidazol 800mg TID for 3days Plus
3. Diloxanid furoate 500mg TID for 10days or
4. Iodoqinol 650mg TID for 21days followed by
5. Chloroquine 500mg (Salt) daily for 14days. (Table 22)

d. Ameboma or extraintestinal diseases:

As for hepatic abscess but not including Chloroquine. [7]

Table 22 Treatment of amebiasis.[1]

Clinical Setting	Drugs of Choice and Adult Dosage	Alternative Drugs and Adult Dosage
Asymptomatic intestinal infection	Luminal agent: Diloxanide furoate,[2] 500 mg orally three times daily for 10 days	
	or–	
	Iodoquinol, 650 mg orally three times daily for 21 days	
	or–	
	Paromomycin, 10 mg/kg orally three times daily for 7 days	
Mild to moderate intestinal infection	Metronidazole, 750 mg orally three times daily (or 500 mg IV every 6 hours) for 10 days	Luminal agent (see above)plus either–
	or–	Tetracycline, 250 mg orally three times daily for 10 days
	Tinidazole, 2 g orally daily for 3 days	or–
	Plus–	Erythromycin, 500 mg orally four times daily for 10 days
	Luminal agent (see above)	
Severe intestinal infection	Metronidazole, 750 mg orally three times daily (or 500 mg IV every 6 hours) for 10 days	Luminal agent (see above)
	or–	plus either–
	Tinidazole, 2 g orally daily for 3 days	Tetracycline, 250 mg orally three times daily for 10 days
	Plus–	or–
	Luminal agent (see above)	Dehydroemetine [3] or emetine,[2] 1 mg/kg SC or IM for 3–5 days
Hepatic abscess, ameboma, and other extraintestinal disease	Metronidazole, 750 mg orally three times daily (or 500 mg IV every 6 hours) for 10 days	Dehydroemetine [3] or emetine,[2] 1 mg/kg SC or IM for 8–10 days, followed by (liver abscess only) chloroquine, 500 mg orally twice daily for 2 days, then 500 mg daily for 21 days
	or–	
	Tinidazole, 2 g orally daily for 3 days	plus–
	Plus–	Luminal agent (see above)

	Luminal agent (see above)	

1See text for additional details and cautions. 2Not available in the United States. 3Available in the United States only from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta (404-639-3670). [3]

Prevention:

1. No notification
2. No isolation
3. Disinfection of stool
4. Environmental sanitation: Disposal of human faeces
5. Treatment: No prophylaxis
6. No immunization
7. Health education for:
   - Water boiling: Boiling water for 5 min kills cysts [(8)]

[3]

Table Drug Therapy for Amebiasis

Indication	**Therapy**
Asymptomatic carriage	Luminal agent: iodoquinol (650-mg tablets), 650 mg tid for 20 days; *or* paromomycin (250-mg tablets), 500 mg tid for 10 days
Acute colitis	Metronidazole (250- or 500-mg tablets), 750 mg PO or IV tid for 5–10 days,
	plus
	Luminal agent as above
Amebic liver abscess	Metronidazole, 750 mg PO or IV for 5–10 days,
	or
	Tinidazole, 2 g PO once,
	or
	Ornidazole,[a] 2 g PO once,
	plus
	Luminal agent as above

[a]Not available in the United States [(3)]

- Protection of food from fly
- Hand washing after toilet [7]

Prognosis:

1. The mortality rate may be high from untreated:
   - Amebic dysentery
   - Hepatic abscess
   - Ameboma
2. With early treatment the prognosis is good [4] [7]

[4] Uncomplicated invasive intestinal disease and uncomplicated hepatic amoebiasis should normally have a mortality rate of less than 1 per cent. In complicated disease the mortality is much greater and may reach 40 per cent for amoebic peritonitis with multiple gut perforation. Prognosis is usually better in centers where the disease is common and more likely to be recognized early. Late diagnosis increases the probability of complicated disease and mortality rises accordingly. [7]
Unless parasitological cure is achieved, and the gut completely freed of E. histolytica, clinical relapse is quite common, although probably limited by immunological responses. There is so far no evidence of naturally occurring strains of E. histolytica being resistant to normally used drugs. Hepatic scans show that nearly all liver abscesses completely disappear within 2 years; the median resolution time is 8 months. In secondarily infected lesions, bizarre hepatic calcification may be seen years afterwards. Healing of the bowel is remarkably rapid and complete; occasionally fibrous strictures persist after severe dysentery. [7]

Rickettsial Diseases

The rickettsiae are a heterogeneous group of small, obligately intracellular, gram-negative coccobacilli and short bacilli, most of which are transmitted by a tick, mite, flea, or louse vector. (3) (Fig.86)

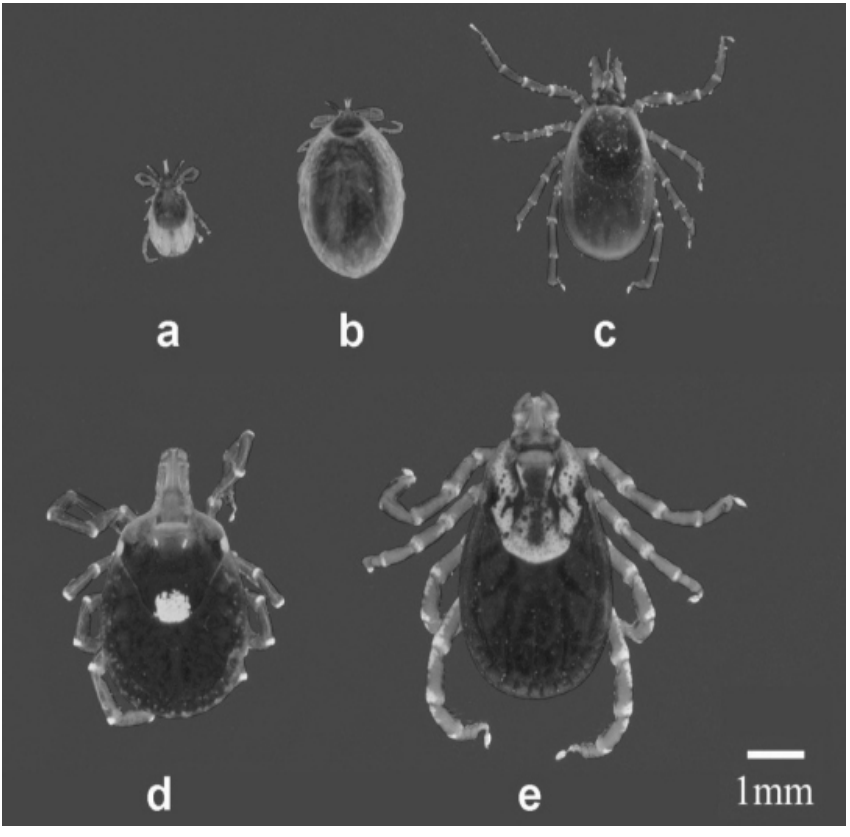
Except for louse-borne typhus[1], humans are incidental hosts. Among rickettsiae, *Coxiella burnetii, Rickettsia prowazekii,* and *R. typhi* have the well-documented ability to survive for an extended period outside the reservoir or vector and to be extremely infectious: inhalation of a single *Coxiella* microorganism can cause pneumonia. High infectivity and severe illness after inhalation make *R. prowazekii, R. rickettsii, R. typhi, R. conorii,* and *C. burnetii* bioterrorism threats. (3)

Clinical infections with rickettsiae can be classified according to 1. The taxonomy and diverse microbial characteristics of the agents, which belong to six genera:

- *Rickettsia*
- *Orientia*
- *Ehrlichia*
- *Anaplasma*
- *Neorickettsia*
- *Coxiella*

2. Epidemiology
3. Clinical manifestations. (3)

[1] Typhus: Gr. Typhos stupor arising from fever. (9)



(Fig. 68)Tick vectors of agents of human rickettsial diseases. An unengaged nymph (a), engorged nymph (b), and adult female (c) of *Ixodes scapularis* (deer tick), the vector of *Anaplasma phagocytophilum,* the cause of human granulocytic anaplasmosis. An adult female (d) of *Amblyomma americanum* (lone star tick), the vector of *Ehrlichia chaffeensis* and *Ehrlichia ewingii,* the causes of human monocytic ehrlichiosis and ewingii ehrlichiosis, respectively. An adult female (e) of *Dermacentor variabilis* (American dog tick), the vector of *Rickettsia rickettsii,* the cause of Rocky Mountain spotted fever. [5]

The clinical manifestations of all the acute presentations are similar during the first 5 days: fever, headache, and myalgias with or without nausea, vomiting, and cough. As the course progresses, clinical manifestations—including occurrence of a macular, maculopapular, or vesicular rash; eschar; pneumonitis; and

meningoencephalitis—vary from one disease to another. Given the 12 etiologic agents with varied mechanisms of transmission, geographic distributions, and associated disease manifestations, the consideration of rickettsial diseases as a single entity poses complex challenges (Table 23).[3]

Table 23 Features of Selected Rickettsial Infections

Disease	Organism	Transmission	Geographic Range	Incubation Period (Days)	Duration (Days)	Rash (%)	Eschar (%)	Lymphadenopathy[a] & Treatment (Rx)
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor andersoni*	United States	2–14	10–20	90	<1	+ Rx: Doxycycline Chloramphenicol
		D. variabilis	United States					
		Amblyomma cajennense, A. aureolatum	Central/South America					
		Rhipicephalus sanguineus	Mexico, United States					
Mediterranean spotted fever[b]	*R. conorii*	Tick bite: *R. sanguineus, R. pumilio*	Southern Europe, Africa, Middle East, Central Asia	5–7	7–14	97	50	+ Rx: Doxycycline Ciprofloxacin
African tick-bite fever	*R. africae*	Tick bite: *A. hebraeum, A. variegatum*	Sub-Saharan Africa, West Indies	4–10	?	50	90	++++ Rx: Doxycycline Ciprofloxacin
Rickettsialpox	*R. akari*	Mite bite: *Liponyssoides sanguineus*	United States, Ukraine, Croatia	10–17	3–11	100	90	+++ Rx: Doxycycline
Flea-borne spotted fever	*R. felis*	Flea (mechanism undetermined): *Ctenocephalides felis*	North and South America, Europe	8–16	8–16	80	15	— Rx: Doxycycline
Epidemic typhus	*R. prowazekii*	Louse feces: *Pediculus humanus corporis,* fleas and lice of flying squirrels, or recrudescence	Worldwide	7–14	10–18	80	None	— Rx: Doxycycline Chloramphenicol
Tick-borne lymphadenopathy	*R. slovaca*	Tick bite: *Dermacentor marginatus, D. reticularis*	Europe	7–9	17–180	5	100	++++ Rx: Doxycycline Ciprofloxacin
Murine typhus	*R. typhi*	Flea feces:	Worldwide	8–16	8–16	80	None	—

		Xenopsylla cheopis, C. felis, others						Rx: Doxycycline
Human monocytotropic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *Amblyomma americanum, D. variabilis*	United States	1–21	3–21	36	None	++ Rx: Doxycycline
Human granulocytotropic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *Ixodes scapularis, I. ricinus, I. pacificus*	United States, Europe, Asia	1–21	3–14	Rare	None	— Rx: Doxycycline
Scrub typhus	*Orientia tsutsugamushi*	Mite bite: *Leptotrombidium deliense,* others	Asia, Australia, New Guinea, Pacific Islands	9–18	6–21	50	35	+++ Rx: Doxycycline Chloramphenicol Azithromycin
Q fever	*Coxiella burnetii*	Inhalation of aerosols of infected parturition material (sheep, dogs, others), ingestion of infected milk or milk products	Worldwide	3–30	5–57	<1	None	— Rx: Doxycycline Ciprofloxacin Ofloxacin

[a]++++, severe; +++, marked; ++, moderate; +, present in a small portion of cases; —, not a noted feature. [b]Eschar is usually present at the bite site. (3)

Epidemic (Louse-Borne) Typhus

The human body louse (*Pediculus humanus corporis*) lives in clothing under poor hygienic conditions and usually in impoverished cold areas. Lice acquire *R. prowazekii* when they ingest blood from a rickettsemic patient. The rickettsiae multiply in the midgut epithelial cells of the louse and are shed in the louse's feces. The infected louse leaves a febrile person and deposits infected feces on its subsequent host during its blood meal; the patient autoinoculates the organisms by scratching. The louse is killed by the rickettsiae and does not pass *R. prowazekii* to its offspring. [3]

Epidemiology:

Epidemic typhus haunts regions afflicted by wars and disasters. An outbreak involved 100,000 people in refugee camps in Burundi in 1997. A small focus occurred in Russia in 1998; sporadic cases have been reported from Algeria, and frequent outbreaks have occurred in Peru. Eastern flying-squirrels (*Glaucomys volans*) and their lice and fleas maintain *R. prowazekii* in a zoonotic cycle. The fleas transmit the infection sporadically to humans. [3]

Brill-Zinsser disease is a recrudescent illness occurring years after acute epidemic typhus, probably as a result of waning immunity. Typhus infection remains latent for years; its reactivation results in sporadic cases of disease in louse-free populations or in epidemics in louse-infested populations. [3]

Rickettsiae are potential agents of bioterrorism. Infections with *R. prowazekii* and *R. rickettsii* have high case-fatality ratios. These organisms cause difficult-to-diagnose diseases, are highly infectious when inhaled as aerosols, and have been selected for resistance to tetracycline or chloramphenicol in the laboratory. [3]

Clinical features:

After an incubation period of ~1 week, the onset of illness is abrupt, with prostration, severe headache, and fever rising rapidly to 38.8°–40.0°C (102°–104°F). Cough is prominent, occurring in 70% of patients. Myalgias are usually severe. In the outbreak in Burundi, the disease was referred to as sutama ("crouching"), a designation reflecting the posture of patients attempting to alleviate the pain. A rash begins on the upper trunk, usually on the fifth day, and then becomes generalized, involving the entire body except the face, palms, and soles. Initially, this rash is macular; without treatment, it becomes maculopapular, petechial, and confluent. The rash often is not detected on black skin; 60% of African patients have spotless epidemic typhus. Photophobia, with considerable conjunctival injection and eye pain, is frequent. The tongue may be dry, brown, and furred. Confusion and coma are common. Skin necrosis and gangrene of the digits as well as interstitial pneumonia may occur in severe cases. Untreated disease is fatal in 7–40% of cases, with outcome depending primarily on the condition of the host. Patients with untreated infections develop renal insufficiency and multiorgan involvement in which neurologic manifestations are frequently prominent. Overall, 12% of patients with epidemic typhus have neurologic involvement. Infection associated with North American flying squirrels is a milder illness; whether this milder disease is due to host factors (e.g., better health status) or attenuated virulence is unknown. [3]

Diagnosis:

Epidemic typhus is sometimes misdiagnosed as typhoid fever in tropical countries. The means even for serologic studies are often unavailable in settings of louse-borne typhus. Epidemics may be recognized by the serologic or immunohistochemical diagnosis of a single case or by detection of *R. prowazekii* in a louse found on a patient. Cross-adsorption indirect fluorescent antibody (IFA) studies can distinguish *R. prowazekii* and *R. typhi* infections. [3]

Treatment:

Doxycycline (200 mg/d, given in two divided doses) is administered orally or—if the patient is comatose or vomiting—intravenously. Although under epidemic conditions a single 200-mg dose has proved effective, treatment is generally continued until 2–3 days after defervescence. Pregnant patients should be evaluated individually and treated with either chloramphenicol early in pregnancy or, if necessary, doxycycline late in pregnancy. [3]

Prevention:

Prevention of epidemic typhus involves control of body lice. Clothes should be changed regularly, and insecticides should be used every 6 weeks to control the louse population. [3]

Endemic Murine Typhus

Definition:

Maxcey distinguished murine typhus, or endemic typhus, from epidemic typhus in 1926. Fleas are usually infected by *R. typhi* when feeding on apparently healthy rats that have blood-borne infection. Humans and other mammals are infected through autoinoculation by scratching a fleabite that is contaminated with feces from an infected flea. Murine typhus, because of its cycle, is more prevalent in hot and humid areas, when rats proliferate. (4)

Epidemiology:

R. typhi is maintained in mammalian host/flea cycles, with rats (*Rattus rattus* and *R. norvegicus*) and the Oriental rat flea (*Xenopsylla cheopis*) as the classic zoonotic niche. Fleas acquire *R. typhi* from rickettsemic rats and carry the organism throughout their life span. Nonimmune rats and humans are infected when rickettsia-laden flea feces contaminate pruritic bite lesions; less frequently, the flea bite transmits the organisms. Transmission also may occur via inhalation of aerosolized rickettsiae from flea feces. Infected rats appear healthy, although they are rickettsemic for ~2 weeks. (3)

Murine typhus occurs mainly in southern Texas and southern California, where the classic rat/flea cycle is absent and an opossum/cat flea (*C. felis*) cycle is prominent. Globally, endemic typhus occurs year-round, mainly in warm (often coastal) areas throughout the tropics and subtropics, where it is highly prevalent though often unrecognized. The incidence peaks from April through June in southern Texas and during the warm months of

summer and early fall in other geographic locations. Patients seldom recall exposure to fleas, although exposure to animals such as cats, opossums, and rats is reported in nearly 40% of cases. [3]

Clinical features:

The incubation period of experimental murine typhus averages 11 days (range, 8–16 days). Headache, myalgia, arthralgia, nausea, and malaise develop 1–3 days before onset of chills and fever. Nearly all patients experience nausea and vomiting early in the illness. [3]

The duration of untreated illness averages 12 days (range, 9–18 days). Rash is present in only 13% of patients at presentation for medical care (usually ~4 days after onset of fever), appearing an average of 2 days later in half of the remaining patients and never appearing in the others. The initial macular rash is often detected by careful inspection of the axilla or the inner surface of the arm. Subsequently, the rash becomes maculopapular, involving the trunk more often than the extremities; it is seldom petechial and rarely involves the face, palms, or soles. A rash is detected in only 20% of patients with darkly pigmented skin. [3]

Pulmonary involvement is frequently prominent; 35% of patients have a hacking, nonproductive cough, and 23% of patients who undergo chest radiography have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions. Bibasilar rales are the most common pulmonary sign. Less common clinical manifestations include abdominal pain, confusion, stupor, seizures, ataxia, coma, and jaundice. Clinical laboratory studies frequently reveal anemia and leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, mildly increased serum hepatic aminotransferases, and prerenal azotemia. Complications may include respiratory failure, hematemesis, cerebral hemorrhage, and hemolysis. Severe illness necessitates the admission of 10% of

hospitalized patients to an intensive care unit. Greater severity is generally associated with old age, underlying disease, and treatment with a sulfonamide; the case-fatality rate is 1%. In a study of children with murine typhus, 50% suffered only nocturnal fevers, feeling well enough for active daytime play. [3]

Diagnosis:

Cultivation, PCR, or cross-adsorption serologic studies of acute- and convalescent-phase sera can provide a specific diagnosis, and an immunohistochemical method for identification of typhus group-specific antigens has been developed. [3]

Treatment:

Nevertheless, most patients are treated empirically with doxycycline (100 mg bid orally for 7–15 days) on the basis of clinical suspicion. Serologic methods are usually used when laboratory confirmation of the diagnosis is sought. [3]

Prevention:

Control of murine typhus was dependent on elimination of the flea reservoir and control of flea hosts, and this remains an important component of control. However, with the recognition of cat fleas as potentially significant reservoirs and vectors, the presence of these flea vectors and their mammalian hosts in suburban and urban areas where close human exposures occur will probably pose increasingly important control problems. [5]

Rocky Mountain spotted fever

RMSF occurs in 48 states (with the highest prevalence in the south-central and southeastern states) as well as in Canada, Mexico, and Central and South America. The infection is transmitted by *Dermacentor variabilis*, the American dog tick, in the eastern two-thirds of the United States and California; by *D. andersoni*, the Rocky Mountain wood tick, in the western United States; by *Rhipicephalus sanguineus* in Mexico and Arizona; and by *Amblyomma cajennense* in Central and South America. Maintained principally by transovarian transmission from one generation of ticks to the next, *R. rickettsii* can be acquired by uninfected ticks through the ingestion of a blood meal from rickettsemic small mammals. [3]

Humans become infected during tick season (in the Northern Hemisphere, from May to September), although some cases occur in winter. The mortality rate was 20–25% in the preantibiotic era and remains at ~3–5% principally because of delayed diagnosis and treatment. The case-fatality ratio increases with each decade of life above age 20. [3]

Pathogenesis:

R. rickettsii organisms are inoculated into the dermis along with secretions of the tick's salivary glands after 6 h of feeding. The rickettsiae spread lymphohematogenously throughout the body and infect numerous foci of contiguous endothelial cells. The dose-dependent incubation period is ~1 week (range, 2–14 days). Occlusive thrombosis and ischemic necrosis are not the fundamental pathologic basis for tissue and organ injury. Instead, increased vascular permeability, with resulting edema, hypovolemia, and ischemia, is responsible. Consumption of

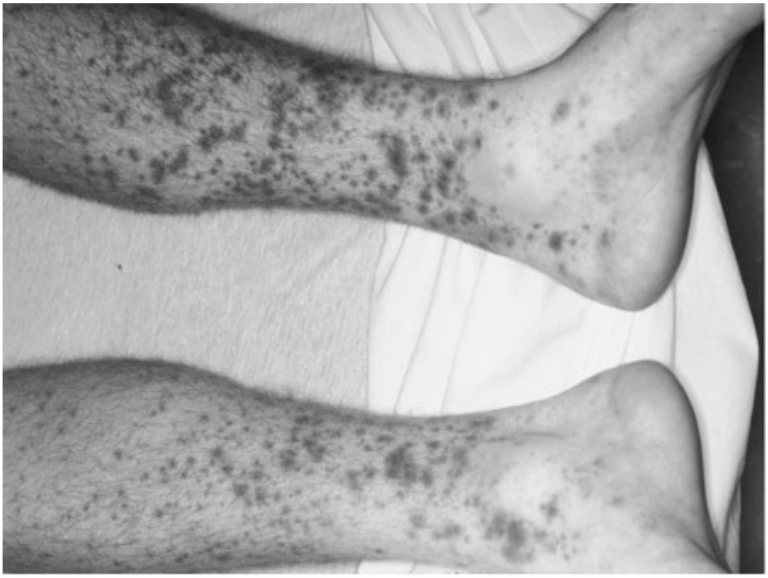
platelets results in thrombocytopenia in 32–52% of patients, but disseminated intravascular coagulation with hypofibrinogenemia is rare. Activation of platelets, generation of thrombin, and activation of the fibrinolytic system all appear to be homeostatic physiologic responses to endothelial injury.[3]

Clinical features:

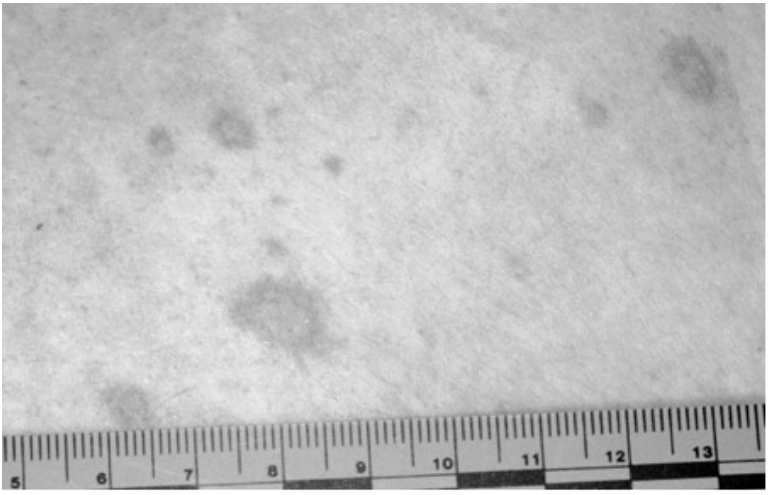
Early in the illness, when medical attention usually is first sought, RMSF is difficult to distinguish from many self-limiting viral illnesses. Fever, headache, malaise, myalgia, nausea, vomiting, and anorexia are the most common symptoms during the first 3 days. The patient becomes progressively more ill as vascular infection and injury advance. In one large series, only one-third of patients were diagnosed with presumptive RMSF early in the clinical course and treated appropriately as outpatients. In the tertiary care setting, RMSF is all too often recognized only when late severe manifestations, developing at the end of the first week or during the second week of illness in patients without appropriate treatment, prompt return to a physician or hospital and admission to an intensive care unit.[3]

The progressive nature of the infection is clearly manifested in the skin. Rash is evident in only 14% of patients on the first day of illness and in only 49% during the first 3 days. Macules (1–5 mm) appear first on the wrists and ankles and then on the remainder of the extremities and the trunk. Later, more severe vascular damage results in frank hemorrhage at the center of the maculopapule, producing a petechia that does not disappear upon compression (Fig. 69). This sequence of events is sometimes delayed or aborted by effective treatment. However, the rash is a variable manifestation, appearing on day 6 or later in 20% of cases and not appearing at all in 9–16% of cases. Petechiae occur in 41–59% of cases, appearing on or after day 6 in 74% of cases that include a rash. Involvement of the palms and soles, often considered

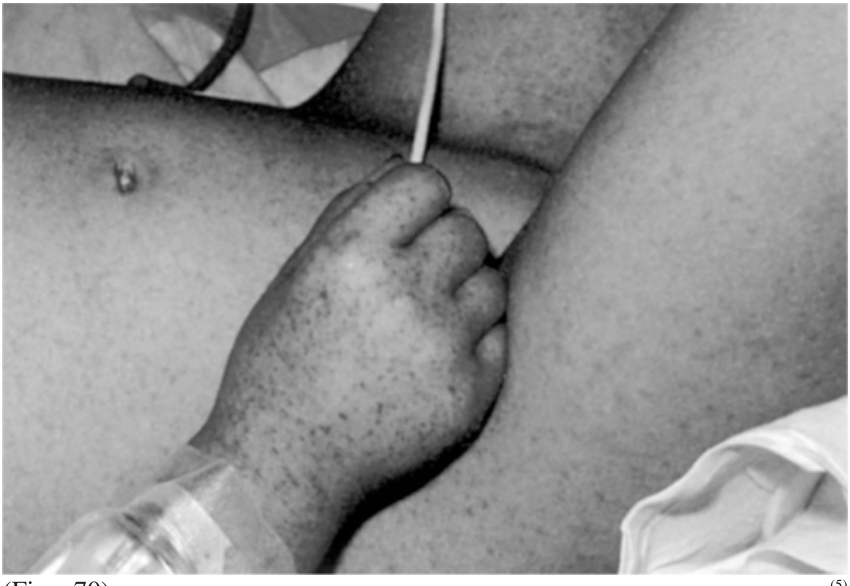
diagnostically important, usually develops relatively late in the course (after day 5 in 43% of cases) and does not develop at all in 18–64% of cases.[3]



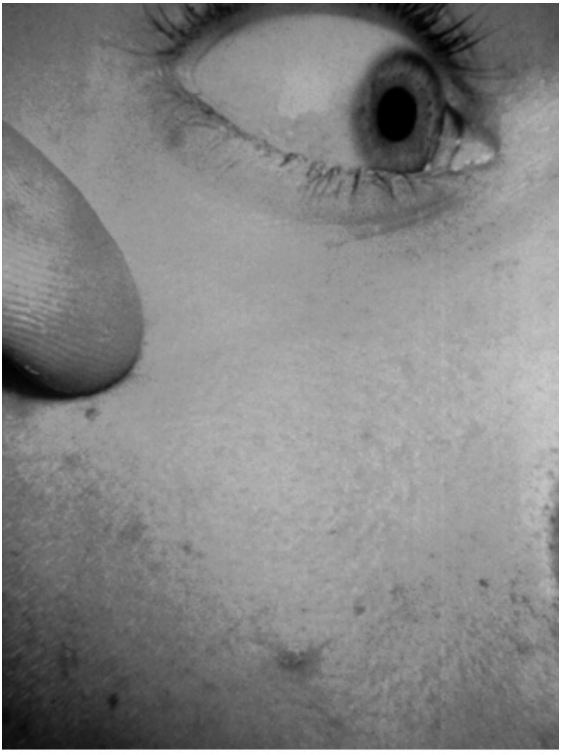
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



(Fig. 69)***Top:*** **Petechial lesions of Rocky Mountain spotted fever** on the lower legs and soles of a young, previously healthy patient. ***Bottom:*** **Close-up of lesions** from the same patient. *(Photos courtesy of Dr. Lindsey Baden; with permission.)*

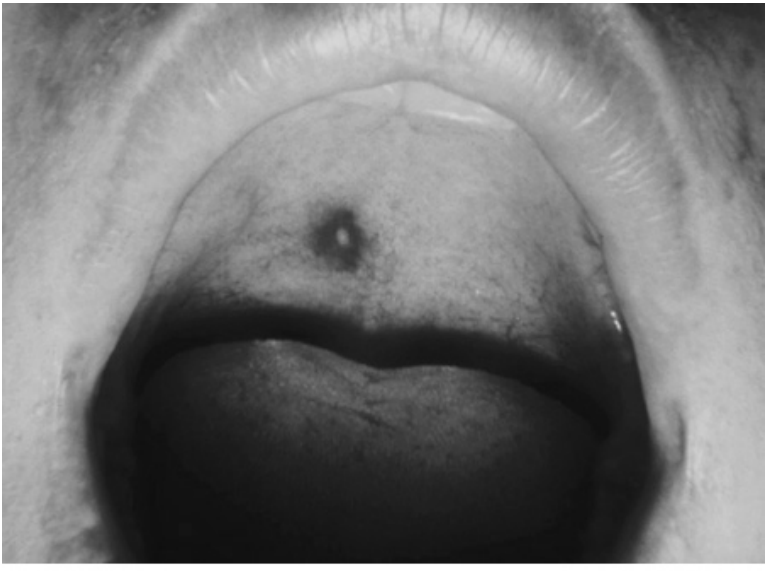


(Fig. 70) Rocky Mountain spotted fever. *(Courtesy of Debra Karp Skopocki, MD.)* [5]



Source: McPhee SJ, Papadakis MA: *Current Medical Diagnosis and Treatment 2009*, 48th Edition: http://www.accessmedicine.com

(Fig. 71)Spotted rash of eye and face due to Rocky Mountain spotted fever. (Public Health Image Library, CDC.)



(Fig. 72)Hard palate lesion caused by Rocky Mountain spotted fever. (Public Health Image Library, CDC.)

Hypovolemia leads to prerenal azotemia and (in 17% of cases) hypotension. Infection of the pulmonary microcirculation leads to noncardiogenic pulmonary edema; 12% of patients have severe respiratory disease, and 8% require mechanical ventilation. [3] Cardiac involvement manifests as dysrhythmia in 7–16% of cases. Besides the preceding respiratory failure, central nervous system (CNS) involvement is the other important determinant of the outcome of RMSF. Encephalitis, presenting as confusion or lethargy, is apparent in 26–28% of cases. Progressively severe encephalitis manifests as stupor or delirium in 21–26% of cases,

as ataxia in 18%, as coma in 10%, and as seizures in 8%. Numerous focal neurologic deficits have been reported. Meningoencephalitis results in cerebrospinal fluid (CSF) pleocytosis in 34–38% of cases; usually there are 10–100 cells/L and a mononuclear predominance, but occasionally there are >100 cells/L and a polymorphonuclear predominance. The CSF protein concentration is increased in 30–35% of cases, but the CSF glucose concentration is usually normal. [3]

Renal failure, often reversible with rehydration, is caused by acute tubular necrosis in severe cases with shock. Hepatic injury with increased serum aminotransferase concentrations (38% of cases) is due to focal death of individual hepatocytes without hepatic failure. Jaundice is recognized in 9% of cases and an elevated serum bilirubin concentration in 18–30%. [3]

Life-threatening bleeding is rare. Anemia develops in 30% of cases and is severe enough to require transfusions in 11%. Blood is detected in the stools or vomitus of 10% of patients, and death has followed massive upper gastrointestinal hemorrhage. [3]

Other characteristic clinical laboratory findings include increased plasma levels of proteins of the acute-phase response (C-reactive protein, fibrinogen, ferritin, and others), hypoalbuminemia, and hyponatremia (in 56% of cases) due to the appropriate secretion of antidiuretic hormone in response to the hypovolemic state. Myositis occurs occasionally, with marked elevations in serum creatine kinase levels and multifocal rhabdomyonecrosis. Ocular involvement includes conjunctivitis in 30% of cases and retinal vein engorgement, flame hemorrhages, arterial occlusion, and papilledema with normal CSF pressure in some instances. [3]

In untreated cases, the patient usually dies 8–15 days after onset. A rare presentation, fulminant RMSF, is fatal within 5 days after onset. This fulminant presentation is seen most often in black males with glucose-6-phosphate dehydrogenase (G6PD)

deficiency and may be related to an undefined effect of hemolysis on the rickettsial infection. Although survivors of RMSF usually return to their previous state of health, permanent sequelae, including neurologic deficits and gangrene necessitating amputation of extremities, may follow severe illness. [3]

Diagnosis:

The diagnosis of RMSF during the acute stage is more difficult than is generally appreciated. The most important epidemiologic factor is a history of exposure to a potentially tick-infested environment within the 12 days preceding disease onset during a season of possible tick activity. However, only 60% of patients actually recall being bitten by a tick during the incubation period.

The differential diagnosis for early clinical manifestations of RMSF (fever, headache, and myalgia without a rash) includes influenza, enteroviral infection, infectious mononucleosis, viral hepatitis, leptospirosis, typhoid fever, gram-negative or gram-positive bacterial sepsis, HME, HGA, murine typhus, sylvatic flying-squirrel typhus, and rickettsialpox. Enterocolitis may be suggested by nausea, vomiting, and abdominal pain; prominence of abdominal tenderness has resulted in exploratory laparotomy. CNS involvement may masquerade as bacterial or viral meningoencephalitis. Cough, pulmonary signs, and chest radiographic opacities may lead to a diagnostic consideration of bronchitis or pneumonia. [3]

At presentation during the first 3 days of illness, only 3% of patients exhibit the classic triad of fever, rash, and history of tick exposure. When a rash appears, a diagnosis of RMSF should certainly be considered. However, many illnesses considered in the differential diagnosis may also be associated with a rash, including rubeola, rubella, meningococcemia, disseminated gonococcal infection, secondary syphilis, toxic shock syndrome, drug hypersensitivity, idiopathic thrombocytopenic purpura,

thrombotic thrombocytopenic purpura, Kawasaki syndrome, and immune complex vasculitis. Conversely, any person in an endemic area with a provisional diagnosis of one of the above illnesses may have RMSF. Thus, if a viral infection is suspected during RMSF season in an endemic area, it should always be kept in mind that RMSF can mimic viral infection early in the course; if the illness worsens over the next couple of days after initial presentation, the patient should return for reevaluation. [3]

The most common serologic test for confirmation of the diagnosis is the indirect immunofluorescence assay. Not until 7–10 days after onset is a diagnostic titer of 1:64 usually detectable. The sensitivity and specificity of the indirect immunofluorescence assay are 94–100% and 100%, respectively. It is important to understand that serologic tests for RMSF are usually negative at the time of presentation for medical care and that treatment should not be delayed while a positive serologic result is awaited. [3]

The only diagnostic test that is useful during the acute illness is immunohistologic examination of a cutaneous biopsy sample from a rash lesion for *R. rickettsii*. Examination of a 3-mm punch biopsy from such a lesion is 70% sensitive and 100% specific. Polymerase chain reaction (PCR) amplification and detection of *R. rickettsii* DNA in peripheral blood is a relatively insensitive approach except when the patient is already in the preterminal state. Rickettsiae are present in large quantities in heavily infected foci of endothelial cells but in relatively low quantities in the circulation. Cultivation of rickettsiae in cell culture is feasible but is seldom undertaken because of biohazard concerns. [3]

Treatment:

The drug of choice for the treatment of both children and adults with RMSF is doxycycline, except when the patient is pregnant or allergic to this drug (see below). Because of the severity of RMSF, immediate empirical administration of doxycycline should

be strongly considered for any patient with a consistent clinical presentation in the appropriate epidemiologic setting. Doxycycline is administered orally (or, in the presence of coma or vomiting, intravenously) at 200 mg/d in two divided doses. For children with suspected RMSF, up to five courses of doxycycline may be administered with minimal risk of dental staining. Other regimens include oral tetracycline (25–50 mg/kg per day) in four divided doses. Treatment with chloramphenicol is advised only for patients who are pregnant or allergic to doxycycline. The antirickettsial drug should be administered until the patient has been afebrile and improving clinically for 2–3 days. Beta-Lactam antibiotics, erythromycin, and aminoglycosides have no role in the treatment of RMSF, and sulfa-containing drugs are likely to exacerbate this infection. There is little clinical experience with fluoroquinolones, clarithromycin, and azithromycin, which are not recommended. The most seriously ill patients are managed in intensive care units, with careful administration of fluids to achieve optimal tissue perfusion without precipitating noncardiogenic pulmonary edema. In some severely ill patients, hypoxemia requires intubation and mechanical ventilation; oliguric or anuric acute renal failure requires hemodialysis; seizures necessitate the use of antiseizure medication; anemia or severe hemorrhage necessitates transfusions of packed red blood cells; or bleeding with severe thrombocytopenia requires platelet transfusions. Heparin is not a useful component of treatment, and there is no evidence that glucocorticoids affect outcome. [3]

Prevention:

Avoidance of tick bites is the only available preventive approach. Use of protective clothing and tick repellents, inspection of the body once or twice a day, and removal of ticks before they inoculate rickettsiae reduce the risk of infection. [3]

Mediterranean Spotted Fever (Boutonneuse Fever)

African Tick-Bite Fever, and Other Tick-Borne Spotted Fevers
R. conorii is prevalent in southern Europe, Africa, and southwestern and south-central Asia. Regional names for the disease caused by this organism include Mediterranean spotted fever, Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan spotted fever. The disease is characterized by high fever, rash, and—in most geographic locales—an inoculation eschar (*tâche noire*) at the site of the tick bite. A severe form of the disease (mortality rate, 50%) occurs in patients with diabetes, alcoholism, or heart failure.[1] (3)

Diagnosis:

Diagnosis of these tick-borne spotted fevers is based on clinical and epidemiologic findings and is confirmed by serology,

[1] *African tick-bite fever*, caused by *R. africae,* occurs in rural areas of sub-Saharan Africa and in the Caribbean islands and is transmitted by *Amblyomma hebraeum* and *A. variegatum* ticks. The average incubation period is 7 days. The mild illness consists of headache, fever, eschar, and regional lymphadenopathy. *Amblyomma* ticks often feed in groups, with the consequent development of multiple eschars. Rash may be vesicular, sparse, or absent altogether. Because of tourism in sub-Saharan Africa, African tick-bite fever is the most frequently imported rickettsiosis in Europe and North America. A similar disease caused by the very closely related *R. parkeri* is transmitted by *A. maculatum* in the United States and *A. triste* in South America. (3)
R. japonica causes *Japanese spotted fever,* which also occurs in Korea. A similar disease in northern Asia is caused by *R. sibirica*. *Queensland tick typhus* due to *R. australis* is transmitted by *Ixodes holocyclus. Flinders Island spotted fever*, found on the island for which it is named as well as in other parts of Tasmania, in mainland Australia, and in southeastern Asia, is caused by *R. honei*. In Europe, patients infected with *R. slovaca* after a wintertime *Dermacentor* tick bite manifest an afebrile illness with an eschar (usually on the scalp) and regional lymphadenopathy. (3)

immunohistochemical demonstration of rickettsiae in skin biopsy specimens, cell-culture isolation of rickettsiae, or PCR of skin biopsy or blood samples. The serologic identification of the etiologic species requires knowledge of all the potential agents as well as expensive, laborious cross-adsorption of the patient's serum. In an endemic area, patients presenting with fever, rash, and/or a skin lesion consisting of a black necrotic area or a crust surrounded by erythema should be considered to have one of these rickettsial spotted fevers. [3]

Treatment:

Successful therapeutic agents include doxycycline (100 mg bid orally for 1–5 days), ciprofloxacin (750 mg bid orally for 5 days), and chloramphenicol (500 mg qid orally for 7–10 days). Pregnant patients may be treated with josamycin (3 g/d orally for 5 days). Data on the efficacy of treatment of mildly ill children with clarithromycin or azithromycin should not be extrapolated to adults or to patients with moderate or severe illness. [3]

Prevention:

MSF is transmitted by tick bites, and Prevention is best accomplished by eliminating tick infestations of dogs, avoiding wooded or grassy areas where ticks reside, using insect repellents containing DEET, wearing protective clothing, and carefully inspecting children who have been playing in the woods or fields. No vaccine is currently available. [5]

Scrub Typhus (Orientia tsutsugamushi)

Scrub typhus is a common and important febrile infectious disease in many parts of the Eastern hemisphere. Recent reports suggest that natural resistance to doxycycline and other antibiotics make selection of appropriate antimicrobial therapy difficult. [5]

Epidemiology:

Scrub typhus is transmitted by the bite of trombiculid mite larvae infected by *O. tsutsugamushi.* These mites, also named chiggers, are vertically infected through their mother. Scrub typhus distribution is limited to a triangle extending between northern Japan, eastern Australia, and eastern Russia and includes the Far East, China, and the Indian subcontinent. All together, 1 billion people may be exposed. Seasonality is determined by the emergence of larvae. In temperate zones, it occurs mainly in autumn and to a lesser extent in spring. *O. tsutsugamushi* species have a wide heterogenicity that may allow the definition of several species, but currently a single species is recognized with many serotypes. The more frequent are Kato, Karp, Gilliam, and Kawasaki. [5]

Clinical features:

The disease occurs in patients exposed to rural or urban foci of scrub typhus after a delay of 10 or more days. The onset is usually sudden and includes fever, headache, and myalgias. Attentive examination may reveal an inoculation eschar at the site of the mite bite and tender draining lymph nodes. Generalized lymphadenopathy and rash may be observed. The symptoms vary

according to organ involvement. Neuromeningeal symptoms are relatively common. Severe forms can be manifested as septic shock. [5]

Leukopenia, thrombocytopenia, and increased levels of hepatic enzymes can occur. Evolution depends on the hosts and strains, and the fatality rate ranges from 0 to 30%. Scrub typhus is not more severe in HIV-infected patients, and surprisingly, HIV suppressive factors appear to be produced during infection. Relapses may occur in this disease. [5]

Diagnosis:

Diagnosis may be difficult. Because the clinical features are frequently not specific, epidemiologic factors are critical. A diagnosis of infectious mononucleosis has erroneously been made in patients with scrub typhus. The bacterium can be detected by culture (in cells or mice) or by PCR in blood and biopsy specimens. Serologically, the technique first used was agglutination of *Proteus mirabilis* serotype OXK in the Weil-Felix reaction. This test lacks sensitivity and specificity and should be replaced by IFA or enzyme-linked immunosorbent assay tests using the three or four major serotypes. [5]

Treatment:

Chloramphenicol was the mainstay of treatment for many years, but now doxycycline is recommended. Single-day treatment with doxycycline is followed by relapses, and even repeated treatment for 2 days at a 7-day interval does not prevent all relapses. Hence, the currently recommended regimen is doxycycline, 100 mg orally twice a day, for 7 days. Cases resistant to doxycycline have been reported, and rifampin (600 mg orally daily) is a reasonable alternative. Prophylaxis is based on the use of repellents. [5]

Prevention:

Prevention is based on avoidance of the chiggers that transmit *O. tsutsugamushi.* Protective clothing is the next most useful mode of prevention. Infection provides immunity to reinfection by homologous but not heterologous strains; however, since natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection. [5]

Rickettsialpox

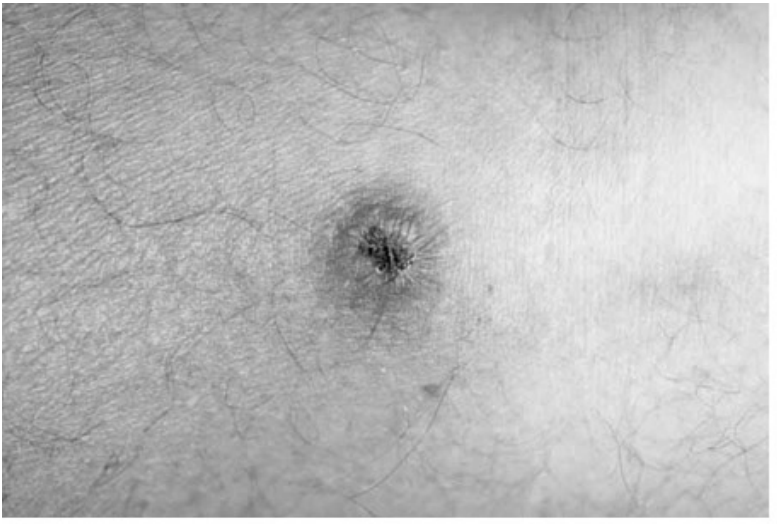
R. akari infects mice and their mites (*Liponyssoides sanguineus*), which maintain the organisms by transovarian transmission. [3]

Epidemiology:

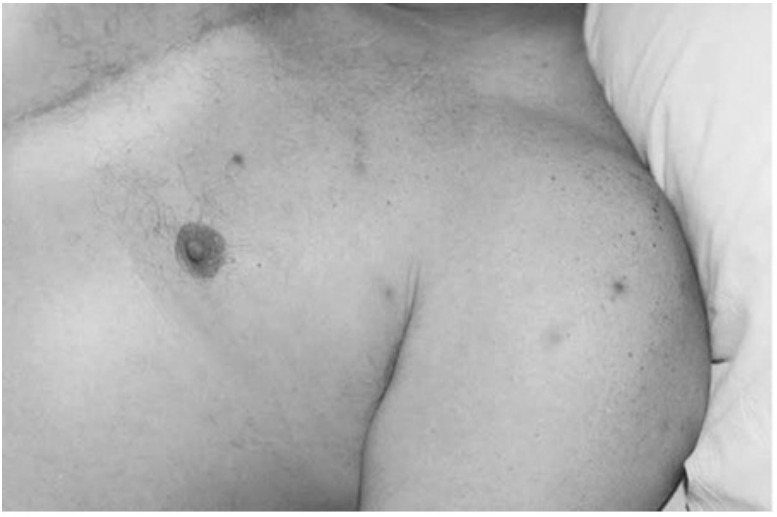
Rickettsialpox is recognized principally in New York City, but cases have also been reported in other urban and rural locations in the United States and in Ukraine, Croatia, and Turkey. [3] Investigation of eschars suspected of representing bioterrorism-associated cutaneous anthrax has revealed that rickettsialpox occurs more frequently than previously realized. [3]

Clinical features:

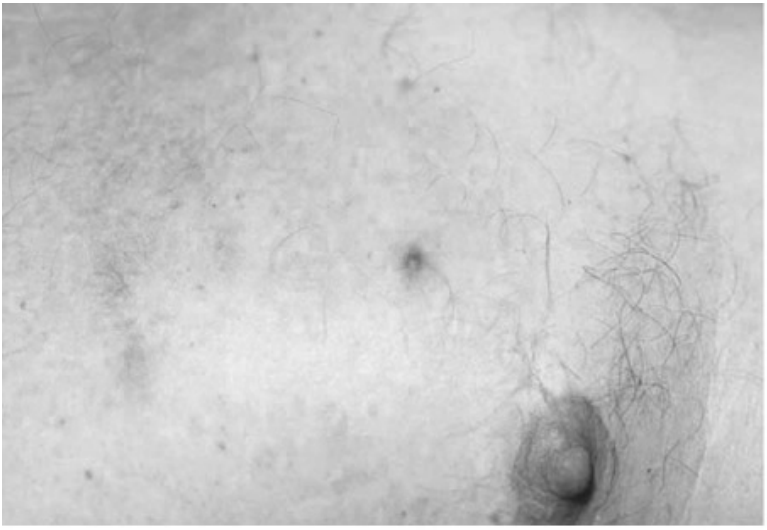
A papule forms at the site of the mite's feeding, develops a central vesicle, and becomes a 1- to 2.5-cm painless black crusted eschar surrounded by an erythematous halo (Fig. 167-2). Enlargement of the regional lymph nodes draining the eschar suggests initial lymphogenous spread. After an incubation period of 10–17 days, during which the eschar and regional lymphadenopathy frequently go unnoticed, onset is marked by malaise, chills, fever, headache, and myalgia. A macular rash appears 2–6 days after onset and evolves sequentially into papules, vesicles, and crusts that heal without scarring (Fig. 73). The rash may remain macular or maculopapular. Some patients develop nausea, vomiting, abdominal pain, cough, conjunctivitis, or photophobia. If untreated, fever lasts 6–10 days. [3]



(Fig. 73)**Eschar at the site of the mite bite in a patient with rickettsialpox.** *(Reprinted from A Krusell et al: Emerg Infect Dis 8:727, 2002. Photo obtained by Dr. Kenneth Kaye.)*



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



(Fig. 74)***Top:*** **Papulovesicular lesions on the trunk of the patient with rickettsialpox** shown in Fig. 167-2. ***Bottom:*** **Close-up of lesions** from the same patient. *(Reprinted from A Krusell et al: Emerg Infect Dis 8:727, 2002. Photos obtained by Dr. Kenneth Kaye.)*

Diagnosis:

Clinical, epidemiologic, and convalescent serologic data establish the diagnosis of a spotted fever group rickettsiosis that is seldom pursued further. [3]

Treatment:

Doxycycline is the drug of choice for treatment. [3]

Q FEVER

Definition:

The name Q fever is derived from "query" to emphasize the surprising aspect of the disease first described in Queensland, Australia, in 1935 by Derrick. The infection in humans is variable in its severity, clinical expression, and natural course (i.e., acute or chronic). It is considered by the CDC to be a potential agent of bioterrorism. Ungulates and pets are the major sources of human infection. [4]

Aetiology:

Coxiella burnetii is a gram-negative bacterium that naturally infects its host's monocytes. It multiplies in an acidic vacuole. Strains are heterogeneous genetically and antigenically and are associated with acute infections of variable severity. *C. burnetii* in vitro generates a deleted, avirulent mutant also named phase II. This mutant exhibits diagnostic antigens that are useful because they are more reactive during acute infection. [4]

Epidemiology:

Q fever is a worldwide zoonosis.

C. burnetii infects a wide range of animals, including mammals, birds, and ticks. Ungulates and pets (cats and dogs) are the most common source of the disease. Mammals are infected through aerosols and may shed *Coxiella* in feces, urine, milk, and birth products. Humans are usually infected by aerosols or less frequently by exposure to milk products. Interhuman infections through sexual intercourse, during delivery, or by blood transfusion have been reported. *Coxiella* survives in the environment and can be spread far by the wind. In the past few

years, major outbreaks were related to sheep and goats. The disease is partly seasonal and related to lambing time. The current geographic repartition is largely unknown. Males have more severe disease but are not more often exposed to Q fever, and middle-aged people are more frequently affected and hospitalized. [4]

Clinical features:

After contamination by *C. burnetii,* 60% of patients seroconvert without apparent disease, 38% experience a self-limited disease, and only 2% require diagnostic evaluation. Months to years after the primary infection, a chronic infection associated with an immunocompromised situation, a cardiac valve lesion, or a vascular prosthesis or aneurysm develops in 0.2 to 0.5% of patients. [4]

Patients with diagnosed acute infection may have a variety of symptoms. Isolated prolonged fever was observed in 14% of more than 1000 patients. Pneumonia was found in 37% and was the only symptom in 17%. This percentage may vary according to the place of study and reach 90% of diagnosed cases. Some cases may be associated with respiratory distress. Hepatitis is found in 60% of patients and is the sole manifestation in 40%. The association of fever and a moderate increase in transaminases is an important clue. Some hepatitides, specifically in middle-aged men, are associated with an inflammatory syndrome and autoantibodies and may be resistant to antimicrobial treatment. Liver biopsy, when performed, exhibits granulomas that may be typified by a lipid vacuole and surrounded by a fibrinoid ring in the form of a doughnut. Less frequently, in 1.5% of cases, patients exhibit a rash. Patients can have specific neurologic manifestations such as meningitis, encephalitis, meningoencephalitis, or peripheral neuropathy. In 1 to 2% of cases, patients have cardiovascular manifestations such as pericarditis or more rarely myocarditis. [4]

Evolution is usually favorable even without treatment, except in special hosts. In pregnant women, symptomatic or not, Q fever compromises the pregnancy. When infected during the first trimester, the patient usually aborts spontaneously. When the patient is infected later, the disease can result in fetal death or prematurity, or the outcome may be normal. Chronic uterine infection may develop in half the patients infected during pregnancy, and they may later experience multiple spontaneous abortions. Thirty to 50% of patients with heart valve or vascular lesions may experience chronic endocarditis within 2 years. This evolution is not prevented by regular treatment. (4)

Patients with Q fever endocarditis have a chronic infection with low-grade fever, progressive degradation of valve function, and progressive heart failure. Fever is intermittent, and vegetations are frequently absent on cardiac echocardiography. Endocarditis is therefore not frequently considered in the initial differential diagnosis. If not diagnosed, the disease progressively worsens and emboli (mainly cerebral) may be observed, as well as renal insufficiency, splenomegaly, and hepatomegaly. Digital clubbing may also be seen. The main clue to the diagnosis in a patient with a valvulopathy is unexplained sickness (unexplained fatigue, weight loss, fever), a biologic abnormality (leukopenia, increased erythrocyte sedimentation rate, thrombocytopenia, increase in hepatic enzymes), or rapid degradation of a prosthetic valve. Chronic osteomyelitis, hepatitis, and infection of an aneurysm and vascular prosthesis have been reported. (4)

Leukopenia may be observed; thrombocytopenia is frequent, as are increases in hepatic enzymes. (4)

Circulating anticoagulant associated with antiphospholipid antibodies may be observed, as may anti–smooth muscle antibodies. During endocarditis, antinuclear antibodies, microhematuria, and rheumatoid factor are frequently found. (4)

Diagnosis:

The diagnosis is based mainly on serology. Direct detection by culture and PCR or immunochemistry in valve, liver, or blood samples is also useful, but serologic evaluation by IFA is the best method. Two antigens (phase I and phase II) can be tested. Acute Q fever is diagnosed when seroconversion or a fourfold increase is obtained with phase II antigen. A single serum test exhibiting IgG antibodies of 200 or greater and IgM of 50 or greater against phase II is also diagnostic. During chronic Q fever, antibodies are at higher titer and directed against both phase I and phase II. IgG against phase I at a titer of 800 or 1600 is diagnostic of chronic infection, as is IgA at 100 or greater. Serology is useful for follow-up of patients with acute Q fever and underlying disease and those with treated chronic Q fever. [(4)]

Treatment:

Treatment is easy during acute Q fever. Doxycycline is the most efficient antimicrobial, and it should be prescribed for 2 weeks. Some patients with hepatitis do not respond well because of an excessive immune response. They rapidly improve with a short course of glucocorticoids. In pregnant women, cotrimoxazole during the entire pregnancy may decrease the chance of an unfavorable outcome. As for endocarditis, bactericidal treatment is necessary. In vitro, antimicrobial efficacy is impaired by the low pH of the vacuole in which *C. burnetii* resides. [(4)]

Hydroxychloroquine increases the pH of this vacuole and restores the bactericidal effect of doxycycline. In patients with endocarditis, the recommended treatment is a combination of doxycycline (200 mg daily) and hydroxychloroquine (600 mg/day, then adjusted to reach a 1-mg/mL plasma concentration). This regimen is prescribed for 18 to 36 months according to serologic results. We recently observed that a more rapid favorable outcome

was obtained with doxycycline serum levels higher than 5μg/mL. Some strains may be resistant to doxycycline, and new macrolides may be an alternative. The major problem with this treatment is photosensitivity; sun exposure should be avoided. An alternative treatment is a combination of doxycycline and ofloxacin for 3 or more years. [4]

Prevention:

Prevention is based on veterinary control in animals. A vaccine is currently available in Australia. [4]

Intestinal Nematodes

More than a billion persons worldwide are infected with one or more species of intestinal nematodes. Table 24 summarizes biologic and clinical features of infections due to the major intestinal parasitic nematodes. These parasites are most common in regions with poor fecal sanitation, particularly in resource-poor countries in the tropics and subtropics, but they have also been seen with increasing frequency among immigrants and refugees to resource-rich countries. Although nematode infections are not usually fatal, they contribute to malnutrition and diminished work capacity. It is interesting that these helminth infections may protect some individuals from allergic disease. Humans may on occasion be infected with nematode parasites that ordinarily infect animals; these zoonotic infections produce diseases such as trichostrongyliasis, anisakiasis, capillariasis, and abdominal angiostrongyliasis. [3]

Table 24 Major Human Intestinal Parasitic Nematodes

	Parasitic Nematode				
Feature	***Ascaris lumbricoides* (Roundworm)**	***Necator americanus, Ancylostoma duodenale* (Hookworm)**	***Strongyloides stercoralis***	***Trichuris trichiura* (Whipworm)**	***Enterobius vermicularis* (Pinworm)**
Global prevalence in humans (millions)	1221	740	50	795	300
Endemic areas	Worldwide	Hot, humid regions	Hot, humid regions	Worldwide	Worldwide
Infective stage	Egg	Filariform larva	Filariform larva	Egg	Egg
Route of infection	Oral	Percutaneous	Percutaneous or autoinfection	Oral	Oral
Gastrointestinal location of worms	Jejunal lumen	Jejunal mucosa	Small-bowel mucosa	Cecum, colonic mucosa	Cecum, appendix
Adult worm size	15–40 cm	7–12 mm	2 mm	30–50 mm	8–13 mm (female)
Pulmonary passage of larvae	Yes	Yes	Yes	No	No
Incubation period[a] (days)	60–75	40–100	17–28	70–90	35–45
Longevity	1 y	*N. americanus*: 2–5 y *A. duodenale*: 6–8 y	Decades (owing to autoinfection)	5 y	2 months
Fecundity (eggs/day/worm)	240,000	*N. americanus*:	5000–10,000	3000–7000	2000

		4000–10,000 *A. duodenale*: 10,000–25,000			
Principal symptoms	Rarely gastrointestinal or biliary obstruction	Iron-deficiency anemia in heavy infection	Gastrointestinal symptoms; malabsorption or sepsis in hyperinfection	Gastrointestinal symptoms, anemia	Perianal pruritus
Diagnostic stage	Eggs in stool	Eggs in fresh stool, larvae in old stool	Larvae in stool or duodenal aspirate; sputum in hyperinfection	Eggs in stool	Eggs from perianal skin on cellulose acetate tape
Treatment	Mebendazole Albendazole Pyrantel pamoate Ivermectin	Mebendazole Pyrantel pamoate Albendazole	1. Ivermectin 2. Albendazole	Mebendazole Albendazole Ivermectin	Mebendazole Pyrantel pamoate Albendazole

[a]Time from infection to egg production by mature female worm. [3]

Ascariasis

A. lumbricoides is the largest intestinal nematode parasite of humans, reaching up to 40 cm in length. Most infected individuals have low worm burdens and are asymptomatic. Clinical disease arises from larval migration in the lungs or effects of the adult worms in the intestines. (3)

Life Cycle:

Adult worms live in the lumen of the small intestine. Mature female *Ascaris* worms are extraordinarily fecund, each producing up to 240,000 eggs a day, which pass with the feces. Ascarid eggs, which are remarkably resistant to environmental stresses, become infective after several weeks of maturation in the soil and can remain infective for years. After infective eggs are swallowed, larvae hatched in the intestine invade the mucosa, migrate through the circulation to the lungs, break into the alveoli, ascend the bronchial tree, and return via swallowing to the small intestine, where they develop into adult worms. Between 2 and 3 months elapse between initial infection and egg production. Adult worms live for 1–2 years. (3)

Epidemiology:

Ascaris is widely distributed in tropical and subtropical regions as well as in other humid areas, including the rural southeastern United States. Transmission typically occurs through fecally contaminated soil and is due either to a lack of sanitary facilities or to the use of human feces as fertilizer. With their propensity for hand-to-mouth fecal carriage, younger children are most affected.

Infection outside endemic areas, though uncommon, can occur when eggs on transported vegetables are ingested. [3]

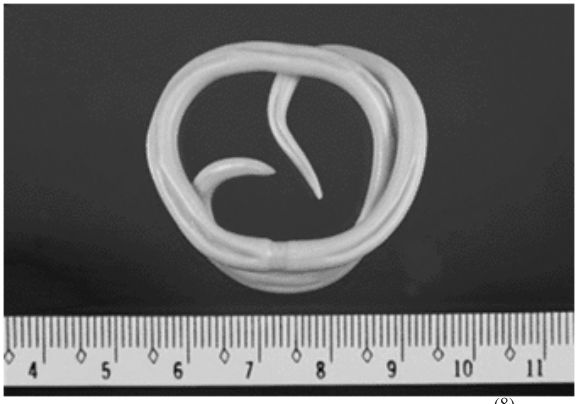
Clinical Features:

During the lung phase of larval migration, ~9–12 days after egg ingestion, patients may develop an irritating nonproductive cough and burning substernal discomfort that is aggravated by coughing or deep inspiration. Dyspnea and blood-tinged sputum are less common. Fever is usually reported. Eosinophilia develops during this symptomatic phase and subsides slowly over weeks. Chest x-rays may reveal evidence of eosinophilic pneumonitis (Löffler's syndrome), with rounded infiltrates a few millimeters to several centimeters in size. These infiltrates may be transient and intermittent, clearing after several weeks. Where there is seasonal transmission of the parasite, seasonal pneumonitis with eosinophilia may develop in previously infected and sensitized hosts. In established infections, adult worms in the small intestine usually cause no symptoms. In heavy infections, particularly in children, a large bolus of entangled worms can cause pain and small-bowel obstruction, sometimes complicated by perforation, intussusception, or volvulus. Single worms may cause disease when they migrate into aberrant sites. A large worm can enter and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, pancreatitis, or (rarely) intrahepatic abscesses. Migration of an adult worm up the esophagus can provoke coughing and oral expulsion of the worm. In highly endemic areas, intestinal and biliary ascariasis can rival acute appendicitis and gallstones as causes of surgical acute abdomen. [3]

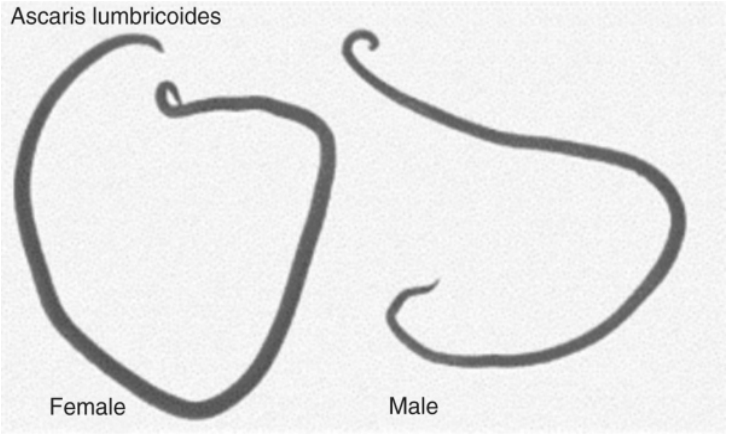
Laboratory Findings:

Most cases of ascariasis can be diagnosed by microscopic detection of characteristic *Ascaris* eggs (65 by 45 m) in fecal samples. Occasionally, patients present after passing an adult

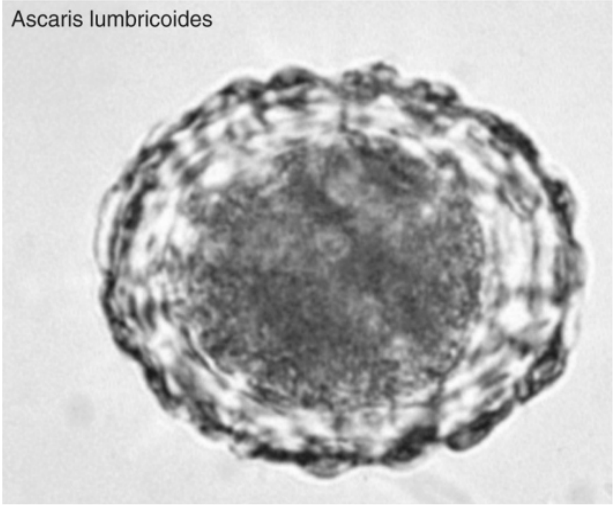
worm—identifiable by its large size and smooth cream-colored surface—in the stool or through the mouth or nose. During the early transpulmonary migratory phase, when eosinophilic pneumonitis occurs, larvae can be found in sputum or gastric aspirates before diagnostic eggs appear in the stool. The eosinophilia that is prominent during this early stage usually decreases to minimal levels in established infection. Adult worms may be visualized, occasionally serendipitously, on contrast studies of the gastrointestinal tract. A plain abdominal film may reveal masses of worms in gas-filled loops of bowel in patients with intestinal obstruction. Pancreaticobiliary worms can be detected by ultrasound and endoscopic retrograde cholangiopancreatography; the latter method also has been used to extract biliary *Ascaris* worms. [3]



(Fig. 75) Ascaris - scale in millimetres. [8]



(Fig. 76) Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: Ascariasis, trichuriasis, and hookworm. Lancet 2006;367:1521–1532.)* [5]



(Fig. 77) Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: Ascariasis, trichuriasis, and hookworm. Lancet 2006;367:1521–1532.)* [5]

Treatment:

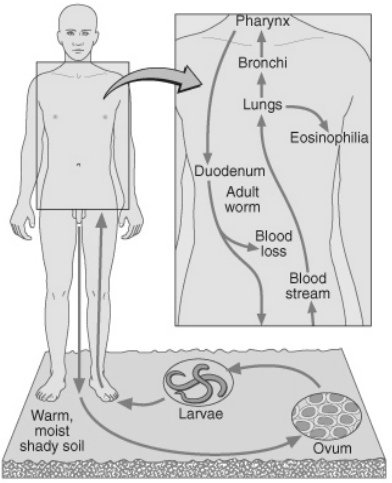
Ascariasis should always be treated to prevent potentially serious complications. Albendazole (400 mg once), mebendazole (500 mg once), or ivermectin (150–200 g/kg once) is effective. These medications are contraindicated in pregnancy, however. Pyrantel pamoate (11 mg/kg once; maximum, 1 g) is safe in pregnancy. Mild diarrhea and abdominal pain are uncommon side effects of these agents. Partial intestinal obstruction should be managed with nasogastric suction, IV fluid administration, and instillation of piperazine through the nasogastric tube, but complete obstruction and its severe complications require immediate surgical intervention.[3]

Hookworm

Two hookworm species (*Ancylostoma duodenale* and *Necator americanus*) are responsible for human infections. Most infected individuals are asymptomatic. Hookworm disease develops from a combination of factors—a heavy worm burden, a prolonged duration of infection, and an inadequate iron intake—and results in iron-deficiency anemia and, on occasion, hypoproteinemia. [3]

Life Cycle:

Adult hookworms, which are ~1 cm long, use buccal teeth (*Ancylostoma*) or cutting plates (*Necator*) to attach to the small-bowel mucosa and suck blood (0.2 mL/d per *Ancylostoma* adult) and interstitial fluid. The adult hookworms produce thousands of eggs daily. The eggs are deposited with feces in soil, where rhabditiform larvae hatch and develop over a 1-week period into infectious filariform larvae. Infective larvae penetrate the skin and reach the lungs by way of the bloodstream. There they invade alveoli and ascend the airways before being swallowed and reaching the small intestine. The prepatent period from skin invasion to appearance of eggs in the feces is ~6–8 weeks, but it may be longer with *A. duodenale*. Larvae of *A. duodenale*, if swallowed, can survive and develop directly in the intestinal mucosa. Adult hookworms may survive over a decade but usually live ~6–8 years for *A. duodenale* and 2–5 years for *N. americanus*. [3]



(Fig. 78) **Ancylostomiasis.** Life cycle of *Ancylostoma.* [2]

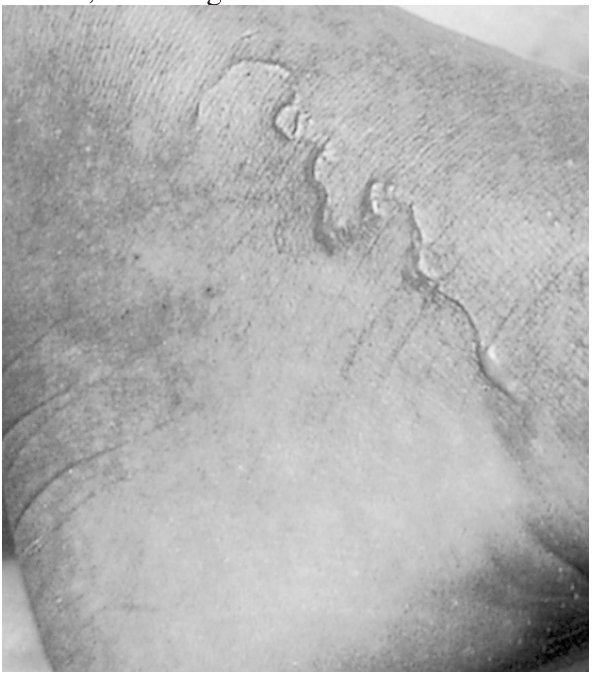
Epidemiology:

A. duodenale is prevalent in southern Europe, North Africa, and northern Asia, and *N. americanus* is the predominant species in the western hemisphere and equatorial Africa. The two species overlap in many tropical regions, particularly Southeast Asia. In most areas, older children have the highest incidence and greatest intensity of hookworm infection. In rural areas where fields are fertilized with human feces, older working adults also may be heavily affected. [3]

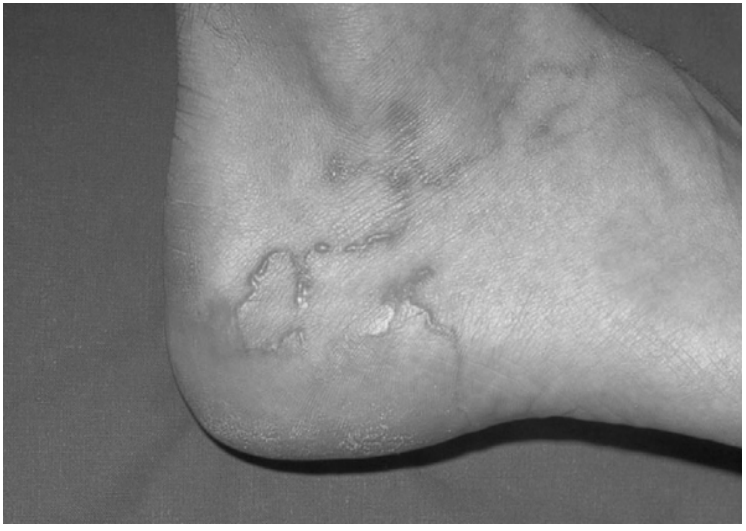
Clinical Features:

Most hookworm infections are asymptomatic. Infective larvae may provoke pruritic maculopapular dermatitis ("ground itch") at the site of skin penetration as well as serpiginous tracks of subcutaneous migration (similar to those of cutaneous larva migrans) in previously sensitized hosts. Larvae migrating through the lungs occasionally cause mild transient pneumonitis, but this condition develops less frequently in hookworm infection than in

ascariasis. In the early intestinal phase, infected persons may develop epigastric pain (often with postprandial accentuation), inflammatory diarrhea, or other abdominal symptoms accompanied by eosinophilia. The major consequence of chronic hookworm infection is iron deficiency. Symptoms are minimal if iron intake is adequate, but marginally nourished individuals develop symptoms of progressive iron-deficiency anemia and hypoproteinemia, including weakness and shortness of breath. [3]



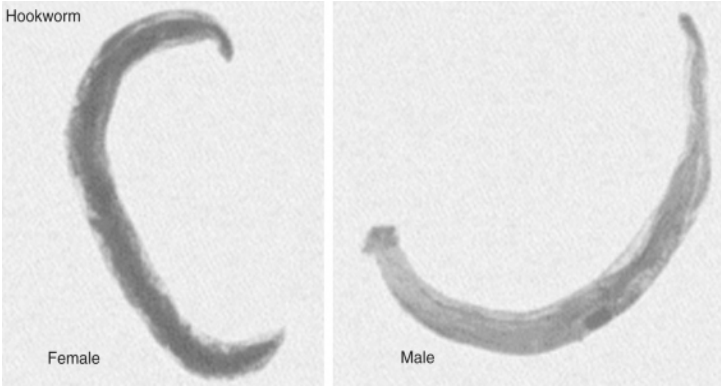
(Fig. 79) Creeping eruption of cutaneous larva migrans. *(From Korting GW: Hautkrankheiten bei Kindern und Jugendlichen. Stuttgart, Germany, FK Schattauer Verlag, 1969.)* [5]



(Fig. 80) **Cutaneous larva migrans.** Red, serpiginous lesions on the side of the foot. In the United States, the dog or cat hookworm (*Ancylostoma caninum* or *Ancylostoma braziliense*) is a common cause. [4]

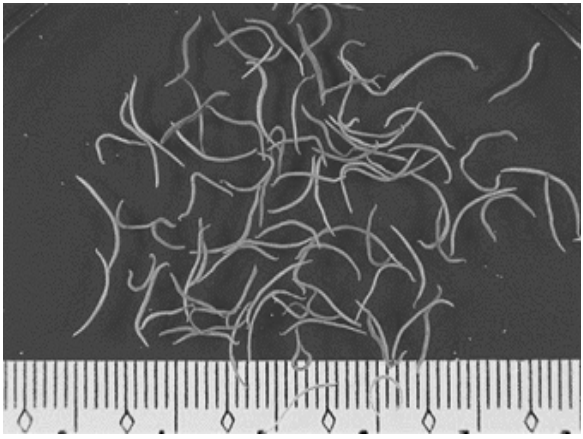
Laboratory Findings:

The diagnosis is established by the finding of characteristic 40- by 60- m oval hookworm eggs in the feces. Stool-concentration procedures may be required to detect light infections. Eggs of the two species are indistinguishable by light microscopy. In a stool sample that is not fresh, the eggs may have hatched to release rhabditiform larvae, which need to be differentiated from those of *S. stercoralis*. Hypochromic microcytic anemia, occasionally with eosinophilia or hypoalbuminemia, is characteristic of hookworm disease. [3]

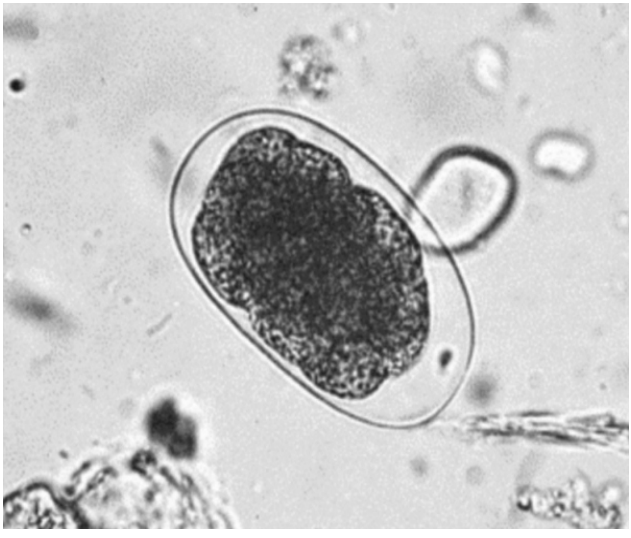


(Fig. 81) Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: Ascariasis, trichuriasis, and hookworm. Lancet 2006;367:1521–1532.)* [5]

(Fig. 82) **Enlargement showing hookworms, *Ancylostoma caninum*, attached to the intestinal mucosa.** Barely visible larvae penetrate the skin (often through bare feet), are carried to the lungs, go through the respiratory tract to the mouth, are swallowed, and eventually reach the small intestine. This journey takes about a week. *(From the Centers for Disease Control and Prevention Image Bank.)* [4]



(Fig. 83) Adult Ancylostoma duodenale - scale in millimetres. (Copyright Viqar Zaman.) [8]



(Fig. 84) Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: Ascariasis, trichuriasis, and hookworm. Lancet 2006;367:1521–1532.)* [5]

Treatment:

Hookworm infection can be eradicated with several safe and highly effective anthelmintic drugs, including albendazole (400 mg once), mebendazole (500 mg once), and pyrantel pamoate (11 mg/kg for 3 days). Mild iron-deficiency anemia can often be treated with oral iron alone. Severe hookworm disease with protein loss and malabsorption necessitates nutritional support and oral iron replacement along with deworming. [3]

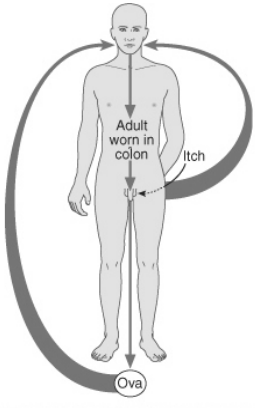
Ancylostoma caninum and *Ancylostoma braziliense A. caninum*, the canine hookworm, has been identified as a cause of human eosinophilic enteritis, especially in northeastern Australia. In this zoonotic infection, adult hookworms attach to the small intestine (where they may be visualized by endoscopy) and elicit abdominal pain and intense local eosinophilia. Treatment with mebendazole (100 mg twice daily for 3 days) or albendazole (400 mg once) or endoscopic removal is effective. Both of these animal hookworm species can cause cutaneous larva migrans ("creeping eruption"). [3]

Enterobiasis (Pinworm)

E. vermicularis is more common in temperate countries than in the tropics. In the United States, ~40 million persons are infected with pinworms, with a disproportionate number of cases among children. [3]

Life Cycle and Epidemiology:

Enterobius adult worms are ~1 cm long and dwell in the cecum. Gravid female worms migrate nocturnally into the perianal region and release up to 10,000 immature eggs each. The eggs become infective within hours and are transmitted by hand-to-mouth passage. From ingested eggs, larvae hatch and mature into adults. This life cycle takes ~1 month, and adult worms survive for ~2 months. Self-infection results from perianal scratching and transport of infective eggs on the hands or under the nails to the mouth. Because of the ease of person-to-person spread, pinworm infections are common among family members. [3]



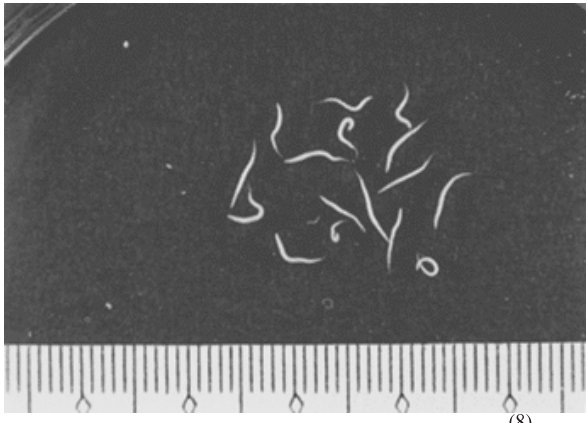
(Fig. 85) **Threadworm.** Life cycle of *Enterobius vermicularis*. [2]

Clinical Features:

Most pinworm infections are asymptomatic. Perianal pruritus is the cardinal symptom. The itching, which is often worse at night as a result of the nocturnal migration of the female worms, may lead to excoriation and bacterial superinfection. Heavy infections have been claimed to cause abdominal pain and weight loss. On rare occasions, pinworms invade the female genital tract, causing vulvovaginitis and pelvic or peritoneal granulomas. Eosinophilia is uncommon. [3]

Diagnosis:

Since pinworm eggs are not released in feces, the diagnosis cannot be made by conventional fecal ova and parasites tests. Instead, eggs are detected by the application of clear cellulose acetate tape to the perianal region in the morning. After the tape is transferred to a slide, microscopic examination will detect pinworm eggs, which are oval, measure 55 by 25 m, and are flattened along one side. [3]



(Fig. 86) Enterobius - scale in millimetres. [8]

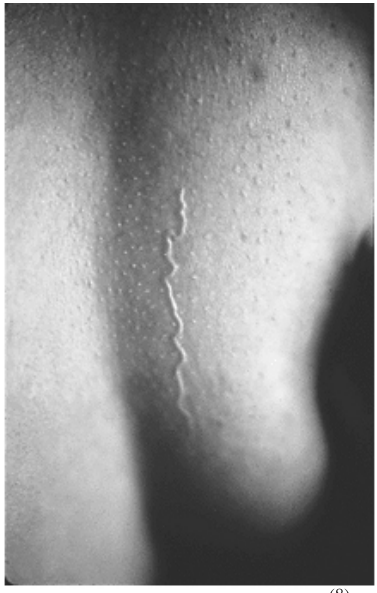
Treatment:

Infected children and adults should be treated with mebendazole (100 mg once), albendazole (400 mg once), or pyrantel pamoate (11 mg/kg once; maximum, 1 g), with the same treatment repeated after 2 weeks. Treatment of household members is advocated to eliminate asymptomatic reservoirs of potential reinfection. [3]

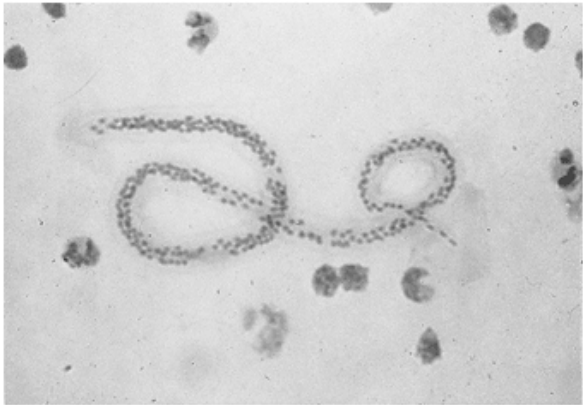
Filarial Infections

Filarial worms are nematodes that dwell in the subcutaneous tissues and the lymphatics. Eight filarial species infect humans (Table 20); of these, four—*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa*—are responsible for most serious filarial infections. Filarial parasites, which infect an estimated 170 million persons worldwide, are transmitted by specific species of mosquitoes or other arthropods and have a complex life cycle including infective larval stages carried by insects and adult worms that reside in either lymphatic or subcutaneous tissues of humans. (Fig 36) The offspring of adults are microfilariae, which, depending on their species, are 200–250 micro m long and 5–7 micro m wide, may or may not be enveloped in a loose sheath, and either circulate in the blood or migrate through the skin. To complete the life cycle, microfilariae are ingested by the arthropod vector and develop over 1–2 weeks into new infective larvae. Adult worms live for many years, whereas microfilariae survive for 3–36 months. The *Rickettsia*-like endosymbiont *Wolbachia* has been found intracellularly in all stages of *Brugia*, *Wuchereria*, *Mansonella*, and *Onchocerca* and is viewed as a possible target for antifilarial chemotherapy. [3]

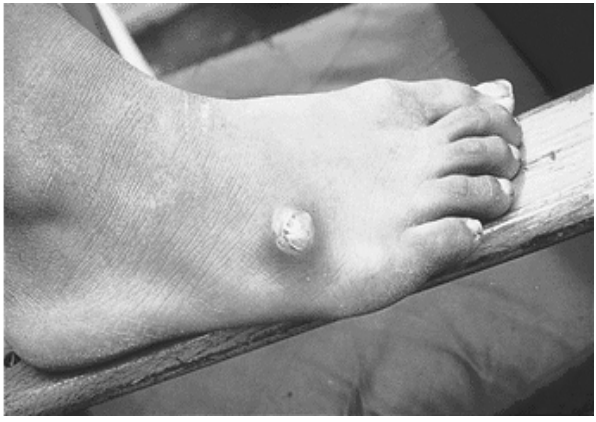
(Fig. 87) Elephantiasis of legs due to filariasis. (Public Health Image Library, CDC.) [7]



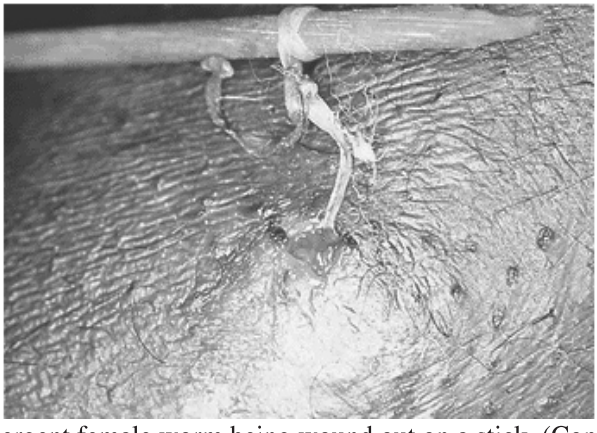
(Fig. 88) Migrating Loa loa. [8]



(Fig. 89) Microfilaria of Wuchereria bancrofti in a blood film from a patient in Samoa. (By courtesy of the Wellcome Museum of Medical Science.) [8]



(Fig. 90) Blister at site of imminent emergence of the female worm. (By courtesy of the late P.E.C. Manson-Bahr.) [8]



(Fig. 91) Emergent female worm being wound out on a stick. (Copyright D.A. Warrell.) [8]

(Fig. 92) Guinea worm in the scrotum. (Copyright D.A. Warrell.) [8]

Table 25 Characteristics of the Filariae

Organism	**Periodicity**	**Distribution**	**Vector**	**Location of Adult**	**Microfilarial Location**	**Sheath**
Wuchereria bancrofti	Nocturnal	Cosmopolitan areas worldwide, including South America and Africa	*Culex* (mosquitoes)	Lymphatic tissue	Blood	+
		Mainly India	*Anopheles* (mosquitoes)			
		China, Indonesia	*Aedes* (mosquitoes)			
	Subperiodic	Eastern Pacific	*Aedes* (mosquitoes)	Lymphatic tissue	Blood	+
Brugia malayi	Nocturnal	Southeast Asia, Indonesia, India	*Mansonia*, *Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+

	Subperiodic	Indonesia, Southeast Asia	*Coquillettidia*, *Mansonia* (mosquitoes)	Lymphatic tissue	Blood	+
B. timori	Nocturnal	Indonesia	*Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+
Loa loa	Diurnal	West and Central Africa	*Chrysops* (deerflies)	Subcutaneous tissue	Blood	+
Onchocerca volvulus	None	South and Central America, Africa	*Simulium* (blackflies)	Subcutaneous tissue	Skin, eye	-
Mansonella ozzardi	None	South and Central America	*Culicoides* (midges)	Undetermined site	Blood	-
		Caribbean	*Simulium* (blackflies)			
M. perstans	None	South and Central America, Africa	*Culicoides* (midges)	Body cavities, mesentery, perirenal tissue	Blood	-
M. streptocerca	None	West and Central Africa	*Culicoides* (midges)	Subcutaneous tissue	Skin	-

(3)

Treatment:

The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. No controlled studies demonstrate that administration of drugs such as diethylcarbamazine modifies the course of acute lymphangitis. Diethylcarbamazine may be given to asymptomatic microfilaremic persons to lower the intensity of parasitemia. The drug also kills a proportion of the adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypertension, and even death may occur,

especially with high microfilarial levels, the dose of diethylcarbamazine should be increased gradually (children, 1 mg/kg PO as a single dose on day 1, 1 mg/kg tid PO on day 2, 1–2 mg/kg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4–14; adults, 50 mg PO on day 1, 50 mg tid PO on day 2, 100 mg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4–14). For patients with no microfilaria in the blood, the full dose (6 mg/kg/day divided tid PO) can be given beginning on day 1. Repeat doses may be necessary to further reduce the microfilaremia and kill lymph-dwelling adult parasites. *W. bancrofti* is more sensitive than *B. malayi* to diethylcarbamazine. Global programs to control and ultimately eradicate lymphatic filariasis currently recommend a single annual dose of diethylcarbamazine (6 mg/kg PO once) often in combination with albendazole (400 mg PO once) for 5 yr. Recent studies have shown that 4 rounds of mass treatment substantially decreased the rate of transmission and clinical symptoms in Papua New Guinea. In co-endemic areas of filariasis and onchocerciasis, mass drug applications with single-dose ivermectin (150 μg/kg PO once) and albendazole are used because of severe adverse reactions with diethylcarbamazine in onchocerciasis-infected individuals. [5]

Trematode Infections

Trematodes, or flatworms, are a group of morphologically and biologically heterogeneous organisms that belong to the phylum Platyhelminthes. Human infection with trematodes occurs in many geographic areas and can cause considerable morbidity and mortality. For clinical purposes, significant trematode infections of humans may be divided according to tissues invaded by adult flukes: blood, biliary tree, intestines, and lungs (Table 21). [3]

Table 26 Major Human Trematode Infections

Trematode	Transmission	Endemic Area(s)
Blood Flukes		
Schistosoma mansoni	Skin penetration by cercariae released from snails	Africa, South America, Middle East
S. japonicum	Skin penetration by cercariae released from snails	China, Philippines, Indonesia
S. intercalatum	Skin penetration by cercariae released from snails	West Africa
S. mekongi	Skin penetration by cercariae released from snails	Southeast Asia
S. haematobium	Skin penetration by cercariae released from snails	Africa, Middle East
Biliary (Hepatic) Flukes		
Clonorchis sinensis	Ingestion of metacercariae in freshwater fish	Far East
Opisthorchis viverrini	Ingestion of metacercariae in freshwater fish	Far East, Thailand

O. felineus	Ingestion of metacercariae in freshwater fish	Far East, Europe
Fasciola hepatica	Ingestion of metacercariae on aquatic plants or in water	Worldwide
F. gigantica	Ingestion of metacercariae on aquatic plants or in water	Sporadic, Africa
Intestinal Flukes		
Fasciolopsis buski	Ingestion of metacercariae on aquatic plants	Southeast Asia
Heterophyes heterophyes	Ingestion of metacercariae in freshwater or brackish-water fish	Far East, North Africa
Lung Flukes		
Paragonimus westermani	Ingestion of metacercariae in crayfish or crabs	Global except North America and Europe

(3)

Treatment:

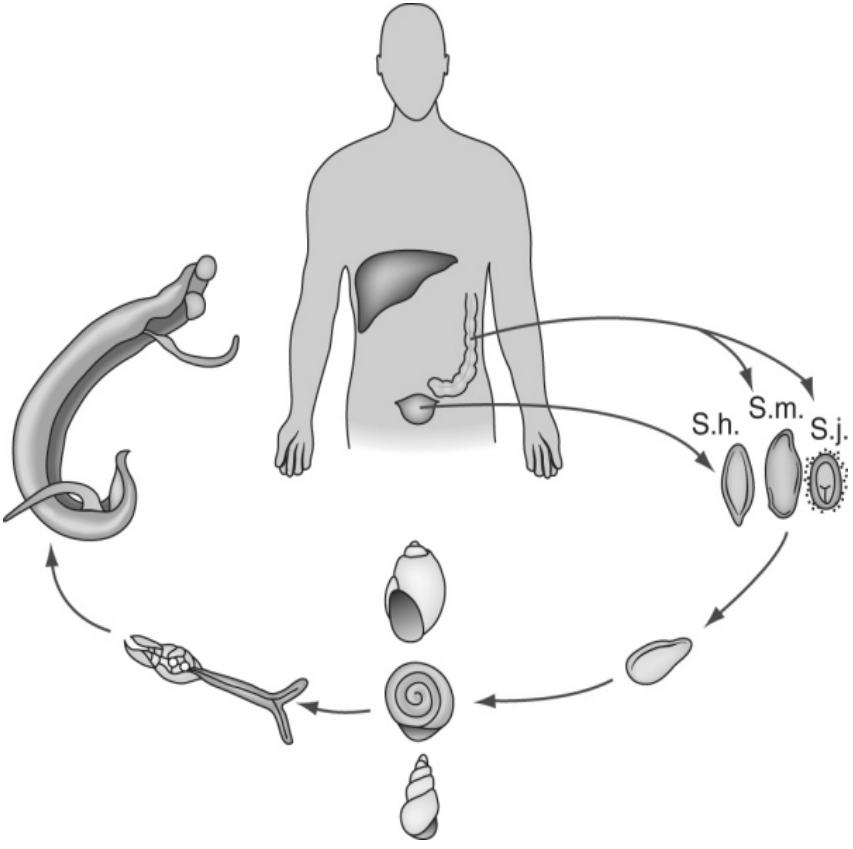
The drug of choice is praziquantel, which—depending on the infecting species (Table 22)—is administered PO as a total of 40 or 60 mg/kg in two or three doses over a single day. (3)

Table 27 Drug Therapy for Human Trematode Infections		
Infection	**Drug of Choice**	**Adult Dose and Duration**
Blood Flukes		
S. mansoni, S. intercalatum, S. haematobium	Praziquantel	20 mg/kg, 2 doses in 1 day
S. japonicum, S. mekongi	Praziquantel	20 mg/kg, 3 doses in 1 day

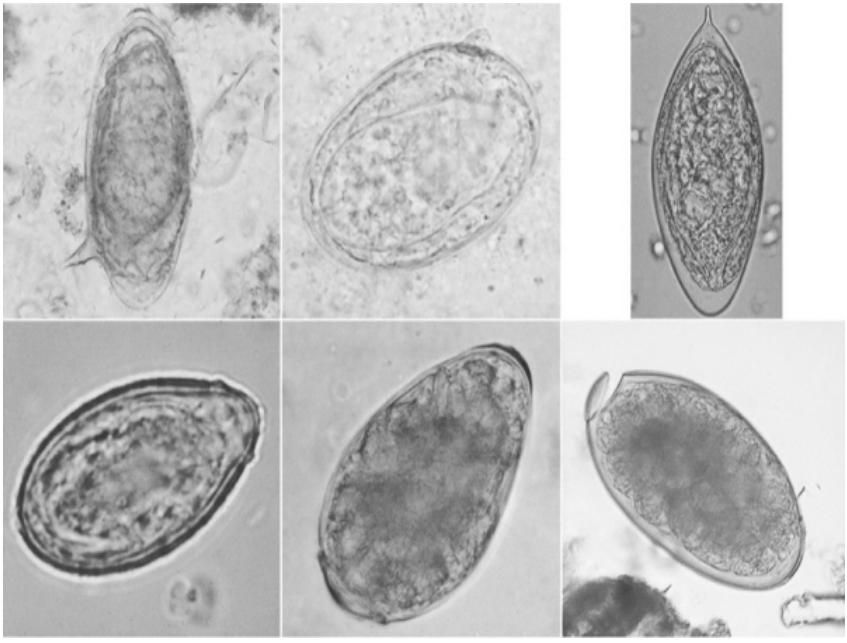
Biliary (Hepatic) Flukes		
C. sinensis, O. viverrini, O. felineus	Praziquantel	25 mg/kg, 3 doses in 1 day
F. hepatica, F. gigantica	Triclabendazole	10 mg/kg once
Intestinal Flukes		
F. buski, H. heterophyes	Praziquantel	25 mg/kg, 3 doses in 1 day
Lung Flukes		
P. westermani	Praziquantel	25 mg/kg, 3 doses per day for 2 days

(3)

(Fig. 93) Geographical distribution of schistosomiasis.



(Fig. 94) Life cycle of schistosomes. Eggs are passed in stools for *Schistosoma mansoni* (S.m.) and *Schistosoma japonicum* (S.j.) and in urine for *Schistosoma haematobium* (S.h.). The eggs hatch in freshwater, miracidia invade specific snail intermediate hosts, and in a few weeks, forked-tail cercariae are liberated. These infective forms penetrate human skin, pass through a migratory phase in the lung and liver, and then pass to their final habitat in the portal venous system (S.m. and S.j.) or the urinary bladder venous plexus (S.h.). Two other species infect humans, although less frequently. *Schistosoma intercalatum* produces terminal spined eggs that may be found in feces, whereas *Schistosoma mekongi* produces eggs similar to but smaller than those of *S. japonicum,* which also may be found in stools. These 2 species of schistosomes have characteristic snail intermediate hosts. *(From Mandell GL, Gennett JE, Dolin R [editors]: Principles and Practice of Infectious Diseases, 6th ed, Vol 2. Philadelphia, Elsevier, 2006, p. 3278.)*



(Fig. 95) Eggs of common human trematodes. Clockwise from upper left: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Clonorchis sinensiss, Pargonimus westermani,* and *Fasiola hepatica* (note the partially open operculum). *(From DPDx, website for laboratory diagnosis of parasitic diseases of the Division of Parasitic Diseases, National Centers for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia [http://www.dpd.cdc.gov/DPDx/].)*

Adult Cestode infection

Infections with **cestodes,** or **tapeworms,** are prevalent on every continent except Antarctica. The key biology that governs disease is whether humans are infected with the intestinal adult stage or the invasive intermediate stage of the parasite (Table 23). No signs or symptoms can clearly be attributed to infection with any adult tapeworm except for *Diphyllobothrium latum.* The intermediate stages of some tapeworms, such as *Taenia solium* and *Echinococcus*, are invasive and form cystic structures that produce tissue damage from mass effect or inflammatory reactions. Infection with the adult worm can be easily diagnosed by finding eggs or segments of adult worms in the stool, whereas the invasive stage of the parasite cannot be observed in any easily sampled fluid. Infection with an intermediate stage, therefore, must be diagnosed by serologic tests, imaging, or invasive procedures. [5]

Table 28 Common Cestode Parasites of Humans, Their Typical Vectors, and Their Usual Symptoms

Parasite Species	Developmental Stage Found in Humans	Common Name	Transmission Source	Symptoms Associated with Infection
Diphyllobothrium latum	Tapeworm	Fish tapeworm	Plerocercoid cysts in fresh water fish	Usually minimal;with prolonged or heavy infection, vitamin B_{12} Deficiency
Hymenolepis nana	Tapeworm, cysticercoids	Dwarf tapeworm	Infected humans	Mild abdominal discomfort
Taenia saginata	Tapeworm	Beef tapeworm	Cysts in beef	Abdominal discomfort, proglottid migration

Parasite Species	Developmental Stage Found in Humans	Common Name	Transmission Source	Symptoms Associated with Infection
Taenia solium	Tapeworm	Pork tapeworm	Cysticerci in pork	Minimal
Taenia solium (*cysticercus cellulosae*)	Cysticerci	Cysticercosis	Eggs from infected humans	Local inflammation, mass effect;if in CNS, seizures, hydrocephalus, arachnoiditis
Echinococcus granulosus	Larval cysts	Hydatid cyst disease	Eggs from infected dogs	Mass effect leading to pain, obstruction of adjacent organs;less commonly, secondary bacterial infection, distal spread of daughter cysts
Echinococcus multilocularis	Larval cysts	Alveolar cyst disease	Eggs from infected canines	Local invasion and mass effect leading to organ dysfunction; distal metastasis possible
Taenia multiceps	Larval cysts	Coenurosis, bladder worm	Eggs from infected dogs	Local inflammation and mass effect
Spirometra mansonoides	Larval cysts	Sparganosis	Cysts from infected copepods, frogs, snakes	Local inflammation and mass effect

Form Mandell GL, Bennett JE, Dolin R (editors): Principles and Practice of Infectious Diseases, 6th ed, Vol 2. Philadelphia, Elsevier, 2005, p 3286. CNS-central nervous system. (5)

Treatment:

1. Fish tapeworm (*Diphyllobothrium latum*): Praziquantel (5–10 mg/kg once) is highly effective. Parenteral vitamin B_{12} should be given if B_{12} deficiency is manifest.

2. Dwarf tapeworm (*Hymenolepis nana*) Praziquantel (25 mg/kg once) is the treatment of choice, since it acts against both the adult worms and the cysticercoids in the intestinal villi. Nitazoxanide (500 mg bid for 3 days) may be used as an alternative.
3. Beef tapeworm (*Taenia saginata*): A single dose of praziquantel (10 mg/kg) is highly effective.
4. Pork tapeworm (*Taenia solium*): Intestinal *T. solium* infection is treated with a single dose of praziquantel (10 mg/kg).[1] Niclosamide (2 g) is also effective.
5. Cysticercosis (*Taenia solium* (*cysticercus cellulosae*)) for the treatment of patients with brain parenchymal cysticerci, most authorities favor antiparasitic drugs, including praziquantel (50–60 mg/kg daily in three divided doses for 15–30 days) or albendazole (15 mg/kg per day for 8–28 days).[2]
6. Hydatid cyst disease (*Echinococcus granulosus*):
   - Surgery has traditionally been the principal definitive method of treatment.
   - Praziquantel (50 mg/kg daily for 2 weeks) may hasten the death of the protoscolices. Medical therapy with albendazole alone for 12 weeks to 6 months results in cure in ~30% of cases and in improvement in another 50%.
7. Coenurosis, bladder worm (*Taenia multiceps*): Both definitive diagnosis and treatment require surgical excision of the lesion. Chemotherapeutic agents generally are not effective.
8. Sparganosis (*Spirometra mansonoides*): Surgical excision is used to treat localized sparganosis. (3)

[1] However, praziquantel occasionally evokes an inflammatory response in the CNS if concomitant cryptic cysticercosis is present. (3)

[2] Both agents may exacerbate the inflammatory response around the dying parasite, thereby exacerbating seizures or hydrocephalus as well. (3)

Taeniasis Saginata

The beef tapeworm *T. saginata* occurs in all countries where raw or undercooked beef is eaten. It is most prevalent in sub-Saharan African and Middle Eastern countries. *T. saginata asiatica* is a variant of *T. saginata* that is found in Asia and for which pigs are the intermediate host. [3]

Etiology and Pathogenesis:

Humans are the only definitive host for the adult stage of *T. saginata*. This tapeworm, which can reach 8 m in length, inhabits the upper jejunum and has a scolex with four prominent suckers and 1000–2000 proglottids. Each gravid segment has 15–30 uterine branches (in contrast to 8–12 for *T. solium*). The eggs are indistinguishable from those of *T. solium*; they measure 30–40 m, contain the oncosphere, and have a thick brown striated shell. Eggs deposited on vegetation can live for months or years until they are ingested by cattle or other herbivores. The embryo released after ingestion invades the intestinal wall and is carried to striated muscle, where it transforms into a cysticercus. When ingested in raw or undercooked beef, this form can infect humans. After the cysticercus is ingested, it takes ~2 months for the mature adult worm to develop. [3]

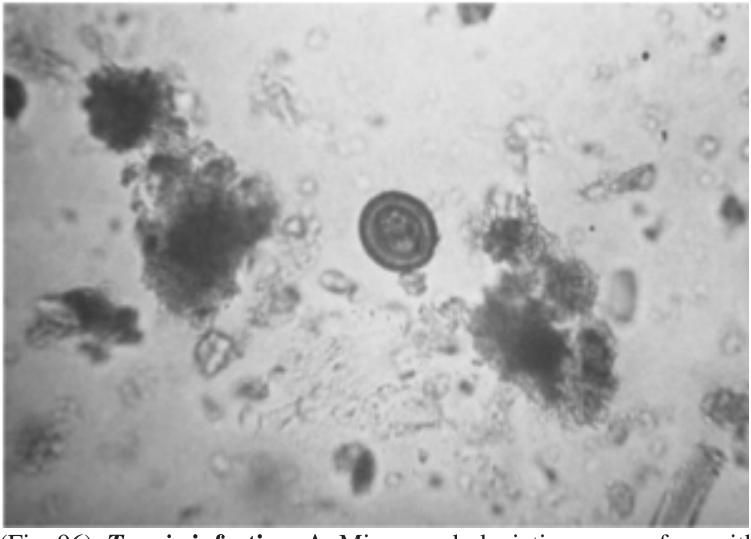
Clinical Manifestations:

Patients become aware of the infection most commonly by noting passage of proglottids in their feces. The proglottids are often motile, and patients may experience perianal discomfort when proglottids are discharged. Mild abdominal pain or discomfort,

nausea, change in appetite, weakness, and weight loss can occur with *T. saginata* infection. [3]

Diagnosis:

The diagnosis is made by the detection of eggs or proglottids in the stool. Eggs may also be present in the perianal area; thus, if proglottids or eggs are not found in the stool, the perianal region should be examined with use of a cellophane-tape swab (as in pinworm infection). Distinguishing *T. saginata* from *T. solium* requires examination of mature proglottids or the scolex. Serologic tests are not helpful diagnostically. Eosinophilia and elevated levels of serum IgE may be detected. [3]



(Fig. 96) ***Taenia* infection. A,** Micrograph depicting an egg from either a *Taenia saginata* or *Taenia solium* cestode (i.e., tapeworm). The eggs of *T. saginata* and *T. solium* are rounded or subspherical with a thick, radially striated brown shell. The diameter is 31 to 43µm. Inside each shell is an embryonated oncosphere with six hooks. [4]

Treatment:

A single dose of praziquantel (10 mg/kg) is highly effective. [3]

Prevention:

The major method of preventing infection is the adequate cooking of beef; exposure to temperatures as low as 56°C for 5 min will destroy cysticerci. Refrigeration or salting for long periods or freezing at –10°C for 9 days also kills cysticerci in beef. General preventive measures include inspection of beef and proper disposal of human feces. [3]

Hymenolepiasis Nana

Infection with *Hymenolepis nana*, the dwarf tapeworm, is the most common of all the cestode infections. *H. nana* is endemic in both temperate and tropical regions of the world. Infection is spread by fecal/oral contamination and is common among institutionalized children. (3)

Etiology and Pathogenesis:

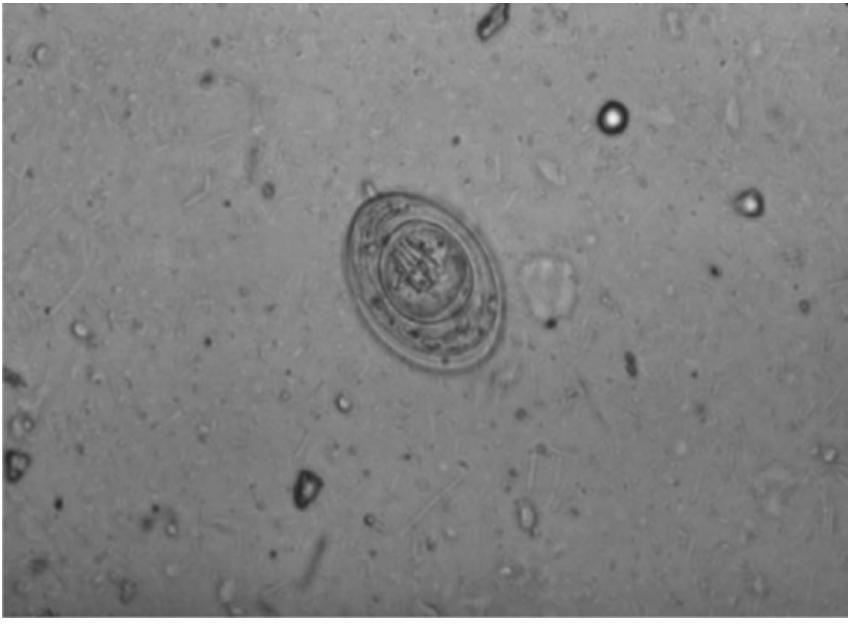
H. nana is the only cestode of humans that does not require an intermediate host. Both the larval and adult phases of the life cycle take place in the human. The adult—the smallest tapeworm parasitizing humans—is ~2 cm long and dwells in the proximal ileum. Proglottids, which are quite small and are rarely seen in the stool, release spherical eggs 30–44 m in diameter, each of which contains an oncosphere with six hooklets. The eggs are immediately infective and are unable to survive for >10 days in the external environment. *H. nana* can also be acquired by the ingestion of infected insects (especially larval meal-worms and larval fleas). When the egg is ingested by a new host, the oncosphere is freed and penetrates the intestinal villi, becoming a cysticercoid larva. Larvae migrate back into the intestinal lumen, attach to the mucosa, and mature into adult worms over 10–12 days. Eggs may also hatch before passing into the stool, causing internal autoinfection with increasing numbers of intestinal worms. Although the life span of adult *H. nana* worms is only ~4–10 weeks, the autoinfection cycle perpetuates the infection. (3)

Clinical Manifestations:

H. nana infection, even with many intestinal worms, is usually asymptomatic. When infection is intense, anorexia, abdominal pain, and diarrhea develop. [3]

Diagnosis:

Infection is diagnosed by the finding of eggs in the stool. [3]



(Fig. 97) **Micrograph depicting an egg from a *Hymenolepis nana* tapeworm, or cestode.** *H. nana* eggs are oval or subspherical in shape, 40 to 60µm×30 to 50µm in size—smaller than those of *Hymenolepis diminuta.* On the inner membrane are two poles from which four to eight polar filaments spread out between its two membranes. [3]

Treatment:

Praziquantel (25 mg/kg once) is the treatment of choice, since it acts against both the adult worms and the cysticercoids in the intestinal villi. Nitazoxanide (500 mg bid for 3 days) may be used as an alternative. [3]

Prevention:

Good personal hygiene and improved sanitation can eradicate the disease. Epidemics have been controlled by mass chemotherapy coupled with improved hygiene. [3]

Human immunodeficiency virus (HIV) and AIDS

Definition:

The definition of AIDS is complex, however we should not focus on whether AIDS is present but should view HIV disease as a spectrum ranging from primary infection with or without the acute symptom to the asymptomatic stage and to the advanced disease. [3]

- AIDS was first recognized in USA in the summer of 1981 in five homosexual men in Los Angeles with pneumocystis carinii pneumonia and 26 homosexual in New York and Los Angeles with Kaposi's sarcoma. [3]
- In 1983 HIV was isolated from a patient with lymphadenopathy. [3]
- In 1984 HIV was demonstrated to be the causative agent of AIDS. [3]
- In 1986 HIV-2 was first identified in West Africa. [3]

Etiology:

1. The causative agent: The etiologic agent is HIV
2. The characteristics of agent:
   - RNA virus
   - Belong to the family of retrovirus
   - Has two groups:
     a. HIV-1
     b. HIV-2

- The common cause of HIV disease is HIV-1
- HIV-2 was first identified in West Africa. [3]

Epidemiology:

1. Prevalence/Incidence:
   - Pandemic disease
   - Epidemic disease
   - Has sporadic cases
   - Global total: 40 million in 2003
   - In 2003 newly infected cases are 5 million
   - Has >14000 new infection each day [3]
2. Geographical variation: Worldwide disease, in 2003 worldwide estimation are:
   - Sub Sahara Africa 26,6million
   - South and southeast Asia 6,4million
   - Latin America 1,6million
   - Eastern Europe and central Asia 1,5million
   - East Asia and Pacific 1milllion
   - Global total 40million [3]
3. Age group:
   - Any age but common in adult
   - Worldwide 37million adult cases
   - 2/3 of women cases are in Sub Sahara Africa
   - In Sub Sahara Africa 50% cases are women
   - 3million cases are children
   - In USA 70% cases are men and 30% cases are women [3]
4. Seasonal variation: No any seasonal variation
5. Route of transmission:
   - Homosexual route
   - Heterosexual route
   - Through blood and blood products

- Transplacental route
- Via breast milk [3]

6. Reservoir of infection: Human
7. Incubation period: 2-4 weeks [6]
8. Infectivity period: Lifelong

Pathogenesis:

1. Entry of virus into the bloodstream
2. Cleared to the spleen and other lymphoid organs
3. Replication in spleen and lymphoid organs
4. Then lead to viremia and dissemination of viruses
5. Dendritic cells play role in the initiation of HIV infection
6. Dendritic cells increase infectivity of HIV to target cells
7. Target cells (CD4 T cells or helper T cells) infection
8. Virus replication in CD4 T cells leads to a burst of viremia
9. Rapid dissemination of viruses to other lymphoid organs and brain
10. Appearance of acute HIV syndromes [3]
11. Infection of T4 (CD4) and B lymphocytes causes immunodeficiency
12. Macrophages act as reservoir for HIV and serve to disseminate
13. HIV can directly infect brain, renal tubular cells and GI epithelium [7]

Pathophysiology:

Clinically, the syndromes caused by HIV infection are usually by one of three known mechanism:

1. Immunodeficiency:
   - This is a result of the direct effect of HIV upon immune cells.
   - Tow features of HIV immunodeficiency are:

The low incidence of certain infection such as listeriosis and aspergillosis.
The frequent occurrence of certain neoplasm such as lymphoma or Kaposi's sarcoma.

- The latter complication is seen primarily in bisexual men.

2. Autoimmunity/allergy & hypersensitivity reaction:
   - This is a result of disordered cellular immune function or B lymphocyte dysfunction, the example of both are:
     Lymphocytic infiltration of organ e.g. lymphocytic interstitial pneumonia
     Autoantibody production e.g. immunologic thrombocytopenia
   - These phenomena may be the only clinically apparent disease or may be coexist with obvious immunodeficiency.
   - HIV infected patients have higher rate of allergic reaction to unknown allergen.
3. Direct HIV infection of some organs:
   - May cause neurologic, renal and gastrointestinal dysfunction.
   - See discussion in pathogenesis

Clinical features:

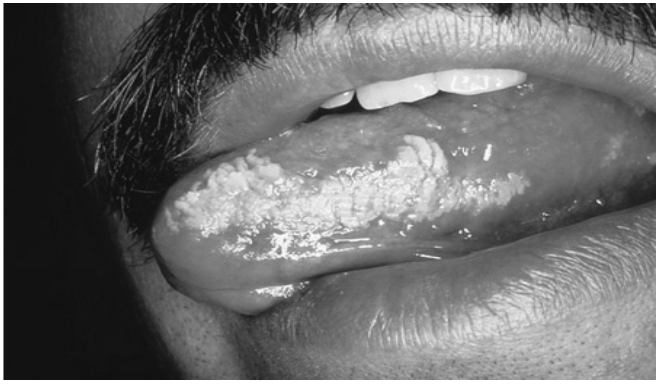
1. Asymptomatic for years
2. Systemic complaints:
   - Fever
   - Night sweat
   - Weight loss
   - Anorexia
   - Nausea
   - Vomiting
3. Sinopulmonary diseases:

a. Pneumocystis pneumonia
b. Other infectious pulmonary diseases:
   - Viral pneumonia
   - Mycobacterial tuberculosis
   - Haemophilus influenza
   - Pseudomonas aerogenosa
c. Non infectious pulmonary diseases:
   - Kaposi's sarcoma
   - Non Hodgkin's lymphoma
   - Interstitial pneumonitis
d. Sinusitis:
   - Sinus congestion
   - Discharge
   - Headache
   - Fever

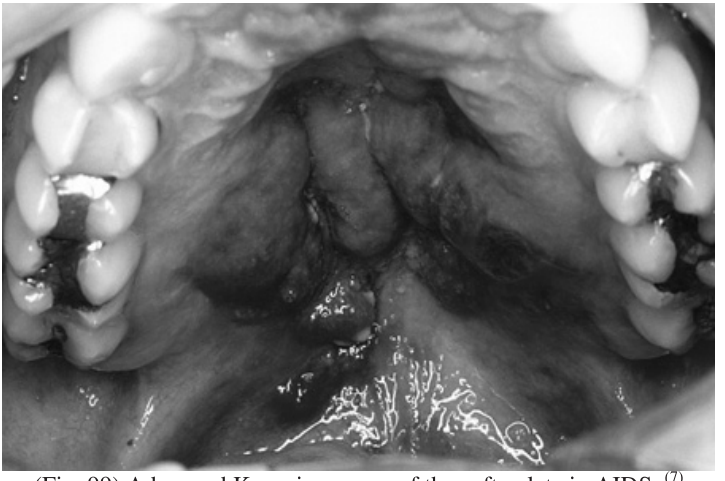
4. Central nervous system diseases:
   - Toxoplasmosis
   - CNS lymphoma
   - AIDS dementia complex
   - Cryptococcal meningitis
   - HIV myelopathy
   - Progressive multifocal leukoencephalopathy
5. Peripheral nervous system syndromes:
   - Inflammatory polyneuropathies
   - Sensory neuropathies
   - Mononeuropathies
6. Rheumatologic manifestations:
   - Arthritis:
     Suppurative
     Fungal
     Mycobacterial

- Reiter's syndrome (Reactive arthritis):
- Psoriatic arthritis
- Sicca syndrome
- Lupus erythematosis

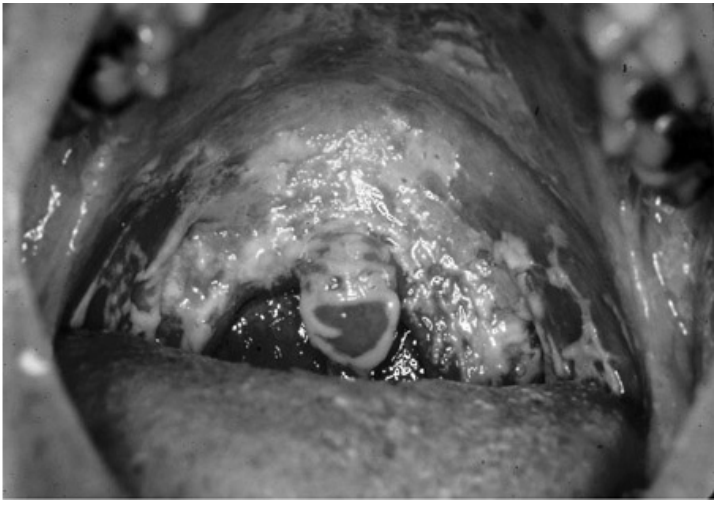
7. Myopathy:
   - Proximal muscle weakness
   - Muscle tenderness due to Zidovudine (Antiviral)
8. Retinitis:
   - Visual changes
   - Cytomegalovirus retinitis
   - Herpes virus infection
   - Toxoplasmosis
9. Oral lesion:
   - Oral candidiasis
   - Hairy leukoplakia (Fig. 37)
   - Angular cheilitis
   - Angular fissures
   - Gingival diseases
   - Kaposi's sarcoma (Fig. 38)
   - Aphthous ulcer (Fig. 39)
   - Warts [7]

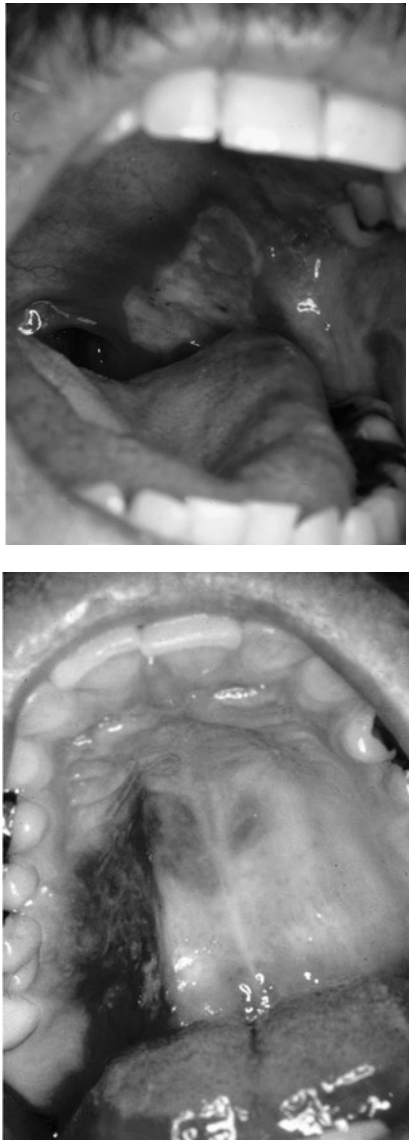


(Fig. 98) Oral hairy leukoplakia of the lateral border of the tongue in an HIV-infected patient. [7]



(Fig. 99) Advanced Kaposi sarcoma of the soft palate in AIDS. [7]





(Fig. 100) **Various oral lesions in HIV-infected individuals.** ***A.*** Thrush. ***B.*** Hairy leukoplakia. ***C.*** Aphthous ulcer. ***D.*** Kaposi's sarcoma. [7]

10.Gastrointestinal manifestations:

a. Esophageal diseases:

- Candidal esophagitis
- Herpes simplex
- Cytomegalovirus infection

b. Hepatic diseases:

- Mycobacterial diseases
- Cytomegalovirus diseases
- Hepatitis B virus
- Hepatitis C virus
- Lymphoma
- Toxicity of drugs in HIV diseases

c. Biliary diseases:

- Cholecystitis
- Sclerosing cholangitis
- Papillary stenosis
- Syndrome with
  Nausea
  Vomiting
  Right upper quadrant pain

e. Enterocolitis:

May be due to:

- Bacteria:
  Campylobacter
  Salmonella
  Shigella
- Viruses:
  Cytomegalovirus
  Adenovirus
- Protozoan:
  Cryptosporidium

Entamoeba histolytica
Giardia
Isospora
Microsporidium

Common manifestation:

- Watery diarrhea
- Fever
- Abdominal pain

f. Other disorders:

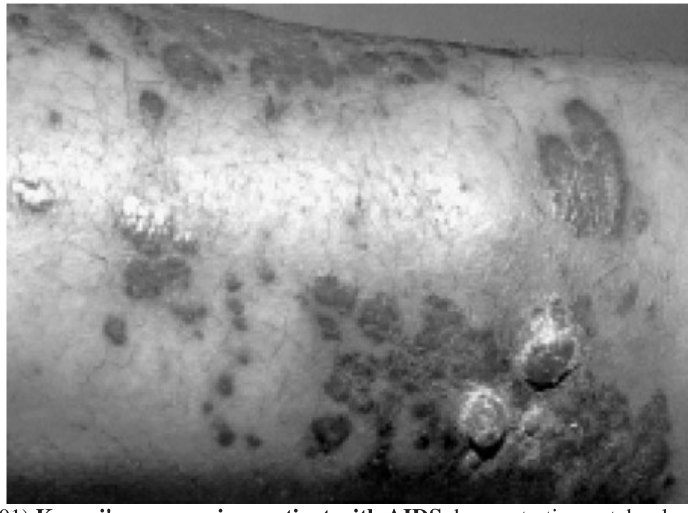
- Gastropathy
- Malabsorption
- Infections:
  Campylobacter
  Salmonella
  Shigella
- Helicobacter pylori is common

11. Endocrinologic manifestations:

- Mild adrenal abnormalities
- Mild abnormalities of thyroid function

12. Skin manifestations:

- Herpes simplex infection
- Herpes zoster
- Molluscum contagiosum
- Bacillary angiomatosis: due to:
  Bartonella henselea
  Bartonella Quintana
- Kaposi's sarcoma (Fig. 40)
- Seboric dermatitis
- Xerosis
- Psoriasis



(Fig. 101) **Kaposi's sarcoma in a patient with AIDS** demonstrating patch, plaque, and tumor stages. [7]

13. HIV related malignancies:
    - Kaposi's sarcoma
    - Non Hodgkin's lymphoma
    - Hodgkin's diseases
    - Anal dysplasia and squamous cell carcinoma
    - Cervical dysplasia and neoplasia
14. Gynecologic manifestations:
    - Vaginal candidiasis
    - Cervical dysplasia and neoplasia
    - Pelvic inflammatory diseases
15. Inflammatory reactions:
    - Cytomegalovirus retinitis
    - Focal lymphadenitis
    - Granulomatus masses
    - Tuberculosis
    - Cryptococcal meningitis [7]

Investigations:

1. HIV RNA by PCR
2. Immune complex–dissociated p24 antigen capture assay
3. HIV RNA by bDNA
4. HIV RNA by NucliSens [3]
5. Complete blood count(In advanced HIV infection):
   - Anemia
   - Neutropenia
   - Thrombocytopenia
6. Absolute CD4 lymphocyte count
7. CD4 lymphocyte percentage
8. Western blot
9. HIV rapid antibody test
10. HIV viral load tests (Table 29)
11. HIV enzyme-linked immunosorbent assay (ELISA) [7]

Table 29 Characteristics of Tests for Direct Detection of HIV

Test	Technique	Sensitivity[a]	Cost/Test[b]
Immune complex–dissociated p24 antigen capture assay	Measurement of levels of HIV-1 core protein in an EIA-based format following dissociation of antigen-antibody complexes by weak acid treatment	Positive in 50% of patients; detects down to 15 pg/mL of p24 protein	$1–2
HIV RNA by PCR	PCR amplification of cDNA generated from viral RNA (target amplification)	Reliable to 40 copies/mL of HIV RNA	$75–150
HIV RNA by bDNA	Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification	Reliable to 50 copies/mL of HIV RNA	$75–150
HIV RNA by NucliSens	Isothermic nucleic acid amplification with internal controls	Reliable to 80 copies/mL of HIV RNA	$75–150

[a]Sensitivity figures refer to those approved by the US FDA. [b]Prices may be lower in large volume settings. ***Note:*** EIA, enzyme immunoassay; PCR, polymerase chain reaction. [3]

Treatment:

Treatment for HIV infection can be divided into four categories:

1. Therapy for opportunistic infections and malignancies (Table 30)
2. Antiretroviral treatment (Table 31)
3. Hematopoietic stimulating factors
4. Prophylaxis of opportunistic infections. (7)

Table 30 Treatment of AIDS-related opportunistic infections and malignancies.[1]

Infection or Malignancy	Treatment	Complications
Pneumocystis jiroveci infection[2]	Trimethoprim-sulfamethoxazole, 15 mg/kg/d (based on trimethoprim component) orally or intravenously for 14–21 days.	Nausea, neutropenia, anemia, hepatitis, drug rash, Stevens-Johnson syndrome.
	Pentamidine, 3–4 mg/kg/d intravenously for 14–21 days.	Hypotension, hypoglycemia, anemia, neutropenia, pancreatitis, hepatitis.
	Trimethoprim, 15 mg/kg/d orally, with dapsone, 100 mg/d orally, for 14–21 days.[3]	Nausea, rash, hemolytic anemia in G6PD[3]-deficient patients. Methemoglobinemia (weekly levels should be < 10% of total hemoglobin).
	Primaquine, 15–30 mg/d orally, and clindamycin, 600 mg every 8 hours orally, for 14–21 days.	Hemolytic anemia in G6PD-deficient patients. Methemoglobinemia, neutropenia, colitis.
	Atovaquone, 750 mg orally three times daily for 14–21 days.	Rash, elevated aminotransferases, anemia, neutropenia.
	Trimetrexate, 45 mg/m^2 intravenously for 21 days (given with leucovorin calcium) if intolerant of all other regimens.	Leukopenia, rash, mucositis.
Mycobacterium avium complex infection	Clarithromycin, 500 mg orally twice daily with ethambutol, 15 mg/kg/d orally (maximum, 1 g). May also add:	Clarithromycin: hepatitis, nausea, diarrhea; ethambutol: hepatitis, optic neuritis.
	Rifabutin, 300 mg orally daily.	Rash, hepatitis, uveitis.
Toxoplasmosis	Pyrimethamine, 100–200 mg orally as loading dose	Leukopenia, rash

	followed by 50–75 mg/d, combined with sulfadiazine, 4–6 g orally daily in four divided doses, and folinic acid, 10 mg daily for 4–8 weeks; then pyrimethamine, 25–50 mg/d, with clindamycin, 2–2.7 g/d in three or four divided doses, and folinic acid, 5 mg/d, until clinical and radiographic resolution is achieved.	
Lymphoma	Combination chemotherapy (eg, modified CHOP, M-BACOD, with or without G-CSF or GM-CSF). Central nervous system disease: radiation treatment with dexamethasone for edema.	Nausea, vomiting, anemia, leukopenia, cardiac toxicity (with doxorubicin).
Cryptococcal meningitis	Amphotericin B, 0.6 mg/kg/d intravenously, with or without flucytosine, 100 mg/kg/d orally in four divided doses for 2 weeks, followed by:	Fever, anemia, hypokalemia, azotemia.
	Fluconazole, 400 mg orally daily for 6 weeks, then 200 mg orally daily.	Hepatitis.
Cytomegalovirus infection	Valganciclovir, 900 mg orally twice a day for 21 days with food (induction), followed by 900 mg daily with food (maintenance).	Neutropenia, anemia, thrombocytopenia.
	Ganciclovir, 10 mg/kg/d intravenously in two divided doses for 10 days, followed by 6 mg/kg 5 days a week indefinitely. (Decrease dose for renal impairment.) May use ganciclovir as maintenance therapy (1 g orally with fatty foods three times a day).	Neutropenia (especially when used concurrently with zidovudine), anemia, thrombocytopenia.
	Foscarnet, 60 mg/kg intravenously every 8 hours for 10–14 days (induction), followed by 90 mg/kg once daily. (Adjust for changes in renal function.)	Nausea, hypokalemia, hypocalcemia, hyperphosphatemia, azotemia.
Esophageal candidiasis or recurrent vaginal candidiasis	Fluconazole, 100–200 mg orally daily for 10–14 days.	Hepatitis, development of imidazole resistance.
Herpes simplex infection	Acyclovir, 400 mg orally three times daily until healed; or acyclovir, 5 mg/kg intravenously every 8 hours for severe cases.	Resistant herpes simplex with chronic therapy.
	Famciclovir, 500 mg orally twice daily until healed.	Nausea.
	Valacyclovir, 500 mg orally twice daily until healed.	Nausea.
	Foscarnet, 40 mg/kg intravenously every 8 hours, for acyclovir-resistant cases. (Adjust for changes in renal function.)	See above.
Herpes zoster	Acyclovir, 800 mg orally four or five times daily for 7 days. Intravenous therapy at 10 mg/kg every 8 hours for ocular involvement, disseminated disease.	See above.
	Famciclovir, 500 mg orally three times daily for 7 days.	Nausea.
	Valacyclovir, 500 mg orally three times daily for 7 days.	Nausea.
	Foscarnet, 40 mg/kg intravenously every 8 hours for acyclovir-resistant cases. (Adjust for changes in renal function.)	See above.
Kaposi sarcoma		

Limited cutaneous disease	Observation, intralesional vinblastine.	Inflammation, pain at site of injection.
Extensive or aggressive cutaneous disease	Systemic chemotherapy (eg, liposomal doxorubicin). Interferon-alpha (for patients with CD4 > 200 cells/mcL and no constitutional symptoms). Radiation (amelioration of edema).	Bone marrow suppression, peripheral neuritis, flu-like syndrome.
Visceral disease (eg, pulmonary)	Combination chemotherapy (eg, daunorubicin, bleomycin, vinblastine).	Bone marrow suppression, cardiac toxicity, fever.

For treatment of *Mycobacterium tuberculosis* infection, see Chapter 34: Spirochetal Infections. For moderate to severe *P jiroveci* infection (oxygen saturation < 90%), corticosteroids should be given with specific treatment. The dose of prednisone is 40 mg orally twice daily for 5 days, then 40 mg daily for 5 days, and then 20 mg daily until therapy is complete. [3]When considering use of dapsone, check glucose-6-phosphate dehydrogenase (G6PD) level in black patients and those of Mediterranean origin. CHOP, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (Oncovin), and prednisone; modified M-BACOD, methotrexate, bleomycin, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), and dexamethasone; G-CSF, granulocyte-colony stimulating factor (filgrastim); GM-CSF, granulocyte-macrophage colony-stimulating factor (sargramostim). [7]

Table 31 Antiretroviral therapy.

Drug	Dose	Common Side Effects	Special Monitoring [1]	Cost [2]	Cost/Month
Nucleoside reverse transcriptase inhibitors					
Zidovudine (AZT) (Retrovir)	600 mg orally daily in two divided doses	Anemia, neutropenia, nausea, malaise, headache, insomnia, myopathy	No special monitoring	$6.08/300 mg	$365.09
Didanosine (ddI) (Videx)	400 mg orally daily (enteric-coated capsule) for persons ≥ 60 kg	Peripheral neuropathy, pancreatitis, dry mouth, hepatitis	Bimonthly neurologic questionnaire for neuropathy, K^+, amylase, bilirubin, triglycerides	$11.50/400 mg	$344.92
Zalcitabine (ddC) (Hivid)	0.375–0.75 mg orally three times daily	Peripheral neuropathy, aphthous ulcers, hepatitis	Monthly neurologic questionnaire for neuropathy	$2.73/0.75 mg	$245.70
Stavudine (d4T) (Zerit)	40 mg orally twice daily for persons ≥ 60 kg	Peripheral neuropathy, hepatitis, pancreatitis	Monthly neurologic questionnaire for neuropathy, amylase	$7.31/40 mg	$438.61
Lamivudine (3TC) (Epivir)	150 mg orally twice daily	Rash, peripheral neuropathy	No special monitoring	$6.45/150 mg	$386.93

Emtricitabine (Emtriva)	200 mg orally once daily	Skin discoloration palms/soles (mild)	No special monitoring	$12.30/200 mg	$368.93
Abacavir (Ziagen)	300 mg orally twice daily	Rash, fever—if occur, rechallenge may be fatal	No special monitoring	$8.67/300 mg	$519.92
Nucleotide reverse transcriptase inhibitors					
Tenofovir (Viread)	300 mg orally once daily	Gastrointestinal distress	Renal function	$20.47/300 mg	$614.18
Protease inhibitors (PIs)					
Indinavir (Crixivan)	800 mg orally three times daily	Kidney stones	Cholesterol, triglycerides, bilirubin level	$3.05/400 mg	$548.12
Saquinavir hard gel (Invirase)	1000 mg orally twice daily with 100 mg ritonavir orally twice daily	Gastrointestinal distress	Cholesterol, triglycerides	$6.58/500 mg	$789.70 (plus cost of ritonavir)
Ritonavir (Norvir)	600 mg orally twice daily or in lower doses (eg, 100 mg orally once or twice daily) for boosting other PIs	Gastrointestinal distress, peripheral paresthesias	Cholesterol, triglycerides	$10.29/100 mg	$3,703.20 ($617.20 in lower doses)
Nelfinavir (Viracept)	750 mg orally three times daily or 1250 mg twice daily	Diarrhea	Cholesterol, triglycerides	$2.42/250 mg	$680.99
				$6.05/625 mg	$726.40
Amprenavir (Agenerase)	1200 mg orally twice daily	Gastrointestinal, rash	Cholesterol, triglycerides	$0.60/50 mg	$862.20
Fosamprenavir (Lexiva)	For PI-experienced patients: 700 mg orally twice daily and 100 mg of ritonavir 100 orally twice daily. For PI-naïve patients: above or 1400 mg orally twice daily or 1400 mg orally once daily and 200 mg of ritonavir orally once daily	Same as amprenavir	Same as amprenavir	$12.24/700 mg	$734.56–$1469.12(plus cost of ritonavir for lower dose)
Lopinavir/ritonavir (Kaletra)	400 mg/100 mg orally twice daily	Diarrhea	Cholesterol, triglycerides	$7.02/200 mg (lopinavir)	$841.90
Atazanavir (Reyataz)	400 mg orally once daily	Hyperbilirubinemia	Bilirubin level; when used with ritonavir: cholesterol and triglycerides	$16.46/200 mg	$987.41

Tipranavir/ritonavir (Aptivus/Norvir)	500 mg of tipranavir and 200 mg of ritonavir orally twice daily	Gastrointestinal, rash	Cholesterol, triglycerides	$8.94/250 mg (tipranavir) $10.29/100 mg (ritonavir)	$2307.20 (for combination)
Darunavir/ritonavir (Prezista/Norvir)	600 mg of darunavir and 100 mg of ritonavir orally twice daily	Rash	Cholesterol, triglycerides	$ 7.50/300 mg (darunavir) $10.29/100 mg (ritonavir)	$1517.20 (for combination)
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)					
Nevirapine (Viramune)	200 mg orally daily for 2 weeks, then 200 mg orally twice daily	Rash	No special monitoring	$7.73/200 mg	$463.85
Delavirdine (Rescriptor)	400 mg orally three times daily	Rash	No special monitoring	$1.69/200 mg	$303.70
Efavirenz (Sustiva)	600 mg orally daily	Neurologic disturbances	No special monitoring	$17.70/600 mg	$531.04
Entry inhibitors					
Enfuvirtide (Fuzeon)	90 mg subcutaneously twice daily	Injection site pain and allergic reaction	No special monitoring	$38.90/90 mg	$2333.93
Maraviroc (Selzentry)	150–300 mg orally daily	Cough, fever, rash	No special monitoring	$17.40/150 mg or 300 mg	$1044.00
Integrase inhibitor					
Raltegravir (Isentress)	400 mg orally twice daily	Diarrhea, nausea, headache	No special monitoring	$16.20/400 mg	$972.00

[1]Standard monitoring is complete blood count (CBC) and differential, and serum aminotransferases. [2]Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: *Red Book Update, Vol. 27, No. 2,* February 2008. AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions. (7)

Prevention:

Primary prevention:

1. Notification
2. Effective precautions regarding sexual practices
3. Precautions regarding injection drug use
4. Use of perinatal HIV prophylaxis

5. Screening of blood products
6. Infection control practices in the health care setting.
7. Primary care clinicians should routinely obtain a sexual history and provide risk factor assessment of their patients.
8. Because approximately one-fourth of the HIV-infected persons in the United States do not know they are infected, the CDC recommends all adults be routinely tested for HIV.
9. Prior to testing, clinicians should obtain informed consent and review the risk factors for HIV infection with the patient and discuss safer sex and safer needle use as well as the meaning of a positive test.
10. For persons whose test results are positive, information on available medical and mental health services should be provided as well as guidance for contacting sexual or needle-sharing partners. [7]

Secondary prevention:

In the era prior to the development of highly effective antiretroviral treatment, cohort studies of individuals with documented dates of seroconversion demonstrate that AIDS develops within 10 years in approximately 50% of untreated seropositive persons. With currently available treatment, progression of disease has been markedly decreased. In addition to antiretroviral treatment, prophylactic regimens can prevent opportunistic infections and improve survival. Prophylaxis and early intervention prevent several infectious diseases, including tuberculosis and syphilis, which are transmissible to others. Recommendations for screening tests, vaccinations, and prophylaxis are listed in Table 32.

Table 32 Health care maintenance of HIV-infected individuals.
For all HIV-infected individuals:
CD4 counts every 3–6 months
Viral load tests every 3–6 months and 1 month following a change in therapy
PPD
INH for those with positive PPD and normal chest radiograph
RPR or VDRL
Toxoplasma IgG serology
Hepatitis serologies: hepatitis A antibody, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody.
Pneumococcal vaccine
Inactivated influenza vaccine in season
Hepatitis A vaccine for those without immunity to hepatitis A.
Hepatitis B vaccine for those who are hepatitis B surface antigen and antibody negative. (Use 40 mcg formulation at 0, 1, and 6 months; repeat if no immunity 1 month after three-shot series.)
Tetanus/diphtheria vaccine
Human papillomavirus vaccine for HIV-infected women age 26 years or less.
Haemophilus influenzae type b vaccination
Papanicolaou smears every 6 months for women
Consider anal swabs for cytologic evaluation.
For HIV-infected individuals with CD4 < 200 cells/mcL:
Pneumocystis jiroveci prophylaxis (see Prophylaxis of Opportunistic Infections section under Treatment and Table 31–6)
For HIV-infected individuals with CD4 < 75 cells/mcL:
Mycobacterium avium complex prophylaxis (see Prophylaxis of Opportunistic Infections section under Treatment)
For HIV-infected individuals with CD4 < 50 cells/mcL:
Consider CMV prophylaxis

PPD, purified protein derivative; INH, isoniazid; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories; IgG, immunoglobulin G.

HIV Risk for Health Care Professionals:

Epidemiologic studies show that needle sticks occur commonly among health care professionals, especially among surgeons performing invasive procedures, inexperienced hospital house staff, and medical students. Efforts to reduce needle sticks should focus on avoiding recapping needles and use of safety needles whenever doing invasive procedures under controlled circumstances. The risk of HIV transmission from a needle stick with blood from an HIV-infected patient is about 1:300. The risk is higher with deep punctures, large inocula, and source patients with high viral loads.

Prognosis:

With improvements in therapy, patients are living longer after the diagnosis of AIDS. A population-based study conducted in Denmark found that HIV-infected persons at age 25 years without hepatitis C had a life expectancy of 39 additional years. Unfortunately, not all HIV-infected persons have access to treatment. Studies consistently show less access to treatment for blacks, the homeless, and injection drug users. In addition to access to treatment, sustaining lower mortality will require developing new treatments for patients in whom resistance to existing agents develops. For patients whose disease progresses even though they are receiving appropriate treatment, meticulous palliative care must be provided. [7]

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Appendices

A: Barnes-Jewish Hospital Laboratory Reference Values

Reference values for the more commonly used laboratory tests are listed in the following table. These values are given in the units currently used at Barnes-Jewish Hospital and in Systeme International (SI) units, which are used in many areas of the world. Individual reference values can be population and method dependent.

Table 33 Lab Reference Values

Test	Current units	Factor[a]	SI units
Common serum chemistries			
Albumin	3.6â “5.0 g/dL	10	36â “50 g/L
Ammonia (plasma)	9â “33 mcmol/L	1	9â “33 mcmol/L
Bilirubin			
Total[b]	0.3â “1.1 mg/dL	17.1	5.13â “18.80 mcmol/L
Direct	0â “0.3 mg/dL	17.1	0â “5.1 mcmol/L
Blood gases (arterial)			
pH	7.35â “7.45	1	7.35â “7.45
PO_2	80â “105 mm Hg	0.133	10.6â “14.0 kPa
PCO_2	35â “45 mm Hg	0.133	4.7â “6.0 kPa
Calcium			
Total	8.6â “10.3 mg/dL	0.25	2.15â “2.58 mmol/L
Ionized	4.5â “5.1 mg/dL	0.25	1.13â “1.28 mmol/L
CO_2 content (plasma)	22â “32 mmol/L	1	22â “32 mmol/L

Ceruloplasmin	18â “46 mg/dL	0.063	1.5â “2.9 mcmol/L
Chloride	97â “110 mmol/L	1	97â “110 mmol/L
Cholesterol[c]			
Desirable	<200 mg/dL	0.0259	<5.18 mmol/L
Borderline high	200â “239 mg/dL	0.0259	5.18â “6.19 mmol/L
High	â‰¥240 mg/dL	0.0259	6.22 mmol/L
HDL cholesterol[c]	>35 mg/dL	0.0259	>0.91 mmol/L
Copper (total)	75â “145 mg/dL	0.157	11.8â “22.8 mmol/L
Creatinine[b]			
Male, age 4â “20 yr	0.2â “1.2 mg/dL	88.4	18â “106 mcmol/L
Female, age 4â “20 yr	0.2â “1.2 mg/dL	88.4	18â “106 mcmol/L
Male, age 20â “69 yr	0.7â “1.5 mg/dL	88.4	62â “133 mcmol/L
Female, age 20â “69 yr	0.6â “1.4 mg/dL	88.4	53â “124 mcmol/L
Male, age â‰¥70 yr	0.7â “1.7 mg/dL	88.4	62â “150 mcmol/L
Female, age â‰¥70 yr	0.6â “1.5 mg/dL	88.4	53â “133 mcmol/L
Ferritin			
Male adult	20â “323 ng/mL	2.25	45â “727 pmol/L
Female adult	10â “291 ng/mL	2.25	23â “655 pmol/L
Folate			
Plasma	3.1â “12.4 ng/mL	2.27	7.0â “28.1 nmol/L
Red cell	186â “645 ng/mL	2.27	422â “1,464 nmol/L
Glucose, fasting (plasma)	65â “109 mg/dL	0.055	3.58â “6.00 mmol/L
Haptoglobin	30â “220 mg/dL	0.01	0.3â “2.2 g/L
Hemoglobin A1c (estimated)	4.0%â “6.0%	0.01	0.04â “0.06
Iron (total) (age >13 yr)			
Male	45â “160 mcg/dL	0.179	8.1â “31.3 mcmol/L
Female	30â “160 mcg/dL	0.179	5.4â “31.3 mcmol/L
Iron-binding capacity	220â “420 mcg/dL	0.179	39.4â “75.2 mcmol/L
Transferrin saturation	20%â “50%	0.01	0.2â “0.5
Lactate (plasma)	0.7â “2.1 mmol/L	1	0.7â “2.1 mmol/L
Magnesium	1.3â “2.2 mEq/L	0.5	0.65â “1.10 mmol/L
Osmolality	275â “300 mOsm/kg	1	275â “300 mmol/kg
Phosphate	2.5â “4.5 mg/dL	0.323	0.8â “11.45 mmol/L
Potassium (plasma)	3.3â “4.9 mmol/L	1	3.3â “4.9 mmol/L
Protein, total (plasma)	6.5â “8.5 g/dL	10	65â “85 g/L

Sodium	135â “145 mmol/L	1	135â “145 mmol/L
Triglycerides, fasting[c]	<250 mg/dL	0.0113	<2.8 mmol/L
Troponin I			
Normal	0.1 ng/mL	100	60 ng/L
Indeterminant	0.1â “1.4 ng/mL	100	70â “140 ng/L
Abnormal	â‰¥1.5 ng/mL	100	â‰¥150 ng/L
Urea nitrogen	8â “25 mg/dL	0.357	2.9â “8.9 mmol/L
Uric acid[b]	3â “8 mg/dL	59.5	179â “476 mcmol/L
Vitamin B12	180â “1,000 pg/mL	0.738	133â “738 pmol/L
Common serum enzymatic activities			
Aminotransferases			
Alanine (ALT, SGPT)	7â “53 International Units/L	0.01667	0.12â “0.88 mckat/L
Aspartate (AST, SGOT)	11â “47 International Units/L	0.01667	0.18â “0.78 mckat/L
Amylase	25â “115 International Units/L	0.01667	0.42â “1.92 mckat/L
Creatine kinase			
Male	30â “200 International Units/L	0.01667	0.50â “3.33 mc/kat/L
Female	20â “170 International Units/L	0.01667	0.33â “2.83 mc/kat/L
MB fraction	0â “7 International Units/L	0.01667	0â “0.12 mc/kat/L
Gamma-glutamyl transpeptidase (GGT)			
Male	11â “50 International Units/L	0.01667	0.18â “0.83 mckat/L
Female	7â “32 International Units/L	0.01667	0.12â “0.53 mckat/L
Lactate dehydrogenase[b]	100â “250 International Units/L	0.01667	1.67â “4.17 mckat/L
Lipase	<100 International Units/L	0.01667	<1.67 mckat/L
5â ²-Nucleotidase	2â “16 International Units/L	0.01667	0.0â “30.27 mckat/L
Phosphatase, acid	0â “0.7 International Units/L	16.67	0â “11.6 nkat/L

Phosphatase, alkaline[d]			
Age 10â “15 yr	130â “550 International Units/L	0.01667	2.17â “9.17 mc/kat/L
Age 16â “20 yr	70â “260 International Units/L	0.01667	1.17â “4.33 mc/kat/L
Age >20 yr	38â “126 International Units/L	0.01667	0.13â “2.10 mc/kat/L
Common serum hormone values[e]			
ACTH, fasting (8 am, supine)	<60 pg/mL	0.22	<13.2 pmol/L
Aldosterone[f]	10â “160 ng/L	2.77	28â “443 mmol/L
Cortisol (plasma, morning)	6â “30 mg/dL	0.027	0.16â “0.81 mcmol/L
FSH			
Male	1â “8 International Units/L	1	1â “8 International Units/L
Female			
Follicular	4â “13 International Units/L	1	4â “13 International Units/L
Luteal	2â “13 International Units/L	1	2â “13 International Units/L
Midcycle	5â “22 International Units/L	1	5â “22 International Units/L
Postmenopausal	20â “138 International Units/L	1	20â “138 International Units/L
Gastrin, fasting	0â “130 pg/mL	1	0â “130 ng/L
Growth hormone, fasting			
Male	<5 ng/mL	1	<5 mcg/L
Female	<10 ng/mL	1	<10 mcg/L
17-Hydroxyprogesterone			
Male adult	<200 ng/dL	0.03	<6.6 nmol/L
Female			
Follicular	<80 ng/dL	0.03	<2.4 nmol/L
Luteal	<235 ng/dL	0.03	<8.6 nmol/L
Postmenopausal	<51 ng/dL	0.03	<1.5 nmol/L
Insulin, fasting	315 microunits/L	7.18	144 pmol/L
LH			
Male	2â “12 International	1	2â “12 International

	Units/L		Units/L
Female			
Follicular	1â “18 International Units/L	1	1â “18 International Units/L
Luteal	20 International Units/L	1	20 International Units/L
Midcycle	24â “105 International Units/L	1	24â “105 International Units/L
Postmenopausal	15â “62 International Units/L	1	15â “62 International Units/L
Parathyroid hormone	12â “72 pg/mL	â ”	â ”
Progesterone			
Male	<0.5 ng/mL	3.18	<1.6 nmol/L
Female			
Follicular	0.1â “1.5 ng/mL	3.18	0.32â “4.80 nmol/L
Luteal	2.5â “28.0 ng/mL	3.18	8â “89 nmol/L
First trimester	9â “47 ng/mL	3.18	29â “149 nmol/L
Third trimester	55â “255 ng/mL	3.18	175â “811 nmol/L
Postmenopausal	<0.5 ng/mL	3.18	<1.6 nmol/L
Prolactin			
Male	1.6â “18.8 ng/mL	1	1.6â “18.8 mcg/L
Female	1.4â “24.2 ng/mL	1	1.4â “24.2 mcg/L
Renin activity (plasma)[g]	0.9â “3.3 ng/mL/hr	0.278	0.25â “0.91 ng/(L sec)
Testosterone, total			
Male	270â “1,070 ng/dL	0.0346	9.3â “37.0 nmol/L
Female	6â “86 ng/dL	0.0346	0.2â “13.0 nmol/L
Testosterone, free			
Male	9â “30 ng/dL	0.0346	0.3â “11.0 pmol/L
Female	0.3â “1.9 ng/dL	0.0346	0.001â “30.26 pmol/L
Thyroxine, total (T4)	4.5â “12.0 mcg/dL	12.9	58â “155 nmol/L
Thyroxine, free	0.7â “1.8 ng/dL	12.9	10.3â “34.8 pmol/L
uptake[h]	30%â “46%	0.01	0.3â “0.46
Triiodothyronine (T3)	45â “132 ng/dL	0.0154	0.91â “2.70 nmol/L
T4 index[i]	1.5â “4.5	1	1.5â “4.5
TSH	0.35â “6.20 microunits/mL	1	0.35â “6.20 microunits/L

Vitamin D, 1,25-dihydroxy	15â “60 pg/mL	2.4	36â “144 pmol/L
Vitamin D, 25-hydroxy	10â “55 ng/mL	2.49	25â “137 nmol/L
Common urinary chemistries			
Delta-aminolevulinic acid	1.5â “7.5 mg/d	7.6	11.4â “53.2 mcmol/d
Amylase	0.04â “0.30 International Units/min 60â “450 Units/24 hr	16.67	0.6â “75.00 nkat/min
Calcium	50â “250 mg/d	0.250	1.25â “6.25 mmol/d
Catecholamines	<540 mcg/d	â ”	â ”
Dopamine	65â “400 mcg/d	â ”	â ”
Epinephrine	<20 mcg/d	5.5	<110 nmol/d
Norepinephrine	15â “80 mcg/d	5.9	88.5â “472.0 nmol/d
Copper	15â “60 mcg/d	0.0157	0.24â “0.95 mcmol/d
Cortisol, free	9â “53 mcg/d	2.76	25â “146 nmol/d
Creatinine			
Male	0.8â “1.8 g/d	8.84	7.1â “15.9 mmol/d
Female	0.6â “1.5 g/d	8.84	5.3â “13.3 mmol/d
5-Hydroxyindoleacetic acid	<6 mg/d	5.23	<47 mcmol/d
Metanephrine	<1.3 mg/d	5.46	<7.1 mcmol/d
Oxalate			
Male	7â “44 mg/d	11.4	80â “502 mcmol/d
Female	4â “31 mg/d	11.4	46â “353 mcmol/d
Porphyrins			
Coproporphyrin			
Male	0â “96 mcg/d	1.53	0â “110 nmol/d
Female	0â “60 mcg/d	1.54	0â “92 nmol/d
Uroporphyrin			
Male	0â “46 mcg/d	1.2	0â “32 nmol/d
Female	0â “22 mcg/d	1.2	0â “26 nmol/d
Protein	0â “150 mg/d	0.001	0â “0.150 g/d
Vanillylmandelic acid	<8 mg/d	5.05	<40 mcmol/d

(VMA)

Common hematologic values

Coagulation			
Bleeding time[j]	2.5â “9.5 min	60	150â “570 sec
Fibrin degradation products	<8 mcg/mL	â ”	â ”
Fibrinogen[k]	150â “400 mg/dL	0.01	1.5â “4.0 g/L
Partial thromboplastin time (activated)	24â “34 sec	1	24â “34 sec
Prothrombin time[l]	10.5â “14.5 sec	1	10.5â “14.5 sec
INR	0.78â “1.22	â ”	â ”
Thrombin time	11.3â “18.5 sec	1	11.3â “18.5 sec
CBC			
Hematocrit			
Male	40.7%â “50.3%	0.01	0.407â “0.503
Female	36.1%â “44.3%	0.01	0.361â “0.443
Hemoglobin			
Male	13.8â “17.2 g/dL	0.620[m]	8.56â “10.70 mmol/L
Female	12.1â “15.1 g/dL	0.620	7.50â “9.36 mmol/L
Erythrocyte count			
Male	4.5â “5.7 —Á 10^6/microliters	1	4.55.7 10 —Á^{12}/L
Female	3.9â “5.0 —Á 10^6/microliters	1	3.9â “5.0 10 —Á^{12}/L
Mean corpuscular hemoglobin	26.7â “33.7 pg/cell	0.062	1.66â “2.09 fmol/cell
Mean corpuscular hemoglobin concentration	32.7â “35.5 g/dL	0.620	20.3â “22.0 mmol/L
Mean corpuscular volume	80.0â “97.6 mcm^3	1	80.0â “97.6 fL
Red cell distribution width	11.8%â “14.6%	0.01	0.118â “0.146
Leukocyte profile			
Total	3.8â “9.8 —Á 10^3/microliters	1	3.8â “9.8 10 —Á^9/L
Lymphocytes	1.2â “3.3 —Á 10^3/microliters	1	1.2â “3.3 10 —Á^9/L
Mononuclear cells	0.2â “0.7 —Á 10^3/microliters	1	0.2â “0.7 10 —Á^9/L

Granulocytes	1.8â “6.6 —¡ 10^3/microliters	1	1.8â “6.6 10 —¡^{9}/L
Platelet count	140â “440 —¡ 10^3/microliters	1	140â “440 10 —¡^{9}/L
Erythrocyte sedimentation rate			
Male, <50 yr	0â “15 sec		
Male, >50 yr	0â “20 sec		
Female, <50 yr	0â “20 sec		
Female, >50 yr	0â “30 sec		
Reticulocyte count			
Adults	0.5%â “1.5%	0.01	0.005â “0.015
Children	2.5%â “6.5%	0.01	0.025â “0.065
Immunology testing			
Complement (total hemolytic)[n]	118â “226 units/mL		
C3	75â “165 mg/dL	0.01	0.85â “1.85 g/L
C4	12â “42 mg/dL	0.01	0.12â “0.54 g/L
Immunoglobulin			
IgA	70â “370 mg/dL	0.01	0.70â “3.70 g/L
IgM	30â “210 mg/dL	0.01	0.30â “2.10 g/L
IgG	700â “1450 mg/dL	0.01	7.00â “14.50 g/L
Therapeutic agents			
Amitriptyline (+ nortriptyline)	150â “250 mcg/L		
Carbamazepine	4â “12 mg/L	4.23	17â “51 mcmol/L
Clonazepam	10â “50 mcg/mL	3.17	32â “159 nmol/L
Cyclosporine (whole blood)	183â “335 ng/mL		Exact range depends on the type of transplant
Digoxin	0.8â “2.0 mcg/L	1.28	1.0â “2.6 nmol/L
Disopyramide	2â “5 mg/L	2.95	6â “15 mcmol/L
Ethosuximide	40â “75 mg/L	7.08	283â “531 mcmol/L
Imipramine	150â “300 mcg/L	3.57	536â “1071 nmol/L
Desipramine	100â “300 mcg/L	3.75	375â “1,125 nmol/L
Lithium	0.6â “1.3 mmol/L	1	0.6â “1.3 mmol/L
Nortriptyline	50â “150 mcg/L	3.8	190â “665 nmol/L
Phenobarbital	10â “40 mg/L	4.3	43â “172 mcmol/L
Phenytoin	10â “20 mg/L	3.96	40â “79 mcmol/L

(diphenylhydantoin)			
Primidone			
Primidone	5â “15 mg/L	4.58	23â “69 mcmol/L
Phenobarbital	1â “5 mcg/L	4.3	6â “9 mcmol/L
Procainamide	4â “10 mg/L	4.23	17â “42 mcmol/L
Procainamide + *N*-acetylprocainamide	6â “20 mg/L		
Quinidine	2â “5 mg/L	3.08	6.2â “15.4 mcmol/L
Salicylate[o]	20â “290 mg/L	0.0072	0.14â “2.10 mmol/L
Theophylline	10â “20 mg/L	5.5	55â “110 mcmol/L
Valproic acid	50â “100 mg/L	6.93	346â “693 mcmol/L
Antimicrobials			
Amikacin			
Trough	1â “8 mg/L	1.71	1.7â “13.7 mcmol/L
Peak	20â “30 mg/L	1.71	34â “51 mcmol/L
5-Fluorocytosine			
Trough	20â “60 mg/L		
Peak	50â “100 mg/L		
Gentamicin			
Trough	0.5â “2.0 mg/L	2.09	1.0â “4.2 mcmol/L
Peak	6â “10 mg/L	2.09	12.5â “20.9 mcmol/L
Ketoconazole			
Trough	1 mg/L	â ”	â ”
Peak	1â “4 mg/L	â ”	â ”
Sulfamethoxazole			
Trough	75â “120 mg/L	â ”	â ”
Peak	100â “150 mg/L	â ”	â ”
Tobramycin			
Trough	0.5â “2.0 mg/L	2.14	1.1â “4.3 mcmol/L
Peak	6â “10 mg/L	2.14	12.8â “21.4 mcmol/L
Trimethoprim			
Trough	2â “8 mg/L	â ”	â ”
Peak	5â “15 mg/L	â ”	â ”
Vancomycin			
Trough	5â “15 mg/L	0.69	3.5â “10.4 mcmol/L
Peak	20â “40 mg/L		13.8â “27.0

mcmol/L

ACTH, adrenocorticotropic hormone; fL, femtoliter; fmol, femtomole; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; INR, international normalized ratio; katal, mole/sec; kPa, kilopascal; LH, luteinizing hormone; µkat, microkatal; nkat, nanokatal; pmol, picomole; TSH, thyroid-stimulating hormone.

[a]A more complete list of multiplication factors for converting conventional units to SI units can be found in *Ann Intern Med* 1967;106:114, and in *The SI for the Health Professions.* Geneva: World Health Organization, 1977.

[b]Variation occurs with age and gender. This range includes both genders and persons older than 5 yr.

[c]National Institutes of Health Congress Development Panel on Triglycerides, HDL, and Coronary Artery Diseases, *JAMA* 1993;269:505.

[d]Higher values (up to 350 µU/mL) can be normal in persons younger than 20 yr.

[e]Because most hormones are measured by immunologic techniques and because hormones may vary in molecular weight (e.g., gastrin), most are expressed as mass/L. The reference ranges are method dependent.

[f]Supine, normal unit diet; in the upright position, the reference range is 40â “310 ng/L.

[g]High-sodium diet, supplemented with sodium, 3 g/d.

[h]Replaces T_3 resin uptake.

[i]T_4 ·. (T uptake).

[j]Template modified after Ivy.

[k]Determined by the Clauss method.

[l]Normal ranges for prothrombin times vary according to the reagent used. Therefore, we report an INR with all prothrombin times ordered.

[m]This factor assumes a unit molecular weight of 16,000; assuming a unit molecular weight of 64,500, we have a multiplication factor of 0.156.

[n]CH_{50} is the reciprocal of dilution of sera required to lyse 50% of sheep erythrocytes.

[o]Therapeutic range for treatment of rheumatoid arthritis [(1)]

International Systems of units

Notes on International Systems of units (SI Units)

Système International (SI) units are a specific subset of the metre-kilogram-second system of units and were agreed upon as the everyday currency for commercial and scientific work in 1960, following a series of international conferences organised by the International Bureau of Weights and Measures. SI units have been adopted widely in clinical laboratories, but non-SI units are still used in many countries. For that reason, values in both units are given for common measurements throughout this textbook and commonly used non-SI units are shown in this appendix. However, the SI unit system is recommended.

Table 34 Examples of basic SI units

Length	metre (m)
Mass	kilogram (kg)
Amount of substance	mole (mol)
Energy	joule (J)
Pressure	pascal (Pa)
Volume	The basic SI unit of volume is the cubic metre (1000 litres). For convenience, however, the litre (l) is used as the unit of volume in laboratory work.

Table 35 Examples of decimal multiples and submultiples of SI units

Factor	*Name*	*Prefix*
10^{6}	mega-	M
10^{3}	kilo-	K
10^{-1}	deci-	D
10^{-2}	centi-	C
10^{-3}	milli-	M
10^{-6}	Micro-	M
10^{-9}	nano-	N

10^{-12}	pico-	P
10^{-15}	Femto-	F

Exceptions to the use of SI units

By convention, blood pressure is excluded from the SI unit system and is measured in mmHg (millimetres of mercury) rather than pascals.

Mass concentrations (e.g. g/l, μg/l) are used in preference to molar concentrations for all protein measurements, and for substances which do not have a sufficiently well-defined composition.

Some enzymes and hormones are measured by 'bioassay', in which the activity in the sample is compared with the activity (rather than the mass) of a standard sample which is provided from a central source. For these assays, results are given in standardised 'units', or 'international units', which depend upon the activity in the standard sample and may not be readily converted to mass units. (2)

Pregnancy and Medical Therapeutics

Using medications during pregnancy or lactation always creates discussion between the patient and the physician. There is a continuous balance among treating a maternal condition for the safety of the mother, treating a maternal condition for the safety of the fetus, and potential drug toxicity to the fetus. (1)

It is important to remember that the risk to the embryo or fetus changes throughout gestation, such that many of the more teratogenic medications can be relatively safe during certain parts of the pregnancy or during lactation.

Many factors play a role in the possible teratogenic nature of a medication, such as the genetic susceptibility of the fetus, maternal ability to absorb and metabolize medications, other environmental factors, the developmental stage of the embryo or fetus, dose and duration of exposure, activity of metabolites, and drugâ “drug interactions.

Placental transport is very important and occurs more readily with medications that are of low molecular weight, lipid soluble, nonpolar, and nonprotein bound.Gestational timing of medications is very important.

There is thought to be an â œall-or-noneâ phenomenon for an embryo during the first 2 weeks after conception. It is during this time that exposure to a teratogen is believed to either cause enough damage to the embryo that death or a spontaneous miscarriage occurs, or no damage or sufficient repair occurs such that there are no lasting effects. This is a common period of fetal exposure, given that many women may not yet know they are pregnant.

The first trimester is the very important time of organogenesis, during which both adequate control of maternal disease states (e.g., diabetes), and limiting exposure to teratogens (e.g., radiation exposure and many medications) are equally important and may require consultation with an obstetrician or maternal fetal medicine specialist.

The remainder of pregnancy is a period of cell growth and differentiation

that can be inhibited by certain medications in varying doses and duration of exposure.

Finally, lactation represents a time during which certain medications may be transported to the fetus through breast milk. The cellular mechanisms through which this occurs are different than during placental transport, and certain medications (e.g., warfarin) that can be teratogenic or cause disastrous complications when passage occurs in utero can be very safe during lactation, given transportation in only an inactive form. (1)

Risk Factor Categories:

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, there is no evidence of a risk in later trimesters, and the possibility of fetal harm appears remote. Very few drugs have sufficient safety profiles, and therefore the table excludes this category. The only medications classified as category A are each of the vitamins when used in Recommended Dietary Allowance (RDA)-recommended doses, levothyroxine, the antiemetic doxylamine, and the electrolytes potassium citrate, potassium chloride, and potassium gluconate. (1)

Category B: Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester, and there is not evidence of a risk in the later trimesters. (1)

Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. These drugs should only be given if the potential benefit justifies the potential risk to the fetus. (W)

Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk, as if the drug is needed in a (1)

life-threatening situation or for serious diseases for which safer drugs are ineffective or cannot be used. (1)

Category X: Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. These drugs are contraindicated in women who are or may become pregnant. (1)

Table 36 Pregnancy and Medical Therapeutics

Class of medication	Category B	Category C	Category D	Category X
Analgesics	Acetaminophen	Triptans	*	Dihydroergotamine
	Diclofenac*	(antimigraine)		Ergotamine
	Hydromorphone*	Aspirin*		
	Ibuprofen*	Butalbital		
	Indomethacin*	Butorphanol*		
	Meperidine*	Celecoxib*		
	Methadone*	Codeine*		
	Naproxen*	Fentanyl*		
	Oxycodone*	Hydrocodone*		
	Oxymorphone*	Ketorolac*		
		Morphine*		
		Propoxyphene*		
		Sufentanil*		
		Tramadol		
Anesthetics	Halothane	Nitrous oxide		
	Isoflurane	Sevoflurane		
	Ketamine			
	Lidocaine (local)			
	Propofol			
	Ropivacaine (local)			
Antibiotics	Azithromycin	Gentamycin	Quinine	
	Aztreonam	Bacitracin	Streptomycin	
	Cephalosporins	Chloramphenicol	Tetracyclines	
	Clavulanate	Chloroquine		
	Clindamycin	Clarithromycin		
	Ethambutol	Dapsone		
	Meropenem	Imipenem-		
	Metronidazole	cilastatin		
	Penicillins	Isoniazid		
	Polymyxin B	Linezolid		
	Sulbactam	Pyrazinamide		
	Tazobactam	Quinolones**		

	Vancomycin	Rifampin		
		Spectinomycin		
		Sulfonamides		
		Trimethoprim		
Anticonvulsants	Magnesium sulfate	Ethosuximide	Carbamazepine	
		Gabapentin	Clonazepam	
		Lamotrigine	Diazepam	
		Levetiracetam	Phenobarbital	
		Oxcarbazepine	Phenytoin	
		Topiramate	Primidone	
		Zonisamide	Valproic acid	
Antidepressants/	Buproprion	Aripiprazole	Alprazolam	Other
antipsychotics/	Buspirone	Chlorpromazine	Chlordiazepoxide	benzodiazepines
anxiolytics	Zolpidem	Clozapine	Clonazepam	
		Haloperidol	Diazepam	
		Olanzapine	Lithium	
		Quetiapine	Lorazepam	
		Risperidone	Midazolam	
		SSRIs[a]	Oxazepam	
		TCAs		
		Thioridazine		
		Ziprasidone		
Antifungals	Amphotericin B	Caspofungin		
	Clotrimazole	Fluconazole		
		Griseofulvin		
		Ketoconazole		
		Miconazole		
		Nystatin		
		Terconazole		
Antihistamines	Cetirizine	Fexofenadine		
	Chlorpheniramine	Hydroxyzine		
	Diphenhydramine	Promethazine		
	Loratadine			
	Meclizine			
Antilipemics	Cholestyramine	Clofibrate		Statins
	Colestipol	Gemfibrozil		
	Niacin[b]			
Antiretrovirals[c]	Atazanavir	Efavirenz		
	Didanosine	Indinavir		
	Emtricitabine	Lamivudine		
	Ritonavir	Lopinavir		
	Saquinavir	Nevirapine		
	Tenofovir	Zidovudine		
Antivirals	Acyclovir	Amantadine		
	Famciclovir	Foscarnet		
	Valacyclovir	Ganciclovir		
		Oseltamivir		
		Rimantadine		
Bisphosphonates		Alendronate	Pamidronate	
		Ibandronate		

		Risedronate		
Cardiovascular drugs	Methyldopa Hydrochlorothiazide[d]	Acetazolamide Adenosine Calcium-channel blockers Clonidine Digoxin Esmolol Flecainide Hydralazine Isosorbides Labetalol[d] Metoprolol[d] Minoxidil Nitroglycerin (B/C) Nitroprusside Prazosin Propranolol[d] Terazosin	ACE Inhibitors Amiodarone ARBs Atenolol	
Dermatology	Azelaic acid Clindamycin Erythromycin	Benzoyl peroxide Tretinoin (topical)	Doxycycline	Isotretinoin
Gastrointestinal	Cimetidine Famotidine Lactulose Lansoprazole Loperamide Meclizine Mesalamine Metoclopramide Ondansetron Opium tincture Orlistat Pantoprazole Ranitidine Sucralfate Ursodiol	Docusate Droperidol Kaolin Mineral oil Omeprazole Prochlorperazine Promethazine Senna Simethicone		Misoprostol
Hematologic	Argatroban Clopidogrel Dalteparin Dypyridamole Enoxaparin Lepirudin	Alteplase Epoetin alfa Filgrastim Heparin Pentoxifylline Streptokinase	Aminocaproic acid	Warfarin
Hormones	Acarbose Desmopressin Insulin Metformin Somatostatin Troglitazone	Adrenal hormones[e] Calcitonin Glipizide Glyburide Melatonin	Methimazole Propylthiouracil Tamoxifen Hydroxyprogesterone[f]	Danazol Estrogens Iodide[131] Leuprolide Mifepristone Testosterone

	Vasopressin	Repaglinide
	Micronized	Rosiglitazone
	progesterone	Tolbutamide
Respiratory	Acetylcysteine	Albuterol
	Budesonide	Corticosteroids
	Cromolyn sodium	(inhaled)
	Ipratropium	Dextromethorphan
	Montelukast	Guaifenesin
	Zafirlukast	Salmeterol
		Theophylline
Urologic	Oxybutynin	Tolterodine
	Phenazopyridine	Trospium

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

*All of these can be considered category D if used in large doses or for prolonged duration.

**Although classified as category C by the manufacturer, use with caution, given concern for floroquinolone-induced fetal cartilage damage. This is somewhat controversial, but most obstetricians avoid their use in pregnancy.

[a]Recent data suggest that there may be concern for increased risk of persistent pulmonary hypertension with exposure in the latter half of pregnancy or neonatal withdrawl syndromeâ ”although usually self-limitedâ ”with exposure in the third trimester. Fluoxitine is the most studied and has been followed the longest, and setraline still has a good safety profile. Much of this is still hotly debated in the literature.

[b]Considered category C if used in doses for lipid treatment or above RDA doses.

[c]Efavirenz is generally not recommended in the first trimester. Consider consultation with a specialist who has experience in HIV and pregnancy because there are specific recommendations for treating HIV in pregnancy that differ from nonpregnant treatment regimens.

[d]There is concern for use of beta-blockers in the second and third trimesters given reports of intrauterine growth restriction and reduced placental weights, although labetalol has the most safety data of the class. Diuretics should not be used to treat gestational hypertension.

[e]Adrenal hormones (e.g., cortisol, dexamethasone, hydrocortisone, and prednisone) are generally regarded as category C, although some argue that one should try to avoid use during the first trimester, given some concern for teratogenic data in animals and human epidemiologic studies.

[f]Avoid in the 1st trimester. The American college of Obstetrics & Gynecology (ACOG) supports its use in pregnancy if history of spontaneous preterm delivery. [(1)]

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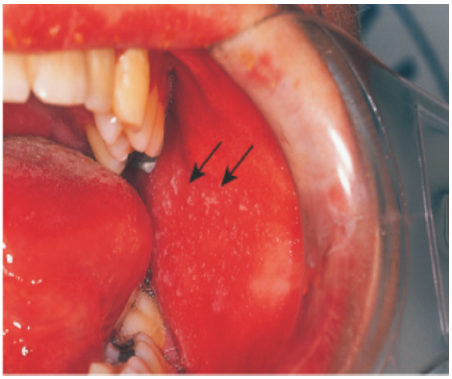
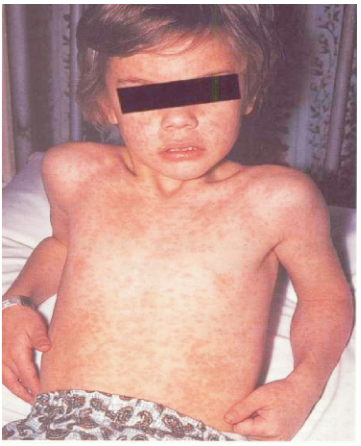
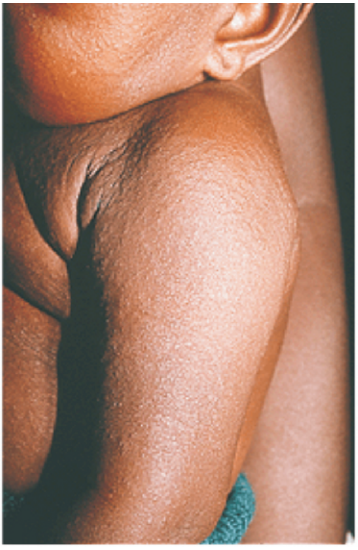


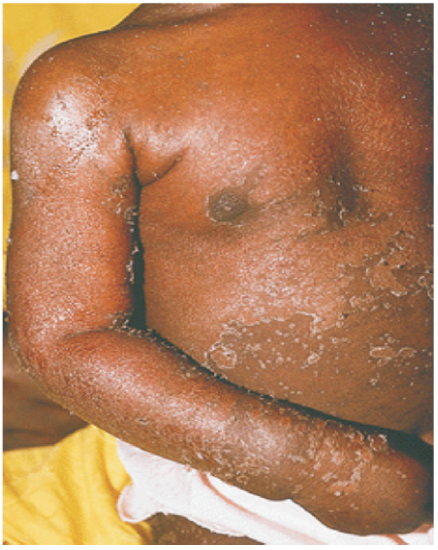
(Fig 11) Koplik's spots (arrows) seen on buccal mucosa in the early stages of measles. (2)



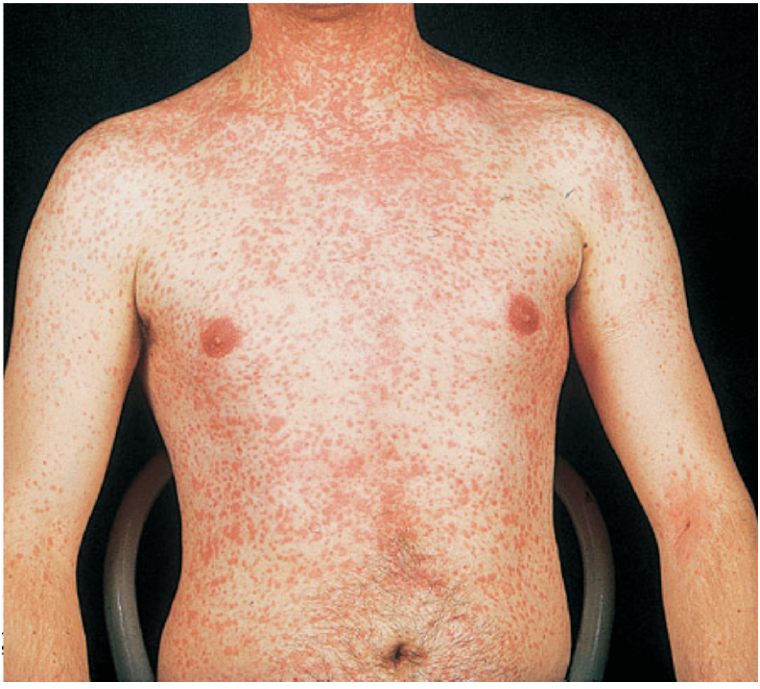
(Fig 12) Typical measles rash. (2)



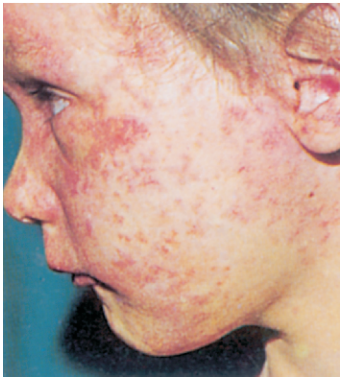
(Fig. 13) Measles rash (African). (8)



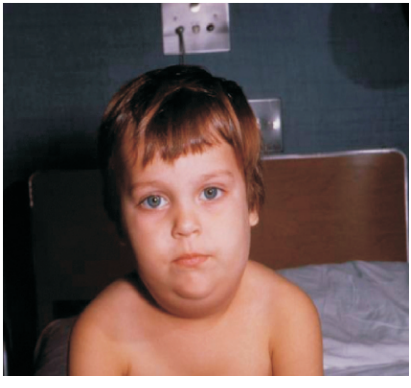
(Fig. 14) Measles rash (African). (8)



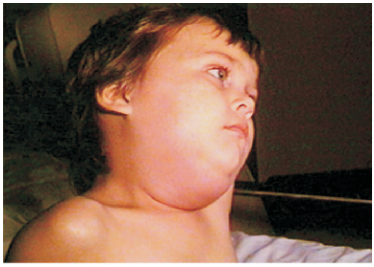
(Fig 15) **In measles, discrete erythematous lesions** become confluent as the rash spreads downward. (3)



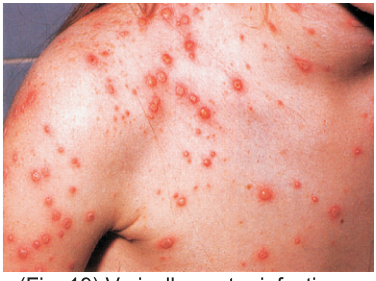
(Fig. 16) Rash of rubella (5)



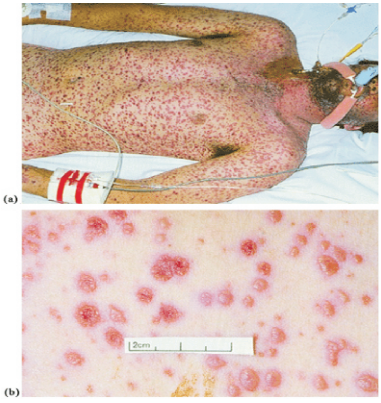
(Fig. 18- A) A child with mumps showing parotid swelling (5)



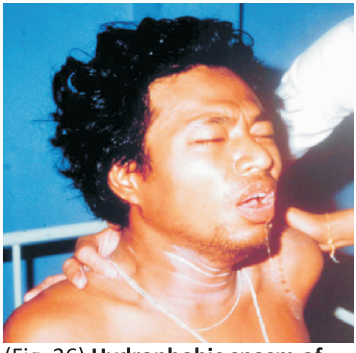
(Fig. 18- B)**Child with mumps**. Note the classic submandibular and preauricular enlargement of the parotid gland. (3)



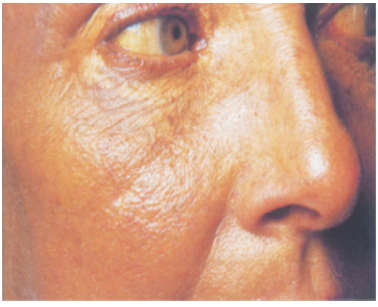
(Fig. 19) Varicella-zoster infections. Adolescent with varicella lesions in various stages(5)



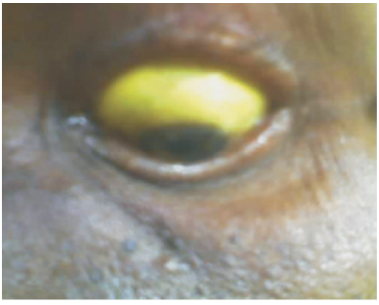
(Fig. 21) (a) **Severe chickenpox** also involving the lungs. (b) Details of the rash. (8)



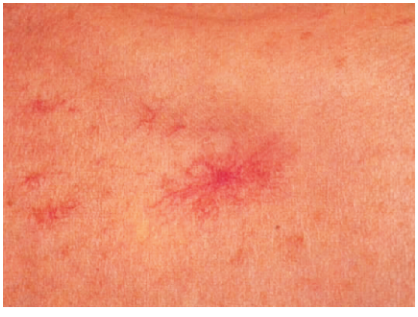
(Fig. 26) **Hydrophobic spasm of inspiratory muscles associated with terror** in a patient with encephalitic (furious) rabies who is attempting to swallow water. (3)



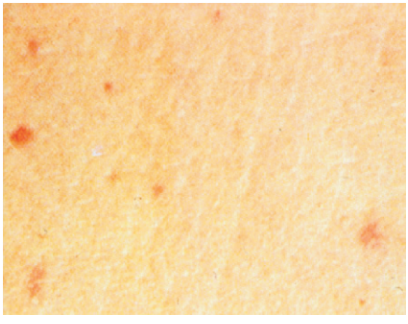
(Fig. 27) Jaundice (4)



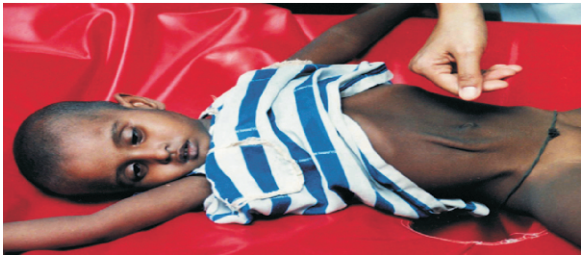
(Fig. 28) Scleral icterus (4)



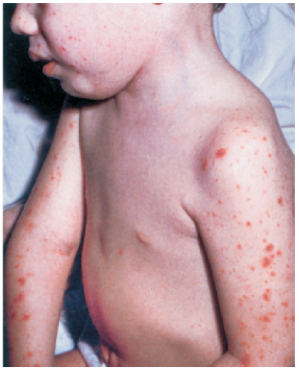
(Fig. 29) Vascular spider (7)



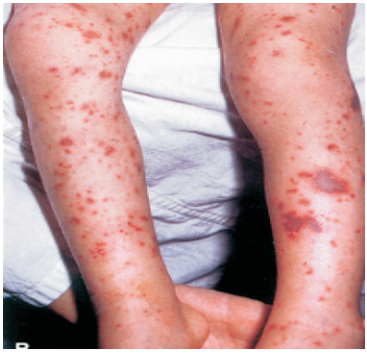
(Fig. 31) "**Rose spots," the rash of enteric fever** due to S. Typhi or S. Paratyphi. (3)



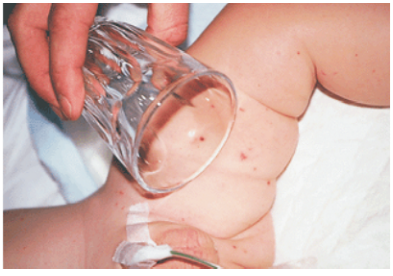
(Fig. 34) A child, lying on a cholera cot, showing typical signs of severe dehydration from cholera. The patient has sunken eyes, lethargic appearance, and poor skin turgor, but within 2 hr was sitting up, alert, and eating normally. (5)



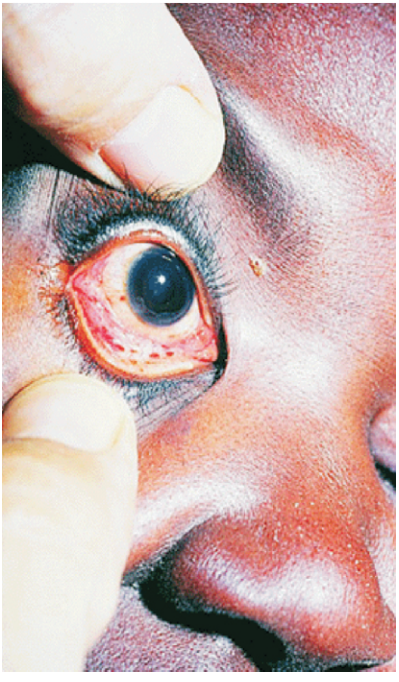
(Fig. 35) Meningococcal petechial rash (5)



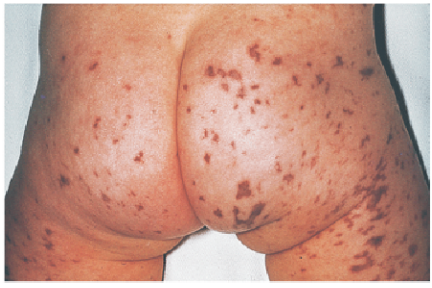
(Fig. 36) Meningococcal infections. This image shows the lower extremities of the patient (5)



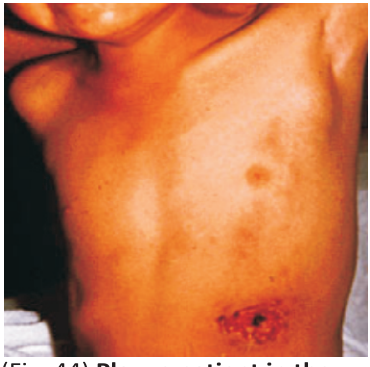
(Fig. 38) The â€ glass testâ€™ used to differentiate haemorrhagic skin lesions from viral or drug rash in an infant with meningococcal meningitis caused by Neisseria meningitidis group B. There was complete recovery after 5 days treatment with benzylpenicillin. (8)



(Fig. 40) Conjunctival petechiae in a Nigerian boy with meningococcal meningitis. (Copyright D.A. Warrell.) (8)

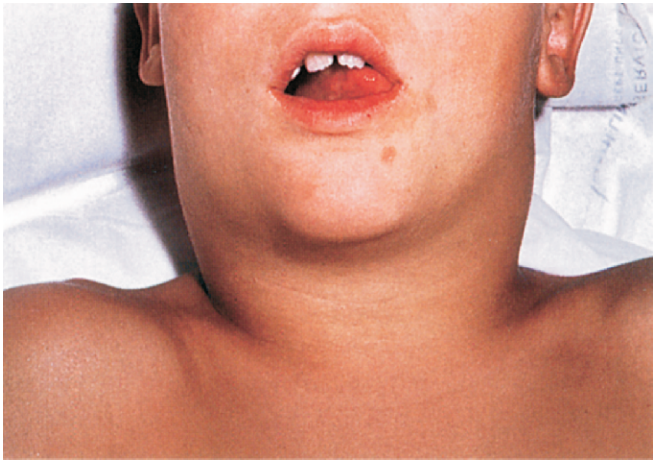


(Fig. 41) The rash of meningococcal septicaemia in an English child. (8)

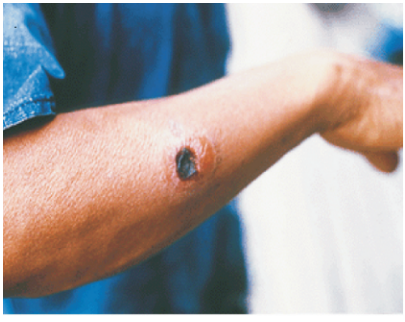


(Fig. 44) **Plague patient in the southwestern United States** with a left axillary bubo and an unusual plague ulcer and eschar at the site of the infective flea bite. (3)

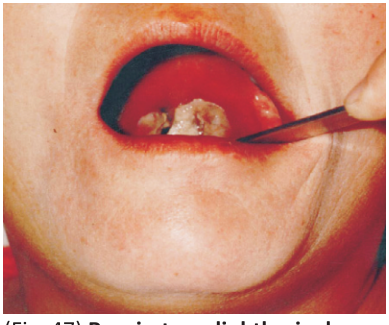
(Fig. 42) Healing vasculitic rash in a Brazilian boy with meningococcal meningitis and meningococcaemia (Copyright D.A. Warrell.) (8).



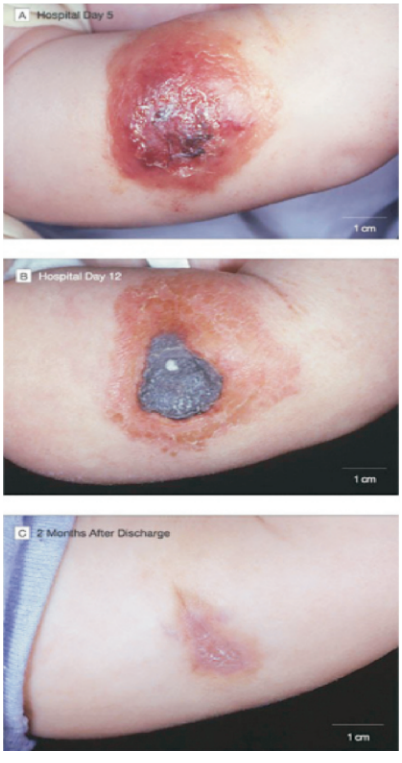
(Fig. 45) **Diphtheria. Bull-neck appearance** of diphtheritic cervical lymphadenopathy in a 13 yr old boy (5).



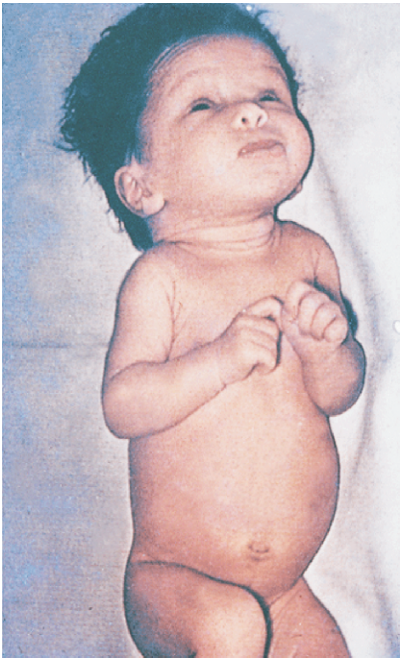
(Fig. 49) Cutaneous anthrax lesion on the forearm on day 10 showing an ulcer with a depressed black eschar. (8)



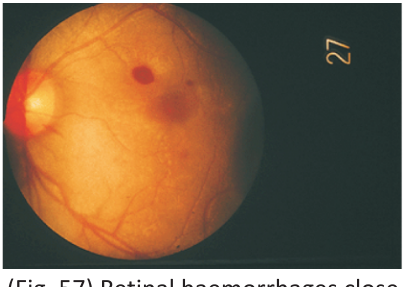
(Fig. 47) **Respiratory diphtheria due to toxigenic C. diphtheriae** producing exudative phsaryngitis in a 47-year-old woman with neck edema and a pseudomembrane extending from the uvula to the pharyngeal wall. (3)



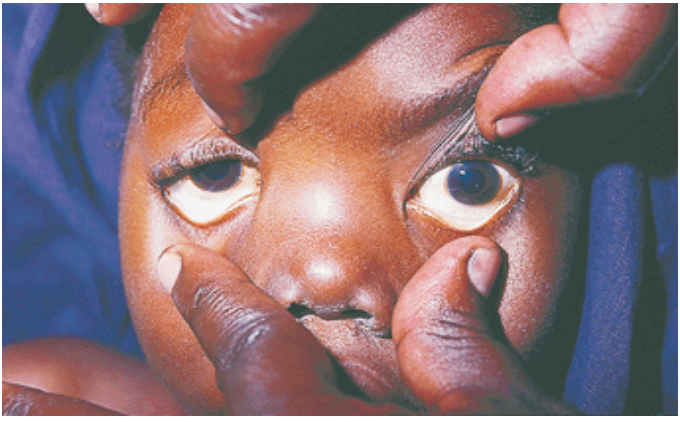
(Fig. 48) **The lesion of cutaneous anthrax**. (4)



(Fig. 54) **Characteristic facies in neonatal tetanus** (8)

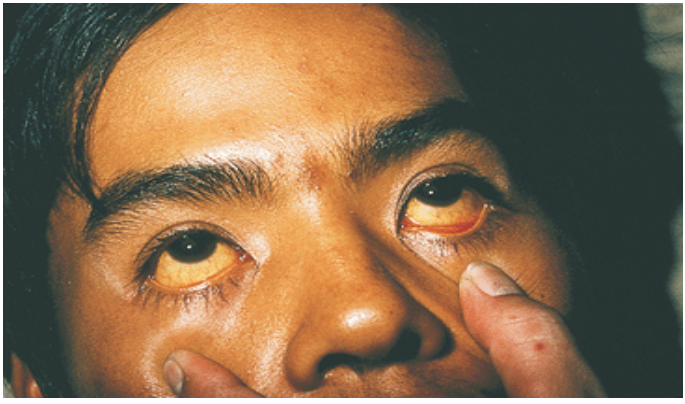


(Fig. 57) Retinal haemorrhages close to the macula in a Thai patient with cerebral malaria. (Copyright D.A. Warrell.) (8)

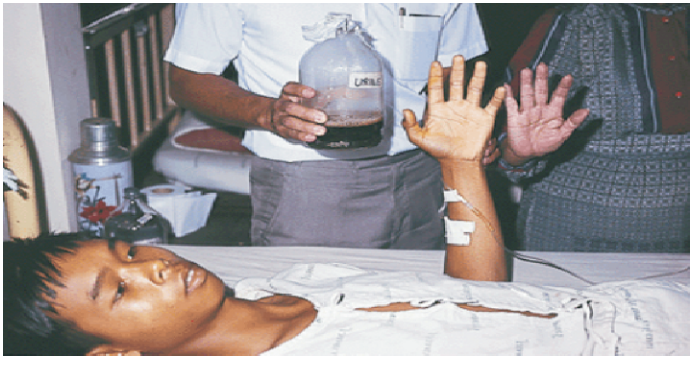


(Fig. 58) Profound anaemia (haemoglobin 1.2 g/dl) in a Kenyan child with P. falciparum parasitaemia. (Copyright D.A. Warrell.) (8)

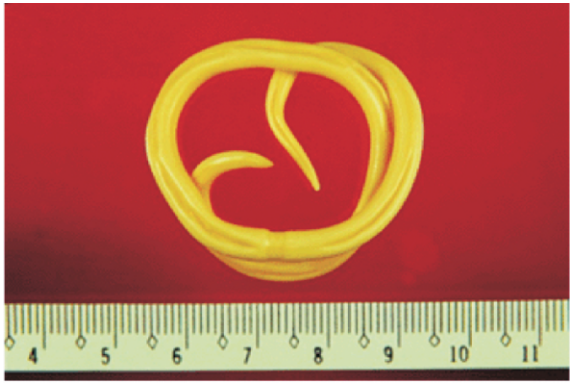
(Fig. 59) Cerebral malaria. Spontaneous systemic bleeding in a Thai patient with disseminated intravascular coagulation. (Copyright D.A. Warrell.) (8)



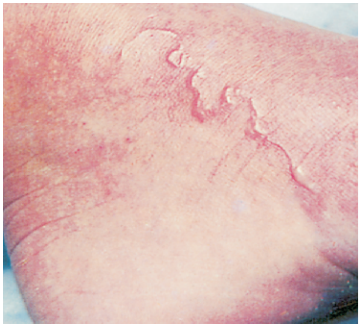
(Fig. 60) Deep jaundice in a Vietnamese man with severe falciparum malaria. (Copyright D.A. Warrell.) (8)



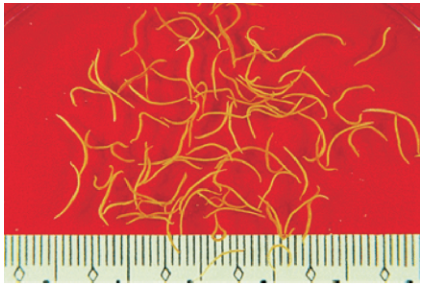
(Fig. 61) Intravascular haemolysis in a Karen patient with glucose 6-phosphate dehydrogenase deficiency in whom treatment with an oxidant drug resulted in haemoglobinuria and anaemia (normal hand in comparison). (Copyright D.A. Warrell.) (8)



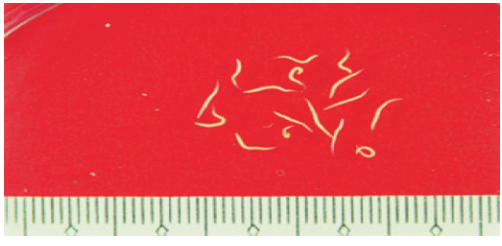
(Fig. 75) Ascaris - scale in millimetres. (8)



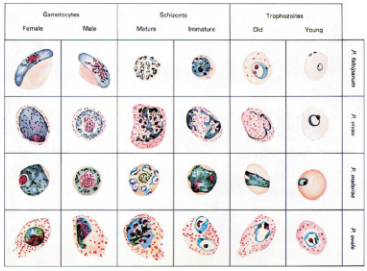
(Fig. 79) Creeping eruption of cutaneous larva migrans. (N)



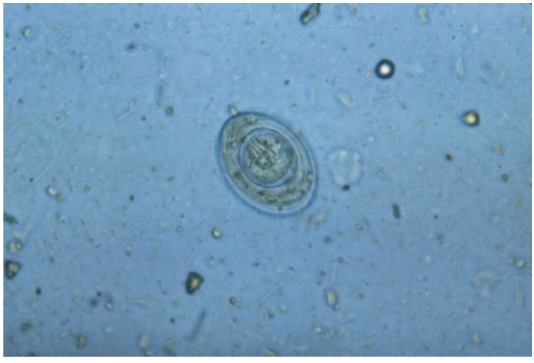
(Fig. 83) Adult Ancylostoma duodenale - scale in millimetres. (Copyright Viqar Zaman.) (O)



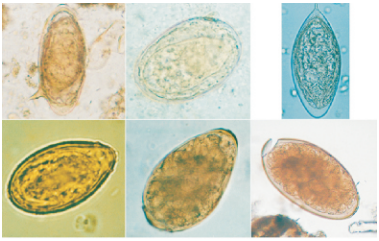
(Fig. 86) Enterobius - scale in millimetres. (O)



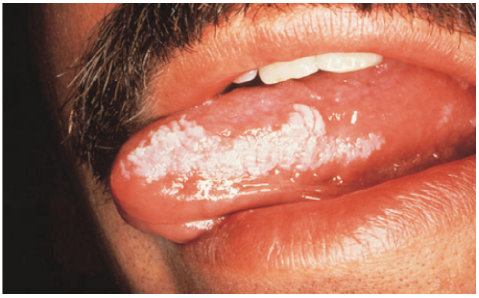
(Fig. 64) Malaria parasites developing in erythrocytes. (By courtesy of The Wellcome Trust.) (8)



(Fig. 97) Micrograph depicting an egg from a Hymenolepis nana tapeworm, or cestode. H. nana eggs are oval or subspherical in shape, 40 to 60?m×30 to 50?m in size-smaller than those of Hymenolepis diminuta. On the inner membrane are two poles from which four to eight polar filaments spread out between its two membranes. (3)



(Fig. 95) Eggs of common human trematodes. Clockwise from upper left: Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Clonorchis sinensiss, Pargonimus westermani, and Fasiola hepatica (note the partially open operculum



(Fig. 98) Oral hairy leukoplakia of the lateral border of the tongue in an HIV-infected patient. (7)

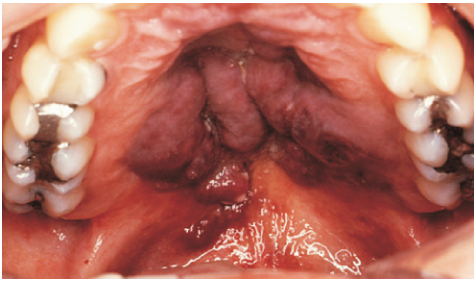
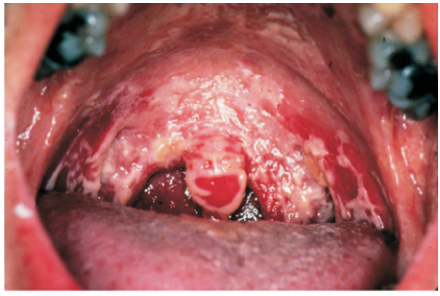
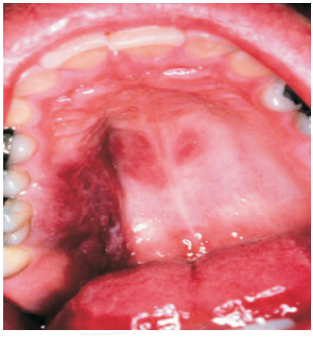
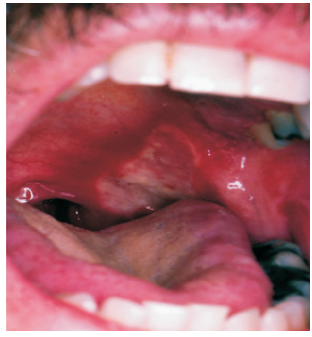


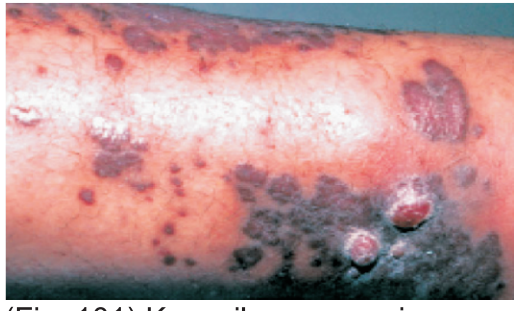
Fig. 99) Advanced Kaposi sarcoma of the soft palate in AIDS. (7)







(Fig. 100) Various oral lesions in HIV-infected individuals.
A. Thrush. B. Hairy leukoplakia. C. Aphthous ulcer.
D. Kaposi's sarcoma. (7)



(Fig. 101) Kaposi's sarcoma in a patient with AIDS demonstrating patch, plaque, and tumor stages. (7)

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د چاپ نېټه	۱۳۹۱
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اداري او تخنیکي چارې یې په آلمان کې د افغانیک موسسې لخوا ترسره شوې دي.

دکتاب د محتوا او لیکنې مسؤلیت دکتاب په لیکوال او اړوندی پوهنځی پورې اړه لري. مرسته کوونکې او تطبیق کوونکي ټولنې په دې اړه مسؤلیت نه لري.

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