„VICTOR BABEŞ" UNIVERSITY
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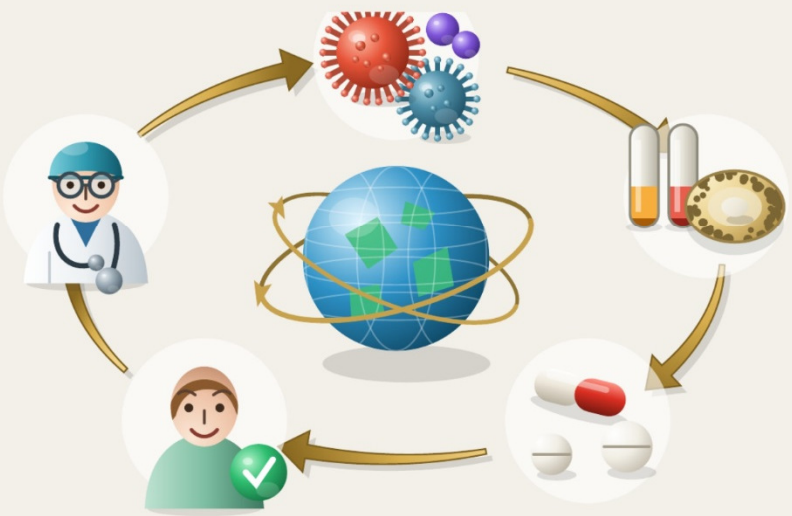
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INFECTIOUS DISEASES

PRACTICAL WORK GUIDE

for 6th-year General Medicine students



GHIDURI ȘI ÎNDRUMĂTOARE DE LABORATOR

„Victor Babeș" Publishing House
Timișoara, 2026

Editura „Victor Babeş”

Piața Eftimie Murgu nr. 2, cam. 316, 300041 Timișoara

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https://www.umft.ro/ro/organizare-evb/

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Indicativ CNCSIS: 324

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ISBN 978-606-786-669-8

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This book is the English translation of the original Romanian edition:

Lăzureanu EV (coord.), Laza R, Marinescu AR, Herlo A, Novăcescu TG, Grădiștean IM. Boli infecțioase. Îndreptar de lucrări practice pentru studenții anului VI, Medicină generală. Timișoara: Editura „Victor Babeș”; 2026. ISBN 978-606-786-662-9.

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CHAPTER 1

Antibiotics and antibiotic therapy

Prof. Elena-Voichița Lăzureanu, MD, PhD

Antibiotics are drugs used exclusively for the treatment and prevention of bacterial infections. They act either as bactericidal agents, by directly killing bacteria (e.g. penicillin, vancomycin, gentamicin), or as bacteriostatic agents, by halting their multiplication (e.g. erythromycin, doxycycline, chloramphenicol).

Antibiotics are not effective against viruses (influenza virus, SARS-CoV-2, rotavirus, etc.), fungi (Candida, Cryptococcus, etc.) or parasites (Giardia lamblia, Trichinella spiralis, etc.).

Antibiotics are classified by spectrum of activity as follows:

- Narrow spectrum: active only against a specific group of bacteria (e.g. penicillin, oxacillin, vancomycin)
- Broad spectrum: active against a wide variety of different bacteria (e.g. amoxicillin-clavulanic acid, ceftriaxone, meropenem)

Antibiotic therapy is the therapeutic approach that consists of using antibiotics to treat or prevent a bacterial infection. It is a fundamental branch of anti-infective therapy and is based on the principle of selective toxicity: killing or inhibiting the target bacteria without harming the cells of the host.

According to its clinical purpose, antibiotic therapy is divided into:

- **Curative antibiotic therapy**: treatment given to cure an existing infection that has been documented clinically or by laboratory tests.
- **Prophylactic antibiotic therapy**: short-term administration, in the absence of infection, to prevent its occurrence (e.g. surgical prophylaxis before an operation).

According to the certainty of the diagnosis, antibiotic therapy is structured as follows:

1. **Empirical/first-line therapy** (presumptive): initiated immediately, before the causative bacterium is known with

certainty. The antibiotic is chosen on the basis of the clinical signs, the most likely pathogens and medical guidelines, after biological samples have been collected.

2. **Targeted therapy** (documented): treatment is adjusted once laboratory results are available (identification of the bacterium by culture and antimicrobial susceptibility testing), choosing the most effective antibiotic with the narrowest possible spectrum.

When choosing the right antibiotic, it is important to identify the type of infection: community-acquired or nosocomial.

Characteristic	Community-acquired infection	Nosocomial infection (healthcare-associated)
Place of acquisition	Outside a healthcare facility	During or as a result of medical care
Time of onset	Present on admission in a patient with no contact with the healthcare system	Not present or incubating on admission; develops subsequently
Examples	Community-acquired pneumonia, urinary tract infection, influenza, gastroenterocolitis	Ventilator-associated pneumonia, surgical wound infection, catheter-related bloodstream infection
Organisms	More often community flora	More often hospital organisms, sometimes multidrug-resistant
Antibiotic resistance	Generally lower	May be high, due to selection of resistant organisms

1.1. MAJOR CLASSES OF ANTIBIOTICS

The major classes of antibiotics are presented in the table below**:**

Antibiotic class	Representative examples	Main target organisms	Common infections treated
Beta-lactams Mechanism of action: inhibit cell wall synthesis			
Penicillins	Penicillin G, V, amoxicillin, ampicillin, oxacillin, piperacillin	Streptococci, staphylococci, *Enterococcus*, *Listeria*, *Pseudomonas* (extended-spectrum agents)	Tonsillitis, otitis, sinusitis, pneumonia, skin infections, endocarditis, syphilis.
Cephalosporins	Cefalexin (1st gen.), cefuroxime (2nd gen.), ceftriaxone (3rd gen.), cefepime	*Streptococcus pneumoniae*, *E. coli*, *Klebsiella*, *Proteus*,	Urinary tract infections, severe pneumonia, bacterial meningitis,

	(4th gen.), ceftaroline (5th gen., anti-MRSA)	*Pseudomonas* (4th gen.)	intra-abdominal infections, sepsis.
Carbapenems	Meropenem, imipenem, ertapenem	Multidrug-resistant Gram-negative bacteria (ESBL), anaerobes, *Pseudomonas aeruginosa (but not ertapenem!)*	Severe nosocomial (hospital-acquired) infections, peritonitis, severe sepsis.
Monobactams	Aztreonam	Aerobic Gram-negative bacteria only (*Pseudomonas*, *E. coli*)	Severe urinary or respiratory infections
Macrolides & ketolides Mechanism of action: inhibit protein synthesis (50S)	Azithromycin, clarithromycin, erythromycin, telithromycin	Atypical bacteria (*Mycoplasma*, *Chlamydia*, *Legionella*), *Campylobacter*, streptococci	Atypical pneumonia, upper respiratory tract infections, STIs (chlamydia), *H. pylori*-associated ulcer.
Fluoroquinolones Mechanism of action: inhibit DNA gyrase and topoisomerase IV	Ciprofloxacin, levofloxacin, moxifloxacin	*E. coli*, *Pseudomonas*, *Salmonella*, *Shigella*, atypical bacteria	Complicated urinary tract infections, community-acquired pneumonia, gastrointestinal infections, acute bacterial sinusitis.
Tetracyclines Mechanism of action: inhibit protein synthesis (30S)	Doxycycline, minocycline, tigecycline (glycylcycline)	*Borrelia*, *Rickettsia*, *Chlamydia*, *Mycoplasma*, *Propionibacterium acnes*, MRSA	Lyme disease, spotted fever, acne, sexually transmitted infections.
Aminoglycosides Mechanism of action: inhibit protein synthesis (30S); bactericidal effect	Gentamicin, amikacin, tobramycin, neomycin	Aerobic Gram-negative bacilli (*Pseudomonas*, *Klebsiella*, *Enterobacter*)	Sepsis, complicated urinary tract infections, endocarditis (in combination), ocular/topical infections.
Glycopeptides & lipoglycopeptides Mechanism of action: inhibit cell wall synthesis	Vancomycin, teicoplanin, dalbavancin	Resistant Gram-positive bacteria only (MRSA, ampicillin-resistant *Enterococcus*, *Clostridioides difficile*)	Severe skin infections, osteomyelitis, MRSA endocarditis, pseudomembranous colitis (oral vancomycin).

Lincosamides Mechanism of action: inhibit protein synthesis (50S)	Clindamycin, lincomycin	Gram-positive bacteria, anaerobic bacteria (*Bacteroides fragilis*)	Dental infections, osteomyelitis, pelvic infections, lung abscesses, acne (topical use).
Streptogramins Mechanism of action: disrupt the bacterial outer membrane	Quinupristin/dalfopristin	Staphylococci (MRSA), *Enterococcus faecium* resistant to vancomycin	Severe nosocomial infections caused by multidrug-resistant Gram-positive bacteria
Lipopeptides Mechanism of action: lyse the cell membrane	Daptomycin	Multidrug-resistant Gram-positive bacteria only (MRSA, VRE)	Complicated skin infections, bacteremia, right-sided bacterial endocarditis.
Sulfonamides & trimethoprim Mechanism of action: inhibit folic acid synthesis	Sulfamethoxazole + trimethoprim	*Staphylococcus aureus* (including MRSA), *E. coli*, *Pneumocystis jirovecii*	Uncomplicated urinary tract infections, exacerbations of bronchitis, *Pneumocystis* pneumonia (in immunocompromised patients).
Nitroimidazoles Mechanism of action: generate free radicals that damage DNA	Metronidazole, tinidazole	Anaerobic bacteria (*Clostridium*, *Bacteroides*), protozoa (*Giardia*, *Trichomonas*)	Vaginitis, amebiasis, giardiasis, intra-abdominal infections, prophylaxis in colorectal surgery.
Nitrofurans Mechanism of action: damage bacterial DNA	Nitrofurantoin	*E. coli*, *Enterococcus*, *Staphylococcus saprophyticus*	Acute uncomplicated cystitis (lower urinary tract infections only).
Fosfomycins Mechanism of action: inhibit the first step of cell wall synthesis	Fosfomycin	*E. coli*, *Enterococcus*, ESBL-producing Gram-negative bacteria	Acute uncomplicated cystitis (single-dose treatment).
Rifamycins Mechanism of action: inhibit RNA polymerase	Rifampicin	Mycobacterium tuberculosis, staphylococci (in prosthesis-associated infections, in combination)	TB, endocarditis (in combination)

1.2. RESERVE ANTIBIOTICS

The most important reserve antibiotics are:

1. Beta-lactams and combinations with beta-lactamase inhibitors: piperacillin-tazobactam, ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam.
    - Target organisms: carbapenem-resistant Enterobacterales (CRE), multidrug-resistant (MDR) Pseudomonas aeruginosa, and Klebsiella pneumoniae producing carbapenemase (KPC/class A) and OXA-48 (class D)
    - Indications: ventilator-associated pneumonia, complicated intra-abdominal infections and severe hospital-acquired urinary tract infections.
2. Glycylcyclines: tigecycline, eravacycline.
    - Target organisms: Acinetobacter baumannii, MRSA, vancomycin-resistant enterococci (VRE) and anaerobes. Not active against Pseudomonas aeruginosa!
    - Indications: complicated skin and soft-tissue infections, severe intra-abdominal infections.
3. Polymyxins: colistin (polymyxin E), polymyxin B.
    - Target organisms: extensively drug-resistant (XDR) Gram-negative “superbugs”, particularly Acinetobacter baumannii, Pseudomonas aeruginosa and Klebsiella pneumoniae.
    - Indications: sepsis and severe hospital-acquired infections when no other option is effective any longer. They carry a very high risk of toxicity (nephrotoxicity and neurotoxicity).
4. Oxazolidinones and lipopeptides: linezolid, tedizolid, daptomycin.
    - Target organisms: multidrug-resistant Gram-positive bacteria: MRSA (methicillin-resistant Staphylococcus aureus) and VRE (vancomycin-resistant Enterococcus).
    - Indications: severe pneumonia (linezolid), bacteremia and infective endocarditis (daptomycin). Daptomycin is not used in pneumonia because it is inactivated by pulmonary surfactant.
5. Siderophore cephalosporins: cefiderocol.
    - Target organisms: carbapenem-resistant aerobic Gram-negative bacteria (including metallo-beta-lactamase producers, against which other new options fail).
    - Indications: respiratory, urinary or systemic infections in patients with limited treatment options.

Table of bacteria and effective antibiotics

Bacteria	Effective antibiotic classes/subclasses
Gram-positive	Penicillins, cephalosporins (especially 1st generation), glycopeptides, lipopeptides, oxazolidinones, macrolides
Gram-negative	Aminoglycosides, fluoroquinolones, 3rd–4th generation cephalosporins, carbapenems, monobactams, polymyxins
Anaerobes	Metronidazole, carbapenems, penicillins with β-lactamase inhibitors, clindamycin
Atypical bacteria	Macrolides, tetracyclines, respiratory fluoroquinolones
Methicillin-resistant staphylococci	Vancomycin, linezolid, daptomycin, ceftaroline, sometimes co-trimoxazole (depending on susceptibility)
Pseudomonas aeruginosa	Piperacillin/tazobactam, ceftazidime, cefepime, cefiderocol, meropenem/imipenem ± β-lactamase inhibitors, aztreonam ± avibactam, ciprofloxacin, levofloxacin, aminoglycosides, polymyxins, IV fosfomycin
Enterococci	Ampicillin, vancomycin (if susceptible), linezolid, daptomycin

The most common adverse reactions to antibiotics are presented in the following table:

Antibiotic class	Common examples	Specific adverse reactions	Risk of *Clostridioides difficile*
Penicillins	Amoxicillin, ampicillin	Allergy, anaphylactic shock, simple diarrhea, candidiasis.	**Common** (increased risk with beta-lactamase inhibitor combinations).
Cephalosporins	Cefalexin, ceftriaxone	Cross-allergy with penicillin, nausea, liver test abnormalities.	**Very common** (especially 2nd and 3rd generations).
Fluoroquinolones	Ciprofloxacin, levofloxacin	Tendinitis/tendon rupture, arrhythmias, neurological impairment.	**Very common** (one of the main classes implicated).
Lincosamides	Clindamycin	Severe abdominal pain, nausea, skin rash.	**Very common** (the highest risk reported per dose).
Sulfonamides / diaminopyrimidines	Trimethoprim**,** co-trimoxazole	Skin rash, hyperkalemia (elevated potassium), rare blood disorders.	**Moderate** / **low** (much lower risk than with cephalosporins or fluoroquinolones).

Macrolides	Clarithromycin, azithromycin	Severe gastric discomfort, cardiac rhythm disturbances, altered taste.	**Moderate** / **rare**.
Tetracyclines	Doxycycline, minocycline	Photosensitivity, tooth discoloration in children, esophageal irritation.	**Rare** (considered among the safest from a microbiological standpoint).
Aminoglycosides	Gentamicin, amikacin	Renal toxicity, hearing and balance impairment.	**Rare** (very little effect on colonic anaerobic bacteria).

To preserve the efficacy of these drugs, hospitals apply strict rules for their administration.

- Conditional initiation: they are given only after the organism has been isolated in the laboratory and an antibiogram has confirmed resistance to the standard lines of therapy.
- Special approval: their prescription often requires the approval of an infectious diseases specialist or of an antimicrobial stewardship committee.
- Toxicity monitoring: many of these molecules require regular monitoring of renal function (colistin, daptomycin) or of the complete blood count (linezolid).

1.3. PRINCIPLES OF ANTIBIOTIC THERAPY IN PREGNANCY

1. Antibiotics considered safe (first-line) in pregnancy

These classes have not shown adverse effects on the fetus in controlled clinical studies and are widely used for respiratory, urinary or gynecological infections.

- Penicillins: amoxicillin, ampicillin, penicillin G, oxacillin, including combinations with inhibitors (amoxicillin-clavulanic acid, piperacillin-tazobactam).
- Cephalosporins (all generations): cefalexin (1st gen.), cefuroxime (2nd gen.), ceftriaxone (3rd gen.), cefepime (4th gen.).
- Monobactams: aztreonam.
- Some macrolides: erythromycin and azithromycin are considered safe.
  Note: clarithromycin should be avoided (higher risk category).

2. Antibiotics to be used with caution (only if the maternal benefit outweighs the fetal risk)

They are administered only in severe infections where safe options have failed, or according to the antibiogram in nosocomial infections.

- Carbapenems: meropenem and ertapenem are relatively safe, but imipenem is preferably avoided (animal studies have shown a risk of embryotoxicity).
- Glycopeptides: vancomycin (intravenous) is used only in severe MRSA infections and requires strict monitoring of maternal serum levels.
- Clindamycin (lincosamides): safe for topical/intravaginal use; used with caution systemically.
- Fosfomycin: safe and widely used as a single dose in uncomplicated cystitis in pregnant women.

3. Contraindicated antibiotics (proven toxic/teratogenic effects)

These molecules carry clear risks for fetal development and must be avoided completely, except in extreme life-threatening situations with no alternative.

- Tetracyclines (doxycycline, minocycline): CONTRAINDICATED in the second and third trimesters. They bind to calcium in developing bone structures, causing dental enamel hypoplasia, irreversible yellow-brown discoloration of the fetal teeth and slowed bone growth.
- Fluoroquinolones (ciprofloxacin, levofloxacin): CONTRAINDICATED. They have an affinity for connective tissue and may cause arthropathy, described as lesions of the growth cartilage in fetuses.
- Aminoglycosides (gentamicin, amikacin, tobramycin): CONTRAINDICATED (except when the mother's life is at risk, e.g. severe sepsis). They cross the placenta and carry an increased risk of fetal ototoxicity (they can cause congenital deafness by damaging the vestibulocochlear nerve, cranial nerve VIII) and nephrotoxicity.
- Sulfonamides/trimethoprim:
    - *Trimethoprim* is a folic acid antagonist; when given in the first trimester, it increases the risk of neural tube defects (e.g. *spina bifida*).
    - *Sulfonamides* given in the third trimester compete with bilirubin for binding sites on serum albumin, increasing

the risk of severe nuclear jaundice (kernicterus) in the newborn.

- Nitrofurantoin: safe in the first and second trimesters for lower urinary tract infections, but CONTRAINDICATED at term (weeks 38–42) because of the risk of triggering hemolytic anemia in the newborn (glucose-6-phosphate dehydrogenase deficiency).

1.4. PRINCIPLES OF ANTIBIOTIC THERAPY IN CHILDREN

Antibiotic therapy in children must be adapted to age, body weight and organ (hepatic, renal) impairment, with careful monitoring of the clinical course and of adverse reactions.
Certain antibiotic classes are not used, or are used only as a last resort, because of their toxic effects on the child's development:

- Tetracyclines: contraindicated in children under 8 years of age. They are deposited in tooth enamel and bone, causing permanent yellow-brown discoloration of the teeth and slowed bone growth.
- Fluoroquinolones: generally contraindicated in children and adolescents. They may damage the articular growth cartilage and cause tendon injury.
- Sulfonamides: contraindicated in the first 2 months of life. They can trigger severe kernicterus (brain damage due to bilirubin accumulation).

Specific and common adverse reactions in children:

- Severe gastrointestinal disturbances: diarrhea, vomiting and epigastric pain are the most common. Children's intestinal flora is fragile and easily destroyed by antibiotics, which favors secondary infections (e.g. enterocolitis).
- Skin allergies: allergic skin reactions are relatively common, especially with penicillins (amoxicillin, ampicillin) and cephalosporins. A simple rash may sometimes be mistaken for an allergy; the physician must therefore determine whether it is a drug reaction or a sign of the disease (as happens in infectious mononucleosis). Antibiotics can trigger Stevens-Johnson syndrome, which may have an unfavorable course.
- Ear and kidney toxicity (aminoglycosides, e.g. gentamicin, amikacin): used only in hospitals for severe infections, these drugs require close monitoring.

- Oral ulcers and candidiasis: destruction of the beneficial bacteria of the gut microbiome may favor oral or gastrointestinal candidiasis.
- Clostridioides difficile colitis: when the beneficial bacteria disappear, this bacterium overgrows and releases toxins A and B, causing colitis. In children under 1 year of age: this bacterium is normally present (as “asymptomatic carriage”) in more than 30–50% of healthy infants. They lack the mature receptors that would allow the toxin to cause disease. Guidelines therefore do not recommend testing for C. difficile in children under 1 year of age, except in extremely rare cases (congenital diseases), because a positive result is usually a mere coincidence and the diarrhea has another cause (for example, a virus). In children aged 1 to 3 years: carriage remains fairly high. Testing is performed only if the physician has ruled out other causes (rotavirus, Salmonella, etc.).

1.5. ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship is a set of coordinated medical interventions and strategies aimed at optimizing antibiotic use in order to improve patient treatment and reduce bacterial resistance. It promotes the use of the right antibiotic, at the correct dose, by the optimal route of administration and for a strictly limited duration.

The 5 “Rs” of stewardship (core principles)

- Right route: choosing between intravenous administration (in severe infections) and oral administration.
- Right dose: rigorous dose adjustment according to the patient's weight, age and renal function.
- Right duration (timing): using the shortest course of treatment that ensures cure.
- Right target: rapid switch from a broad (empirical) spectrum to a narrow spectrum once the bacterium has been isolated in the laboratory (de-escalation).
- Right indication: complete avoidance of antibiotics in viral infections such as the common cold, influenza or COVID-19.

Why is this program vital?

1. It prevents antimicrobial resistance (AMR): reducing unnecessary use lowers the number of “super-resistant” bacteria in hospitals and in the community.

2. It protects the patient: it reduces the risk of serious secondary infections, such as *Clostridioides difficile* enterocolitis.
3. It reduces costs: optimized treatment shortens hospital stays and reduces the waste of expensive drugs.

1.6. ANTIMICROBIAL RESISTANCE (AMR)

Antimicrobial resistance (AMR), or bacterial resistance, is the ability of bacteria to survive and multiply in the presence of antibiotics that would normally kill them or stop their growth. In terms of how it arises, there are 2 main types of bacterial resistance.

The 2 main types of resistance

1. Natural (intrinsic) resistance

This is an innate and permanent characteristic of an entire bacterial species.

- All bacteria of that species are resistant because they lack the target on which the antibiotic acts or have a natural barrier (pulmonary surfactant inactivates daptomycin in lung infections).
- Example: *Mycoplasma* has no cell wall and is therefore naturally resistant to penicillins, as these antibiotics can act only by destroying the cell wall; Pseudomonas aeruginosa is intrinsically resistant to ertapenem.

2. Acquired resistance

It occurs in a bacterium that was normally susceptible to an antibiotic.

- It is the result of a genetic change and represents a major clinical problem.
- It can arise through two mechanisms:
    - Spontaneous genetic mutations in the bacterium's own DNA.
    - Horizontal gene transfer from another bacterium (via plasmids or bacteriophages).

Bacteria use 4 physical or chemical strategies to block the antibiotic:

- Enzymatic inactivation: the bacterium produces enzymes that destroy the antibiotic (such as the *beta-lactamases of the Ambler classification*).

- Efflux pumps: the bacterium develops microscopic “pumps” that expel the antibiotic from the cell before it can take effect.
- Membrane impermeability: alteration of protein channels (porins), blocking the entry of the antibiotic into the bacterium.
- Target modification: the bacterium slightly changes its internal structure so that the antibiotic can no longer bind to it.

Inappropriate antibiotic use accelerates acquired resistance through artificial selective pressure, a process by which we kill the weak bacteria and help only the strong ones to survive and multiply. A bacterial colony always contains a small percentage of bacteria that have undergone random genetic mutations and have become resistant. When the antibiotic is misused, we eliminate the competitors of these “superbugs”, giving them free space and resources to colonize the body.

The Ambler classification is a molecular system that divides beta-lactamase enzymes into four main classes (A, B, C and D), based on their amino acid sequence and structure. These enzymes are produced by bacteria to destroy beta-lactam antibiotics (such as penicillins).

1.6.1. AMBLER MOLECULAR CLASSIFICATION

The table below brings together the *Ambler molecular classification*, the chemical structure of the active site, the main associated enzymes, the antibiotics destroyed and the current therapeutic options:

Ambler class	Mechanism / active site	Specific enzymes (examples)	Which antibiotics become USELESS?	Which new antibiotics / combinations RESCUE treatment?
Class A *(serine enzymes)*	Uses a serine residue to cleave the beta-lactam ring.	ESBL (CTX-M, SHV, TEM) KPC (*K. pneumoniae* carbapenemase), GES (carbapenemase variants)	Penicillins, cephalosporins (1st–4th gen.). With KPC/GES: carbapenems (meropenem, imipenem) are also completely destroyed.	Ceftazidime-avibactam Meropenem-vaborbactam *For simple ESBL producers*: standard carbapenems (meropenem).

Class B *(metallo-beta-lactamases)*	Require zinc ions (Zn^{2+}) to hydrolyze the antibiotic.	NDM (New Delhi, e.g. NDM-1, NDM-5), VIM (Verona integron-encoded), IMP	All major beta-lactams: penicillins, cephalosporins and carbapenems. *Exception*: aztreonam is structurally resistant.	Cefiderocol Aztreonam + ceftazidime-avibactam *Non-beta-lactam alternatives*: colistin, tigecycline.
Class C *(serine enzymes)*	Chromosomal enzymes, often inducible in *Pseudomonas* or *Enterobacter*.	AmpC: CMY, DHA, FOX	Penicillins, 1st, 2nd- and 3rd-generation cephalosporins (ceftriaxone, ceftazidime), monobactams.	Cefepime (4th-gen. cephalosporin); carbapenems (meropenem); ceftazidime-avibactam
Class D *(serine enzymes)*	Also called oxacillinases; they show great variability between species.	OXA-48 (common in *Klebsiella*); OXA-23, OXA-24/40, OXA-58 (in *Acinetobacter*)	Penicillins and carbapenems (high-level resistance to meropenem). *Note:* OXA-48 may leave 3rd-generation cephalosporins partially intact.	Ceftazidime-avibactam (blocks OXA-48) Sulbactam-durlobactam (specific for the OXA enzymes of *Acinetobacter*) or high-dose ampicillin/ sulbactam + cefiderocol/ colistin

Table of antibiotics (beta-lactam and non-beta-lactam) and their activity against Gram-negative bacteria

Antibiotic	ESBL or AmpC producer	KPC producer	NDM producer	OXA-48 producer	Carbapenem-resistant P. aeruginosa	Carbapenem-resistant A. baumannii	S. maltophilia
Aztreonam-avibactam	**YES**	**YES**	**YES**	**+/-**	**+/-**	**NO**	**YES**
Cefiderocol	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Ceftazidime-avibactam	**YES**	**YES**	**NO**	**+/-**	**NO**	**NO**	**NO**
Ceftolozane-tazobactam	**YES**	**NO**	**NO**	**NO**	**+/-**	**NO**	**+/-**
Colistin	**YES**	**+/-**	**+/-**	**+/-**	**+/-**	**+/-**	**+/-**
Eravacycline	**YES**	**YES**	**YES**	**YES**	**NO**	**YES**	**YES**
Fosfomycin	**YES**	**+/-**	**+/-**	**+/-**	**+/-**	**NO**	**NO**
Imipenem-relebactam	**YES**	**YES**	**NO**	**+/-**	**YES**	**NO**	**NO**
Meropenem-vaborbactam	**YES**	**YES**	**NO**	**NO**	**NO**	**NO**	**NO**
Tigecycline	**YES**	**YES**	**YES**	**YES**	**NO**	**YES**	**YES**

The hypervirulent strain of *Klebsiella pneumoniae* (hvKP) is a hypermucoviscous, extremely aggressive variant of the classic bacterium, capable of causing severe and potentially fatal invasive infections in young and otherwise completely healthy individuals. The World Health Organization (WHO) has issued a global alert about its rapid spread, as the new strains combine this extreme virulence with resistance to last-line antibiotics (carbapenems). Unlike the classic form (cKP), which affects only vulnerable or hospitalized patients, the hypervirulent variant has dangerous biological features:

- Hypermucoviscous phenotype: the bacterium produces an extremely thick polysaccharide capsule, visible in the laboratory by the "string test" (formation of a mucoid string longer than 5 mm when the colony is touched).
- Overactive siderophores: it produces molecules that capture iron from the human body 10–100 times more efficiently than normal strains, feeding the bacterium and accelerating its multiplication.
- Metastatic dissemination: it has the unique ability to spread via the bloodstream from a single focus to multiple distant organs within an extremely short time.

Early identification is vital for patient survival. Standard management involves diagnosis and treatment as follows:

- Molecular diagnosis: specific genetic tests (for the virulence genes *iucA*, *iroN*, *peg-344*).
- Surgical drainage: large abscesses of the liver or other organs must be drained percutaneously to allow the antibiotics to act.
- Targeted antibiotic therapy: aggressive regimens based strictly on the antibiogram. For convergent strains (hypervirulent + multidrug-resistant), physicians resort to new antibiotic combinations such as ceftazidime-avibactam (CZA) or to reserve antibiotics (tigecycline, polymyxins).

The main mistakes that accelerate antibiotic resistance

1. Stopping treatment early

- What happens: the patient feels better after 2–3 days and stops the antibiotic.
- The mechanism: the first doses kill only the most susceptible bacteria. Bacteria with partial or moderate resistance survive.

- The result: the infection recurs, but this time the colony consists only of the descendants of the surviving bacteria and has become resistant to that antibiotic.

2. Underdosing or failure to follow the dosing schedule

- What happens: taking a lower dose (for example, one tablet instead of two), not observing the dosing interval (every 12 hours instead of every 8 hours) or failing to adjust the dose in obese patients results in underdosing.
- The mechanism: the blood concentration of the antibiotic falls below the minimum level required to kill the bacteria (the minimum inhibitory concentration, MIC).
- The result: the bacteria have time to activate their defense systems (such as efflux pumps or enzyme production) and become resistant.

3. Self-medication in viral infections

- What happens: taking antibiotics for conditions caused by viruses (common cold, influenza, most sore throats).
- The mechanism: antibiotics have no effect whatsoever on viruses. Instead, they directly attack the microbiota (the normal, beneficial bacterial flora of the gut and skin).
- The result: the destruction of beneficial bacteria leaves room for opportunistic and resistant bacteria to grow and to transfer their resistance genes via plasmids.

4. Use of broad-spectrum antibiotics without an antibiogram

- What happens: physicians prescribe, or patients request, “strong” antibiotics (broad-spectrum agents that kill dozens of bacterial species) for trivial infections, without a prior bacterial culture.
- The mechanism: instead of destroying a single target, billions of harmless bacteria are destroyed.
- The result: enormous, widespread selective pressure is created in the body, favoring the emergence of MDR (multidrug-resistant) bacteria and the development of toxigenic Clostridioides difficile.

1.6.2. CLASSIFICATION BY SEVERITY

By severity, there are 3 classes of antibiotic resistance:

1. MDR (multidrug-resistant)

- Definition: the bacterium is resistant to at least one antibiotic in 3 or more different antimicrobial categories (classes) tested.
- Clinical significance: standard first-line treatment fails. Physicians must resort to reserve (second-line) antibiotics, which are often more expensive or have more adverse effects.
- Common example: *Escherichia coli* or *Staphylococcus aureus* (MRSA) simultaneously resistant to penicillins, cephalosporins and fluoroquinolones.

Example antibiogram for an MDR Staphylococcus aureus strain: MRS phenotype

Blood culture

Growth of **Staphylococcus aureus**

Antibiogram

BLOOD CULTURE - Disk diffusion method

Organism name: **Staphylococcus aureus**

ANTIBIOTIC	INTERPRETATION
Linezolid	S
Trimethoprim-sulfamethoxazole	S
Gentamicin	S
Tigecycline	S
Tetracycline	R
Ciprofloxacin	R
Levofloxacin	R
Moxifloxacin	R
Oxacillin	R
Erythromycin	R
Clindamycin	R

MRS phenotype **= methicillin (oxacillin) resistance = resistance** to:

- Penicillins
- Beta-lactam/beta-lactamase inhibitor combinations (amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam)
- Cephalosporins (except those with anti-MRSA activity: *ceftaroline*, *ceftobiprole*)
- Carbapenems

4. XDR (extensively drug-resistant)

- Definition: the bacterium is resistant to almost all antibiotic classes. It remains susceptible to no more than two of the available antibiotic classes.

- Clinical significance: treatment options are extremely limited, and physicians are forced to use complex antibiotic combinations or drugs that are highly toxic to the body (such as colistin).
- Common example: hospital strains of *Acinetobacter baumannii* or *Pseudomonas aeruginosa* resistant to all commonly used antibiotics, including carbapenems.

Urine culture

Growth of **Acinetobacter baumannii >100 000 CFU/ml**

Antibiogram

URINE CULTURE - Disk diffusion method

Organism name: **Acinetobacter baumannii**

Carbapenemase: **Positive**

ANTIBIOTIC	INTERPRETATION
Imipenem	R
Meropenem	R
Doripenem	R
Ampicillin+sulbactam	R
Trimethoprim-sulfamethoxazole	R
Amikacin	R
Gentamicin	R
Tobramycin	R
Cefiderocol	S
Colistin	S

5. PDR (pandrug-resistant)

- Definition: the bacterium is resistant to absolutely all antibiotics in all classes recommended for testing.
- Clinical significance: the infection is practically untreatable with current antibiotics. This is the most feared scenario in medicine, with extremely high patient mortality. Physicians can only resort to experimental therapies (such as bacteriophage therapy).

Example antibiogram for PDR Klebsiella pneumoniae – sputum

SPUTUM - Disk diffusion method

Organism name: **Klebsiella pneumoniae**
Carbapenemase: **Positive**
MBL: **Positive**

ANTIBIOTIC	MIC	INTERPRETATION
Amoxicillin+clavulanic acid	>=128	R
Ceftriaxone	>=128	R
Ceftazidime	>=64	R
Cefepime	>=64	R
Ceftolozane/Tazobactam	>=16	R
Ceftazidime/Avibactam	>=16	R
Aztreonam	>=16	R
Trimethoprim-sulfamethoxazole	>=128	R
Piperacillin+tazobactam	>=64	R
Levofloxacin	>=128	R
Moxifloxacin	>=64	R
Ertapenem	>=32	R
Imipenem	>=32	R
Meropenem	>=32	R
Amikacin	>=32	R
Tobramycin	>=64	R
Gentamicin	>=64	R
Cefiderocol	>=32	R
Colistin	>=64	R

CARBAPENEMASE-PRODUCING PHENOTYPE (OXA-48, NDM). DO NOT TREAT WITH CARBAPENEMS!!!
(NDM = New Delhi metallo-beta-lactamase)

In *Klebsiella*, synergism *in vitro* was observed between Aztreonam and Ceftazidime/Avibactam, suggestive of MBL (metallo-beta-lactamase) production. The simultaneous combination of the 2 antibiotics may be a potentially effective therapeutic option, even though the strain is resistant to each antibiotic individually. Clinical correlation and consultation with an infectious diseases specialist are recommended.

Of course, for organisms with MDR, XDR or PDR resistance, the minimum inhibitory concentration (MIC) is also important; depending on its value, some antibiotics may be effective at increased doses and with prolonged administration, even if the organism appears to be resistant.

This table details the remaining therapeutic options for MDR, XDR and PDR bacteria, divided into the two major categories of hospital pathogens: Gram-negative (the most prone to extreme resistance) and Gram-positive.

Resistance profile	Remaining treatment options (Gram-negative) *(e.g. Klebsiella, Pseudomonas, Acinetobacter, E. coli)*	Remaining treatment options (Gram-positive) *(e.g. Staphylococcus aureus – MRSA, Enterococcus – VRE)*
MDR ***(multidrug-resistant)***	Carbapenems (meropenem, imipenem); 4th-generation cephalosporins (cefepime); fluoroquinolones (if susceptible); aminoglycosides (gentamicin)	Glycopeptides (vancomycin, teicoplanin); lincosamides (clindamycin); linezolid or doxycycline
XDR ***(extensively drug-resistant)***	New reserve combinations: ceftazidime-avibactam, ceftolozane-tazobactam. Polymyxins: colistin. Glycylcyclines: tigecycline. Siderophore cephalosporin: cefiderocol.	Oxazolidinones: linezolid, tedizolid. Lipopeptides: daptomycin. Anti-MRSA cephalosporins: ceftaroline. Streptogramins: quinupristin-dalfopristin.
PDR ***(pandrug-resistant)***	No functional standard antibiotic. Massive, experimental doses or extreme combinations of 3–4 molecules are attempted (e.g. colistin + extended-infusion meropenem + fosfomycin).	No functional standard antibiotic. Experimental molecules or atypical combinations are used (e.g. very high doses of daptomycin combined with ceftaroline).

When a bacterium becomes PDR and no longer responds to any antibiotic, medical teams turn to alternative strategies:

- Bacteriophage therapy: use of specific viruses that attack and destroy only bacterial cells, leaving human cells intact.
- Barrier synergism: combining 3–4 antibiotics to which the bacterium is individually resistant, in the hope that a simultaneous attack on several cellular structures will weaken it (e.g. destruction of the cell wall by a beta-lactam allows an aminoglycoside to enter, even if both appear as “Resistant” on the antibiogram).
- Immunomodulators and monoclonal antibodies: therapies that aggressively stimulate the patient's immune system to clear the infection without the help of antibiotics.

1.6.3. ANTIBIOTIC SYNERGISM

Antibiotic synergism is the phenomenon in which the combined action of two or more antibiotics is **significantly more potent** than the sum of the individual effects of each antibiotic taken separately. Synergism is not a mere coincidence; it relies on strict biochemical mechanisms

by which one antibiotic paves the way for, or potentiates the effect of, the other.

The most important antibiotic synergisms are classified according to the mechanism by which the drugs act together:

1. *Cell wall inhibition + protein synthesis blockade (the most classic synergism)*

The beta-lactam antibiotic damages the bacterial wall, facilitating entry of the aminoglycoside into the cell, where it blocks the ribosomes.

- Penicillin (or ampicillin) + gentamicin: used as the standard regimen in infective endocarditis caused by *Enterococcus faecalis* or *Streptococcus*.
- Ceftazidime (or piperacillin-tazobactam) + tobramycin (or amikacin): used in severe respiratory sepsis caused by *Pseudomonas aeruginosa*.

2*. Sequential double blockade of the same metabolic pathway*
Two substances act at different steps of the same bacterial metabolic pathway (folic acid synthesis), blocking it completely.

- Sulfamethoxazole + trimethoprim (co-trimoxazole/Biseptol): taken separately, they are only bacteriostatic, but together they become strongly bactericidal. It is the treatment of choice for *Pneumocystis jirovecii* pneumonia and for urinary tract infections.

3. *Membrane disruption + permeabilization for other classes (reserve synergisms)*
A polymyxin is used as a "detergent" to penetrate the outer membrane of extensively drug-resistant (XDR) Gram-negative bacteria, allowing another antibiotic to enter, even though the standard antibiogram showed the bacterium to be resistant to both.

- Colistin + meropenem: a life-saving combination in severe infections with carbapenemase-producing *Klebsiella pneumoniae* (KPC).
- Colistin + rifampicin: rifampicin does not normally act on Gram-negative bacteria, but colistin paves the way for it. Used against *Acinetobacter baumannii*.

4. *Protecting the antibiotic with a "shield" (beta-lactam + inhibitor)*
The inhibitor has no antibacterial effect of its own, but neutralizes the resistance enzymes (beta-lactamases) secreted by the bacterium, allowing the antibiotic to do its job.

- Amoxicillin + clavulanic acid (Augmentin): clavulanic acid inactivates beta-lactamases, allowing amoxicillin to kill otherwise resistant bacteria.
- Piperacillin + tazobactam (Tazocin): widely used in hospitals for intra-abdominal and nosocomial infections.
- Ceftazidime + avibactam (Zavicefta): a reserve combination for multidrug-resistant (MDR) Gram-negative bacteria.

5. *Double blockade of the cell wall (beta-lactam + beta-lactam synergism)*

Each antibiotic binds to different penicillin-binding proteins (PBPs) on the bacterial wall, achieving complete destruction of its structure.

- Ampicillin + ceftriaxone: a modern regimen used for endocarditis caused by *Enterococcus faecalis*, offering efficacy similar to that of the ampicillin + gentamicin regimen, but with much lower renal toxicity.

1.6.4. ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis is the administration of an antibiotic to a person without an active bacterial infection in order to prevent the occurrence of infection under conditions of increased risk. The aim is not to eradicate an already established infection, but to prevent infection by ensuring an effective antimicrobial concentration at the moment of exposure to contamination. The fundamental principle is: right antibiotic + right dose + right timing + minimum effective duration.

Antibiotic prophylaxis is indicated when:

1. The risk of infection is significant:

- surgical procedures with a risk of infection;
- clean-contaminated procedures;
- certain contaminated procedures, depending on the circumstances;
- procedures in which the occurrence of infection would have serious consequences.

2. Post-procedural infection would have severe consequences

- prosthetic implants;
- certain cardiovascular procedures;
- certain orthopedic procedures involving prosthetic material;
- procedures in which infection of the implanted material would be difficult to treat.

3. There is a particular individual risk

Prophylaxis may be indicated in certain situations in high-risk patients; however, not every patient with comorbidities automatically requires a prophylactic antibiotic.

A prophylactic antibiotic should not be administered routinely:

- in procedures with a very low risk of infection, when the benefit is negligible;
- merely because a drain or catheter is present;
- to artificially prolong prophylaxis after surgery;
- as a substitute for asepsis, antisepsis and correct surgical technique;
- “just to be safe”, without a clear indication.

Principles of correct antibiotic selection. The aim is not to cover all possible bacteria. The prophylactic antibiotic must cover the microorganisms most likely to be involved in the respective procedure, and it should:

1. achieve effective concentrations in the operated tissue;
2. have low toxicity;
3. have as narrow a spectrum as possible;
4. be administered at an adequate dose;
5. be adapted to the local epidemiological situation.

Cefazolin is one of the main antibiotics used in surgical prophylaxis. It covers mainly: *Staphylococcus aureus* susceptible to methicillin; streptococci; some Gram-negative bacilli. It is frequently used in: general surgery; vascular surgery; cardiac surgery; orthopedics; thoracic surgery; many clean procedures.

Alternatives in β-lactam allergy, depending on the procedure and the type of allergy, are clindamycin or vancomycin, in selected situations. Vancomycin should not be used routinely instead of cefazolin; its use is reserved for particular situations, for example MRSA risk/colonization, according to the local protocol.

In colorectal surgery, coverage is required for Gram-negative bacilli and anaerobes: cefazolin + metronidazole, or amoxicillin/clavulanate, depending on the protocol.

The antibiotic must be administered so that an effective tissue concentration is present at the time of incision. For most antibiotics, the interval is 60 minutes before incision. For antibiotics that require slower administration, particularly vancomycin or fluoroquinolones, administration should be started earlier, generally within 120 minutes before incision. A single dose is usually sufficient. The dose is repeated intraoperatively if:

- the procedure is very long and exceeds the redosing interval of the antibiotic;
- major bleeding occurs;
- there are other situations that lower the antimicrobial concentration below the effective level.

  Prophylaxis should be as short as possible. In most procedures a single dose is sufficient; if continuation is necessary, it should generally last <24 hours.

Part I: SINGLE-ANSWER multiple-choice questions (only one correct answer)

1. What is the main mechanism of action of antibiotics of the penicillin class?

A) Inhibition of bacterial protein synthesis
B) Inhibition of bacterial cell wall synthesis [correct]
C) Alteration of the cytoplasmic membrane
D) Inhibition of nucleic acid synthesis
E) Inhibition of protein synthesis at the 50S subunit

2. Which antibiotic is used orally for the treatment of pseudomembranous colitis caused by Clostridioides difficile?

A) Gentamicin
B) Vancomycin [correct]
C) Injectable metronidazole
D) Ciprofloxacin
E) Azithromycin

3. Which of the following antibiotics belongs to the macrolide class?

A) Amikacin
B) Ceftriaxone
C) Azithromycin [correct]
D) Doxycycline
E) Gentamicin

4. Which antibiotic combination shows a classic synergism used in the treatment of Enterococcus faecalis endocarditis?

A) Ciprofloxacin + doxycycline
B) Ampicillin + gentamicin [correct]
C) Erythromycin + clindamycin
D) Vancomycin + linezolid
E) Tetracycline + dalbavancin

5. In which Ambler class are KPC-type carbapenemases classified?

A) Class A [correct]
B) Class B
C) Class C
D) Class D
E) Class E

6. Which antibiotic is contraindicated in pregnant women?

A) Amoxicillin [correct]
B) Ciprofloxacin
C) Clarithromycin
D) Tetracycline
E) Trimethoprim/sulfamethoxazole

7. Which of the following antibiotics is a fourth-generation cephalosporin that is stable against AmpC enzymes (Class C)?

A) Cefalexin
B) Cefuroxime
C) Ceftriaxone
D) Cefepime [correct]
E) Cefiderocol

8. Which antibiotic is contraindicated in the treatment of pneumonia because it is completely inactivated by pulmonary surfactant?

A) Linezolid
B) Daptomycin [correct]
C) Ceftaroline
D) Tigecycline
E) Doxycycline

9. The bla_OXA-48 gene confers resistance to carbapenems. In which hospital bacterial species is it most frequently isolated?

A) *Pseudomonas aeruginosa*
B) *Klebsiella pneumoniae* [correct]
C) *Staphylococcus aureus*
D) *Streptococcus pyogenes*
E) Clostridioides difficile

10. Which of the following defines an XDR (extensively drug-resistant) bacterium?

A) Resistance to a single commonly used antibiotic
B) Resistance to 3 antibiotic classes
C) It remains susceptible to at most two of the antibiotic categories tested [correct]
D) Absolute resistance to all known antibiotics
E) No antibiotic resistance

Part II: MULTIPLE-ANSWER multiple-choice questions (two or more correct answers)

16. Which of the following antibiotics belong to the carbapenem group?

A) Meropenem [correct]
B) Imipenem [correct]
C) Aztreonam

D) Ertapenem [correct]
E) Cefiderocol

17. Which antibiotic classes act by inhibiting protein synthesis at the level of bacterial ribosomes?

A) Penicillins
B) Macrolides [correct]
C) Aminoglycosides [correct]
D) Tetracyclines [correct]
E) Streptogramins

18. What are the valid therapeutic options in a severe infection with an NDM-1-producing bacterium (Ambler Class B)?

A) Ceftazidime-avibactam
B) Cefiderocol [correct]
C) Aztreonam + ceftazidime-avibactam [correct]
D) Piperacillin-tazobactam
E) Trimethoprim-sulfamethoxazole

19. Which antibiotics can be used successfully to treat infections caused by MRSA (methicillin-resistant Staphylococcus aureus)?

A) Vancomycin [correct]
B) Amoxicillin
C) Linezolid [correct]
D) Ceftaroline (fifth-generation cephalosporin) [correct]
E) Doxycycline

20. Which antibiotics are considered “bactericidal”?

A) Cephalosporins [correct]
B) Tetracyclines
C) Fluoroquinolones [correct]
D) Penicillins [correct]
E) Chloramphenicol

21. What are the major risks associated with the inappropriate or excessive use of broad-spectrum antibiotics in hospital wards?

A) Selection of multidrug-resistant strains (MDR, XDR) [correct]

B) Occurrence of secondary Clostridioides difficile infections [correct]
C) Complete and irreversible destruction of human DNA
D) Increased incidence of invasive fungal infections (e.g., candidiasis) [correct]
E) Increased incidence of parasitic infections

22. Which of the following characteristics are true for bacteria producing Ambler Class C enzymes (AmpC)?

A) They are mainly cephalosporinases [correct]
B) They are strongly inhibited by clavulanic acid
C) They are susceptible to carbapenems [correct]
D) They are completely inactive against ceftriaxone
E) They are relevant for tetracyclines

23. Which rules must be followed when collecting blood cultures to ensure the accuracy of bacteriological tests?

A) Samples are collected before initiation of antibiotic therapy [correct]
B) A single bottle is drawn from the old central catheter
C) Strict aseptic rules are followed to avoid contamination with skin bacteria [correct]
D) At least two sets of bottles (aerobic and anaerobic) are collected [correct]
E) Samples are collected after the antibiotic has been started

24. What are the correct criteria for classifying a bacterium as PDR (pandrug-resistant)?

A) Resistance to all antibiotics of the penicillin class
B) Resistance to all antibiotics in all therapeutic categories tested [correct]
C) It is a superbug that is practically untreatable with standard regimens [correct]
D) It is able to survive only in the presence of oxygen
E) It has no antibiotic resistance

25. Which beta-lactamase inhibitors belong to the “reserve” group capable of restoring the efficacy of the partner molecules against carbapenemases?

A) Clavulanic acid

B) Avibactam [correct]
C) Vaborbactam [correct]
D) Sulbactam alone
E) Sulfamethoxazole

1.7. CLINICAL CASES

Case 1: The respiratory viral infection trap

Case presentation: A 4-year-old boy (weight: 16 kg) is brought to the office with a low-grade fever of 37.8°C, dry cough, nasal obstruction and dysphagia. Symptoms began 48 hours earlier. On clinical examination: diffusely congested pharynx, no lateral cervical lymphadenopathy. Normal lung auscultation. Laboratory tests: no inflammatory changes.

What is the appropriate therapeutic approach?
A) Oral antibiotic
B) Intramuscular antibiotic
C) No antibiotic is recommended [correct]
D) Topical antibiotic
E) Intravenous antibiotic

Correct answer:

Correct choice: No antibiotic is recommended! The diagnosis is acute rhinopharyngitis, which at this age is of viral etiology in >85% of cases.
Appropriate treatment: symptomatic (antipyretics: paracetamol; nasal hygiene with saline and suction; oral antiseptic) and pathogenic (anti-inflammatory: ibuprofen).

Case 2: Assessing age-related risks and contraindications

Case presentation: A 6-year-old girl (weight: 20 kg) presents with fever of 39°C, severe odynophagia and headache, of sudden onset 24 hours earlier. Clinically: hyperemic, intensely congested tonsils with white pultaceous exudates and tender submandibular lymphadenopathy. The rapid bacteriological test on the pharyngeal swab is positive for group A beta-hemolytic Streptococcus.

Which antibiotic is recommended?
A) Amoxicillin [correct]
B) Doxycycline

C) Gentamicin
D) Linezolid
E) No antibiotic is recommended

Correct answer:

The error: Doxycycline (tetracycline class) is strictly contraindicated in children under 8 years of age. It chelates calcium in hard tissues, causing enamel dysplasia, permanent yellow-brown discoloration of the teeth and slowed bone growth.
Correct choice: Amoxicillin. Amoxicillin is the treatment for streptococcal pharyngotonsillitis.

Case 3: Adult with C. difficile colitis

Case presentation: Seven days ago, an 87-year-old man completed a 10-day course of amoxicillin-clavulanic acid given for maxillary surgery. Today he returns to the doctor with multiple (more than 10/day) watery, very foul-smelling stools, accompanied by abdominal cramps and fever of 38.2°C. A stool test confirms the presence of Clostridioides difficile toxins A and B.

Which antibiotic is recommended?
A) Oral clarithromycin
B) Oral tetracycline
C) Oral vancomycin [correct]
D) Intravenous vancomycin
E) No antibiotic is recommended

Correct answer:

Mechanism: The previous broad-spectrum treatment destroyed the normal intestinal flora, allowing proliferation of the opportunistic bacterium *C. difficile* and release of necrotizing toxins.
Contraindication: Antisecretory agents and peristalsis inhibitors (e.g., loperamide) are prohibited. Blocking intestinal motility prevents toxin elimination, leading to toxic megacolon, perforation and septic shock.
Correct choice: Orally administered vancomycin. *Caution: vancomycin is not given intravenously for this condition, because it does not reach the intestinal lumen in therapeutic concentrations.*

Case 4: Urinary tract infection in a pregnant patient

Case presentation: A 26-year-old woman, 28 weeks pregnant, presents to the doctor complaining of dysuria, urinary frequency and suprapubic pain for 24 hours. She has no fever and no flank pain. Urinalysis shows leukocyturia and positive nitrites.

Which antibiotic is recommended?
A) Oral ciprofloxacin
B) Oral nitrofurantoin
C) Oral vancomycin
D) Oral trimethoprim/sulfamethoxazole
E) Oral fosfomycin [correct]

The error: Fluoroquinolones (such as ciprofloxacin) are strictly contraindicated in pregnancy. They cross the placenta and may cause arthropathy (damage to the fetal growth cartilage). Sulfonamides should also be avoided in the third trimester (risk of kernicterus in the fetus), as should nitrofurantoin in the last weeks of pregnancy (risk of hemolytic anemia in the newborn).
Correct choice: The first-line antibiotics that are safe in pregnancy are fosfomycin trometamol (single 3 g oral dose), amoxicillin-clavulanic acid (Augmentin 1 g every 12 hours for 5-7 days) or cefalexin.

Case 5: Community-acquired pneumonia and the risk of QT prolongation

Case presentation: A 68-year-old man with known hypertension and chronic atrial fibrillation controlled with amiodarone, with no healthcare contact in the past year, presents with fever of 38.5°C, cough with rusty sputum and right-sided pleuritic chest pain. Chest radiography confirms an alveolar infiltrate in the right lower lobe. The patient is hemodynamically stable, without respiratory compromise, and can be treated at home.

Which antibiotic is recommended?
A) Amoxicillin/clavulanic acid + doxycycline, orally [correct]
B) Azithromycin + doxycycline, orally
C) Fluoroquinolone
D) Carbapenem
E) Oral fosfomycin

Correct answer:

The error: Macrolides (clarithromycin, erythromycin, azithromycin) prolong the QT interval on the electrocardiogram. The patient is already taking amiodarone (an antiarrhythmic that itself markedly prolongs the QT interval). Their combination is contraindicated, as it massively increases the risk of malignant ventricular arrhythmias (such as *torsades de pointes*), which can cause cardiorespiratory arrest. Quinolones in an adult with comorbidities (heart disease) may slightly prolong the QT interval; the risk is lower, but caution is required.

Guideline recommendation: a much safer combination from a cardiac standpoint is amoxicillin-clavulanic acid combined with doxycycline.

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CHAPTER 2

MENINGEAL IRRITATION SYNDROME

Assoc. Prof. Ruxandra Laza, MD, PhD

2.1. CLINICAL ORIENTATION

Meningitis, an important chapter of infectious pathology and equally of medical emergencies, is an extremely serious, contagious infectious disease of multiple etiologies, characterized by the association, in variable proportions, of 3 major syndromes: the infectious syndrome, the meningeal syndrome and the encephalitic syndrome.

I. *The infectious syndrome* is the first to develop; it includes fever with or without chills, flushed facies and sweating.

II. *The meningeal syndrome* can be divided semiologically into 2 components:

A. *Symptoms secondary to intracranial hypertension* (due to CSF overproduction and meningocerebral edema):

- headache is particularly intense, continuous and perceived as "helmet-like". It does not respond to usual analgesics (acetylsalicylic acid, metamizole, etc.). It worsens after efforts that increase intra-abdominal pressure (coughing, defecation) and on compression of the jugular veins. It is relieved by applying an ice pack to the head or after intracranial pressure is lowered by CSF removal at lumbar puncture, by depletive therapy or by vomiting;
- photophobia, or intolerance to light, makes the patient keep the eyes closed or turned toward the darkest area of the room;
- effortless, "explosive", "central-type", morning, projectile vomiting, not preceded by nausea, which relieves the headache.

Signs suggestive of the diagnosis:

- *pulse-temperature dissociation*: fever associated with bradycardia;
- *bulging fontanelle in the newborn*; however, this sign is often absent because of the dehydration resulting from vomiting, sometimes diarrhea and/or diaphoresis. In this age group and in young children, a characteristic cry may also occur (*the encephalitic cry*).

B. Manifestations of the *neuroradiculitis process (or signs of meningeal irritation*):

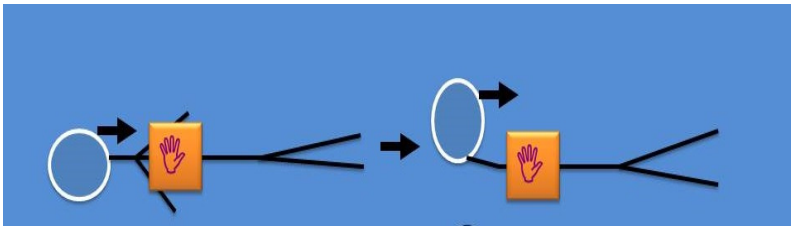
Subjective:

- *spinal pain* radiating to the chest and limbs;
- *cutaneous hyperesthesia*: pain on touching the skin or the muscle masses.

Objective:

- *meningeal streak (tache cérébrale)*: caused by vasomotor disturbances; it is a white line flanked by 2 erythematous stripes, appearing after mechanical stimulation with a needle or fingernail, and is frequent in bacterial meningitis;
- presence of *muscle contractures* due to intraspinal neuroradiculitis;
- presence of *characteristic antalgic postures*:
  - *lateral recumbency in triple flexion* (knees, hips, spine, neck);
  - *the "gun-dog" position* (en chien de fusil): lateral decubitus, with the gaze turned toward the darkest part of the room, flexion of the lower limbs and trunk, and hyperextension of the head. This position represents a *passive component of the contracture syndrome*, because no maneuver by the examiner is needed to demonstrate it.
  - positions of *opisthotonus*: contracture of the extensor muscles of the trunk, or *emprosthotonus*: a posture resembling the position of the fetus in the uterus (rare).
- when contractures are less marked, they are demonstrated by means of *nerve root stretch maneuvers* (the active component of the contracture syndrome):
  - *at the level of the **head**:*

✔ *nuchal rigidity: tested with the patient in the supine position; flexion of the head onto the chest is attempted, with the examiner's hand placed under the nuchal region. Normally the maneuver can be performed easily, but in the presence of meningeal irritation it meets resistance or flexion is not possible.*



✔ *neck cramp:* attempted flexion of the head onto the trunk reveals contracture of the entire spine (present especially in bacterial meningitis)*;*

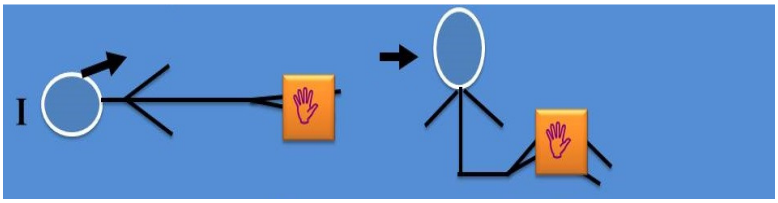
✔ *Brudzinski neck sign:* tested in the same way as nuchal rigidity, but somewhat more vigorously. It is positive when the maneuver results in flexion of the knees.



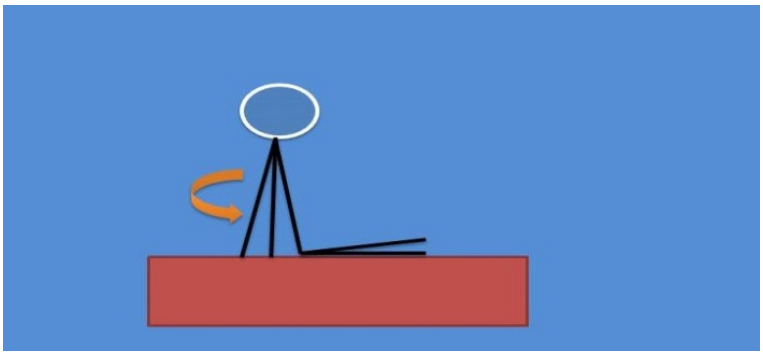
✔ *the nucho-mydriatic sign* (Flatau): flexion of the head onto the trunk is associated with mydriasis;

- *at the trunk:*

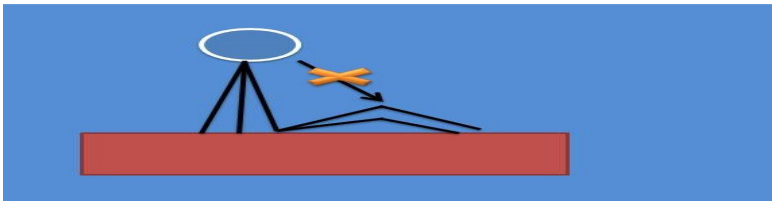
✔ Kernig I (trunk) sign: with the patient in the supine position, flexion of the trunk onto the axis of the lower limbs is attempted, with the examiner's hand placed under the **scapulae**/shoulders of the patient. It is positive when it causes flexion of the knees.



✔ tripod sign: when asked to sit up, the patient supports himself with the upper limbs placed behind, in order to maintain the sitting position, forming a tripod.

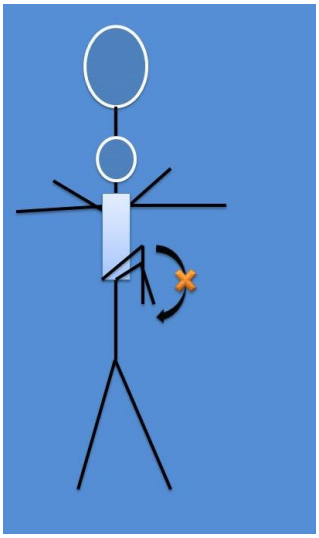


✔ kiss sign: the patient is unable to touch the knees with the lips from the sitting position. It is useful especially in children.



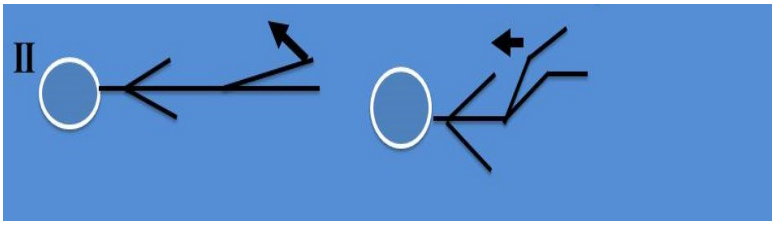
✔ suspension test in infants (spring sign): of real

✔ value in infants and young children, performed as follows: the child is suspended by the axillae. In the presence of meningeal irritation, the child flexes the thighs onto the pelvis and the legs onto the thighs. When extension is attempted and after it has been achieved, the limbs return to their initial position, just like a spring.

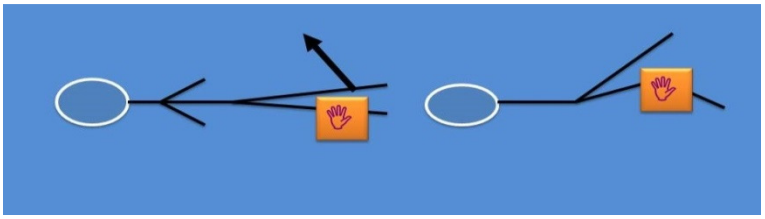


- *at the lower limbs*:

✔ Kernig II (limb) sign: with the patient in the supine position, raising of the extended lower limbs is attempted. In a patient with meningeal irritation syndrome, this maneuver produces flexion of the knees and pain in the posterior thighs and calves.



✔ contralateral Brudzinski sign: with the patient in the supine position, the examiner flexes one lower limb at the hip and knee, then abruptly extends the leg on the thigh. The sign is positive when flexion of the opposite (contralateral) knee occurs and/or violent pain is felt in the gastrocnemius and posterior thigh muscles.



✔ quadriceps compression sign.

In infants, the diagnostic difficulty stems from the limited feasibility of performing and interpreting the classic meningeal signs, as well as from the frequent presence of atypical symptoms: digestive and respiratory disturbances. In bacterial meningitis, the meningeal syndrome is usually complete and well expressed.
Important: the absence of classic meningeal signs does NOT exclude meningitis. The presentation may be atypical, and the diagnosis is not based on a single clinical test.

III. *The encephalitic syndrome* reflects extension of the inflammatory process to the CNS and manifests as altered consciousness, ranging from mere drowsiness, slowed speech and delayed responses to temporal and spatial disorientation, amnestic disturbances, psychomotor agitation and coma. In infants, upward gaze fixation, the encephalitic cry, seizures (tonic, clonic or tonic-clonic), trismus and

bruxism (teeth grinding, in children) are seen. The following may also occur:

- Pontobulbar disturbances: tachypnea, dyspnea alternating with apnea, sometimes Cheyne-Stokes respiration;
- Diencephalic disturbances: hyperthermia/hypothermia, glycosuria;
- Focal signs: paresis and paralysis, pyramidal, extrapyramidal and cerebellar disturbances, due to underlying cerebral edema or to complications (abscesses, subdural effusions).

In the elderly, encephalitic signs are more frequent, owing to lower tolerance to hypoxia and to the arterial hypotension induced by the inflammatory process.

Skin signs are frequently present: herpes labialis (in meningococcal meningitis), hemorrhagic, petechial rashes of particular significance, suggesting a severe, toxic form of bacterial meningitis.





When the clinical examination is suggestive of meningeal irritation syndrome, further paraclinical investigation is indicated to establish the etiology.

2.2. LUMBAR PUNCTURE: DIAGNOSTIC VALUE

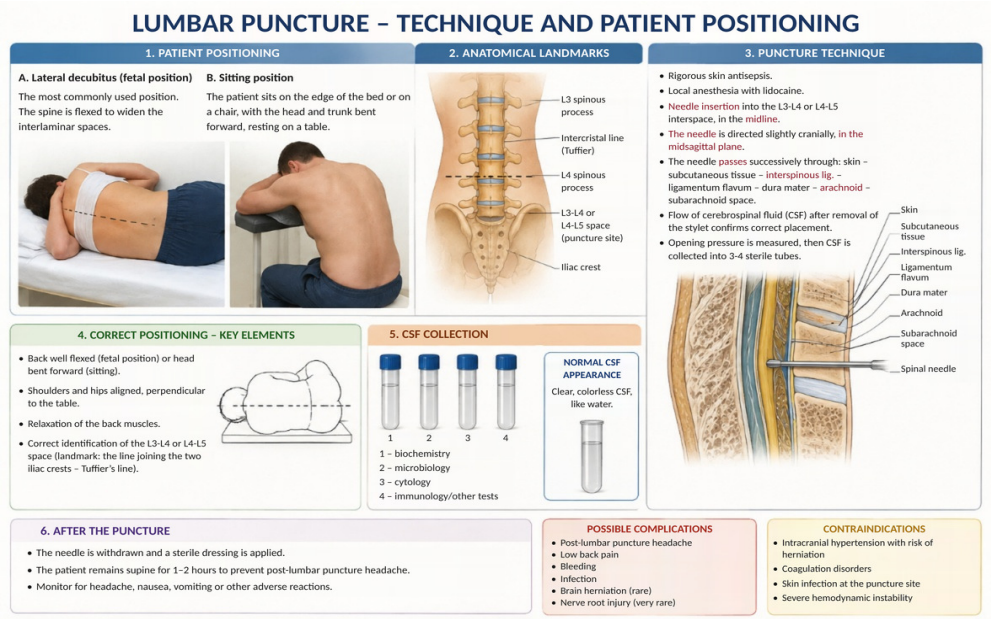
Lumbar puncture (LP) moves the diagnosis from meningeal syndrome to a disease: meningitis.
Lumbar puncture technique: incidents and accidents:
Positioning of the patient is extremely important for performing this maneuver under the best possible conditions. Two positions are used:

- The sitting position, with the back at the edge of the bed, the **knees flexed toward the abdomen** and the head flexed;
- The lateral decubitus position, with the knees drawn up to the chest and the head flexed, with a pillow placed between the knees to avoid distortion of the bony landmarks.

The landmarks used are the iliac crests and the line joining them. This line usually passes through the L3-L4 intervertebral space. By then palpating the spinous processes, the middle of the L3-L4 or L4-L5 space is determined and the needle insertion site is established. A special single-use spinal needle with a stylet, 20 or 22G in size, is used. After rigorous skin asepsis, the needle is inserted perpendicular

to the middle of the L3-L4 or L4-L5 interspace; after passing through the skin, the needle is angled 10-20 degrees cranially and advanced slowly.

Passage through the interspinous ligament is associated with increased resistance, as is passage through the ligamentum flavum, after which a sensation of “give” is felt, similar to that of entering a vein, indicating that the subarachnoid space has been entered. The stylet is withdrawn and cerebrospinal fluid begins to drip.



Incidents and accidents:

- Dry tap: either because of deficient technique or because of local conditions (healed spinal fracture, ligament ossification), the subarachnoid space cannot be entered. In these circumstances, if the puncture is considered absolutely necessary for the diagnosis, it is useful to attempt it at another level or by the suboccipital route.
- A traumatic tap is due to accidental vascular injury and yields hemorrhagic CSF. In this case, the fluid can be collected in several tubes to see whether it clears, or a new puncture can be attempted one space higher. In a traumatic tap, it is useful to estimate the leukocyte/erythrocyte ratio, which is normally 1/1000.

In subarachnoid hemorrhage, the fluid is uniformly hemorrhagic throughout the puncture and does not clot when left in the tube. Over time, the erythrocytes sediment and the supernatant is clear or xanthochromic (yellow), depending on the age of the hemorrhage.

When the tube is shaken, the erythrocytes are released from the sediment and the fluid becomes hemorrhagic again.
Post-lumbar puncture syndrome usually occurs within the first 24 hours after the procedure and manifests as intense headache accompanied by nausea or vomiting and vertigo, especially in the upright position and when walking. Back pain and pain in the lower limbs, of variable intensity, may also occur. The only treatment is rest and administration of analgesics or Cofedol. Nevertheless, symptoms may persist for up to 10-14 days.

2.3. BIOCHEMICAL AND CYTOLOGICAL PARAMETERS OF CEREBROSPINAL FLUID: NORMAL VALUES AND PATHOLOGICAL CHANGES

Normal CSF is normotensive (at lumbar puncture the CSF flows steadily, drop by drop) and has the following characteristics:

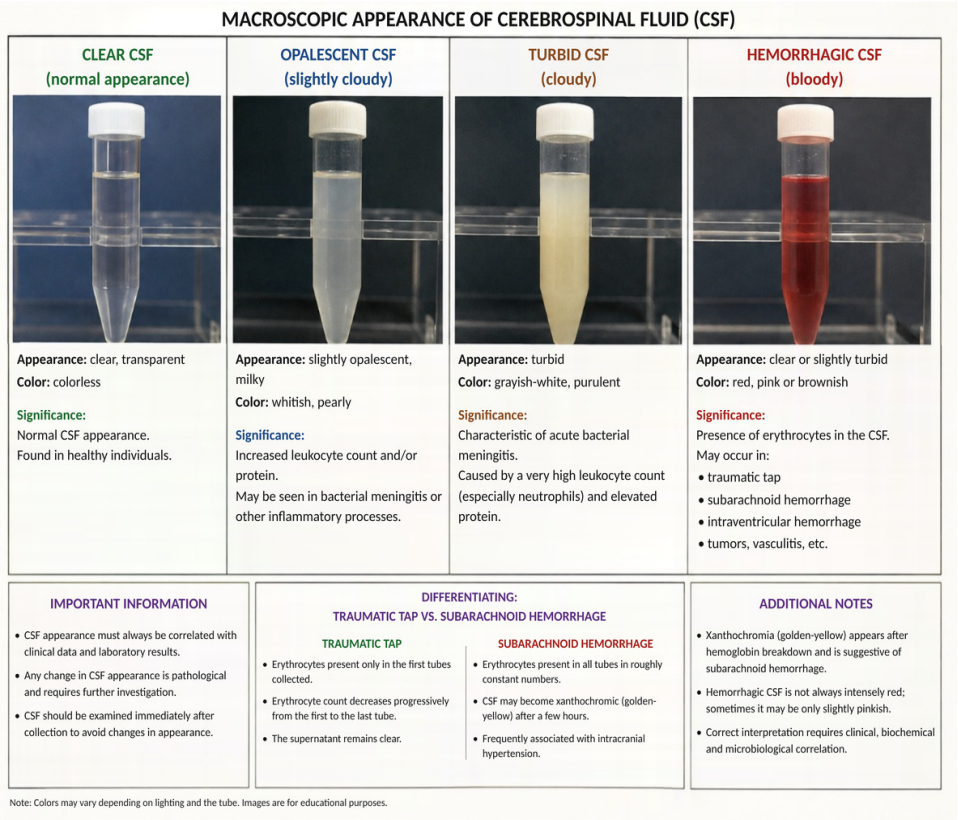
- appearance: clear, like “spring water”;
- pressure: normotensive, drop by drop;
- cellularity: a few lymphocytes (2-5/mm^3); counting is performed in a Fuchs-Rosenthal chamber after lysis of the CSF erythrocytes (possibly present owing to a traumatic tap) with acetic acid; differential cell count: for example, 90% lymphocytes, 10% monocytes.
- CSF protein: 15-45 mg/dl; 0.15-0.45 g/l;
- a value expressed qualitatively by the Pandy reaction = negative;
- CSF glucose: 1/2-2/3 of the blood glucose value; 50-80 mg/dl;
- CSF chloride: 720-750 mg/dl (mg%);
- lactic acid: 0.99-2.88 mg/l; 1.3-2.4 mmol/l.

CSF findings define the following terms:

Meningism	Meningeal reaction	Meningitis
Meningeal irritation syndrome with **normal CSF**	Meningeal irritation syndrome with **minimal changes** in the CSF	Meningeal irritation syndrome with **suggestive changes** in the CSF

Pathogens, depending on the taxonomic class to which they belong, cause certain particular CSF changes:

Type of meningitis	CSF appearance	Pandy reaction	Cellularity (per mm^3)	CSF glucose	CSF protein	CSF chloride	Lactic acid
Viral (serous, aseptic) meningitis	clear or slightly opalescent	+ / - +	500 polymorphous lymphocytes	normal	slightly increased	usually normal	normal
Bacterial meningitis	cloudy ("cabbage broth")	++++	>1000 PMN	markedly decreased	increased	usually normal	markedly increased
Tuberculous meningitis	clear, slightly opalescent, xanthochromic or hemorrhagic	++++	500 monomorphous lymphocytes	markedly decreased	markedly increased	usually decreased	increased
Meningitis decapitated (partially treated) by antibiotics	opalescent or clear	++ (+)	500 PMN and lymphocytes	decreased	increased	usually normal	usually normal



Important: these are indicative patterns, not absolute criteria. Results must be interpreted together with the clinical picture and microbiological investigations.

Formulating a correct diagnosis in a therapeutically useful time frame requires good knowledge of the possible deviations from the classic clinical and CSF findings; in this respect, the following should be remembered:

- not all pyogenic meningitides have purulent cerebrospinal fluid (CSF);
- the cerebrospinal fluid may be clear in very severe meningitis, in an areactive patient, or when the CSF is examined at a very early stage of the disease;
- even when the cell count is only minimally above normal values, the CSF smear may show a high density of organisms (meningococci and pneumococci give the slide, on microscopic examination, a "*pure culture*" appearance). This cytobacterial peculiarity requires bacteriological examination (smear and culture) of any clear CSF, even if the cellular reaction is absent or minimal (but the clinical picture is severe).

In bacterial meningitis, the CSF remains clear (on macroscopic examination) in 2 situations:

- *decapitated bacterial meningitis*, due to administration of antibiotics before CSF collection, and
- in *hyperacute, fulminant forms of the disease* (Waterhouse-Friderichsen syndrome).

An essential problem is the differentiation, in a therapeutically useful time frame, of viral meningitis from tuberculous meningitis. Such confusion can be fatal for the patient because of delayed therapy. The following data from the history, the epidemiological investigation and the physical examination are of particular value.

	Viral meningitis	***Tuberculous meningitis***
History	No significant data	Family or personal history of TB
Onset symptoms	Fever, myalgia, respiratory catarrh	Insidious onset, with a clinical syndrome of tuberculous impregnation
Clinical picture	Acute febrile syndrome, meningeal syndrome +/-	Febrile syndrome, Well-expressed meningeal syndrome, Encephalitic syndrome with basal localization and cranial nerve involvement, pathognomonically the abducens (external oculomotor) nerve ->** A FEBRILE MENINGEAL SYNDROME WITH OCULOMOTOR NERVE PALSY POINTS TO TUBERCULOUS MENINGITIS!**
Course	Benign, self-limiting, with recovery, possibly with sequelae	Progressive worsening in the absence of antituberculous treatment
Paraclinical investigations	Chest X-ray: interstitial pneumonia	Fundoscopy: choroidal tubercles; Chest X-ray: miliary TB, pulmonary TB (not a mandatory requirement for the diagnosis of meningitis)
CSF	Clear, hypertensive, Pandy +/++, cells “in the hundreds”, rarely > 1500/mm^3, 90% polymorphous lymphocytes, protein 0.4-0.8 g/l, chloride, glucose and lactic acid normal. Culture and latex agglutination negative.	Clear or hemorrhagic, hypertensive, sometimes hypotensive, Pandy +++/++++, cells “in the tens”, < 500/mm^3, 80-90% small, monomorphous, mature lymphocytes in the sediment, markedly increased protein, 0.5-3 g/l, chloride decreasing over time, glucose markedly decreased through consumption, increased lactic acid; cultures may become positive after 45 days; latex agglutination negative

Thus, the usual distinctions between meningitis with clear, purulent or hemorrhagic CSF are welcome and didactically evocative of a particular etiological framework, but in clinical practice there are numerous forms that do not fit these patterns, numerous intermediate aspects and some deviations dictated by the stage of the disease, by specific properties of the pathogen involved or by the particular immune response of the host.

If the CSF collected is purulent and/or the cellularity suggests a bacterial etiology, the CSF is centrifuged and a Gram-stained smear is prepared from the sediment. *Direct microscopy*, when positive, allows rapid identification of the organism and initiation of antibiotic therapy based on the criterion of greatest probability. *Cultures* on standard media will identify the organism, and the antibiogram will reveal its specific antimicrobial susceptibility. In tuberculous meningitis, the etiological diagnosis is difficult: none of the laboratory diagnostic methods exceeds 60% sensitivity, namely culture on Löwenstein-Jensen medium and BACTEC Myco/F Lytic.

In addition to bacteriological investigation, a minimum *immunological examination* is required (latex agglutination, coagglutination, counterimmunoelectrophoresis, ELISA). Identification of soluble bacterial or fungal antigens in the CSF by latex agglutination or counterimmunoelectrophoresis is a very useful method of etiological diagnosis in decapitated meningitis, in which the CSF no longer contains viable bacteria able to grow in culture. Antigens derived from the bacterial wall persist in the CSF and can be identified when brought into contact with specific antibodies.

Identification in the CSF, by molecular biology methods (PCR), of nucleic acids specific to the various etiologies of meningitis is a modern and rapid method of etiological diagnosis that allows early initiation of appropriate antibiotic therapy. It is a syndromic test that simultaneously detects several agents of meningitis/encephalitis. It is useful for rapid etiological diagnosis, but it has variable sensitivity, does not cover all etiologies and may yield false-positive/false-negative results; therefore, the result must be interpreted together with the clinical picture, CSF cytobiochemical data, culture and other specific tests. Which etiologies does it frequently identify? Depending on the panel: *Viruses***:** *Herpes simplex virus / HSV-1*, *HSV-2*, *VZV*, *Enterovirus*, human herpesvirus *HHV-6*, *Cytomegalovirus, Human parechovirus*; *Bacteria***:** *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus agalactiae* (group B), *Escherichia coli* K1, *Listeria monocytogenes*; Fungi**:** *Cryptococcus neoformans/gattii*.

It is very useful for lumbar puncture to be preceded by imaging investigations (computed tomography, magnetic resonance imaging). If such an investigation is not available, at least a *fundoscopic examination* is performed to exclude papilledema, together with as complete a neurological examination as possible to exclude a focal lesion, after which lumbar puncture is performed as an emergency.
The question nevertheless remains: which patients with suspected meningitis should mandatorily undergo cranial CT/MRI before lumbar puncture, in order to avoid possible complications ranging from minor to the most severe (cerebellar tonsillar herniation, which is life-threatening)?
The following situations point to the need for cranial CT/MRI before lumbar puncture:

a) immunocompromised status: HIV infection/AIDS, immunosuppressive therapy, post-transplant status;
b) personal history of CNS disease: stroke, focal infection, space-occupying lesion;
c) new-onset seizures within one week before presentation;
d) papilledema;
e) focal neurological deficit: dilated nonreactive pupils, ocular motility abnormalities, abnormal visual fields, fixed gaze, limb paralysis.

Practical principle: if lumbar puncture has to be postponed, collection of blood cultures and initiation of appropriate antimicrobial treatment must not be unjustifiably delayed.

The 2025–2026 WHO guidelines emphasize that, if bacterial meningitis is suspected, antimicrobial treatment must not be unjustifiably delayed by lumbar puncture.

2.4. MENINGITIS: A MEDICAL EMERGENCY

The attribute "*early*" applied to recognition of the disease is supported by the following statements, which have become "*primary truths*" of clinical observation: "every hour of delay may be decisive", "meningococcemia kills faster than any other infectious disease", "the chance of recovery from tuberculous meningitis becomes minimal if treatment has not been started within the first 14 days of illness".
An excessively intense inflammatory response may lead to blockage of the subarachnoid space, arachnoiditis, hydrocephalus and/or cranial nerve lesions.

Post-meningitic neurological sequelae include: motor lesions (paresis, spasticity), seizures, psychological sequelae (cognitive, perceptual and behavioral deficits) and deafness (due to involvement of cranial nerve VIII in the purulent process, or damage to the cochlea or central pathways through thrombophlebitis and cerebral anoxia).

Treatment: patients with meningitis must be hospitalized, and the disease is subject to mandatory named notification. Treatment is complex and includes:

I. *Etiological treatment*: immediately after collection of blood cultures and of CSF by LP, antibiotic treatment is started as an emergency. Factors to be kept in mind include the susceptibility of the pathogen involved and the ability of the drug to penetrate and achieve an effective bactericidal concentration in the CSF.

II. *Pathogenetic treatment*:
   - maintaining adequate cerebral perfusion and reducing raised intracranial pressure are essential to prevent potentially life-threatening complications;
   - mannitol and hypertonic glucose are administered to reduce intracranial pressure;
   - the use of corticosteroids (usually dexamethasone 0.15 mg/kg every 6 hours for 2-4 days) as adjunctive treatment for bacterial meningitis improves outcomes.

III. *Symptomatic treatment*:
   - control and prevention of seizures with anticonvulsant medication;
   - antipyretic and antiemetic agents, etc.

Practical approach in suspected bacterial meningitis:

Bacterial meningitis is a **medical emergency**. In a patient with clinical suspicion, the following steps are required: rapid assessment of severity; monitoring of vital functions; collection of blood cultures, when this is possible without delaying treatment; lumbar puncture, when safe and indicated; initiation of empirical antimicrobial treatment as soon as possible; subsequent adjustment of treatment according to the etiological agent and antibiogram; monitoring for neurological and systemic complications. The empirical antimicrobial regimen depends on *the patient's age, risk factors, the epidemiological context and local protocols*.

2.5. REVIEW QUESTIONS

Basic questions

1. What is meningeal irritation syndrome?
2. What are the main symptoms of meningeal syndrome?
3. What is nuchal rigidity (neck stiffness)?
4. How is nuchal rigidity tested correctly?
5. How is the Kernig sign elicited?
6. What does the Brudzinski sign represent?
7. What is the “gun-dog” (chien de fusil) position?
8. What are the main infectious etiologies of meningitis?

Clinical-level questions

9. What is the significance of purpura in the context of an acute febrile syndrome?
10. What are the main investigations required when meningitis is suspected?
11. Which parameters should be analyzed in the CSF?
12. What does the CSF typically look like in bacterial meningitis?
13. How can bacterial CSF be broadly distinguished from viral CSF?
14. Which features suggest tuberculous meningitis?
15. In which situations should brain imaging be considered before lumbar puncture?
16. Why is bacterial meningitis a medical emergency?
17. What must not be delayed when lumbar puncture has to be postponed?

Mini self-check test

1. Which of the following is a meningeal sign?

A. Babinski
B. Kernig
C. Romberg
D. Hoffmann

Answer: B

2. The Brudzinski neck sign consists of:

A. passive extension of the lower limbs
B. involuntary flexion of the lower limbs on passive flexion of the neck
C. extension of the great toe
D. absence of deep tendon reflexes

Answer: B

3. In bacterial meningitis, the CSF most frequently shows:

A. lymphocytic predominance and increased CSF glucose
B. neutrophilic predominance and decreased CSF glucose
C. decreased CSF protein
D. severe hypocellularity

Answer: B

4. Altered consciousness associated with meningeal syndrome suggests:

A. migraine only
B. meningoencephalitis or other brain involvement
C. neuralgia only
D. absence of CNS involvement

Answer: B

5. Fever + petechiae/purpura + rapid deterioration of the general condition particularly suggest:

A. meningococcemia
B. migraine
C. trigeminal neuralgia
D. tension-type headache

Answer: A

2.6. CLINICAL CASE PRESENTATIONS

2.6.1. Meningitis with opalescent CSF – difficulties in etiological classification

A well-conducted history and a correctly performed clinical examination allow a meningeal, meningoencephalitic or meningomyelitic syndrome to be diagnosed without particular difficulty. Establishing a diagnosis of meningism, meningeal reaction or meningitis requires cytological, biochemical and microbiological examination of the cerebrospinal fluid. Often, the information obtained does not allow a definite etiology to be established or contains elements that point towards a false etiology.
The patient presented illustrates the stages of positive and differential diagnosis of serous meningitis, prolonged form.
C.I., a 15-year-old female student from an urban area, was hospitalized for 27 days in the 2nd Infectious Diseases Clinic, Timișoara.

History of present illness: at the time of admission, *ill for 8 days*. *Onset* with fever (38-39˚C), diffuse headache, nausea and repeated vomiting. On *day 2 of illness* she was admitted to the local hospital and received mannitol, hydrocortisone hemisuccinate (HHS), metoclopramide and Algocalmin; the improvement of her complaints led her to request discharge. *Two days later*, the recurrence of the same complaints led to readmission; she received ampicillin, hydrocortisone hemisuccinate (HHS), mannitol and Algocalmin.
The persistence of low-grade fever and vomiting and the appearance of objective signs of meningeal irritation led to her transfer to the Infectious Diseases Clinic, Timișoara.

Personal history is notable for: measles at 3 years of age; one convulsive seizure at 5 years. *The epidemiological history* reveals no other cases of illness.
*Physical examination***:** clear sensorium, able to stand and to walk with minimal support. Moderate nuchal rigidity, trunk Kernig sign, well-marked Brudzinski neck sign. No cranial nerve involvement, no motor deficit, no coordination disorders, flexor plantar response, patellar and Achilles reflexes present, symmetrical, normokinetic. Good nutritional status, normal height, 60 kg. Skin without rash, lymph nodes within normal limits, lungs and heart without auscultatory changes, BP 120/60 mmHg, HR 80/min. Pharynx of normal color. Abdomen soft,

liver palpable 2 cm below the costal margin, of normal consistency, spleen not palpable. Continent micturition.

During hospitalization she had low-grade fever (37-37.2˚C) in the first 17 days and 3 episodes of vomiting in the first 4 days; bowel movements remained normal.

The diagnosis of *MENINGEAL SYNDROME* being well supported by subjective and objective findings, and with no history requiring special precautions before lumbar puncture, the next stage followed: confirming the disease, recognizing meningitis proper, and identifying the etiological framework or even the causative agent.

The findings of *lumbar puncture* **(LP)** were: opalescent cerebrospinal fluid (CSF), slightly increased pressure, Pandy ++++, 1100 cells/mm^3, 94% lymphocytes, protein 2.4 g/l, chloride 7.02 g/l, glucose 30 mg/dl; direct examination and culture: no microorganisms.

At this stage of the investigations, the diagnosis retained is: *ACUTE MENINGITIS WITH OPALESCENT CSF, OF UNDETERMINED ETIOLOGY***.**

Ceftriaxone 2 g/day and dexamethasone 2 × 8 mg/day are started.

We considered the diagnostic classification mentioned above *unsatisfactory and open to revision,* for the following reasons:

- ✔ an infectious syndrome lasting 8 days, 6 of them without antibiotic treatment, with no significant deterioration of the general clinical condition;
- ✔ the absence of clinical findings suggestive of a suppurative focus capable of seeding the meninges; the high percentage of lymphocytes in the CSF differential count; the 24-36 hours of antibiotic treatment (ampicillin) cannot be invoked as having induced the shift in CSF cellularity.

In initiating antibiotic treatment, we took into account the following reasoning: the LP findings proved etiologically inconclusive; for a tuberculous etiology, since the useful therapeutic window had not yet been exceeded, specific therapy was not the first priority; the risk of clinical deterioration, together with the possible involvement of an inflammatory focus adjacent to the leptomeninges.

Corticosteroid therapy was considered necessary because of the risk of organization of fibrinous deposits on the leptomeninges and of its subsequent consequences.

Paraclinical investigations performed after the first day of hospitalization showed: 3 direct CSF examinations for Koch bacillus (BK) = negative; CSF culture for common flora = sterile; chest X-ray =

no active lesions; PPD 2 U = Palmer III (post-vaccination reaction); gastric lavage: BK negative; Hb 14 g%, Hct 44%, WBC 4600/mm^3, differential: S67% L29% M5% E3%, Plt 170000/mm^3, ESR 15-30 mm/h/2h, blood glucose 90 mg%, Fb 3.1 g/l, CRP negative, ALT/AST = 65/186 U/l, serum protein electrophoresis 7.5 g%, 51-4-10-14-20%; blood culture sterile.

CSF dynamics:

	Day 10	Day 12	Day 19	Day 35
Appearance	**opalescent**	**slightly opalescent**	**clear**	**clear**
Pandy	**+++**	**+++**	**+++**	**+**
Cells	**1250**	**925**	**142**	**92**
Differential count	**96% lymphocytes**	**96% lymphocytes**	**98% lymphocytes**	**98% lymphocytes**
Protein g/l	**1,8**	**1,28**	**1,08**	**0,58**
Chloride g/l	**7,05**	**7**	**7,15**	**7,2**
Glucose mg/dl	**51**	**35**	**54**	**40**

The clinical course was relatively good. The sensorium remained clear; she had low-grade fever of 37-37.2°C during the first 16 days after admission and 3 further episodes of vomiting in the first 4 days; nausea and headache resolved. From day 6 after admission there were no objective signs of meningeal irritation; by day 21 of hospitalization ALT and AST had returned to normal.

The clinical course, together with the cytobiochemical dynamics of the CSF, led to the discontinuation of antibiotic therapy on day 11 of hospitalization and to the decision not to start antituberculous treatment.

The diagnosis retained is: ***ACUTE SEROUS MENINGITIS, PROLONGED FORM, DECLINE / CONVALESCENCE STAGE, UNCOMPLICATED.*** *INTRAINFECTIOUS HEPATITIS.*

The diagnosis of serous meningitis did not follow the rigorous path of positive diagnosis; in our patient *the diagnosis was based on the*

dynamics of the course and not on isolation of the pathogen or on specific serology.

Along the same lines, we could not retain a diagnosis of acute viral meningitis either. The diagnosis of serous meningitis was based on the slow normalization of the CSF and on the maintenance of a good clinical condition (the term "serous" is reserved for cases in which the etiology cannot be specified; most often it is viral).

A CSF protein level of 0.58 g/l and a cell count of 92 cells/mm^3, almost exclusively lymphocytes, on day 35 of illness lead to classification as a *prolonged form* and, with regard to the *stage of evolution*, as decline/convalescence. The absence of encephalitic or arachnoid manifestations allows the meningitis to be considered *uncomplicated*.

The presence of hepatocytolysis during the first 21 days of illness drew attention to the involvement of a virus with meningeal and hepatic tropism; the markers specific for viruses with primary and facultative hepatic tropism were negative.

*Particular feature of the case***:** the limited diagnostic value of the CSF, especially as it fell into a zone of exceptions, one that blurs the boundary between the cytobiochemical patterns typical of viral, tuberculous or bacterial etiology.

Differential diagnosis: the biphasic course of the clinical picture drew attention to a *bacterial etiology*. Considering that *in the first part of the illness* the manifestations of the infectious-inflammatory syndrome and of intracranial hypertension predominated, and that only *in the last days* did objective signs of meningeal irritation appear, the existence of *meningitis secondary to a suppurative process adjacent to the leptomeninges* could not be left out of the diagnostic reasoning. Nor could we leave out the existence of a *paucibacterial meningitis,* arising in the context of a vigorous inflammatory response of the host, or of a *"decapitated" bacterial meningitis* (through the conversion of cellularity and the absence of organisms in the CSF sediment at the end of the 36 hours of antibiotic treatment).

The lack of significant change in CSF parameters after 5 days of antibiotic treatment and the virtually exclusive persistence of lymphocytes in the CSF differential count, together with the maintenance of a relatively good clinical condition, led to the discontinuation of antibiotics and to the exclusion of pyogenic agents.

The fact that on day 12 of illness CSF protein showed a second decrease compared with the values recorded at the first puncture,

together with the fact that the clinical condition improved progressively, supported ruling out tuberculous meningitis. The chest X-ray findings and the 3 negative direct CSF examinations for BK pointed in the same direction.
Based on the known clinical and CSF data, we have no evidence supporting the involvement of viruses belonging to the enterovirus, myxovirus, adenovirus or herpesvirus families. Given the cytobiochemical CSF values and the slow normalization of these CSF changes, what remains under consideration is **the possible involvement of lymphocytic choriomeningitis virus (family Arenaviridae).**

*Treatment***:** the risk of worsening of the disease course and the absence of a major element delimiting the etiology within the shortest possible time after admission call for a therapeutic approach covering the etiologies under consideration as broadly as possible.
Starting from a possible bacterial etiology, *ceftriaxone 2 g/day was introduced.*
The significantly elevated CSF protein (2.4 g/l), together with the risk of organization of fibrinoid deposits and the tendency towards loculation, obstruction of the interventricular foramina or development of arachnoiditis, justified the addition of *corticosteroid therapy*: *dexamethasone 0.8 mg/kg, 8 days.* Attenuation of the fibroblastic and connective tissue reaction and of exudate formation contributes both to preventing certain complications and sequelae and to potentiating the antimicrobial action of antibiotics.
The complaints secondary to the intracranial hypertension syndrome required the administration of *anti-edema (depletive*) medication: 20% mannitol, 1 mg/kg, 4 days.
The history of an isolated convulsive episode led to the initiation of *sedative treatment*, as maintenance therapy.
Reduced appetite and nausea led to the initiation of *metabolic support medication: 10% glucose*, *vitamins B1 and B6*. To relieve certain complaints (headache, nausea), *Algocalmin and metoclopramide were administered.*
Hygienic and dietary treatment aimed at maintaining skin and mucosal hygiene and ensuring thermal comfort, a minimum of environmental comfort and psychological support.
Given the slow dynamics of the CSF changes, alongside a favorable clinical course, antibiotic therapy was discontinued on day 8 of hospitalization. The clear downward trend of CSF protein led to the discontinuation of corticosteroid therapy on day 8 of hospitalization.

Depletive medication was administered during the first 3 days of hospitalization.

*Course and prognosis***:** the absence of an encephalitic component throughout the illness**,** together with the CSF dynamics recorded over the 5 punctures, allows us to state that *the short-term outcome* will be good. Among *the longer-term consequences,* the following may be kept in mind: episodic headache, emotional instability. *Neither complications* (interventricular block, arachnoiditis) nor *sequelae* (EEG abnormalities of the diffuse irritative type, abnormalities in the epileptic spectrum) are expected.

She was discharged on day 27 after admission. At discharge: afebrile, good appetite, no headache, walking normally.

The patient's clinical condition remained good at 3 and 6 months after discharge.

2.6.2. RECURRENT PNEUMOCOCCAL MENINGITIS

Meningeal localization of pneumococcal infection continues to carry a high potential for severity, unpredictable, almost fulminant courses, neurosensory and psychomotor sequelae, as well as a significant tendency to recur.

The severity and the tendency to relapse are directly related both to the pathogenic properties of the pneumococcus and to the presence of unfavorable circumstances on the part of the host. Thus, through the polysaccharide components of its capsule, the pneumococcus resists phagocytosis and, by stimulating local fibrin production, creates the conditions for "self-rescue" within the fibrin mass, by limiting antibiotic penetration and hence its bactericidal effect. This may explain the multidrug resistance reported in some pneumococcal strains (especially serotypes 6, 14, 19 and 23).

The host is clearly disadvantaged in the following conditions: open craniocerebral trauma (skull fracture + craniocerebral wound and/or scalp wound); closed head injury; surgical procedures; medical procedures.

Besides the recurrent nature of the disease, the patient presented below draws attention to a particular host condition (congenital deafness – cochlear implant). The first episode of purulent meningitis occurred at the age of 1 year and 9 months, the second episode 5 months after placement of the cochlear implant, and the third episode 2 weeks after discharge.

The child Ț. D., aged 1 year and 9 months, was hospitalized for 19 days in the 2nd Infectious Diseases Clinic, Timișoara.

At the time of admission, he had been ill for 6 days. Onset with low-grade fever of 37.3˚C and agitation. On days 2 and 3 he remained febrile (39-39.7˚C); on day 4 he was seen by a physician, who recommended symptomatic treatment; on day 5 he became more adynamic and drowsy; on day 6 he was admitted to the local hospital, where a lumbar puncture was performed; the finding of purulent CSF led to his transfer to the 2nd Infectious Diseases Clinic with a diagnosis of acute purulent meningitis.
Personal history: first child, born at term, birth weight 3050 grams, APGAR score 9, breastfed for 1 month, then fed cow's milk in appropriate dilutions, dietary diversification from 5 months. At the age of 1 year he was diagnosed with profound bilateral hearing loss; no other illnesses in the first year of life.
Family history: father with insulin-dependent type 1 diabetes mellitus and spontaneous pneumothorax.

On *physical examination*: altered general condition, drowsy, responds to painful stimuli, intermittent crying during the examination, follows with his eyes. Moderate nuchal rigidity, Brudzinski neck sign; active limb movements possible. Good nutritional status, normal height and weight (10 kg), head circumference 47 cm; skin of normal color, subcutaneous tissue normally represented, muscle tone preserved. Lateral cervical lymph nodes mobile, under 0.7 cm. Pharynx of normal color. Dentition: 2 lower and upper central incisors, 2 lower and upper lateral incisors, 4 first molars. Normally shaped chest, no auscultatory changes, respiratory rate 30/minute; heart sounds regular, clear, HR = 110/minute. Abdomen soft, liver palpable 2 cm below the costal margin, spleen at the costal margin, normal bowel movements; spontaneous micturition.

Laboratory tests: lumbar puncture: purulent CSF, Pandy ++++, 3200 cells/mm^3, 100% polymorphonuclear cells, protein 4.5 g/l, chloride 7.2 g/l, glucose 4 mg/dl, lactate 4.2 mmol/l (37.8 mg/dl). On *direct examination*: lanceolate Gram-positive cocci arranged in pairs. *CSF culture*: Streptococcus pneumoniae; susceptible to: amikacin 30 mm, Meronem 28 mm, ampicillin, vancomycin, rifampicin 20 mm; resistant to: penicillin, co-trimoxazole.
White blood cell count: 13500/mm^3; differential: 85% N, 10% L, 4% M, 1% E; Hct 32%, Hb 11 g%, Plt 230000/mm^3; ESR 133-141 mm/h/2h; fibrinogen 6.8 g‰, ALT 52 U/l; *blood culture* sterile; pharyngeal swab: 10 colonies of Staphylococcus aureus; chest X-ray: normal; ENT consultation: normal tympanic membranes.

Ceftriaxone 500 mg every 12 hours, dexamethasone 2 × 2 mg/day and 20% mannitol 3 × 50 ml/day were started.

CSF dynamics:

Date	Cells/mm³	Cytology	Pandy	Protein mg/dl	Lactate mmol/l	Glucose mg/dl
Day 4 after admission	1500	76% PMN	++++	168	3,8 (34.2 mg/dl)	58
Day 8 after admission	60	20% PMN	+	60	2.6 (23.4 mg/dl)	52
Day 14 after admission	14		-	35	1,8 (1.22 mg/dl)	55

Good clinical course, with no objective signs of meningeal irritation from day 7 of hospitalization; afebrile from day 5. Follow-up ESR: 60/84 mm/h/2h; WBC: 9800/mm³. Duration of antibiotic therapy: 18 days.
After discharge, the clinical condition remained relatively good, except for the hearing loss already noted, which led to repeated ENT reassessments and ultimately to the decision to perform cochlear implantation (ENT Clinic, Timișoara).
The second admission, at the age of 4 years, took place 2 years and 3 months after the first admission and 6 months after cochlear implantation. At the time of admission, he had been ill for 4 days. Onset with fever of 39˚C, joined from day 3 by headache, photophobia, vomiting (2-3 episodes), adynamia and drowsiness. On day 4 of illness, after an 8-hour stay in the Pediatrics department, he was transferred to the Infectious Diseases Clinic with suspected meningitis.

On *physical examination***:** impaired general condition: febrile, drowsy, adynamic; normal gaze. Mediocre nutritional status, moderately underweight (13 kg); skin without rash, no lymph node enlargement, lungs and heart without auscultatory changes, pharynx of normal color, bowel transit present; spontaneous micturition. Nuchal rigidity

well marked, Brudzinski neck sign and trunk Kernig sign positive, active movements present, patellar and Achilles reflexes preserved, equivocal plantar response.
Laboratory tests: lumbar puncture: purulent CSF, Pandy ++++, 18000 cells/mm^3, 94% polymorphonuclear cells, protein 408 mg/dl (4.08 g/l), chloride 700 mg/dl (7 g/l), glucose 37 mg/dl, lactate 4.5 mmol/l (40.5 mg/dl). On *direct examination*: lanceolate Gram-positive cocci arranged in pairs, extracellular. *CSF culture*: negative.
White blood cell count: 29600/mm^3; differential: 88% N, 6% L, 4% M, 1% E; Hct 35%, Hb 11 g%, Plt 419000/mm^3; ESR 115-120 mm/h/2h; fibrinogen 14 g‰, ALT 21 U/l; protein electrophoresis: total protein 6.71 g%; 42-9.5-20.7-14.6-13.2%; *blood culture* sterile; *pharyngeal swab: no beta-hemolytic Streptococcus.* Chest X-ray: normal; ENT consultation: normal tympanic membranes. EEG: normal-voltage theta-delta tracing, without focal signs. Fundoscopy: normal optic disc margins, pale retina.
Meropenem 500 mg every 8 hours, HHS 100 mg every 12 hours and 20% mannitol 3 × 60 ml/day were started. Good clinical course. *Follow-up lumbar puncture* (5 days after admission): clear CSF, Pandy +, 84 cells/mm^3, 90% lymphocytes, protein 0.68 g/l, chloride 710 mg/dl, lactate 2 mmol/l (18 mg/dl), glucose 67 mg/dl.
Afebrile from day 4 of hospitalization, with no objective signs of meningeal irritation from day 6. At discharge: follow-up ESR: 30/62 mm/h/2h; WBC: 20700/mm^3; differential: 76% N, 18% L, 5% M, 1% E; fibrinogen: 5.5 g‰; blood glucose 68 mg%. Duration of antibiotic therapy: 11 days.
He returned to the clinic 5 days later (*third admission*). At the time of admission, he had been ill for 20 hours. Onset during the night with left ear pain, repeated vomiting (3-4 episodes) and frontal headache. After an initial examination at the ENT Clinic, he was referred to our clinic with suspected meningitis.
On *physical examination:* altered general condition, febrile, psychomotor agitation, well-marked nuchal rigidity, positive Brudzinski neck sign, brisk, symmetrical patellar and Achilles reflexes; flexor plantar response. Respiratory rate 30/minute, HR 120/minute. Skin without rash; no other abnormal physical findings.
Laboratory tests: lumbar puncture: purulent CSF, Pandy ++++, 5500 cells/mm^3, 100% polymorphonuclear cells, protein 2.8 g/l (280 mg/dl), glucose 73 mg/dl, lactate 5.8 mmol/l (52.3 mg/dl). On *direct examination*: encapsulated Gram-positive cocci arranged in pairs, extracellular. *CSF culture*: Streptococcus pneumoniae; susceptible to: Ciprinol 25 mm, levofloxacin 23 mm, pefloxacin 22 mm, vancomycin

21 mm, chloramphenicol 21 mm, rifampicin 20 mm; resistant to: penicillin.
White blood cell count: 22300/mm³; differential: 85% N, 7% L, 5% M, 3% E; Hct 34%, Hb 11.3 g%, Plt 425000/mm³; ESR 95-115 mm/h/2h; fibrinogen 6.8 g‰, ALT 10 U/l; blood glucose 110 mg%; blood culture: sterile; pharyngeal swab: no beta-hemolytic Streptococcus; chest X-ray: normal; ENT consultation: normal tympanic membranes.
Meropenem 500 mg every 8 hours, dexamethasone 2 × 2 mg/day and 20% mannitol 3 × 60 ml/day were started. Relatively good clinical course, afebrile from day 5, with no objective signs of meningeal irritation from day 7. Follow-up lumbar puncture (5 days after admission): clear CSF, Pandy +, 70 cells/mm³, 90% lymphocytes, protein 0.36 g/l, chloride 724 mg/dl, glucose 62 mg/dl, lactate 2.2 mmol/l (19.8 mg/dl). On day 20 of hospitalization (20.VI.06): clear CSF, Pandy -, 48 cells/mm³, protein 0.29 g/l (29 mg/dl), chloride 715 mg/dl, glucose 48 mg%, lactate 1.5 mmol/l (13.5 mg/dl). ESR 15-30 mm/h/2h; fibrinogen 1.8 g‰, ALT 20 U/l. Duration of antibiotic therapy: 22 days.

Discussion: while the diagnosis of pneumococcal meningitis posed no particular difficulties, certain aspects of the disease course and of the host's particular features raise questions and invite comment.
Thus, the patient's age at the first admission (1 year and 9 months) places him, in terms of susceptibility, in the risk group of extreme ages (< 2 years; > 65 years). Nasopharyngeal colonization with pneumococci begins at 2 months of age and lasts on average 6 months for a given serotype. Within the commensal nasopharyngeal flora, the carriage rate in children is 20-40%. The carrier state is favored by certain environmental conditions (group settings, cold season), but also by genetic predisposition.
The meningeal involvement can be considered primary, since the history revealed no signs of another, non-invasive infection (tonsillitis, sinusitis, otitis).
The likely route of entry into the subarachnoid space remains the lymphatic route from the nasopharynx.
The 5-day delay in starting antibiotic therapy (at the first admission), together with preserved consciousness, suggests the involvement of a less toxigenic serotype with reduced invasive properties.
The relatively moderate reactivity of the subarachnoid space, compared with the intensity of the systemic inflammatory syndrome (ESR, fibrinogen, WBC count), suggests, on the one hand, a more limited stimulation of the inflammatory process by the polysaccharide

constituents of the capsule of the pneumococcus involved and, on the other hand, substantial inflammatory activity of systemic cellular mediators (interleukin-1, tumor necrosis factor α).
Although susceptibility to pneumococcal infection is general, it is greatly favored by host and environmental factors (craniocerebral trauma, surgery, cold season). As regards host factors, the only definite risk factor in this patient is age (< 2 years), i.e. the insufficiency of cellular and humoral defense mechanisms.
In our opinion, the hearing deficit noted in the first year of life, classified as profound hearing loss (ENT Clinic) and not associated with other clinical or laboratory abnormalities, cannot be implicated as a predisposing host factor.
The absence of malformations in the ancestors or of infectious or toxic insults during embryo-fetal development does not exclude a genetic disorder as the cause of the deafness, i.e. of deaf-mutism.
The cochlear implant, as a hearing prosthesis reserved for profound sensorineural deafness, may be invoked as a risk factor for the second episode of meningitis.
The persistence of pneumococci sheltered within fibrinopurulent deposits cannot be avoided without early diagnosis, adequate and prolonged antibiotic therapy (no less than 14 days), and corticosteroid therapy adapted to the extent of the inflammatory exudate in the subarachnoid space and to the degree of encephalitic or neuritic involvement.
The emergence of antibiotic resistance requires careful surveillance of the susceptibility of pneumococcal strains circulating in a given area, as well as a more appropriate selection of the antibiotics included in susceptibility testing.
Prevention of pneumococcal infections in persons at major risk (lymphoproliferative syndromes, monoclonal gammopathies, HIV infection) can be ensured by administration of immunoglobulins and, in chronic and metabolic diseases and in splenectomized patients, by administration of the Pneumo 23 Mérieux vaccine.

2.6.3. MENINGOENCEPHALITIS OF MIXED ETIOLOGY

It is important to note that, although rare, meningitis of mixed etiology does exist, and the treatment regimen must be designed to cover both etiological agents; otherwise the outcome would be unfavorable. Once collected, the CSF must be fully exploited from every point of view.
The high proportion of secondary meningeal involvement requires appropriate monitoring of the primary suppurative foci; the same

attention must be paid to meningitis with a history of head trauma, meningosinus or meningonasal fistulas and ventriculoperitoneal shunts, as these may favor recurrences.
The patient presented below illustrates a pattern of evolution of tuberculous infection which, over 7 months of follow-up, went through the following diagnostic classifications: 1. Possible tuberculous meningoencephalitis. Hydrocephalus with ventriculoperitoneal drainage; 2. E. coli meningoencephalitis; 3. Tuberculoma.
C.D., aged 2 years and 9 months, was hospitalized for 14 days in the 2nd Infectious Diseases Clinic, Timișoara.
T*he child had sustained traumatic brain injury (TBI) inflicted by another person 18 days before admission to our Clinic* (according to the grandmother, who accompanied the child).
O*n days 5-6 after the TBI*, the child woke up during the night complaining of headache and had repeated vomiting.
He was admitted to the Pediatrics Department in Caransebeș, where he was assessed neurologically and by ENT, without any pathological findings. During observation the child became drowsy, with repeated projectile vomiting, and was therefore transferred after 5 days to the Louis Țurcanu Hospital, Timișoara.
A *contrast-enhanced cerebral CT* was performed, revealing basal meningeal thickening, hydrocephalus and bilateral mastoiditis, for which the child was transferred to our clinic.

Condition on admission: impaired general condition, afebrile, consciousness preserved, unable to maintain the sitting position, no signs of meningeal irritation, but with mild rigidity on passive mobilization. No response to verbal stimuli; responds to painful stimuli by whimpering. In the supine position he falls asleep instantly and shows bronchoplegia. SaO2 - 100%, HR - 85 beats/min.
Lumbar puncture was not performed because of the risk of tonsillar herniation.
Treatment was started with mannitol 60 ml, then 3 × 30 ml/day, dexamethasone 4 × 1.8 ml/day, ceftriaxone 2 × 600 mg/day and vancomycin 4 × 180 mg/day.

After 24 hours the course was favorable, and on the third day he was moving independently, climbing up and down stairs, conscious, cooperative, without focal neurological signs.
Four days later the general condition changed: the child remained conscious but developed contractures and tremor of the left lower

limb and focal neurological signs, with left central facial palsy and left hemiparesis.
Strictly supervised antituberculous treatment (DOT) was added, 7/7 regimen, H150, R150, E200, P250, and vancomycin was replaced with ciprofloxacin 3 × 100 mg/day.
He was assessed by pediatric neuropsychiatry, and Depakine was recommended in progressively increasing doses.
Because of respiratory disturbances and the persistence of the convulsive syndrome despite anticonvulsant treatment, the child *was transferred to the Infectious Diseases intensive care unit.*
Cerebral MRI + angiography: Tetraventricular hydrocephalus. Massive cerebral edema.
H**e** was transferred to the Neurosurgery department for ventricular drainage, with the diagnosis: POSSIBLE TUBERCULOUS MENINGOENCEPHALITIS. HYDROCEPHALUS. CONVULSIVE SYNDROME. LEFT HEMIPARESIS

The child was transferred back from Neurosurgery 24 hours after external ventricular drainage, with a postoperative course assessed as favorable.
*Neurosurgical consultation***:** Patient under observation for TB meningoencephalitis, in remission. Internal hydrocephalus with functional EVD. Recommendation: non-contrast cerebral CT.
*Non-contrast cerebral CT***:** status post drained supratentorial triventricular hydrocephalus; drainage tube with its tip on the interventricular septum, which is slightly displaced to the left. Lateral ventricles and third ventricle dilated, bifrontal distance 4 cm, third ventricle 1.3 cm, with discrete periventricular interstitial edema adjacent to the frontal and occipital horns. Fourth ventricle of normal size. Extracerebral CSF spaces of normal appearance. A 4 mm hypodense fluid-density lesion of sequelar appearance is visible in the left thalamus. No infratentorial lesions visible on CT. Orbits of normal appearance. Mucosal thickening and encysted secretions in the right maxillary sinus. Bilateral otomastoiditis.
He continued to be monitored in the Infectious Diseases intensive care unit. Treatment consisted of Meronem IV for 18 days, ciprofloxacin IV for 30 days and dexamethasone for 30 days, combined with isoniazid 100 mg, rifampicin 100 mg, pyrazinamide 300 mg and ethambutol 100 mg, and Depakine 1.2 ml every 8 hours.
The course was slowly favorable, with no new findings during monitoring. He was transferred to the Dr. Nicolae Robănescu Children's Rehabilitation Center, Bucharest.

He was readmitted (24 days) 4 months after the transfer to the Rehabilitation Clinic. At the time of admission, he had been ill for 3 days. Onset with fever, watery vomiting (6/day) and irritative cough. He was admitted the same day to the Pediatrics Department in Caransebeș, where treatment with cefotaxime, gentamicin, dexamethasone and Algocalmin was started, with improvement of the clinical condition for 1 day. Subsequently the fever recurred, and the patient became drowsy and developed vomiting, myoclonus and fasciculations in the left hemibody, for which he was referred to the Emergency Department of the Louis Țurcanu Hospital:
Contrast-enhanced head CT: ventriculoperitoneal shunt with a right parietal entry site and its tip in the right lateral ventricle (in contact with the choroid plexuses). Symmetrical cerebral hemispheres. Moderately enlarged lateral ventricles. Moderately enlarged third ventricle, transverse diameter 12.7 mm. Fourth ventricle of normal size and appearance. Brainstem with rare millimetric porencephalic lesions. No obvious contrast enhancement.

A **lumbar puncture** was performed: *purulent CSF under increased pressure, Pandy ++++,* cells 10918/mm^3, PMN 85%, Ly 4%, Mo 11%, CSF protein 1.44 g/l (144 mg/dl), glucose 0.18 mg/dl, lactate 6.8 mmol/l (61.3 mg/dl); *CSF culture: Escherichia coli*; antibiogram: S – Meronem, imipenem, ertapenem, amikacin, ciprofloxacin, levofloxacin, Biseptol, cefoxitin.
He was referred to our Clinic. *On admission*: severe general condition; febrile; drowsy, poorly cooperative, with psychomotor agitation during the examination; complains of intense headache; well-marked meningeal signs; pale skin; normal cardiopulmonary auscultation; abdomen moving with respiration, soft, bowel transit present and normal; unable to stand.
Laboratory: infectious/inflammatory syndrome (CRP 167.75 mg/l, procalcitonin 1.34 ng/ml, leukocytosis 19330/µl, ESR 15 mm/h).
Bacteriology: blood culture: ESBL-producing E. coli.
The following *treatment* was started: meropenem 40 mg/kg every 8 hours (17 days), vancomycin 15 mg/kg every 6 hours (7 days), Ciprinol 400 mg/day (7 days); IV corticosteroids, depletive agents, anticonvulsants and gastric protectants.
Of note, the grandmother (the child's caregiver) had not administered the antituberculous treatment at home, and it was not reintroduced into the initial treatment regimen, in view of possible hypersensitivity reactions to rifampicin.

Neurosurgical consultation: Diagnosis – Secondary internal hydrocephalus operated with a right ventriculoperitoneal shunt with a medium-pressure valve. Status post possible tuberculous meningoencephalitis. Headache syndrome. *Neurological*: conscious, cooperative, no signs of intracranial hypertension, slight nuchal rigidity, no lateralizing signs or signs of spinal cord involvement at the time of examination. Subjectively, headache; afebrile at the time of examination.

Chest X-ray: no pulmonary consolidation, no mediastinal or hilar lymphadenopathy.
He was febrile during the first 3 days after admission, with impaired general condition, drowsiness, myoclonus in the left hemibody and well-marked signs of meningeal irritation. He was reassessed by pediatric neuropsychiatry and the anticonvulsant dose was increased.
The subsequent course was slowly favorable, with diminution and then disappearance of the signs of meningeal irritation and with recovery of digestive tolerance.
Corticosteroid doses were gradually tapered over 7 days, in line with the clinical improvement, but 48 hours after corticosteroid discontinuation the child developed low-grade fever, intense headache, intermittent vomiting and myoclonus in the left hemibody.

Pediatric neuropsychiatry consultation: neurological examination: currently no acute focal symptoms, no signs of intracranial hypertension (ICH). *Psychiatric examination*: anxious behavior with easy crying, emotional outbursts at minimal frustration. *EEG:* waking tracing with a medium- and low-voltage theta background rhythm, multiple movement artifacts predominantly in the frontal leads, irritative in the posterior leads.

Diagnosis: Acute E. coli meningoencephalitis, secondary internal hydrocephalus with ventriculoperitoneal shunt. Convulsive seizures. *Recommendations*: Continue drug treatment with Depakine syrup 3 × 1.8 ml.
N*eurosurgical consultation*: Functional valve.

*Contrast-enhanced cerebral MRI***:** Peripherally gadolinium-enhancing nodular lesion in the head of the left caudate nucleus – tuberculoma? toxoplasmosis? Subcentimetric sequelar lesions, supratentorial bilaterally and in the left middle cerebellar peduncle. Drained

hydrocephalus, supratentorial ventriculomegaly. No periventricular edema. Bilateral otomastoiditis.

*Lumbar puncture (after 5 days of treatment)***:** *clear CSF, Pandy +, leukocytes 450/mm³, CSF glucose 16 mg/dl, CSF protein 49.6 mg/dl, lactate 4.18 mmol/l (37.66 mg/dl), differential count: disrupted cells, approximately 70% lymphocytes, 30% PMN, rare red blood cells*. Culture and genetic test pending.

*Pulmonology consultation***:** reintroduction of antituberculous treatment, continuation phase H150R150 7/7, up to 9 months.
Under DOT the course was favorable, with defervescence and improvement of the pain complaints after approximately 72 hours.
He was discharged in good general condition, with the following recommendations:
1. Continue DOT {H150, R150} 7/7, up to 9 months; 2. Continue Depakine 3 × 0.8 ml/day PO, as recommended by pediatric neuropsychiatry; prednisone 15 mg/day and Nexium 1 mg/kg/day via the family physician; 3. Reassessment at the clinic in one month, or at any time if needed.
Of note, by 3 months after discharge the child had not attended any assessment at the clinic and was practically lost to follow-up.
Discussion: The clinical case presented illustrates one of the not infrequent situations encountered in practice in which the disease presents with “borrowed” manifestations. The history comprises a succession of exacerbations and remissions over a period of approximately 7 months.

At the first admission, *the clinical diagnosis* of *meningoencephalitic syndrome* was well supported by subjective and objective findings.
However, the diagnosis of *bacterial meningitis* did not follow the rigorous pathway of positive diagnosis: the neuroimaging finding (contrast-enhanced cranial CT) of hydrocephalus required precautions before performing the LP, which is in practice the step that confirms the disease, establishes meningitis as such, and identifies the etiological framework or even the causative agent. For a tuberculous etiology, since the therapeutic window had not yet been exceeded, specific therapy was not brought to the forefront.
Eight days after admission (day 23 of illness), the clinical picture became dominated by neurological manifestations: contractures and tremor of the left lower limb, and focal neurological signs, with left central facial palsy and left hemiparesis.

The classification as *tuberculous meningoencephalitis* was based on elements of the disease course and not on isolation of the pathogen or on evidence from specific serology.
The progressive nature of the disease required neurosurgical management of the hydrocephalus, with external ventricular drainage.
A new admission, 4 months after transfer to the Rehabilitation Clinic, was prompted by the recurrence of left-sided hemicranial headache, with fever and vomiting. Revisiting the history in the newly arisen clinical context revealed discontinuation of the antituberculous treatment (stopped by the grandmother approximately 1 month earlier) and the child's belonging to a family environment with poor living conditions (father with pulmonary TB who had abandoned treatment).

The initial diagnosis of *purulent meningitis*, well supported by the CSF cytological and biochemical findings, benefited from a convincing etiological argument: the identification of ESBL-producing E. coli in the CSF culture. Isolation of the same organism in blood culture as well, in our child, who carried a ventriculoperitoneal shunt, points to hematogenous seeding of the meninges.
A tuberculous etiology was not supported by the CSF examination (direct examination, pellicle, culture). The newly emerged clinical complaints, together with the CSF cytological and biochemical parameters (control puncture after 12 days of antibiotic treatment showing 450 cells/mm^3, positive Pandy test, low CSF glucose), led us to maintain the classification of tuberculous meningitis, confirmed by the appearance of a tuberculoma on cranial MRI.
Under the newly established identity, the clinical manifestations acquired coherence.

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CHAPTER 3
FEBRILE RASH SYNDROME

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Febrile rash syndrome, or febrile exanthem, is defined as an eruption appearing on the skin, with or without other associated symptoms. An enanthem may or may not be part of the course of an exanthem and represents an eruption appearing on the mucous membranes.

Early diagnosis is important, both for identifying conditions with a potentially severe course and instituting appropriate treatment, and for isolating the patient in order to limit transmission of the infection. In this respect, the epidemiological investigation is extremely important and should include data such as exposure to vectors, history of international travel, contact with sick individuals, vaccination history and childhood diseases, etc.

The patient's history includes the usual data, with emphasis on the exanthem and/or enanthem. A complete physical examination is performed by systems, with emphasis on the characteristics of the eruption (lesion appearance, distribution, accompanying signs and symptoms, evolution of the exanthem over time, etc.).

3.1. PRIMARY SKIN LESIONS

- ✓ Macule: flat, erythematous lesion less than 1 cm in diameter;
- ✓ Plaque: raised, erythematous lesion more than 1 cm in diameter;
- ✓ Papule: firm, raised lesion without fluid content, less than 0.5 cm in diameter;
- ✓ Nodule: solid, raised lesion of variable size, larger than a papule;
- ✓ Vesicle: small lesion with clear content;
- ✓ Bulla: large vesicle with clear, serous (straw-colored) or hemorrhagic content;
- ✓ Pustule: similar to a vesicle, but with cloudy, purulent content;
- ✓ Purpura: multiple hemorrhagic spots, red to violaceous in color, that do not blanch on pressure;
- ✓ Petechiae: small hemorrhagic spots less than 1 cm;
- ✓ Ecchymosis: large hemorrhagic spot, more than 1 cm.

In order to establish the appropriate therapeutic approach, the etiology of the exanthem must be determined. A first step is identifying

the etiological agent and making the differential diagnosis between infectious and non-infectious conditions (autoimmune vasculitis, allergic dermatoses, etc.). Table 1 summarizes the main characteristics of the exanthem in the most common febrile eruptive diseases.

Table 1. Characteristics of febrile eruptive diseases

Disease	**Etiology**	**Description**	**Affected group/ Epidemiological factors**	**Clinical syndrome**
Measles	Paramyxovirus	Discrete lesions that become confluent, as extensive skin eruptions, starting at the hairline, sparing the palms and soles; Koplik spots	Unimmunized individuals	Cough, conjunctivitis, coryza, severe prostration
Rubella	Togavirus	Spreads downward from the hairline, clears in the same order in which it spreads; Forchheimer spots	Unimmunized individuals	Lymphadenopathy, arthritis
Infectious mononucleosis	Epstein-Barr virus	Diffuse maculopapular eruption (5% of cases; 90% if penicillin is administered); urticaria, petechiae in some cases; periorbital edema (50%); palatal petechiae (25%)	Adolescents, young adults	Hepatosplenomegaly, pharyngitis, cervical lymphadenopathy, atypical lymphocytosis, heterophile antibodies
Other viral exanthems	Echoviruses 2, 4, 9, 11, 16, 19 and 25; coxsackieviruses A9, B1, B5, etc.	A wide range of skin manifestations that may mimic rubella or measles	Affects children more often than adults	Nonspecific viral syndromes
Hand, foot and mouth disease	Coxsackievirus A16	Tender vesicles, oral erosions; 0.25 cm papules on the hands and feet, with an erythematous rim, evolving into fragile vesicles	Summer and autumn; primarily children under 10 years of age; multiple family members	Transient fever

Scarlet fever	Group A beta-hemolytic Streptococcus	Diffuse erythema that blanches on pressure, beginning on the face and spreading to the trunk and extremities; circumoral pallor; “sandpaper” skin texture; accentuation of linear erythema in the skin folds (Pastia's lines); white enanthem evolving into a red “strawberry” tongue; desquamation in the second week	Most common in children aged 2 to 10 years; usually follows group A streptococcal pharyngitis	Fever, pharyngitis, headache
Varicella (chickenpox)	Varicella-zoster virus	Macules (2-3 mm) that evolve into papules, then vesicles (sometimes umbilicated), on an erythematous base (“dewdrops on a rose petal”); pustules that subsequently crust; lesions appear in crops; may involve the scalp and mouth; intensely pruritic	Usually affects children; 10% of adults are susceptible; most common in late winter and spring	Malaise; usually a mild course in healthy children; more severe forms with complications in adults and immunocompromised children

Exanthem subitum (roseola) is caused by human herpesvirus 6 and is most common among children under 3 years of age. As in erythema infectiosum, the rash usually appears after the fever has subsided. It consists of pink to rose-colored macules and papules of 2-3 mm, which rarely coalesce, appear first on the trunk and sometimes on the extremities (sparing the face), and fade within 2 days.

Although *drug reactions* cause numerous manifestations, including urticaria, drug-induced exanthematous eruptions are the most common and are often difficult to distinguish from viral exanthems. Drug eruptions are usually more intensely erythematous and pruritic than viral exanthems, but this distinction is not reliable. A history of newly used medications and the absence of prostration may help differentiate a drug-related skin eruption from an eruption of other etiology. The rash may persist for up to 2 weeks after the causative agent is discontinued.

Some population groups are more prone than others to drug-induced skin eruptions. Among HIV-infected patients, 50-60% develop a rash in response to sulfonamides; 90% of patients with Epstein-Barr virus mononucleosis who are given ampicillin develop a rash.

In the evaluation of individuals with centrally distributed maculopapular eruptions, *rickettsial diseases* should also be considered. The usual setting for an outbreak of epidemic typhus is war or natural disaster, in which people are exposed to body lice. Endemic typhus or leptospirosis (the latter caused by a spirochete) may be seen in urban settings where rodents proliferate.

Erythema migrans, *the skin eruption of Lyme disease*, typically presents as single or multiple annular plaques. If untreated, erythema migrans lesions usually resolve within a month, but they may persist for more than a year. Southern tick-associated rash illness (STARI) presents with a rash similar to erythema migrans, but it is less severe than Lyme disease and often occurs in regions where Lyme disease is not endemic. Erythema marginatum, the rash of acute rheumatic fever, has a distinctive pattern of spreading and shifting transient annular lesions.

Collagen vascular diseases may cause fever and rash. Patients with systemic lupus erythematosus typically develop a sharply demarcated erythematous eruption on the cheeks (malar rash) in a butterfly distribution, as well as other skin manifestations.

Still's disease is characterized by an evanescent, salmon-colored eruption on the trunk and proximal extremities that coincides with fever spikes.

3.2. PRACTICAL CASES

A. A 6-year-old male patient from a rural area presents with a 7-day history of high fever (T max = 40°C), dysphagia and loss of appetite, and a 1-day history of a fine maculopapular rash on the face and neck. On examination: intensely congested pharynx, oral aphthae, febrile T = 39°C, tachycardic HR = 140 bpm, fine maculopapular rash on the face, neck, and anterior and posterior chest (Photo 1). At home he had been treated with oral paracetamol and metamizole drops.

   Personal physiological history: not vaccinated according to the Ministry of Health schedule, first pregnancy, first birth, attends school (preparatory grade), reported contact with a confirmed measles case.

Past medical history: allergic to ibuprofen and cow's milk protein.

Questions:

1. *What is the main diagnostic suspicion:
   a. Suspected measles
   b. Suspected varicella
   c. Suspected scarlet fever
   d. Allergic dermatosis
   e. Erythema multiforme

2. What can support the positive diagnosis:
   a. Attending a community setting (school)
   b. Contact with a confirmed case
   c. Lack of vaccination
   d. Contact with an unconfirmed case
   e. Allergy to ibuprofen

Clinical and laboratory course: normal leukocyte count, lymphomonocytosis on the differential count, CRP = 1 mg/L (NR 0-5 mg/L), ALT = 145 U/L (NR 0-34 U/L), AST = 100 U/L (NR 11-34 U/L), normal renal function, measles virus IgM = positive. From the second day of admission, the rash generalized, extending down to the lower limbs (Photo 1). From the 3rd day of admission, the patient became afebrile.

3. *What is the definitive diagnosis:
   a. Scarlet fever
   b. Measles
   c. Varicella
   d. Rubella
   e. Adenovirus infection



Photo 1. Measles exanthem (photos from the infectious diseases course for students – personal collection – unpublished)

4. What is a possible cause of the hepatocellular injury (cytolysis) syndrome:
   a. Possibly drug-induced toxicity
   b. It may be a satellite hepatitis
   c. Transaminases are normal
   d. GGT must be measured to exclude drug toxicity
   e. It may be due to paracetamol use

Clinical and laboratory course: after 2 afebrile days, isolated febrile spikes reappear (T = 38°C), with a dry cough predominantly at night and a band-like ("helmet") headache. Laboratory findings: WBC = 18,300/µL (NR 4,000-10,000/µL) with neutrophilia, CRP = 80 mg/L (NR 0-5 mg/L), ALT = 100 U/L (NR 0-34 U/L), AST = 70 U/L (NR 11-34 U/L), normal renal function. No clinical signs of meningeal irritation. Lung auscultation: within normal limits.

5. Which investigations do you consider useful in this case:
   a. Chest X-ray
   b. Sinus X-ray
   c. ENT consultation
   d. Nothing needs to be done; this is the normal course of the disease
   e. Lumbar puncture

6. *What do you think is the most likely cause:
   a. Acute sinusitis
   b. Basal pneumonia
   c. Acute otitis
   d. Meningitis
   e. Encephalitis

Investigations: sinus X-ray – complete opacification of the maxillary sinus. ENT consultation – acute sinusitis, requiring antibiotic therapy combined with nasal decongestants.

7. What treatment do you propose in this case:
   a. IV azithromycin
   b. IV moxifloxacin
   c. IV meropenem
   d. IV ceftriaxone
   e. IV gentamicin

8. What treatment would you have proposed for uncomplicated measles (limit yourself to the case presented above):
   a. Oral rehydration
   b. Vitamin therapy
   c. Antipyretics
   d. Parenteral hydration
   e. Oral ibuprofen

B. A 6-year-old male patient from a rural area presents with a 2-day history of fever (T max = 38.6°C), dysphagia and loss of appetite, and a 1-day history of a rough, fine maculopapular rash on the anterior chest. On examination: intensely congested pharynx, depapillated/raspberry tongue (Photo 2), tachycardic HR = 140 bpm, febrile T = 38°C, rough fine maculopapular rash on the anterior chest. At home he had been treated with oral paracetamol and methylene blue.
Personal physiological history: not vaccinated according to the Ministry of Health schedule, first pregnancy, first birth, attends school (preparatory grade). Reportedly, 3 classmates are absent because of acute tonsillitis.
Past medical history: recurrent viral respiratory infections.

Questions:

9. *What is the main diagnostic suspicion:
   a. Suspected measles
   b. Suspected varicella
   c. Suspected scarlet fever
   d. Allergic dermatosis
   e. Erythema multiforme

10. What can support the positive diagnosis:
   a. Attending a community setting (school)
   b. Contact with a confirmed case
   c. Lack of vaccination
   d. Contact with an unconfirmed case
   e. Distribution of the rash

Clinical and laboratory course: leukocytosis with neutrophilia and eosinophilia on the differential count, CRP = 84 mg/L (NR 0-5 mg/L), ESR = 20 (0-5/h), ALT = 14 U/L (NR 0-34 U/L), AST = 10 U/L (NR 11-34 U/L), normal renal function, blood glucose = 80 mg/dL (NR 70-100 mg/dL), ASO titer below 200 (NR below 200), throat swab culture for pathogenic flora = positive for *group A beta-hemolytic Streptococcus*. From the second day of admission, the tongue became depapillated from tip to base, and the patient became afebrile (Photo 2).



Photo 2. Raspberry tongue (photos from the infectious diseases course for students – personal collection – unpublished)

11. *What is the definitive diagnosis:
    a. Scarlet fever
    b. Measles
    c. Varicella
    d. Rubella
    e. Adenovirus infection

12. Therapeutic management:
    a. There is no etiological treatment
    b. Antibiotic treatment is required
    c. The antibiotic of choice is penicillin
    d. Penicillin skin testing is not performed
    e. Penicillin skin testing is mandatory

13. *In case of penicillin allergy:
    a. Moldamin is administered
    b. Levofloxacin is the first-line option
    c. Oral clarithromycin may be administered

d. There is no such thing as penicillin allergy
e. Oral Ospen may be administered

14. Post-streptococcal syndrome:
    a. Is a complication of an acute infection with *group A beta-hemolytic Streptococcus*
    b. The patient requires treatment with Moldamin
    c. It is assessed in the laboratory by the ASO titer
    d. It does not cause distant complications
    e. Acute rheumatic fever may result from the post-streptococcal syndrome

15. Complications of scarlet fever:
    a. Septic shock
    b. Adenophlegmon
    c. Sinusitis
    d. Otitis
    e. Urinary tract infection

16. Differential diagnosis of scarlet fever:
    a. Infectious mononucleosis
    b. Enteroviral infections
    c. Acute rotavirus enterocolitis
    d. Salmonellosis
    e. Acute pneumonia

C. A 35-year-old male patient from an urban area presents with a 4-day history of fever (T max = 38.6°C) and loss of appetite, and a 2-day history of a generalized polymorphic rash (intensely pruritic maculopapular and vesicular lesions) (Photo 3).

On examination: coated tongue, tachycardic HR = 148 bpm, febrile T = 38°C, generalized polymorphic rash (Photo 3). At home he had been treated with oral paracetamol and a topical menthol paste.

Personal physiological history: vaccinated according to the Ministry of Health schedule, works in IT, contact with his son, a confirmed varicella case.

Past medical history: none.



Photo 3. Polymorphic rash (photos from the infectious diseases course for students – personal collection – unpublished)

Questions:

17. *What is the main diagnostic suspicion:
    a. Suspected infectious mononucleosis
    b. Varicella
    c. Suspected scarlet fever
    d. Allergic dermatosis
    e. Erythema multiforme

18. Is a laboratory work-up required to confirm the positive diagnosis?
19. Does the case presented above require hospital admission?
20. What treatment do you propose?
21. What are the complications of the condition presented?

Answers to Case C:

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D. A 14-year-old male patient from an urban area presents with a 7-day history of fever (T max = 39°C), loss of appetite, dysphagia and bilateral laterocervical polyadenopathy. He had been treated at home with clarithromycin 500 mg, 1 tablet twice daily for 5 days, without improvement of symptoms.

On examination: coated tongue, tachycardic HR = 148 bpm, febrile T = 40°C, erythematous pharynx with pultaceous tonsillar exudate (Photo 4), bilateral laterocervical lymphadenopathy, mobile lymph nodes of 2/3 cm, tender on deep palpation, hepatosplenomegaly on deep palpation. No other abnormal findings on physical examination.

Personal physiological history: vaccinated according to the Ministry of Health schedule, 8th-grade pupil, no known infectious contact.

Past medical history: none.



Photo 4. Acute erythematous-pultaceous tonsillitis (photos from the infectious diseases course for students – personal collection – unpublished)

Questions:

22. *Which serological test would you need for the diagnosis:
a. Throat swab culture for pathogenic flora
b. Measles virus IgM
c. Rubella virus IgM
d. EBV anti-VCA IgM antibodies
e. EBV anti-VCA IgG antibodies

23. *What is the most likely diagnosis:
a. Scarlet fever
b. Measles
c. Infectious mononucleosis
d. Acute leukemia
e. Streptococcal tonsillitis

24. What are the common complications of infectious mononucleosis:
a. Splenic rupture
b. Autoimmune hemolytic anemia
c. Bacterial superinfections
d. Abdominal aortic rupture
e. Relapse

Correct answers:
1. a
2. abc
3. b
4. abde
5. bc
6. a
7. cde
8. bcde
9. c
10. ad
11. a
12. bce
13. c
14. abce
15. abcd
16. ab
17. b

18. the positive diagnosis of varicella is based on epidemiological, clinical and laboratory evidence, with the note that in most cases a clinical diagnosis is sufficient.
19. hospital admission for varicella is required if complications develop; in the present case, the patient is at the height of the disease, with typical symptoms.
20. antiviral treatment with acyclovir is indicated for all adults who develop varicella, regardless of their immune status, because the risk of severe forms and death from varicella in adults is 25 times higher than in children.
21. bacterial superinfection of skin lesions; primary varicella pneumonia; varicella croup; neurological complications; rare visceral involvement – hepatitis, pancreatitis, appendicitis, etc.
22. d
23. c
24. abc

3.3. KEY POINTS

3.3.1. Measles

Measles is a highly contagious infectious disease caused by the measles virus. It occurs in individuals not previously immunized by vaccination or prior disease.

Transmission is in most cases via the respiratory route, and contagiousness is very high (95% of previously unimmunized individuals who come into contact with a confirmed case are at risk of developing the disease).

Clinically, the disease has two periods: the pre-eruptive period (with high fever, catarrhal symptoms, enanthem – erythematous pharyngitis, hemorrhagic palatal stippling and Koplik spots – and neurological manifestations such as irritability, headache or even encephalitic features) and the eruptive period (an exanthem that spreads progressively in a craniocaudal direction, maculopapular, erythematous and velvety to the touch); during this period, measles croup, acute bronchiolitis or measles pneumonia may also occur.

Laboratory diagnosis: nonspecific findings (absence of an inflammatory syndrome, normal leukocyte count or leukopenia with a tendency to lymphomonocytosis) and serological findings (presence of IgM anti-measles antibodies). Note: the presence of IgG anti-measles antibodies indicates immunity against measles acquired in the past, either after the disease or after MMR vaccination. In some

cases, the laboratory work-up may also reveal a hepatocellular injury syndrome (satellite hepatitis due to the viral infection, or drug toxicity – especially related to the medication taken by the patient at home).

The complications (Table 2) of this disease are: those caused by the virus itself (measles pneumonia, measles croup, capillary bronchiolitis and neurological complications), those caused by measles-induced immunosuppression (bacterial superinfections, TB reactivation, candidiasis, parasitic infections, etc.), and those determined by the underlying host condition (giant cell pneumonia, cervicomediastinal emphysema, measles keratitis, inclusion body encephalitis).

Approximately 30% of patients develop at least one complication; the risk is highest under 5 years and over 20 years of age, in pregnant women, in malnourished individuals (vitamin A deficiency) and in the immunocompromised. In pregnancy, measles increases the risk of miscarriage, prematurity and low birth weight, without being teratogenic as rubella is.

Table 2. Complications of measles

Complication	Frequency	Essential clinical notes
Acute otitis media	7–9%	The most common complication; risk of residual hearing loss
Diarrhea	~8%	Dehydration and secondary malnutrition, especially in infants
Pneumonia	1–6%	Viral (Hecht giant cell) or secondary bacterial; the main cause of death
Laryngotracheitis / croup	variable	Upper airway obstruction in infants and young children
Keratitis, corneal ulcer	variable	Associated with vitamin A deficiency; a cause of blindness in resource-limited settings
Acute post-infectious encephalitis	~1/1.000	2–30 days after the rash; ~15% mortality, ~25% neurological sequelae
MIBE (measles inclusion body encephalitis)	rare	Exclusively in the immunocompromised; latency of weeks to months; often fatal
SSPE	see SSPE section	Latency of years; invariably fatal
Death	1–3/1.000*	*in high-resource countries; 5–10% in resource-poor settings or in malnourished individuals

Treatment is mainly symptomatic. Antibiotic treatment is used strictly in case of bacterial superinfection.

Measles infection selectively destroys memory B and T lymphocytes. Mina et al. (*Science*, 2015) showed, using population data, an increase in mortality from other infections for 2–3 years after measles; the same group (*Science*, 2019), using VirScan, demonstrated the loss of 11–73% of the antibody repertoire already present, while Petrova et al. (*Science Immunology*, 2019) documented incomplete reconstitution of the memory B-cell pool. Practical consequence: after measles, the child again becomes vulnerable to pathogens to which he or she was already immune, and some previous immunizations may require reassessment; this phenomenon accounts for a substantial part of the indirect mortality attributed to the disease.

3.3.2. SSPE – subacute sclerosing panencephalitis

Pathogenesis of SSPE (Dawson disease): it is a chronic progressive encephalitis caused by the persistence in neurons of a defective measles virus, with mutations predominantly in the M protein gene, which prevent the assembly of complete virions and allow cell-to-cell spread, sheltered from the humoral immune response. The mean latency is 7–10 years (reported extremes: under 1 year to over 30 years), and the male-to-female ratio is 2–3:1. Risk factors identified in the literature include young age at infection, rural residence, crowding, low socioeconomic status and having an older sibling who brings the infection into the household.
Incidence – why the “classic” estimates are outdated. Studies from the last two decades have substantially revised the risk compared with textbook values, particularly for infection during the first year of life.

The differences between estimates do not reflect different biology but different denominators: reported measles cases are underestimated to a variable extent (Khetsuriani et al. recalculate 1:2,792 under a hypothetical scenario of 50% underreporting), and cohorts differ in age at infection, duration of follow-up and access to neurological diagnosis. The constant finding across all studies is that young age at infection is the strongest risk factor. A recent Algerian series (47 children aged 2–6 years, 2020–2022) found 87% unvaccinated and 83.8% infected before one year of age, while also noting a shortening of latency compared with classic descriptions – an observation reported independently in other recent series as well, with cases diagnosed even at toddler age.

Clinical and paraclinical features: Jabbour staging: I – behavioral changes and cognitive decline; II – massive periodic myoclonus, seizures, ataxia; III – rigidity, decerebrate posturing, autonomic dysfunction; IV – vegetative state, akinetic mutism, death. Diagnosis: EEG with Radermecker periodic complexes synchronous with the myoclonic jerks, high CSF anti-measles IgG titers with an elevated antibody index (intrathecal synthesis), oligoclonal bands, and, at a late stage, cortical atrophy and white matter hyperintensity on MRI. The teaching pitfall is stage I: declining school performance and behavioral changes are often attributed to a psychiatric disorder or to the family context, and the diagnosis is made only when myoclonus appears. Inosine pranobex, intraventricular interferon alfa and ribavirin are palliative; the course is invariably fatal, with a median survival of 1–3 years.

Relevance for Romania: because of the latency, SSPE is the "delayed echo" of epidemics: cases diagnosed today correspond to the waves of 10–12 years ago, and children infected during the 2023–2025 epidemic – especially infants, too young to be vaccinated and protected only by herd immunity – constitute the at-risk population for the next decade. Applying the conservative estimates from the literature to the nearly 28,000 pediatric cases of the last three years, dozens of SSPE cases can be anticipated in the coming years. This is the strongest argument against the label of "a trivial childhood disease" and, at the same time, the reason why protecting infants is a collective, not an individual, responsibility.

Epidemiological situation in Romania:

Between January 1, 2023 and December 31, 2025, the National Institute of Public Health (INSP) confirmed 35,736 measles cases and 30 deaths. The age distribution shows the pattern of an epidemic in a largely susceptible population: 27,720 cases (77.6%) in children under 15 years and 3,188 (8.9%) in adolescents aged 15–19 years. The peak was reached in 2024; in 2025 the number fell to approximately 4,198 cases, but transmission continued into 2026, which shows that the decline reflects partial depletion of susceptible cohorts rather than interruption of viral circulation.

The European comparison explains why Romania is the textbook case of the region. Over the period February 1, 2024 – January 31, 2025, the ECDC recorded 32,265 cases in the EU, of which 27,568 were in Romania – over three quarters of the total; the second-ranked country, Italy, reported 1,097 cases. Even after the 2025 decline, Romania continued to account for more than half of EU

cases. The formal consequence: the country is among the states of the WHO European Region in which measles is considered endemic – the virus circulates continuously, not only through importations – which means loss of elimination status and additional surveillance obligations, including genotyping to document transmission chains.

The geographic distribution is extremely uneven and overlaps the map of vaccination coverage: the major outbreaks were concentrated in counties with coverage below 50%, in communities with poor access to a family physician, with populations not registered on family physicians' lists, or with high mobility. For the clinical rotation discussion, it is worth remembering that in a population with an R0 of 12–18, 50% coverage does not provide “half the protection” but practically no barrier to transmission: every case, whether imported or autochthonous, quickly finds a transmission chain.

The reported mortality (30 deaths) is almost certainly an underestimate of the true burden, as it includes neither indirect deaths from infections occurring during the period of post-measles immunosuppression nor future cases of SSPE.

Situation in the EU/EEA and globally:

EU/EEA: between December 1, 2024 and November 30, 2025, the 30 countries reported 8,826 cases, of which 72.0% were laboratory-confirmed. Among cases with known age, 40.0% occurred in children under 5 years and 33.7% in persons aged 15 years and older – a concrete argument against the label of “an exclusively pediatric disease”. Among cases with known vaccination status, 79.9% were unvaccinated, 10.3% had received a single dose, 7.9% two or more doses, and 1.7% an unknown number of doses; the small proportion of cases in fully vaccinated persons corresponds to the expected secondary vaccine failure and does not contradict vaccine efficacy.

Eight to ten deaths per year were reported (France, Romania, the Netherlands), with a case fatality rate of 0.10–0.13%. In the winter months of 2025–2026, reports fell below 150 cases per month across the EU/EEA (November 2025: 83 cases, most of them in Poland, Germany, Italy and Spain; February 2026: 139 cases in 11 countries, with 15 countries reporting zero cases), with active outbreaks reported in Bulgaria, Latvia, France and Spain. Seasonality is marked – a low in late summer and an increase in January–March – so winter declines should not be interpreted as the end of the epidemic.

Globally: the WHO estimates approximately 11 million cases and 95,000 deaths for 2024, mostly in unvaccinated or incompletely

vaccinated children under 5 years of age. Global coverage was 84% for the first dose and 76% for the second, leaving about 30 million children underprotected. Mortality decreased by 88% between 2000 and 2024 (approximately 58 million deaths averted), but incidence is rising: 59 countries reported large or disruptive outbreaks, nearly three times as many as in 2021, and a quarter of these were in countries previously declared measles-free, including Canada and the USA. In 2024, the European Region reported the highest number of cases in the last 25 years, approximately 20% of the global total; in 2025, cases fell by about 75% in Europe and Central Asia, but more than 200,000 people in the region have fallen ill over the last three years. The “more cases, fewer deaths” paradox is explained by the shift of outbreaks away from low-income countries, where case fatality is highest, toward middle- and high-income countries.

Vaccination coverage in Romania:

INSP data show progressive erosion: in 2024, coverage for the first MMR dose was reported at around 80% nationally, and for the second dose at around 60%. County-level assessment, however, reveals the real dispersion: only one county exceeded 70% (Bihor, 73.8%), 14 counties ranged between 50.6% and 67.4%, 24 counties between 31.3% and 49.7%, and three counties were below 30%, the lowest being Argeș (23.7%). NGOs working in the field report, in the cohorts they assessed, acceptance rates of 47.4% for the first dose and as low as 20% for the second in some communities. The second dose, scheduled at 5 years of age, is the weakest link, as it comes after the end of the frequent contacts with the family physician during the first year of life.

3.3.3. Measles vaccines (Table 3)

All current measles vaccines are live attenuated vaccines derived from the wild-type Edmonston strain isolated in 1954. They are administered subcutaneously, are lyophilized, reconstituted immediately before use, and are markedly heat- and light-sensitive (cold chain mandatory, prompt use after reconstitution). The monovalent vaccine is practically no longer used in Europe; the MMR (measles–mumps–rubella) and MMRV (tetravalent, with a varicella component) combinations are used instead.

Table 3. Measles vaccination

Attenuated strain	Common products	Notes
Enders–Edmonston (Moraten)	M-M-RVaxPro, ProQuad	The most widely used worldwide; derived from the Edmonston strain isolated in 1954
Schwarz	Priorix, Priorix-Tetra	European standard; similar immunogenicity and reactogenicity
Edmonston–Zagreb	monovalent, WHO programs	Immunogenic even at 6–9 months; used in mass campaigns in endemic areas
AIK-C, CAM-70, Leningrad-16	national programs outside Europe	Not available in the EU; useful when taking the vaccination history of patients from other regions

Schedule in Romania: dose 1 at 12 months, dose 2 at 5 years, free of charge, through the family physician.

"Zero" dose: in an epidemic context or before travel to an endemic area, it may be administered between 6 and 11 months of age; it does not count toward the schedule – the child subsequently receives both standard doses, because residual maternal antibodies blunt the immune response.

Efficacy: ~93% after one dose, 97–99% after two doses, with protection usually lifelong. Minimum interval between doses: 4 weeks. Persons born before 1957–1960 are presumed to have natural immunity.

Contraindications: severe immunosuppression (including low CD4 count), pregnancy – conception should be avoided for one month after vaccination – and previous anaphylaxis to the vaccine or to any of its components. It may be administered concomitantly with inactivated vaccines at different sites; with other injectable live vaccines, either simultaneously or at an interval of ≥4 weeks. Administration of immunoglobulins or blood products requires postponement of vaccination, depending on the preparation and dose.

Post-exposure prophylaxis: vaccine within the first 72 hours in eligible susceptible persons; standard immunoglobulin within the first 6 days in infants under 12 months, susceptible pregnant women and the immunocompromised.

Safety: fever and transient rash in 5–15% of vaccinees, at 7–12 days; lymphadenopathy, transient arthralgia (especially in adolescent girls, due to the rubella component); self-limited immune thrombocytopenia, rare. Febrile seizures are slightly more frequent after the first dose of MMRV than after MMR and varicella vaccines given separately, which is why some guidelines prefer MMR for the

first dose. The association with autism has been repeatedly refuted, most robustly by the Danish cohort of Hviid et al. (2019, Annals of Internal Medicine), including 657,461 children.

3.3.4. Varicella

Varicella is a highly contagious infectious disease that can occur at any age. Transmission is from person to person, via the respiratory route through nasopharyngeal secretions, but also through contact with uncrusted vesicular skin lesions.

Clinical picture: a polymorphic rash (macule–papule–vesicle–pseudopustule–crust) that is intensely pruritic and centripetal in distribution (abundant on the face, neck and trunk, sparse on the limbs); general signs – fever, chills, odynophagia, malaise, generalized small lymph node enlargement (micropolyadenopathy).

The positive diagnosis is based on epidemiological, clinical and laboratory evidence, with the note that in most cases a clinical diagnosis is sufficient. The most widely used serological tests are ELISA assays, which can distinguish IgM anti-VZV antibodies from IgG anti-VZV antibodies.

The complications (Table 4) of varicella are: primary varicella pneumonia (more common in adults, pregnant women, the immunocompromised and newborns), varicella croup, neurological complications (encephalitis, meningitis, etc.), Reye syndrome (in children with varicella given aspirin), bacterial superinfection of skin lesions, and, in rare cases, involvement of other viscera – hepatitis, pancreatitis, appendicitis, etc.

Approximately 1 in 50 cases develops complications, and the high-risk groups are infants, adults, pregnant women, newborns and the immunocompromised. A prospective Swiss pediatric surveillance study (2021–2023) found, among 224 children hospitalized for varicella: skin complications in 54% of cases (including 52 S. pyogenes infections), musculoskeletal complications in 13%, neurological complications in 12%, two ischemic strokes, ICU admission in 14%, surgical interventions in 18% and death in 1% – at a hospitalization rate of 12.6 per 10,000 cases. Most of the hospitalized children were previously healthy, which contradicts the idea that severe forms occur only in those with comorbidities.

Table 4. Complications of varicella

Complication	Frequency	Key clinical notes
Bacterial skin superinfection	most common	S. aureus and group A streptococcus; the main cause of hospitalization
Invasive group A streptococcal infection	rare, severe	Necrotizing fasciitis, toxic shock; varicella is a major risk factor
Acute cerebellar ataxia	~1/4.000	The most common neurological complication; prognosis generally good
Encephalitis	~1/50.000	More common and more severe in adults; seizures, coma
Varicella pneumonia	rare in children	The most common complication in adults; increased risk in smokers and pregnant women
Ischemic stroke / VZV vasculopathy	rare	May occur weeks to months after the episode, including in healthy children
Thrombocytopenia, hepatitis, arthritis	rare	Usually self-limiting
Reye syndrome	historical	Associated with aspirin use – contraindicated in varicella
Death	1–3/100,000 cases	Significantly higher risk in adults, pregnant women, neonates and immunocompromised patients

Antiviral etiological treatment with aciclovir is indicated for all adults who develop varicella, regardless of their immune status, because the risk of severe disease and death from varicella in adults is 25 times higher than in children. Immunocompromised patients who develop varicella have a firm indication for treatment. Immuno-competent children with mild varicella may be treated symptomatically only.

Varicella and pregnancy: maternal infection during the first 20 weeks may result in congenital varicella syndrome (limb hypoplasia, dermatomal skin scarring, chorioretinitis, microcephaly, cortical atrophy), with an overall risk below 2%. The most severe situation is neonatal varicella: if the maternal rash appears between 5 days before and 2 days after delivery, the newborn receives the virus without protective maternal antibodies, and mortality in the absence of prophylaxis has historically been reported as high as ~30%. Management includes specific immunoglobulin and aciclovir. Varicella pneumonia in pregnancy is likewise a medical emergency. In practice, serological status is worth documenting in any pregnant woman with a negative or uncertain history of varicella, and vaccination should be given before pregnancy.

The "invisible" burden: the cost-effectiveness argument for universal vaccination rests not only on severe disease but also on the indirect burden: 7–10 days of isolation for each sick child, parental absenteeism, exclusion of susceptible contacts from childcare and school settings, and the risk to younger siblings and immunocompromised relatives in the household. In European economic analyses, indirect costs usually account for the majority of the total cost of the disease – which is why some countries have adopted UVV even in the absence of significant mortality.

The epidemiological situation in Romania:

By volume, varicella is the most frequently reported rash illness in Romania. CNSCBT/INSP data show 29,503 cases in 2022 (national incidence 154.25 per 100,000 population, up from the pandemic years but below the 2019 level) and 31,642 cases in 2023. Age-specific incidence rates for 2023 show the classic pattern of a disease not controlled by vaccination: over 1,116 cases per 100,000 in the 5–9-year age group and approximately 998 per 100,000 in the 1–4-year age group. No deaths have been reported in recent years, which does not mean there is no burden – deaths from varicella are rare, but hospitalizations and complications are frequent and under-recorded.

Interpreting the figures: unlike measles, varicella is massively underreported: the diagnosis is clinical, most cases never reach a physician, and reporting is aggregate rather than case-based. Seroepidemiological estimates suggest that, in a population without routine vaccination, virtually the entire birth cohort contracts the disease by adulthood – which implies a true number of the order of 150,000–200,000 cases per year in Romania, compared with the ~30,000 reported. Romanian pediatricians point out that, over the last 15 years, hundreds of thousands of children have needlessly gone through the disease even though an effective vaccine is available. In 2026, increases in cases were also reported among adults, with the season extending beyond the cold months and hospital admissions for severe disease – the pattern expected in a population in which a growing proportion of people reach adulthood without having had the disease and without being vaccinated.

The situation in Europe:

Reported annual incidence varies enormously between countries, more because of surveillance systems than because of true epidemiology: 300–1,291 per 100,000 in Western Europe (France, the Netherlands, Germany, the United Kingdom), 164–1,240 in

Southern Europe (Italy, Spain, Portugal) and up to approximately 350 per 100,000 in Eastern Europe (Poland, Romania). Vaccination policies are equally heterogeneous: approximately 16 European countries have adopted universal varicella vaccination of children (UVV) – nationwide in countries such as Germany, Greece, Cyprus, Latvia and Lithuania, and regionally in Italy and Spain – whereas about 17 countries recommend vaccination only for susceptible adolescents and risk groups. Romania belongs to the second category, with no routine vaccination.

Evidence from universal programs: a systematic review published in 2025 (41 studies from 5 of the 16 European countries with UVV) found a significant reduction in varicella incidence (IRR 0.46; 95% CI 0.39–0.54) and in hospitalizations (IRR 0.60; 95% CI 0.53–0.69) after the programs were introduced. The authors highlight two points useful for clinical rotation discussions: to date, no conclusive increase has been identified either in incidence among older age groups or in the burden of herpes zoster – the argument that delayed the decision in many countries – and the factor most strongly associated with vaccine acceptance is an explicit recommendation from the physician. Heterogeneity across studies remains high, and differences in surveillance between countries limit direct comparisons.

3.3.5. VZV vaccines (Table 5)

Varicella vaccines are live attenuated, all derived from the Oka strain, isolated in Japan in 1974 from a child with varicella. They are given subcutaneously, are heat-sensitive and are reconstituted immediately before use. For zoster there is, separately, a non-replicating recombinant vaccine with an entirely different mechanism and indication.

Table 5. VZV vaccination

Strain / type	Products	Notes
Oka/Merck (live attenuated)	Varivax (monovalent), ProQuad (MMRV)	Oka strain isolated in Japan (1974), attenuated by serial passage
Oka/RIT (live attenuated)	Varilrix (monovalent), Priorix-Tetra (MMRV)	European standard; same parent strain, different manufacturing process
Recombinant gE + AS01B (non-replicating)	Shingrix (RZV) – for zoster only	Does not prevent varicella; targets reactivation in adults
Oka/Merck high dose (live)	Zostavax (ZVL) – for zoster only	Withdrawn/progressively replaced by RZV because of waning efficacy

Schedule in Romania: two doses, the first from 12 months of age, the second usually at 4–6 years (minimum interval 4–8 weeks in unvaccinated older children, adolescents and adults). A single dose leaves a significant proportion of individuals susceptible.

Efficacy: ~80–85% after one dose against any form of disease, but 97–99% against moderate and severe disease; ~92% against any form after two doses. "Breakthrough" varicella – in vaccinated individuals – is atypical: fewer than 50 lesions, often maculopapular, low-grade fever, yet contagious, and therefore easily missed diagnostically.

In Romania: the varicella vaccine is not included in the National Immunization Program; it is dispensed on prescription, at the patient's expense. The direct methodological consequence: unlike MMR, there are no national vaccination coverage data for varicella.

Any figure in circulation comes from sales estimates or local studies, not from a population register – a distinction worth emphasizing to students.

Post-exposure prophylaxis: vaccination within 72 hours (up to 5 days) of contact prevents or attenuates the disease in eligible susceptible individuals. Specific anti-VZV immunoglobulin (or, if unavailable, standard immunoglobulin) for exposed newborns, susceptible pregnant women and immunocompromised patients, ideally within 96 hours.

Contraindications: severe immunosuppression, pregnancy (conception should be avoided for one month after vaccination), anaphylaxis to a vaccine component. In patients with HIV, vaccination may be considered if the CD4 count is above the recommended thresholds.

Safety: local reactions, fever, and a localized varicella-like rash in 3–5% of vaccinees. Transmission of the vaccine strain to contacts is exceptional and occurs practically only from vaccinees who develop a rash. The risk of febrile seizures is higher after the first dose of MMRV than after MMR and varicella vaccines given separately – which is why many guidelines prefer separate administration for the first dose. The vaccine strain can establish latency and reactivate as zoster, but at lower rates than after natural infection.

3.3.6. Herpes zoster

After varicella, VZV remains latent in the spinal and cranial sensory ganglia. Reactivation, favored by declining cell-mediated immunity (age, immunosuppression, malignancy, stress,

corticosteroid therapy), produces zoster: a painful vesicular rash, typically unilateral, confined to one or two dermatomes. Incidence is approximately 3–5 cases per 1,000 person-years in the general population and rises steeply after the age of 50; the lifetime cumulative risk is estimated at about 30% for a person who has had varicella. Forms of particular clinical relevance are herpes zoster ophthalmicus (V1 branch, risk of keratitis and vision loss), Ramsay Hunt syndrome (geniculate ganglion: facial palsy, hearing loss, vertigo) and disseminated zoster in immunocompromised patients.

Complications: the most common is postherpetic neuralgia – pain persisting more than 90 days after the rash – which occurs in 5–30% of patients, with frequency and severity rising markedly with age, and is often refractory to treatment. Cohort studies have also documented a transiently increased risk of stroke and cardiovascular events in the months following an episode of zoster, especially after herpes zoster ophthalmicus. Antiviral treatment (aciclovir, valaciclovir, famciclovir) started within 72 hours of rash onset shortens the duration of the illness and partially reduces the risk of postherpetic neuralgia.

Zoster vaccination: the first vaccine, ZVL (Zostavax), live attenuated with a high dose of the Oka strain, has an efficacy that wanes rapidly: 51.3% in the first years, 39.6% at 3.3–7.8 years and 21.1% at 4.7–11.6 years after vaccination. It has been progressively replaced by RZV (Shingrix), a non-replicating recombinant vaccine containing VZV glycoprotein E and the AS01B adjuvant, given in two doses 2 months apart. In the pivotal ZOE-50 and ZOE-70 trials, efficacy against zoster was 97.2% in adults vaccinated at ≥50 years and 91.3% in those aged ≥70 years. The final analysis of the long-term follow-up study ZOE-LTFU, published in 2025, shows efficacy maintained at 79.8% at 11 years after initial vaccination, with humoral and cellular immune responses plateauing above prevaccination levels and with no serious adverse events attributed to the vaccine. Being non-replicating, RZV can also be given to immunocompromised patients, in whom ZVL was contraindicated.

Situations requiring attention: zoster in a child or a young adult without obvious risk factors calls for evaluation for underlying immunosuppression – first and foremost HIV infection, but also hematological malignancies or undisclosed immunosuppressive treatment. There are also forms without a rash (zoster sine herpete), with isolated radicular pain, in which the diagnosis is made by PCR for VZV DNA in CSF or blood; PCR of vesicular fluid remains the reference method when the rash is atypical. An episode of zoster

does not contraindicate subsequent vaccination – on the contrary, vaccination is recommended, usually a few months after the episode has resolved, to prevent recurrences.

In Europe, zoster vaccination is recommended in 17 of the 27 EU member states (63%), but fully reimbursed in only 7; the age from which it is recommended varies – ≥50 years in 4 countries, ≥60 in 5 and ≥65 in 7. Romania has no national zoster vaccination program, and commercial availability must be checked case by case.

3.3.7. Scarlet fever

Scarlet fever is an acute bacterial infection caused by group A beta-hemolytic Streptococcus. It most commonly affects school-age children and is rarely seen in adults. Transmission is usually airborne, but also occurs through direct contact with contaminated objects.

Clinical picture: onset is often abrupt, with fever of 38–39 °C, chills, malaise, dysphagia and a coated tongue, followed in the full-blown stage by an exanthem (a rough, micropapular erythematous rash that spares the face, palms and soles, is not pruritic, and shows the Grozovici–Pastia sign – horizontal ecchymotic lines – in the flexural creases) and an enanthem ("flaming red" pharynx, hyperemic, enlarged tonsils with or without pultaceous exudate, the characteristic tongue changes of the lingual cycle).

Laboratory diagnosis: leukocytosis with neutrophilia, with or without eosinophilia, a marked inflammatory syndrome; throat swab culture for pathogenic flora demonstrates group A beta-hemolytic Streptococcus.

The complications of the disease are: early (hemorrhagic rash, septic shock, toxic nephritis, toxic myocarditis, etc.) and late (acute rheumatic fever – ASO titer, poststreptococcal glomerulonephritis, erythema nodosum, Henoch–Schönlein purpura).

The AHA and IDSA guidelines are concordant: penicillin remains the treatment of choice, as no resistance of S. pyogenes to penicillins has been documented. The standard regimens are: oral penicillin V for 10 days (250 mg 2–3 times daily in children, 500 mg twice daily in adolescents and adults); amoxicillin 50 mg/kg/day (maximum 1 g) once daily for 10 days – the preferred option in children for adherence; or intramuscular benzathine penicillin G as a single dose (600,000 IU below 27 kg, 1,200,000 IU above 27 kg), useful when adherence is uncertain. In allergic patients: a narrow-spectrum oral cephalosporin (if the reaction was not anaphylactic),

clindamycin or macrolides – the latter with the caveat of regionally variable resistance, which is why guidelines do not recommend them as first choice. The 10-day duration is required for eradication, not for symptom relief, which occurs within 24–48 hours.

The evidence: a meta-analysis of antibiotic interventions in suspected GAS pharyngitis shows a 70% reduction in the attack rate of acute rheumatic fever, and up to 80% for intramuscular penicillin, with one case of acute rheumatic fever prevented per 50–60 patients treated. The "classic" 3% rate comes from epidemic studies in military settings (1950s–1960s); under endemic conditions the true rate is substantially lower. This is a good example of how a figure obtained in an epidemic context comes to be cited as a universal value.

3.3.8. Acute rheumatic fever – treatment and secondary prophylaxis

The diagnosis is based on the Jones criteria as revised by the AHA in 2015, which introduced different thresholds for high-risk populations and accepts subclinical carditis detected by echocardiography. Treatment of the acute episode includes: (1) GAS eradication – a full course of penicillin, even if the throat swab is negative at the time of diagnosis; (2) anti-inflammatory therapy – salicylates or naproxen for arthritis and fever, with corticosteroids reserved for severe carditis with heart failure; (3) treatment of heart failure; (4) for Sydenham chorea, rest and, if needed, carbamazepine or valproic acid. Anti-inflammatory drugs relieve symptoms but have not been shown to alter the course of valvular heart disease.

Secondary prophylaxis is the intervention with the greatest impact: benzathine penicillin G 1,200,000 IU (600,000 IU below 27 kg) intramuscularly every 4 weeks – every 3 weeks in high-incidence areas or in patients with recurrences. Oral alternatives: penicillin V 250 mg twice daily or, in case of allergy, a macrolide.

After the acute infection, patients should be monitored with ASO titer, inflammatory markers, urinalysis with urine sediment, physical examination and ECG.

3.3.9. Acute poststreptococcal glomerulonephritis

It follows infection with nephritogenic strains, 1–2 weeks after pharyngitis or 3–6 weeks after a skin infection, with a peak between 3 and 10 years of age and a male predominance (~2:1). The reported annual incidence in resource-limited countries is approximately 9.5–28.5 cases per 100,000; in Europe it is now sporadic. Treatment is

supportive: salt and fluid restriction, loop diuretics for volume overload, antihypertensives, and treatment of the complications of hypervolemia (acute pulmonary edema, hypertensive encephalopathy). The antibiotic is given for eradication and to limit transmission, not to modify the course of the nephritis. Immunosuppression and corticosteroid pulse therapy are reserved for rapidly progressive forms with crescents on biopsy; renal biopsy is not routine but is indicated in case of diagnostic uncertainty, atypical course or rapid deterioration of renal function. Renal replacement therapy is rarely required. Short-term prognosis in children is excellent, but microscopic hematuria may persist for 1–2 years, and recent studies report persistent proteinuria and a risk of chronic kidney disease in a minority – hence the risk-stratified follow-up recommended in the standard of care published in Nephrol Dial Transplant (2025). Unlike acute rheumatic fever, no secondary prophylaxis is given – recurrences are exceptional.

3.3.10. Other poststreptococcal entities

Poststreptococcal reactive arthritis: shorter latency than in acute rheumatic fever (under 10 days), non-migratory arthritis, often of the lower limbs, with a poor response to salicylates. Management is controversial; many centers recommend antistreptococcal prophylaxis for 12 months with echocardiographic evaluation – if carditis develops, the patient is reclassified as having acute rheumatic fever and prophylaxis is continued according to the table above.

PANDAS / **PANS**: the association between streptococcal infection and the abrupt onset of obsessive-compulsive symptoms or tics remains unconfirmed by robust prospective studies and does not appear as an entity in the major infectious diseases guidelines. Prolonged antibiotic therapy or immunotherapy outside clinical trials is not recommended; a reasonable approach is standard treatment of a documented streptococcal infection and psychiatric evaluation of the symptoms.

3.3.11. Infectious mononucleosis

Infectious mononucleosis is a communicable, self-limiting infectious disease caused by the Epstein–Barr virus, characterized by fever, tonsillopharyngitis, lymphadenopathy and the presence of atypical lymphocytes in peripheral blood. Etiology and epidemiology:

Epstein–Barr virus (EBV, human herpesvirus 4) is a DNA virus of the family Herpesviridae, with tropism for B lymphocytes and the oropharyngeal epithelium. The infection is ubiquitous, with over 90% of the adult population having antibodies. The source of infection is humans, either ill or asymptomatic carriers, who shed the virus intermittently in saliva for months or years after primary infection. Transmission occurs predominantly through direct contact with saliva ("the kissing disease"), more rarely through blood transfusion or organ transplantation. The incubation period is long, 30–50 days. In countries with low socioeconomic status, primary infection occurs in childhood and is usually asymptomatic or paucisymptomatic; the classic clinical form of mononucleosis occurs mainly in adolescents and young adults (15–25 years).

Pathogenesis: after initial replication in the oropharyngeal epithelium, the virus infects B lymphocytes, which it immortalizes and activates polyclonally, with production of heterophile antibodies. The cellular immune response, dominated by cytotoxic CD8+ T lymphocytes, is responsible for the clinical manifestations and for the appearance of atypical lymphocytes (Downey cells) in peripheral blood, which are in fact activated T lymphocytes, not infected B lymphocytes. After recovery, EBV persists latently in memory B lymphocytes for life, with possible reactivations, usually asymptomatic in immunocompetent individuals.

Clinical picture: the disease begins with a prodromal period (3–5 days) manifested by fever, headache, fatigue, myalgia, sweating, loss of appetite and malaise. The full-blown stage lasts on average 2–3 weeks and is characterized by high fever (39–40 °C), acute tonsillopharyngitis, which may be pseudomembranous, follicular or erythematous, generalized lymphadenopathy, splenomegaly, hepatomegaly, a macular or maculopapular exanthem (arms, trunk, especially after administration of ampicillin or amoxicillin), and eyelid or periorbital edema.

The positive diagnosis is based on epidemiological, clinical and laboratory evidence. The patient has marked leukocytosis with lymphomonocytosis in the absence of a specific inflammatory syndrome.

Specific serological tests for diagnosis: IgM antibodies against EBV VCA (detectable in the first months of illness), IgG antibodies against EBV VCA (persist for life and are useful in assessing previous exposure). The laboratory diagnosis may be supplemented by the heterophile antibody test (the Paul–Bunnell–Hăngănuțiu reaction or rapid Monospot-type tests), positive in 85–90% of adults in weeks 2–3

of illness but frequently negative in children under 4 years of age. Anti-EBNA antibodies appear late, 6–12 weeks after onset, so their presence virtually rules out a recent primary infection. Detection of viral DNA by PCR is reserved for severe forms or immunocompromised patients. Moderate hepatocellular injury (transaminases elevated 2–5-fold) is present in most patients, even in the absence of clinical hepatomegaly.

The complications of infectious mononucleosis are: hematological (autoimmune hemolytic anemia), neurological (Guillain–Barré syndrome, Bell's facial palsy, acute myelitis, etc.), splenic rupture, upper airway obstruction, bacterial superinfections, etc.

Treatment is symptomatic; there is NO specific antiviral treatment. Antipyretics, analgesics and nonsteroidal anti-inflammatory drugs are generally given.

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CHAPTER 4
JAUNDICE SYNDROME. VIRAL HEPATITIS

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4.1. JAUNDICE SYNDROME — DEFINITION AND CLINICAL RECOGNITION

Jaundice is the yellow discoloration of the skin, sclerae and mucous membranes caused by the accumulation of bilirubin in tissues. It becomes visible when total bilirubin exceeds 2–2.5 mg/dL, i.e., approximately twice the upper limit of normal. Between 1.5 and 2 mg/dL the discoloration is seen only in the sclerae, in natural light — scleral subicterus, easily missed under the artificial lighting of hospital wards.

The order in which the signs appear is of practical value. The urine darkens before any change in the skin, so asking about urine color dates the onset of hyperbilirubinemia more accurately than the moment when the patient or family noticed the yellowing. The sclerae follow, being rich in elastin, a protein with a high affinity for bilirubin, and then the skin. Resolution occurs in the reverse order, the sclerae being the last to clear.

Bilirubin diffuses into albumin-rich fluids — ascites, transudates, cerebrospinal fluid — but is absent from saliva, tears and pancreatic juice. Edematous areas, scars and the skin of a paralyzed limb remain uncolored, because deposition depends on local perfusion.

Not every yellow skin means jaundice. In carotenemia — high intake of carrots, pumpkin, beta-carotene supplements, hypothyroidism — the color is orange, predominates on the palms, soles and nasolabial folds, and the sclerae remain white. Discoloration induced by mepacrine or by exposure to picric acid also spares the sclerae. Conversely, in a patient with severe anemia jaundice may be masked by pallor, and in a patient with hyperpigmented skin it should be sought on the sublingual mucosa and the hard palate.



Photo 1. Intense cutaneous jaundice with a greenish-earthy hue in an elderly patient. The discoloration uniformly involves the skin of the trunk; comparison with the examiner's hand shows how intense it is. A few reddish punctate lesions are also visible on the flank. The sclerae become discolored before the skin and remain the most reliable site to look for jaundice, examined in natural light.

4.2. BILIRUBIN METABOLISM

Between 250 and 350 mg of bilirubin are produced daily. Approximately 80–85% derives from the hemoglobin of senescent red blood cells destroyed by macrophages of the reticuloendothelial system, and the remainder from ineffective erythropoiesis in the bone marrow and from other hemoproteins — cytochromes, myoglobin, catalases. Iron is recycled, globin is catabolized, and the porphyrin ring is cleaved by heme oxygenase to form biliverdin, which is then reduced to bilirubin.

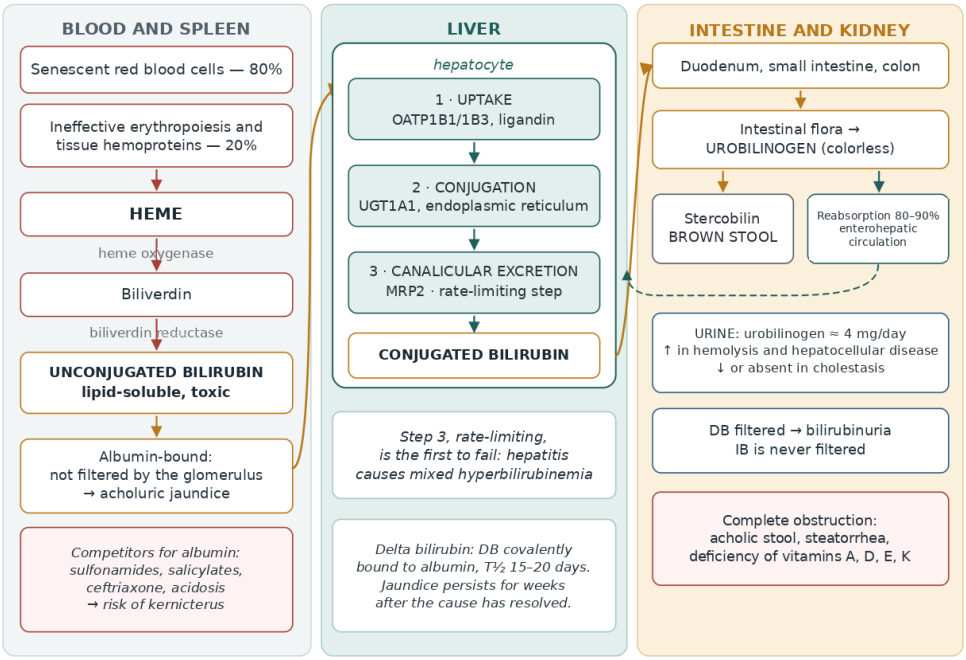


Figure 1. Bilirubin metabolism: production, plasma transport, the three hepatic steps, the enterohepatic circulation and renal elimination.

Unconjugated bilirubin is lipid-soluble and circulates bound to albumin. In this form it is not filtered by the glomerulus, which explains the absence of bile pigments from the urine in hemolytic jaundice. Binding to albumin weakens in acidosis, hypoalbuminemia and in the presence of drugs that compete for the same binding sites: salicylates, sulfonamides, ceftriaxone, free fatty acids. In the newborn, the free fraction crosses the blood–brain barrier and binds to neurons of the basal ganglia — the reason why ceftriaxone is contraindicated in the first four weeks of life. At the sinusoidal pole of the hepatocyte, bilirubin is taken up via the OATP1B1 and OATP1B3 transporters, without its albumin carrier. This is followed by conjugation with glucuronic acid by UDP-glucuronosyltransferase (UGT1A1), yielding the water-soluble mono- and diglucuronides. Canalicular excretion via the MRP2 pump is ATP-dependent and is the rate-limiting step of the whole process. The practical consequence is important: any hepatocellular injury affects excretion first and most severely, so that in hepatitis the increase in conjugated bilirubin predominates, even though uptake and conjugation are also impaired.

In the intestine, the bacterial flora deconjugates bilirubin and reduces it to urobilinogen. Part of it is oxidized to stercobilin, which gives stool its brown color; approximately 80% is reabsorbed and re-enters the enterohepatic circulation, and a small fraction reaches the urine, where it normally does not exceed 4 mg/24 h.

Delta bilirubin is the fraction covalently bound to albumin, with a half-life equal to that of albumin (approximately 20 days). It is not filtered by the kidney and explains why jaundice persists for weeks after the resolution of biliary obstruction or after recovery from hepatitis, while bilirubinuria has already disappeared. The phenomenon does not indicate persistence of the disease.

4.3. PATHOPHYSIOLOGY OF HYPERBILIRUBINEMIA

The disturbance may occur at any of the four steps. Overproduction, reduced uptake and defective conjugation cause unconjugated hyperbilirubinemia; defective canalicular excretion and biliary obstruction cause conjugated hyperbilirubinemia. The working convention is simple: jaundice is considered unconjugated when indirect bilirubin accounts for more than 80–85% of the total, and conjugated when the direct fraction exceeds 50%.

The level at which the bilirubin chain breaks is illustrated in Figure 3. In practice, pure mechanisms are rare. Hepatocellular disease interferes simultaneously with all three hepatic steps, and in cirrhosis hepatocellular jaundice may be associated with hemolysis and intrahepatic cholestasis. The classification nevertheless remains useful because it guides the first steps of the investigation.

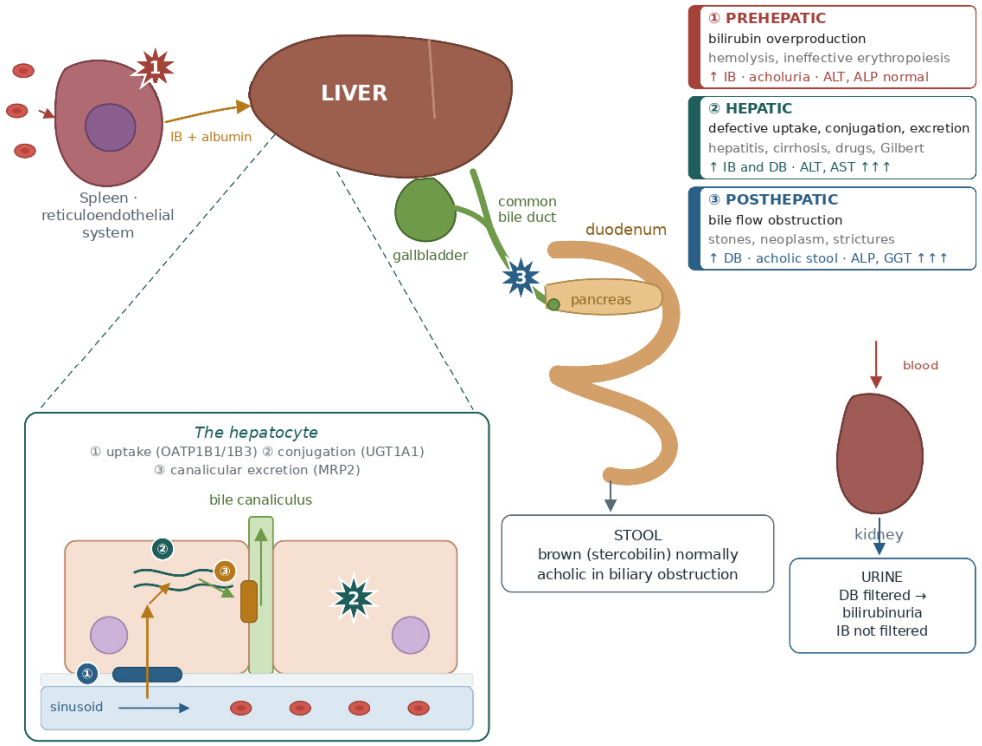


Figure 2. The three levels at which the bilirubin chain can break: 1 prehepatic overproduction, 2 hepatocellular defect, 3 biliary obstruction. Inset: the hepatocyte with the three steps and the corresponding transporters.

Table 1. Laboratory profile in the three types of jaundice

	Prehepatic (hemolytic)	Hepatocellular	Posthepatic (cholestatic)
Bilirubin	IB ↑↑, DB normal	IB ↑ and DB ↑ (mixed)	DB ↑↑, IB normal
Urinary bile pigments	Absent	present	marked
Urinary urobilinogen	↑↑	variable	↓ or absent
ALT / AST	Normal	↑↑↑ (often > 10 × ULN)	normal or moderately ↑
ALP / GGT	Normal	normal or slightly ↑	↑↑
Stool	normal / hypercholic	normal / hypocholic	acholic
Other features	anemia, reticulo-cytosis, LDH ↑, haptoglobin ↓	PI ↓, albumin ↓, signs of liver failure	pruritus, cholesterol ↑, steatorrhea

The R ratio = (ALT/ULN) ÷ (ALP/ULN) quantifies this pattern: values above 5 indicate a hepatocellular pattern, below 2 a cholestatic pattern, and between 2 and 5 a mixed pattern.

4.3.1. Clinical consequences of hyperbilirubinemia

Bilirubin itself does not cause pruritus. Cholestatic pruritus is generated by bile acids and by lysophosphatidic acid produced by autotaxin activity, which explains why its intensity does not correlate with the bilirubin level and why it responds to colestyramine, rifampicin or naltrexone, but not to measures that lower bilirubin.
In the newborn, unconjugated bilirubin above 20 mg/dL crosses the blood–brain barrier and causes irreversible damage to the basal ganglia — kernicterus. The risk increases with prematurity, hypoalbuminemia, acidosis and hemolysis. Blue-light phototherapy converts bilirubin into lumirubin, a water-soluble isomer excreted in bile without prior conjugation.
Prolonged cholestasis leads to malabsorption of fat-soluble vitamins. Vitamin K deficiency prolongs the prothrombin time, and the correction test has immediate diagnostic value: in cholestasis, parenteral administration of 10 mg of vitamin K normalizes the prothrombin index within 24–48 hours, whereas in hepatocellular failure it does not change it, because the defect lies in protein synthesis, not in absorption.

4.4. EVALUATION OF THE JAUNDICED PATIENT

Most diagnostic errors in a patient with jaundice stem from a superficial history and from excessive reliance on a single laboratory result. The correct order remains history, physical examination, then investigations.
History
Look for occupational exposure to carbon tetrachloride, trichloroethylene, vinyl chloride or to animal waste and wastewater; contact with patients with hepatitis; consumption of alcohol, paracetamol, supplements and herbal teas, or wild mushrooms; recent travel to endemic areas; blood transfusions, surgical and dental procedures, tattoos, piercings, manicures, injecting drug use; and a family history of jaundice, anemia, splenectomy or gallstones.

The mode of onset is as informative as the laboratory data. Nausea and vomiting preceding the jaundice suggest acute hepatitis or obstruction by gallstones; colicky pain and chills tip the balance toward the latter. Anorexia and progressive deterioration of general condition occur in alcoholic liver disease, chronic hepatitis and liver malignancies.

Clinical examination

The hue of the jaundice provides a diagnostic clue: flavin (pale yellow, with pallor) in hemolytic jaundice, rubin (reddish-yellow) in acute viral hepatitis, verdin (greenish) in prolonged cholestasis, owing to oxidation of bilirubin to biliverdin, and melanic or earthy in liver failure and malignancy.

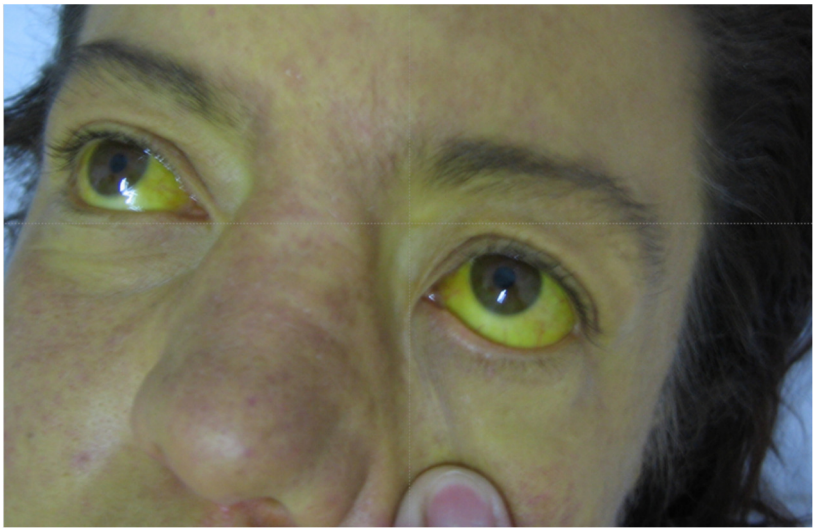


Photo 2. Intense jaundice of the sclerae and facial skin, with a reddish (rubin) hue. This is the usual appearance in acute viral hepatitis.



Photo 3. Cutaneous jaundice with a greenish (verdin) hue in the same patient, in the cholestatic form of acute hepatitis. The greenish color is due to oxidation of bilirubin to biliverdin and appears in prolonged cholestasis.

Palpation of the liver completes the picture. Hepatomegaly of parenchymatous consistency, with a rounded edge and a smooth surface, moving with respiration, occurs in acute viral hepatitis; increased consistency with a sharp edge suggests chronic hepatitis; a small, hard liver with an irregular surface indicates cirrhosis, and a hard, nodular, tender liver suggests metastases. A palpable, non-tender gallbladder in a jaundiced patient — Courvoisier–Terrier sign — points to malignant rather than gallstone obstruction. Spider nevi, palmar erythema, abdominal collateral circulation, ascites, gynecomastia, ecchymoses, splenomegaly and lymphadenopathy should be sought systematically. Jugular venous distension in a patient with hepatomegaly and ascites shifts the diagnosis toward right heart failure or constrictive pericarditis. Encephalopathy and altered consciousness in a patient with rapidly developing jaundice require urgent evaluation for acute liver failure.

Investigations

The first set includes total and fractionated bilirubin, ALT, AST, alkaline phosphatase, GGT, complete blood count with reticulocytes, prothrombin index/INR, albumin and urinalysis. Abdominal ultrasound is the first-line imaging examination and answers the decisive

question — are the bile ducts dilated? MRCP, endoscopic ultrasound and CT complete the evaluation of an obstruction, while ERCP is reserved for situations in which a therapeutic procedure is intended. Liver elastography and serum fibrosis scores have largely replaced biopsy in the evaluation of chronic hepatitis.

4.5. ACUTE VIRAL HEPATITIS

Five primarily hepatotropic viruses cause acute hepatitis in humans: HAV, HBV, HCV, HDV and HEV. All can progress to fulminant forms, and HBV, HCV, HDV and, in immunocompromised patients, HEV can become chronic. In addition, facultatively hepatotropic viruses — EBV, CMV, HSV, VZV, HHV-6, yellow fever virus, hemorrhagic fever viruses — cause hepatitis as part of a systemic infection.

Table 2. Comparative features of hepatitis viruses A–E

	HAV	HBV	HCV	HDV	HEV
Genome	RNA, Picorna-viridae	DNA, Hepadna-viridae	RNA, Flaviviridae	circular RNA, defective virus	RNA, Hepeviridae
Transmission	fecal-oral	parenteral, sexual, vertical	parenteral	As for HBV (requires HBsAg)	fecal-oral, zoonotic (G3, G4)
Incubation (days)	15–45	60–150	15–90	30–45	15–60
Chronicity	no	5–10% in adults, > 90% in newborns	50–85%	coinfection < 5%; superinfection > 80%	only in immunocompromised patients (G3)
Fulminant forms	< 0,5%	≈ 1%	exceptional	up to 20% in coinfection	20% in pregnant women in the 3rd trimester (G1, G2)
Vaccine	yes	Yes	no	indirectly, through HBV vaccination	yes (Hecolin, only in China and Pakistan)

Common clinical picture. The typical icteric form goes through three phases. The pre-icteric phase, lasting 3–7 days, is nonspecific: fatigue, anorexia, nausea, discomfort in the right upper quadrant, sometimes a flu-like syndrome, arthralgia or urticarial rashes (more common in hepatitis B, owing to immune complexes). The icteric phase is heralded by dark urine, followed by jaundice that deepens over 1–2 weeks; paradoxically, the general condition improves as the

jaundice appears in hepatitis A. The convalescent phase lasts weeks, with persistent fatigue. Anicteric and asymptomatic forms are much more common than overt ones, especially in children and in HCV infection. Warning signs requiring admission to a unit with liver transplant capability: prothrombin index below 50% or INR above 1.5, drowsiness or reversal of the sleep–wake cycle, a rapid decrease in liver size, a fall in transaminases with concomitant deepening of jaundice (enzyme–bilirubin dissociation), hypoglycemia, intractable vomiting.

4.5.1. Viral hepatitis A

HAV is a non-enveloped RNA virus of the family Picornaviridae, genus Hepatovirus. The absence of an envelope makes it resistant to gastric acidity, to chlorine in drinking water at usual concentrations, to freezing and to temperatures of 60 °C for one hour; it is inactivated by boiling, autoclaving and chlorination at high concentrations.

Transmission is fecal-oral, directly from person to person or via contaminated water and food — especially shellfish and seafood eaten raw, and vegetables and fruit washed in contaminated water. Fecal shedding is intense for several days before clinical onset and continues for up to three months after the onset of jaundice, which explains the maximal contagiousness during the pre-icteric period, when the diagnosis has not yet been made. Cases cluster in childcare settings, institutions for people with disabilities and areas with poor sanitation.

The virus has no direct cytopathic effect; hepatocyte injury is immune-mediated, through cytotoxic T lymphocytes that recognize viral antigens expressed on the hepatocyte surface. The infection never becomes chronic. Severity increases with age: in children under 6 years of age more than 70% of infections are anicteric, whereas in adults over 50 the risk of a fulminant form is significant.

Clinical picture. The mean incubation period is 21 days (range 10–45). The pre-icteric period lasts 7–14 days and most commonly takes an influenza-like form — moderate fever, headache, myalgia, asthenia — an onset pattern more characteristic of hepatitis A than of the other viral hepatitides. Added to this are anorexia, almost constant and sometimes selective, with aversion to tobacco, nausea, postprandial vomiting, bloating and intermittent pain in the epigastrium or right hypochondrium, aggravated by standing. In children the onset may mimic an acute surgical abdomen, and

operating on a patient in the early stage of acute hepatitis worsens the course of the disease. Jaundice appears after the urine has darkened, 3–7 days earlier, and the stools have become pale. The icteric period lasts 14–21 days, with jaundice proper lasting 7–10 days, mild or absent in children and more intense in the elderly. With its onset the fever subsides and the digestive symptoms abate — the clinical turning point. Persistence or worsening of nausea and vomiting after the onset of jaundice is interpreted as a sign of severity. Physical findings are scant. Hepatomegaly, present in most patients, is moderate, 2–3 cm below the costal margin, more marked in the left lobe, soft, with a rounded lower edge that is tender on palpation; it regresses slowly during convalescence. A rapid day-to-day reduction in liver span heralds massive necrosis. Soft splenomegaly is found in about one third of cases, especially in children, sometimes together with generalized lymphadenopathy.

Anicteric forms far outnumber overt ones: one icteric case for every 20–30 anicteric cases in children and one in 10 in adults. Cholestatic forms occur in 4–10% of adults, with greenish jaundice, troublesome pruritus and a duration of over 30 days, without risk of chronicity. In prolonged forms, asthenia and cytolysis persist for weeks or months. Relapses occur in 1–2% of patients, may be single or repeated, and have a good prognosis. Convalescence lasts 1–3 months, with asthenia often persisting after normalization of transaminases; during this interval physical exertion, stress and surgery may precipitate a relapse.

Diagnosis. IgM anti-HAV confirms acute infection and persists for 3–6 months. IgG anti-HAV antibodies appear during convalescence and persist for life, indicating immunity. Detection of HAV RNA in serum or feces is not performed routinely. Laboratory tests show marked cytolysis, with ALT frequently above 1000 U/L and ALT > AST.

Treatment. There is no etiological therapy; management is common to all acute viral hepatitides — A, B, C and E. Physical and mental rest is recommended, and alcohol is forbidden throughout the illness and during convalescence. The diet is adapted to digestive tolerance, with small, frequent meals of easily digestible foods, without spices and without fried fats; hydration is provided with water, tea, compote and natural fruit juices. The principles and the list of permitted foods are detailed in subchapter 5.6.

Symptomatic treatment includes antiemetics, antispasmodics and choleretics. Hepatotoxic drugs — first and foremost high-dose paracetamol — and oral contraceptives are avoided during the acute episode; vitamin C is avoided, whereas B-group vitamins are allowed.

Corticosteroid therapy is not indicated. Fulminant forms are transferred to a center with access to liver transplantation.

Prevention of hepatitis A

Non-specific measures — hand hygiene, safe drinking water, avoidance of raw shellfish in endemic areas, isolation of the case during the first week after the onset of jaundice — remain essential in outbreak control.

The available vaccines contain whole virus inactivated with formaldehyde and adsorbed on aluminum hydroxide:

- **Havrix** — 1440 ELISA units for adults, 720 units (Havrix Junior) for children aged 1–15 years;
- **Avaxim** — 160 U for adults, 80 U pediatric;
- **Vaqta** — 50 U for adults, 25 U pediatric;
- **Twinrix** — combined hepatitis A + hepatitis B vaccine (720 U HAV + 20 µg HBsAg for adults).

Vaccination schedule: two doses intramuscularly in the deltoid, at 0 and 6–12 months (Avaxim allows an interval of 6–36 months). Seroconversion occurs in over 95% of vaccinees 2–4 weeks after the first dose, and protection after the complete schedule is estimated at no less than 25 years, without boosters. In adults, Twinrix is given at 0, 1 and 6 months, with an accelerated schedule of 0, 7 and 21 days plus a booster at 12 months, useful before urgent departure to an endemic area.

Vaccination is indicated for travelers to endemic areas, sewage and food-service workers, men who have sex with men, drug users, patients with chronic liver disease and those with clotting disorders treated with plasma-derived products. After exposure, susceptible contacts receive the vaccine within 14 days; standard immunoglobulin (0.02 mL/kg IM) is reserved for infants under 12 months, immunocompromised persons, patients with chronic liver disease and those with contraindications to the vaccine.

4.5.2. Viral hepatitis B

HBV is a partially double-stranded DNA virus of the family Hepadnaviridae. The complete infectious particle (Dane particle) measures 42 nm and comprises the envelope bearing HBsAg, the nucleocapsid with HBcAg, the DNA polymerase with reverse transcriptase activity and the circular genome. Ten genotypes, A–J, have been described; genotype D predominates in Romania and is known for its poor response to interferon.

The element that accounts for the current incurability of the infection is covalently closed circular DNA (cccDNA), which persists in the hepatocyte nucleus as a minichromosome, is not affected by nucleos(t)ide analogs and constitutes the reservoir from which the infection can reactivate at any time under immunosuppression. For this reason the realistic therapeutic goal remains suppression of replication, while functional cure — HBsAg loss — is rarely achieved.

Transmission is parenteral, sexual and vertical. HBV is approximately 100 times more infectious than HIV and survives on surfaces for up to seven days. The risk of chronicity depends decisively on age at infection: over 90% in newborns of HBsAg-positive mothers, 20–50% in young children, 5–10% in immunocompetent adults.

Clinical picture. Approximately 90% of acute HBV infections go unnoticed, being asymptomatic or anicteric, and remain undiagnosed — hence their role as a reservoir. Overt forms pass through the same stages as hepatitis A, but each stage is longer.

The mean incubation period is 60–90 days (range 45–180). The pre-icteric period lasts 1–2 weeks and has two almost characteristic onset patterns. The pseudorheumatic syndrome consists of fixed, symmetrical arthralgia or arthritis of the small joints of the hands or the large joints of the limbs, without laboratory evidence of inflammation — the expression of immune complex deposition in the synovium. The cutaneous syndrome manifests as an urticarial rash in persons without an atopic background, more rarely a morbilliform, scarlatiniform or purpuric rash, due to immune complexes deposited in the walls of small dermal vessels. In children, Gianotti-Crosti papular acrodermatitis has been described, with a rash on the limbs, lymphadenopathy and hepatosplenomegaly. The influenza-like onset, common in hepatitis A, is rare here. Jaundice develops more slowly, is more intense and frequently lasts more than three weeks, often with an undulating course; cholestatic forms are more frequent than in hepatitis A. Convalescence lasts 3–6 months. Nine out of ten immunocompetent adults recover, with normalization of ALT, disappearance of HBsAg and appearance of anti-HBs at a protective titer; the rest progress to chronic infection. Fulminant forms occur in approximately 1% of cases.

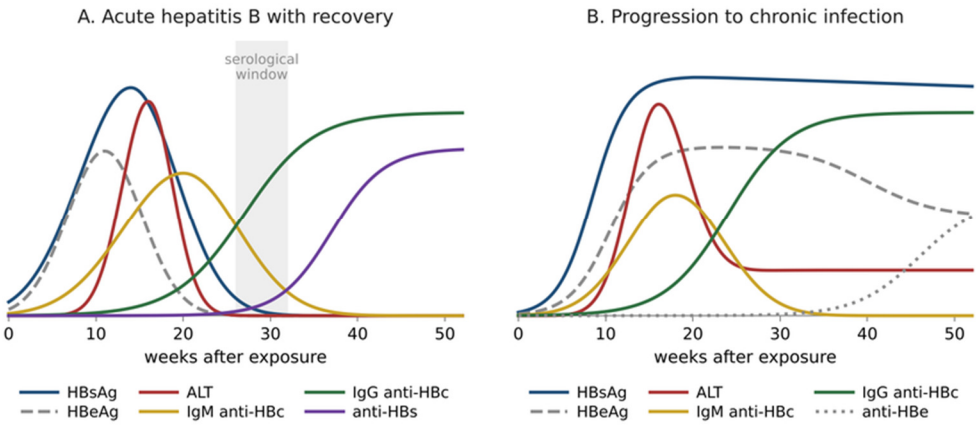


Figure 3. Kinetics of serological markers in HBV infection: A — acute hepatitis with recovery; B — progression to chronic infection.

Interpretation of markers. HBsAg is the first to appear, 1–10 weeks after exposure, and persists beyond 6 months in chronic infection. IgM anti-HBc antibodies appear with the clinical onset and are the marker of acute infection; they remain the only detectable marker during the serological window, the interval between the disappearance of HBsAg and the appearance of anti-HBs. Anti-HBs indicate immunity, either post-infectious — associated with total anti-HBc — or post-vaccination, when anti-HBc are absent. HBeAg indicates active replication; precore mutants do not express it, although replication continues, which is why HBV DNA is the only reliable indicator of replication.

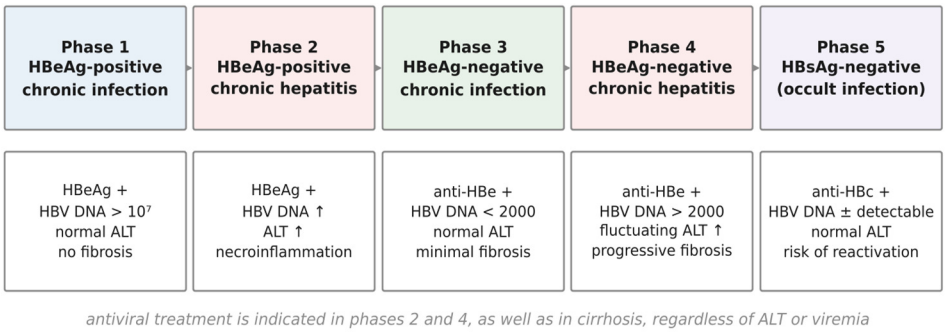


Figure 4. Phases of chronic HBV infection (HBV DNA values expressed in IU/mL).

Treatment of acute hepatitis B

In Romania, acute hepatitis B is a disease subject to mandatory named notification and mandatory hospitalization in an infectious diseases ward. The hygiene and dietary measures are those described for acute hepatitis A: physical and mental rest, abstinence from alcohol, a diet adapted to digestive tolerance, adequate hydration, and symptomatic treatment with antiemetics, antispasmodics and choleretics. Hepatotoxic drugs and vitamin C are avoided; B-group vitamins are allowed.
Common forms are not treated with antivirals: early suppression of replication would shorten the exposure of the immune system to viral antigens and could increase the risk of chronicity. Corticosteroid therapy is contraindicated in acute hepatitis B, because the immunosuppression it induces stimulates viral replication and worsens the prognosis.
Fulminant forms benefit from antiviral treatment with nucleos(t)ide analogs, which inhibit viral replication, together with pathogenetic and symptomatic intensive care measures: cerebral dehydrating agents — mannitol, diuretics — for cerebral edema; a non-absorbable antibiotic (rifaximin), lactulose, high enemas and a low-protein diet for hyperammonemia; 10% glucose infusions and vitamin B1 for hypoglycemia; fresh frozen plasma, blood and hemostatic agents for coagulation disorders; fluid and electrolyte rebalancing, treatment of circulatory collapse and monitoring of urine output. Early corticosteroid therapy remains controversial, being recommended by some authors only in combination with antiviral therapy. Evaluation for liver transplantation is performed early.

Treatment of chronic hepatitis B

The indication for antiviral treatment is established on the basis of three criteria: the level of viral replication, the level of transaminases and the degree of hepatic necroinflammation or fibrosis. Patients with HBV DNA above 2000 IU/mL and ALT above the upper limit of normal and/or at least moderate necroinflammation or fibrosis are treated, regardless of HBeAg status, as are all patients with compensated or decompensated cirrhosis, regardless of viremia and ALT. Patients with HBV DNA above 20,000 IU/mL and ALT above twice the upper limit of normal may also be treated, regardless of fibrosis, as may those with a family history of hepatocellular carcinoma or with extrahepatic manifestations. Two drug classes with different goals are used. Immunomodulatory treatment with pegylated interferon alfa has

a fixed duration of one year and aims at definitive elimination of the virus. Nucleos(t)ide analogs — lamivudine, adefovir, entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide, telbivudine and, in HIV-HBV coinfected patients, emtricitabine — aim to control viral replication, are administered long-term and are discontinued only upon HBs seroconversion, i.e. disappearance of HBsAg with appearance of anti-HBs antibodies.

Table 3. Antiviral medication in chronic hepatitis B

Drug	Daily dose	Remarks
Entecavir (ETV)	0.5 mg PO	First line. 1 mg if lamivudine resistance is present. Taken on an empty stomach.
Tenofovir disoproxil fumarate (TDF)	245 mg PO	First line. Also active against lamivudine-resistant strains. Monitoring of renal function and bone density.
Tenofovir alafenamide (TAF)	25 mg PO	First line. Lower renal and bone toxicity; preferred in patients with reduced eGFR or osteopenia.
Lamivudine, adefovir, telbivudine	—	No longer recommended as first line: low genetic barrier and frequent resistance.
Peginterferon alfa-2a	180 µg SC/week, 48 weeks	Finite duration, no resistance. Candidates: young patients, elevated ALT, low viremia, genotype A or B. Contraindicated in decompensated cirrhosis, autoimmune diseases, severe depression, pregnancy.

Nucleos(t)ide analogs control replication but do not eliminate cccDNA; treatment is indefinite. Discontinuation may be considered in non-cirrhotic patients who have achieved HBe seroconversion and undetectable viremia, after at least 12 months of consolidation, or in HBeAg-negative patients with undetectable HBV DNA for more than three years, always with close monitoring for reactivation. HBs seroconversion is the only firm criterion for discontinuation.

Prophylaxis of reactivation. Before chemotherapy or biological therapy — particularly rituximab — all HBsAg-positive patients and all HBsAg-negative patients with positive anti-HBc must be evaluated. In high-risk patients, entecavir or tenofovir is started 2 weeks before immunosuppression and continued throughout its duration and for a further 6–12 months after its discontinuation. HBV reactivation under rituximab can be fatal.

Specific anti-HBs immunoglobulin (HBIG) provides passive protection for 3–6 months and is always given together with the first dose of vaccine, at different anatomical sites, ideally within 24 hours of exposure: 500 IU intramuscularly for unvaccinated healthcare workers with accidental exposure, 30 IU/kg for newborns of HBsAg-positive mothers, 8 IU/kg (maximum 500 IU) in hemodialysis, as well as after unprotected sexual contact with an infected person.

Recombinant vaccines contain HBsAg produced by genetic engineering in yeast and are administered intramuscularly in the deltoid (in infants, in the thigh):

- **Engerix-B** — 20 µg (adults), 10 µg (pediatric), 40 µg for dialysis and immunocompromised patients;
- **HBVaxPro** / **Recombivax HB** — 5, 10 and 40 µg;
- **Fendrix** — adjuvanted with AS04, intended for patients with renal failure, 0–1–2–6-month schedule;
- **Heplisav-B** — CpG 1018 adjuvant, two doses at 0 and 1 month, in adults over 18 years;
- **Twinrix** — combined A + B; pediatric hexavalent vaccines (Infanrix hexa, Hexacima/Hexyon, Vaxelis), in which HBsAg is coformulated with diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus and Hib.

Schedule in the National Immunization Program (Romania): the first dose of monovalent vaccine in the maternity unit, within 24 hours of birth, followed by three doses of hexavalent vaccine at 2, 4 and 11 months.

Newborns of HBsAg-positive mothers: HBIG 30 IU/kg and the first dose of vaccine within 12 hours of birth, at different anatomical sites, then subsequent doses at 1, 2 and 6 months in preterm infants or those weighing under 2000 g. Efficacy is checked at 9 months of age by measuring HBsAg and anti-HBs.

Children over 1 year, adolescents and adults: three doses, at 0–1–6 months or 0–2–6 months. Accelerated schedules: 0–1–2–12 months, with protection from 3 months, or 0–7–21 days plus a booster at 12 months for Twinrix in adults. Hemodialysis and immunocompromised patients receive a double dose (40 µg) in four administrations (0–1–2–6 months), with annual anti-HBs measurement and a booster when the titer falls below 10 IU/mL. Seroprotection (anti-HBs >10 IU/mL 1–2 months after completing the schedule) reaches 98% in term newborns, over 90% under 40 years of age and 65–75% over 60 years; diabetes, obesity, smoking,

alcohol, male sex and immunosuppression reduce it. Boosters and routine serology are no longer recommended; the titer is checked only in risk groups (healthcare workers, dialysis patients, immunocompromised persons, people with HIV, children of HBsAg-positive mothers, partners of infected persons).

4.5.3. Viral hepatitis D (delta)

HDV is a defective circular RNA virus that requires the HBsAg-bearing envelope of HBV for assembly and for entry into the hepatocyte. Delta infection therefore occurs exclusively in HBV-infected persons and represents the most severe form of chronic viral hepatitis. An estimated 5% of HBsAg carriers worldwide are coinfected.
Simultaneous HBV + HDV coinfection produces an often biphasic acute hepatitis, with a risk of a fulminant form of up to 20% but with chronicity in less than 5%, because resolution of the B infection also entails the disappearance of HDV. Superinfection of a chronic HBsAg carrier is much more serious: it becomes chronic in over 80% of cases, accelerates fibrosis and shortens the interval to cirrhosis and hepatocellular carcinoma.

Clinical picture. The two modes of infection can also be distinguished clinically. Coinfection produces an acute hepatitis that at first sight is indistinguishable from ordinary hepatitis B, but in some patients jaundice and cytolysis follow a biphasic course, with two peaks separated by several days or weeks, corresponding to the successive replication of the two viruses. The risk of a fulminant form is much higher than in hepatitis B alone. The subsequent course follows that of the B infection: resolution of acute hepatitis B, marked by the appearance of anti-HBs, also entails the elimination of HDV.
Superinfection presents differently. In a chronic HBsAg carrier, known or unknown, a distinct acute hepatitis develops: marked asthenia, jaundice, sometimes decompensation of previously silent liver disease. The picture may be mistaken for a spontaneous exacerbation of hepatitis B or for toxic hepatitis. The laboratory clue is a rise in ALT accompanied by a fall in HBV DNA, because HDV inhibits replication of the helper virus. In immunocompromised patients, particularly in HIV coinfection, this inhibition may be absent and the two viruses replicate simultaneously.

Every HBsAg-positive patient must be tested at least once for anti-HDV antibodies, ideally by automatic reflex testing. In those with positive anti-HDV, HDV RNA is determined by PCR to confirm active infection. A sudden worsening of stable chronic hepatitis B, with rising ALT and falling HBV DNA, suggests delta superinfection until proven otherwise.

Treatment. Bulevirtide, a synthetic lipopeptide that mimics the preS1 domain of HBsAg and blocks the NTCP receptor, is the first-line treatment of compensated chronic hepatitis D: 2 mg subcutaneously daily, as monotherapy or in combination with peginterferon. At 48 weeks, approximately half of patients achieve a virological and biochemical response. The optimal duration has not been established; treatment is continued as long as there is benefit, and discontinuation exposes patients to severe flares of hepatitis D and B. Pegylated interferon alfa-2a, 180 µg subcutaneously weekly for 48 weeks, remains the alternative, alone or combined with bulevirtide. The sustained response after discontinuation does not exceed 25–30%, with frequent late relapses. Entecavir and tenofovir have no activity against HDV but are added when HBV DNA exceeds 2,000 IU/mL or in the presence of cirrhosis.
Prevention. There is no HDV vaccine. Hepatitis B vaccination fully protects susceptible persons but offers no benefit to chronic HBsAg carriers, for whom the only protection remains avoidance of parenteral and sexual exposure.

4.5.4. Viral hepatitis C

HCV is a single-stranded RNA virus of the family Flaviviridae, with eight genotypes and numerous subtypes. Its high genetic variability, a consequence of the lack of proofreading activity of the RNA polymerase, explains the circulation of the virus as quasispecies and the absence of a vaccine. In Romania genotype 1b clearly predominates, accounting for over 90% of cases, which is why pretreatment genotyping is no longer routinely required. Transmission is predominantly parenteral: injection drug use, medical procedures with inadequately sterilized instruments, transfusions before the introduction of donor screening in 1992, hemodialysis, tattooing and piercing under improper conditions. Sexual transmission is rare in stable heterosexual couples, but significant among men who have sex with men, particularly in the context of HIV coinfection and

traumatic intercourse. Vertical transmission occurs in 4–8% of cases, a percentage that doubles in HIV coinfection.
Acute hepatitis C is asymptomatic in 70–80% of cases, which explains why most patients present only at the chronic stage. Spontaneous clearance occurs in 15–45% of those infected, more frequently in young women, in those with icteric forms and in carriers of the IL28B CC genotype. The rest develop chronic infection, defined by persistence of HCV RNA beyond 6 months, with slow progression to fibrosis; after 20–30 years, 15–30% develop cirrhosis.

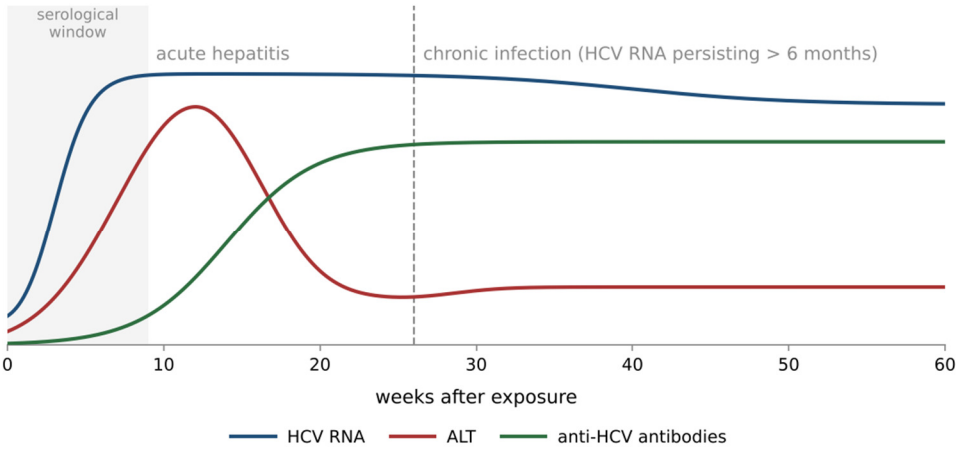


Figure 5. Kinetics of markers in HCV infection and progression to chronicity.

Clinical picture. Acute hepatitis C is the most subtle of the viral hepatitides. The incubation period is 15–90 days, about one month on average, and most infections remain asymptomatic and anicteric, although ALT may exceed the upper limit of normal ten- to twentyfold. Diagnosis in the acute phase is made almost exclusively in systematically monitored persons: injection drug users, healthcare workers after accidental exposure, contacts of a known case.
In overt forms the pre-icteric period is short, about one week, and jaundice is prolonged and follows an undulating course, in parallel with cytolysis. The icteric form, however, has a better prognosis: spontaneous clearance is more frequent in these patients than in those with silent infection. Fulminant forms are exceptional.
Chronic hepatitis C, in turn, remains asymptomatic in most patients for years or decades. When complaints are present, asthenia predominates — non-specific, but sometimes sufficient to prompt a laboratory work-up that uncovers cytolysis. The first clinical signs may

appear only at the stage of cirrhosis, and in patients with extrahepatic manifestations the hepatic picture recedes entirely into the background.

Extrahepatic manifestations are frequent and may dominate the picture: mixed cryoglobulinemia with purpura, arthralgia and peripheral neuropathy, membranoproliferative glomerulonephritis, B-cell non-Hodgkin lymphoma, porphyria cutanea tarda, lichen planus, autoimmune thyroiditis, sicca syndrome, insulin resistance and type 2 diabetes mellitus.

Diagnosis. Screening is performed with anti-HCV antibodies, which appear 4–10 weeks after infection. A positive result indicates contact with the virus, not active infection, and mandates HCV RNA testing. In immunocompromised and dialysis patients serology may be falsely negative, so when infection is suspected, molecular testing is performed directly. Fibrosis is assessed by elastography (FibroScan) or serum scores (FibroTest, FIB-4, APRI).

Direct-acting antiviral treatment

The goal of treatment is cure of the infection, defined as undetectable HCV RNA 12 weeks after the end of therapy. Direct-acting antivirals (DAAs) target key proteins of viral replication: the NS3/4A protease, the NS5A protein and the NS5B polymerase. Combining two molecules with different mechanisms and targets increases antiviral efficacy and reduces the risk of resistance mutations.

Treatment is oral, lasts 8–12 weeks and achieves a virological cure rate of over 95%. Most current regimens consist of a single tablet per day, which considerably increases adherence and lowers the risk of resistance; adverse effects are usually limited to asthenia and mild headache. All patients with chronic HCV infection currently have access to treatment, regardless of the degree of fibrosis. In acute hepatitis C the treatment regimens are identical to those used in chronic infection. The World Health Organization has set the goal of eliminating HCV infection as a public health problem by 2030.

Table 4. Direct-acting antiviral regimens

Combination	Administration	Duration	Indications and remarks
Sofosbuvir/ velpatasvir (Epclusa)	1 tab/day, PO	12 weeks	Pangenotypic (genotypes 1–6), first line. Ribavirin is added in decompensated cirrhosis.
Glecaprevir/ pibrentasvir (Maviret)	3 tab/day, with food	8–16 weeks	Pangenotypic, first line. 8 weeks in treatment-naive patients without cirrhosis; 12 weeks in compensated cirrhosis; 16 weeks in those who have failed previous treatment. Contraindicated in decompensated cirrhosis (Child B/C).
Sofosbuvir/ ledipasvir (Harvoni)	1 tab/day, PO	12 weeks	Genotypes 1, 4, 5 and 6 only.
Grazoprevir/ elbasvir (Zepatier)	1 tab/day, PO	12 weeks	Genotypes 1b and 4 only, in the absence of decompensated cirrhosis.
Ombitasvir/ paritaprevir/ ritonavir ± dasabuvir (Viekirax/Exviera)	PO, daily	12 weeks	Regimen from previous national protocols, now replaced by pangenotypic combinations.
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)	1 tab/day, PO	12 weeks	Retreatment after failure of a previous DAA regimen.

Interactions that must be checked before initiation: amiodarone combined with sofosbuvir may cause severe bradycardia and is contraindicated; enzyme inducers (rifampicin, carbamazepine, phenytoin, St. John's wort) lower DAA concentrations; statins require dose reduction or temporary discontinuation; ethinylestradiol is contraindicated with glecaprevir/pibrentasvir; proton pump inhibitors reduce the absorption of ledipasvir.

Protease inhibitors (glecaprevir, voxilaprevir, grazoprevir) are contraindicated in Child-Pugh B and C decompensated cirrhosis.

Response is assessed by measuring HCV RNA 12 weeks after the end of treatment. Virological cure does not eliminate the risk of

hepatocellular carcinoma in patients who already had cirrhosis or advanced fibrosis (F3–F4): in these patients ultrasound surveillance every six months continues indefinitely. Reinfection remains possible, which is why persons with ongoing exposure require periodic testing.
Prevention. There is no vaccine. Prevention relies on screening of blood and organ donors, the use of single-use equipment, needle and syringe exchange and opioid substitution programs, universal precautions in healthcare facilities and treatment of infected persons, which reduces the reservoir of infection.

4.5.5. Viral hepatitis E

HEV is a non-enveloped RNA virus of the family Hepeviridae, with four genotypes pathogenic for humans that behave very differently. Genotypes 1 and 2 have an exclusively human reservoir, are waterborne and cause large epidemics in South and Southeast Asia, Africa and Central America. Genotypes 3 and 4 are zoonotic, with reservoirs in domestic pigs, wild boar and deer; they are transmitted through consumption of undercooked meat — raw cured sausages, pork liver, game — and are widespread in Europe, including Romania, where seroprevalence exceeds 20% in some studies.
The infection is usually asymptomatic or self-limiting. Two situations, however, are serious. The first is pregnancy: in the third trimester, infection with genotypes 1 and 2 progresses to a fulminant form in up to 20% of pregnant women, with high maternal and fetal mortality. The second is immunosuppression — organ transplant recipients, patients receiving chemotherapy, advanced HIV infection — in which genotype 3 becomes chronic in approximately 60% of cases and can cause cirrhosis within 2–3 years.
Clinical picture. The incubation period is 15–60 days. Asymptomatic forms clearly predominate, regardless of genotype. When the disease is overt, the onset is more florid than in the other viral hepatitides: fever, myalgia, nausea and marked asthenia, followed by jaundice, abdominal pain and hepatomegaly, with elevated ALT. Fever at onset, more consistent here than in hepatitis A or B, may point to the diagnosis in a jaundiced patient returning from an endemic area or after eating undercooked pork or game.
Genotypes 1 and 2 cause mild, self-limiting forms without risk of chronicity — except in pregnant women in the third trimester. Genotypes 3 and 4 remain silent in immunocompetent persons, being symptomatic in only 5–10% of those infected. Patients with pre-

existing chronic liver disease, on the other hand, develop severe forms, up to acute-on-chronic liver failure. In immunocompromised patients chronic infection is usually asymptomatic or manifests only as asthenia and persistent cytolysis, which explains its late diagnosis, sometimes directly at the stage of advanced fibrosis.
Extrahepatic manifestations have also been described: Guillain-Barré syndrome, neuralgic amyotrophy (Parsonage-Turner syndrome), meningoencephalitis, glomerulonephritis, acute pancreatitis.
Diagnosis. IgM anti-HEV indicates acute infection; in immunocompromised patients serology may remain negative, so the diagnosis is made by detecting HEV RNA in serum or feces. Chronicity is defined by persistence of HEV RNA beyond 3 months.
Treatment. Mild and moderate forms resolve spontaneously with supportive treatment. Oral ribavirin remains reserved for severe forms and for decompensation of chronic liver disease, on a weak evidence base. In immunocompromised patients, in whom the infection may become chronic, the first step is reduction of immunosuppression — one third of transplant recipients thereby clear the virus. If HEV RNA persists at three months, ribavirin is given for 12 weeks, with doses adjusted to renal function and hematological tolerance; at the end of treatment the virus is sought in serum and stool, and persistence in either prolongs treatment to six months. Peginterferon alfa remains the salvage option in non-responding liver transplant recipients, but is contraindicated in kidney, pancreas, heart and lung transplant recipients because of the risk of acute rejection. Ribavirin is contraindicated in pregnancy; pregnant women with severe forms (genotypes 1 and 2) are admitted to intensive care, with rapid access to liver transplantation.
Prevention. Non-specific: safe drinking water, avoidance of undercooked pork and game (core temperature of at least 71 °C for 20 minutes), precautions for pregnant women traveling to endemic areas.

4.5.6. Diet in acute hepatitis

No diet shortens acute viral hepatitis and no food hastens the normalization of transaminases. Nutrition covers the energy needs of the regenerating liver and must be tolerated by a patient with nausea and loss of appetite. The risk in the first days is not excess fat but insufficient intake: a patient who does not eat enters catabolism, and hypoglycemia is a sign of severity. An intake of 30–35 kcal/kg/day and

1–1.2 g protein/kg/day is recommended, with carbohydrates as the main energy source; protein restriction is considered only transiently, in hepatic encephalopathy.
Alcohol is forbidden throughout the illness and during convalescence — for one year from onset in the practice of Romanian clinics, for a minimum of six months after normalization of transaminases, and permanently in those with superimposed chronic hepatitis B or C.

Table 5. Foods permitted and to be avoided in acute hepatitis

Category	Permitted	To avoid
Soups and sour soups	Vegetable and cereal-based soups, cream of vegetable soups, skimmed chicken or beef soups, sour soups made with borș (fermented bran) and boiled meatballs	Fatty soups, sour soups thickened with sour cream, cream soups made with roux
Meat	Beef, veal, chicken, turkey — lean, boiled, braised or grilled; lean, lightly salted ham	Pork, lamb, mutton, goose, duck, game; smoked meats, pastrami, cold cuts and sausages; mititei (grilled minced-meat rolls), sarmale (stuffed cabbage rolls), stuffed peppers, fried minced meat; offal (brain, kidneys, drob — lamb offal loaf)
Fish	Lean fish — pike-perch, pike, tench, trout, chub, barbel, cod, hake — poached or grilled	Fatty fish (carp, catfish, beluga, Russian sturgeon, sterlet), salted, smoked, fried or canned fish, fish roe, marinated fish, shellfish
Milk and dairy products	Fresh milk or buttermilk, yogurt, fresh unripened cheese (caș), whey cheese (urdă), desalted telemea; fresh cottage cheese, 300–400 g/day	Sour cream, whipped cream, fatty and fermented cheeses — burduf, cașcaval, processed cheese, Trappist, Swiss-type cheese
Eggs	Soft-boiled or poached Romanian-style (cooked in water, with fresh butter added at the end), at most two per week	Hard-boiled, omelet, fried in lard or oil, dishes made with raw egg yolk
Fats	Fresh butter and vegetable oils (sunflower, olive, corn) added raw, at the end; maximum 40–50 g/day	Lard, bacon fat, tallow, margarine; any fried or overheated fat

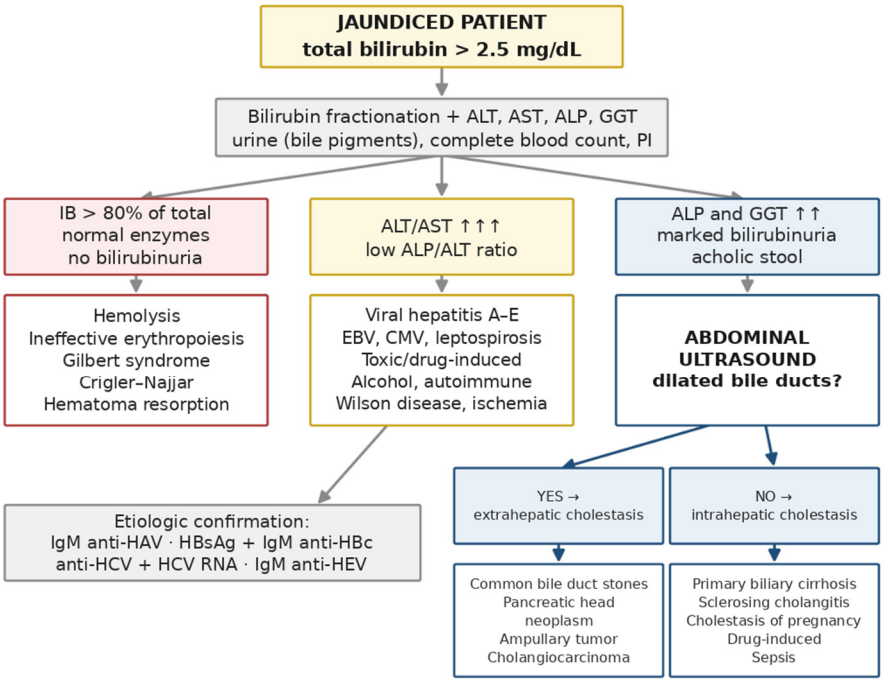
Category	Permitted	To avoid
Cereal products and bread	Rice, semolina, well-cooked pasta, puddings, cottage cheese dumplings (papanași), cereals, biscuits; stale or toasted white bread	Brown bread and fresh bread, leavened doughs, puff pastry, croissants, savory meat pastries, salted pastry sticks
Vegetables	Boiled or baked potatoes, carrots, beetroot, zucchini, spinach, nettles, lettuce, green peas, cauliflower, bell peppers, tomatoes — as purées, sautés, salads dressed with raw oil and lemon juice	Cabbage, onions, garlic, cucumbers, kohlrabi, black radish, eggplant, mushrooms, French fries; dried legumes — beans, peas, lentils, broad beans
Fruit	Apples, pears, apricots, peaches, plums, grapes, raspberries, strawberries, melon, bananas; natural juices and compotes	Walnuts, hazelnuts, almonds, peanuts, pistachios, seeds; figs, dates
Sweets	Honey, jam, marmalade, plum butter (magiun), jellies, Turkish delight, meringues, egg-white foam; semolina or rice puddings, apple or cottage cheese tarts and pies, compotes	Chocolate, cocoa, ice cream, buttercreams or creams rich in egg yolk, doughnuts, crêpes, puff pastries, rich cakes
Seasonings and sauces	Parsley, dill, lovage, tarragon, thyme, bay leaf, caraway, celery; vanilla and lemon zest in desserts; souring with lemon juice, citric acid or mild fruit vinegar; dietetic sauces — white sauce, tomato sauce, vegetable sauce	Black pepper, hot peppers, hot paprika, mustard, horseradish, ketchup, strong vinegar; roux, fried onions, mayonnaise, sour cream–based sauces
Beverages	Water, mint, linden or cherry-stem tea, compote, natural fruit juices, lemonade, orangeade, weak coffee	Any alcoholic beverage, including beer and wine; very cold drinks, cocoa

The recommendations in the table apply to the acute phase and the first weeks of convalescence. They do not replace the nutritional assessment of patients with severe forms, in whom caloric and protein intake is calculated individually.

4.6. DIFFERENTIAL DIAGNOSIS OF JAUNDICE SYNDROME

The first decision when faced with jaundice is not etiological but one of orientation: is the jaundice hepatocellular, cholestatic or hemolytic? Does the patient need a surgical or a medical service? Are there signs of liver failure or sepsis requiring intensive care? The algorithm in Figure 15 starts from bilirubin fractionation and the enzyme profile.

Figure 6. Algorithm for diagnostic orientation in jaundice syndrome.



4.6.1. Jaundice due to unconjugated hyperbilirubinemia

Hemolysis produces a moderate, lemon-yellow (flavin) jaundice — bilirubin rarely exceeds 5 mg/dL if the liver is normal — with anemia, reticulocytosis, elevated LDH, decreased haptoglobin and a positive Coombs test in autoimmune forms. The urine is dark due to hemoglobinuria, not bilirubinuria: bile pigments are absent from the urine, a detail that often settles the diagnosis at the bedside. Infectious causes of hemolysis worth remembering: malaria, Clostridium perfringens sepsis, Mycoplasma pneumoniae infection via cold agglutinins and primaquine-induced hemolysis in patients with G6PD deficiency. Resorption of large hematomas, extensive

pulmonary infarcts and massive transfusions also overload the conjugating capacity.

Gilbert syndrome affects 5–8% of the population and is the most common cause of unconjugated jaundice in young adults. UGT1A1 activity is reduced to about 30% of normal; bilirubin, usually below 4 mg/dL, rises with prolonged fasting, exertion, fever, stress or alcohol consumption. Liver enzymes and blood count are normal and the liver appears normal on ultrasound — no further investigation or treatment is required. Recognizing the syndrome spares the patient repeated investigations. It does, however, have one practical consequence: patients with Gilbert syndrome metabolize irinotecan and atazanavir more slowly.

Crigler-Najjar syndrome is rare: type I, with complete enzyme deficiency, causes neonatal kernicterus and requires phototherapy and liver transplantation; type II, with partial deficiency, responds to phenobarbital. Dubin-Johnson and Rotor syndromes are benign inherited conjugated hyperbilirubinemias, due to a defect in canalicular excretion and in storage, respectively, without progression to liver disease.

4.6.2. Jaundice of infectious causes other than hepatitis A–E

Leptospirosis is the main differential diagnosis of febrile acute hepatitis. Suggestive features are contact with water or soil contaminated with rodent urine, abrupt onset with high fever and chills, intense myalgia — especially in the calves, almost characteristic — subconjunctival hemorrhages, meningeal syndrome and renal involvement. Unlike in viral hepatitis, cytolysis is modest (ALT rarely above 200 U/L), whereas bilirubin may reach very high levels, and leukocytosis with neutrophilia, elevated ESR, raised creatinine and thrombocytopenia complete the picture. Weil syndrome combines jaundice, acute kidney injury and hemorrhagic diathesis. Treatment with penicillin G or ceftriaxone is started on clinical suspicion, without waiting for serological confirmation.

Infectious mononucleosis causes cytolysis in more than 80% of patients but jaundice in fewer than 10%. Pseudomembranous tonsillitis, cervical lymphadenopathy, splenomegaly, lymphocytosis with atypical lymphocytes and anti-VCA IgM establish the diagnosis. A rash appearing after ampicillin administration is a classic clue. Primary cytomegalovirus infection produces a similar picture without tonsillitis; in immunocompromised patients it may cause severe hepatitis.

Sepsis-associated hepatitis occurs in debilitated patients who are catheterized, have undergone surgery or have been transferred from intensive care. The jaundice is predominantly cholestatic, disproportionate to the modest cytolysis, and is accompanied by multiple organ dysfunction. Blood culture is the decisive test. Other infectious causes to keep in mind: liver abscess (pyogenic or amebic), acute cholangitis (Charcot's triad: right upper quadrant pain, fever with chills, jaundice), hepatic tuberculosis, yellow fever and the other viral hemorrhagic fevers in patients returning from endemic areas, and secondary syphilis.

4.6.3. Non-infectious hepatocellular jaundice

Drug-induced toxic hepatitis remains the leading cause of acute liver failure in developed countries. Paracetamol causes centrilobular necrosis with transaminases in the thousands and requires N-acetylcysteine, which is all the more effective the earlier it is given. Other frequently implicated drugs: amoxicillin-clavulanate (the most common cause of drug-induced cholestatic hepatitis), isoniazid, rifampicin, nonsteroidal anti-inflammatory drugs, azole antifungals, methotrexate, amiodarone and anabolic steroids. Dietary supplements and herbal teas must be asked about explicitly, because patients do not report them spontaneously.

Amanita phalloides poisoning follows a characteristic pattern: a latency of 6–24 hours, then a severe gastroenteritic syndrome, a deceptive period of improvement and, at 3–5 days, fulminant liver failure.

Acute alcoholic hepatitis is recognized by an AST/ALT ratio above 2, with absolute values rarely exceeding 300 U/L, markedly elevated GGT, tender hepatomegaly, and fever and leukocytosis that may mimic an infection. Autoimmune hepatitis occurs predominantly in women, with hypergammaglobulinemia and antinuclear, anti-smooth muscle or anti-LKM1 antibodies, and responds to corticosteroid therapy. In any patient under 40 years of age with hepatitis of undetermined cause, Wilson disease must be excluded: low ceruloplasmin, increased urinary copper, Kayser-Fleischer ring, Coombs-negative hemolytic anemia and paradoxically low alkaline phosphatase.

4.6.4. Cholestatic and obstructive jaundice

Extrahepatic cholestasis is recognized on ultrasound by dilation of the bile ducts (Figures 9 and 10). Common bile duct stones present abruptly, after a heavy meal, with biliary colic, fever and chills; the jaundice fluctuates. Carcinoma of the head of the pancreas causes progressive jaundice, initially painless, with intense pruritus, weight loss and a palpable gallbladder. Ampullary tumors (of the ampulla of Vater) present with fluctuating jaundice associated with anemia due to occult gastrointestinal bleeding. Other causes: cholangiocarcinoma, postoperative strictures, chronic pancreatitis of the pancreatic head, a hydatid cyst ruptured into the bile ducts, migrated ascarids, and bulky lymph nodes in the hepatic hilum.
Intrahepatic cholestasis does not dilate the bile ducts. Primary biliary cirrhosis occurs in middle-aged women, with pruritus preceding jaundice by months or years, markedly elevated alkaline phosphatase and positive antimitochondrial antibodies. Primary sclerosing cholangitis is frequently associated with ulcerative colitis and is diagnosed by MR cholangiography. Intrahepatic cholestasis of pregnancy, in the third trimester, presents with generalized pruritus and elevated serum bile acids and carries a fetal risk. To these are added drug-induced cholestasis, cholestasis associated with total parenteral nutrition, postoperative cholestasis and hepatic infiltrative disorders (lymphoma, amyloidosis, sarcoidosis, metastases).

4.7. CLINICAL CASES

Case 1 – Acute HCV hepatitis after occupational exposure, diagnosed in the serological window period

PRESENTATION

A 41-year-old woman, a nurse at a hemodialysis center. Seven weeks earlier she had sustained an accidental needlestick injury with a puncture needle used on a patient known to have chronic HCV infection, HCV RNA positive. The exposure was reported and recorded. At baseline: anti-HCV antibodies negative, ALT 24 U/L, HBsAg negative, anti-HBs 180 mIU/mL after complete vaccination, HIV negative. She now presents with marked fatigue, loss of appetite, nausea and dark urine, of four days' duration. She denies alcohol use, hepatotoxic drugs or supplements.

PHYSICAL EXAMINATION

Afebrile, moderately impaired general condition, body mass index 23. Scleral subicterus, without overt skin jaundice. Liver palpable 2 cm below the costal margin, tender, of elastic consistency; spleen not palpable. No ascites, no collateral circulation, no flapping tremor. BP 115/70 mmHg.

Presumptive diagnosis

Documented percutaneous exposure to a source with positive HCV viremia, followed seven weeks later by a picture of acute hepatitis, points to acute HCV infection even before any testing. The pitfall is that anti-HCV antibodies may still be negative: they usually become positive between weeks 8 and 12 after infection, and at clinical onset only 50–70% of patients have them. A negative result in this interval excludes nothing, and waiting for seroconversion needlessly delays the diagnosis. Confirmation is by HCV RNA.

Acute icteric hepatitis in a person with documented percutaneous occupational exposure to HCV. Suspected acute HCV infection in the serological window period.

LABORATORY INVESTIGATIONS

Laboratory tests and viral markers (day of admission)

Parameter	Value	Reference / interpretation
ALT / AST	1120 / 640 U/L	< 41 / < 40 — severe cytolysis, ALT/AST ratio above 1
Total / direct bilirubin	4.8 / 3.6 mg/dL	< 1.2 / < 0.3 — hepatocellular jaundice
GGT / alkaline phosphatase	180 / 160 U/L	< 60 / 40–130 — mild cholestasis
INR / albumin	1.10 / 4.2 g/dL	0.8–1.2 / 3.5–5.2 — preserved synthetic function
Complete blood count	within normal limits	no cytopenias
Anti-HCV Ab	negative	does not exclude acute infection — window period
HCV RNA	1.8 × 10□ IU/mL	confirms current HCV infection
HCV genotype	1b	guides the antiviral regimen
Anti-HAV IgM, anti-HEV IgM	negative	exclude enterically transmitted hepatitis
HBsAg, anti-HBc IgM	negative	exclude acute hepatitis B
HIV, VDRL, ANA, ASMA	negative	exclude coinfection and autoimmune hepatitis
Abdominal ultrasound	homogeneous liver, non-dilated bile ducts	excludes obstructive jaundice

At week 11 after exposure, anti-HCV antibodies became positive, documenting seroconversion in a person with a negative baseline test — the most robust criterion of acute infection.

Final diagnosis and differential diagnosis

Acute icteric HCV hepatitis, genotype 1b, acquired through percutaneous occupational exposure. Documented anti-HCV seroconversion.

Acute hepatitis B has the same routes of transmission and an overlapping picture, but is excluded by negative HBsAg and anti-HBc IgM in a person with protective post-vaccination anti-HBs. Hepatitis A and E are ruled out serologically. Toxic and drug-induced hepatitis are ruled out by the history, and autoimmune hepatitis by negative autoantibodies. Obstructive jaundice is excluded by ultrasound.

TREATMENT, COURSE AND DISTINCTIVE FEATURES

There is no post-exposure prophylaxis for HCV: neither a vaccine nor immunoglobulins, and antivirals are not given preventively. The correct management after a needlestick injury is monitoring, with HCV RNA at 2–6 weeks and antibodies at 12 and 24 weeks. Once acute infection is confirmed, current guidelines recommend treatment with direct-acting antivirals. The patient received glecaprevir/pibrentasvir for 8 weeks, with undetectable HCV RNA 12 weeks after the end of treatment.

Spontaneous clearance occurs in 20–50% of patients; the rest progress to chronic infection. Anti-HCV antibodies persist after recovery but are not neutralizing and do not protect against reinfection — a point that matters for healthcare workers, in whom exposure may recur. The distinctive feature of this case is that a negative anti-HCV antibody result at clinical onset could have closed the investigation; the diagnosis was made possible only by HCV RNA testing.

QUESTIONS

1. Anti-HCV antibodies: a. appear late, usually 8–12 weeks after infection; b. are neutralizing; c. a negative result excludes acute infection; d. persist after recovery without protecting against reinfection; e. IgM antibodies do not distinguish the acute from the chronic phase.

2. The diagnosis of acute HCV hepatitis is supported by: a. positive anti-HCV IgM; b. detectable HCV RNA in an immunocompetent person with negative anti-HCV antibodies; c. documented anti-HCV

seroconversion; d. ALT above ten times the upper limit of normal; e. scleral and skin jaundice.
3. After a percutaneous occupational exposure to HCV: a. specific immunoglobulins are administered; b. antivirals are given prophylactically; c. HCV RNA is monitored at 2–6 weeks; d. confirmed acute infection is treated with direct-acting antivirals; e. the spontaneous clearance rate is approximately 20%.
Answers. 1 — a, d, e. 2 — b, c; the transaminase level and jaundice reflect severity, not etiology. 3 — c, d, e; for HCV there is neither a vaccine nor effective immunoglobulins, and antivirals are not given prophylactically but only after the infection is confirmed.

Case 2 — Severe acute viral hepatitis A in an adult

PRESENTATION AND EPIDEMIOLOGICAL INVESTIGATION

A 42-year-old man from an urban area, with no known liver disease, unvaccinated against hepatitis A or B. The illness began six days before admission with fever of 38.2 °C, headache, myalgia, nausea, vomiting and epigastric pain — a flu-like and gastrointestinal prodrome, without arthralgia. On day five dark urine and pale stools appeared, and on day six jaundice. The fever subsided with the onset of jaundice, a course characteristic of hepatitis A and useful in differentiating it from a bacterial infection.
The history revealed consumption of well water at a rural household during a visit made four weeks before onset — an interval compatible with the 15–50-day incubation period — and a member of the extended family who had had jaundice six weeks earlier without being investigated. Persistent history-taking also revealed occasional use of "legal highs" (new psychoactive substances), the last intake ten days before onset. This information is hard to obtain, because patients do not volunteer it, and it changes the interpretation of the hepatic picture: any superimposed hepatotoxin aggravates necrosis and accounts for part of the severity.

The incidence of hepatitis A in Romania has declined considerably in recent decades, and cases occur sporadically or in small outbreaks. The reduced viral circulation has a side effect, however: ever larger cohorts of adults reach middle age without natural immunity. In children the infection is often anicteric; in adults icteric forms are the rule, and severe forms occur above the age of 50 or in pre-existing liver disease.

PHYSICAL EXAMINATION AND PRESUMPTIVE DIAGNOSIS

Impaired general condition, afebrile on admission, marked loss of appetite, intense scleral and skin jaundice, coated tongue, congested pharynx. Abdomen soft, tender in the right upper quadrant, with the liver palpable 2 cm below the costal margin, of elastic consistency. Spleen not palpable, no ascites and no collateral circulation. Conscious, oriented, no flapping tremor. BP 118/72 mmHg, HR 76/min, very dark urine, hypocholic stools.

The picture is that of acute hepatitis with hepatocellular jaundice. The absence of colicky pain, fever with chills and completely acholic stools makes obstructive jaundice unlikely from the clinical examination alone. The etiological work-up follows two lines: a viral one, in which the fecal-orally transmitted hepatitides, A and E, are the most likely, and a toxic one, supported by the use of new psychoactive substances. The two are not mutually exclusive. It is a common mistake to look for a single cause of severe acute hepatitis, when a hepatotoxin superimposed on a viral infection explains the severity better than either of them alone.

Severe acute icteric hepatitis of undetermined etiology — viral or toxic, possibly of mixed cause.

LABORATORY DIAGNOSIS

Positive anti-HAV IgM, together with anti-HAV IgG, establishes the diagnosis. Negative HBsAg and anti-HBc IgM and IgG exclude HBV infection; negative anti-HBs indicates a susceptible patient. Also negative: anti-HCV antibodies and HCV RNA, anti-HEV IgM, CMV IgM and EBV VCA IgM, HIV, ANA, ASMA and anti-LKM1, with normal total serum IgG (1180 mg/dL) and normal ceruloplasmin (28 mg/dL). The urine toxicology screen was positive for synthetic cathinones, confirming the reported exposure. Anti-HAV IgM antibodies persist for 3–6 months, occasionally up to 12; a positive result must always be interpreted in the clinical context, otherwise a patient who had hepatitis A a few months earlier may be misdiagnosed.

Ultrasound: slightly enlarged liver (right lobe 16.2 cm), homogeneous structure, non-dilated bile ducts, gallbladder with walls thickened to 6 mm, without stones. The wall thickening reflects the edema of acute hepatitis and hypoalbuminemia, not cholecystitis; misinterpreted, it may lead to an unnecessary cholecystectomy at a time when surgery is contraindicated by coagulopathy.

Time course of laboratory tests

Parameter	Reference	Day 1	Day 5	Day 12	Day 22
ALT / AST (U/L)	< 41 / < 40	3260 / 2480	2980 / 2140	840 / 520	148 / 96
Total / direct bilirubin (mg/dL)	< 1,2 / < 0,3	14,8 / 11,2	**19,4 / 14,6**	9,2 / 6,8	2,8 / 1,9
GGT / alkaline phosphatase (U/L)	< 60 / 40–130	148 / 210	162 / 226	118 / 168	74 / 124
PT (sec) / INR	11–14 / 0,8–1,2	17,2 / 1,44	**18,4 / 1,58**	15,1 / 1,22	13,2 / 1,06
Prothrombin index (%)	> 70	**56**	**50**	72	92
Albumin (g/dL)	3,5–5,2	3,6	3,3	3,5	3,9
Blood ammonia (µmol/L)	15–45	42	56	38	30

The definition of the severe form rests on coagulation, not on the degree of cytolysis: a prothrombin index below 60% or an INR above 1.4, in the absence of encephalopathy. The patient met this criterion from admission, and the functional nadir was reached on day five.

Final diagnosis, treatment and course

Severe acute icteric viral hepatitis A. Superimposed hepatotoxicity due to use of new psychoactive substances (synthetic cathinones).

Hepatitis E should be actively sought and was excluded: transmission is also fecal-oral, the picture is overlapping, and the zoonotic genotype 3 causes sporadic cases in adults in Europe that are mistaken for hepatitis A — with the practical difference that hepatitis E becomes chronic in immunocompromised patients. Toxic hepatitis is not excluded here; rather, it coexists. Wilson disease, which must be ruled out in any severe acute hepatitis under the age of 45, is excluded by normal ceruloplasmin in the absence of hemolysis and of a Kayser-Fleischer ring.

Treatment is supportive, because there is no etiological therapy. Intravenous 10% glucose, arginine, an antiemetic and a gastric antisecretory agent were administered. The key element of management is not pharmacological: stopping any further hepatotoxic exposure, explaining the mechanism and assessing substance use. The coagulopathy required daily monitoring of the prothrombin index and level of consciousness during the first ten days; neither vitamin K nor plasma was given routinely, in the absence of bleeding, because correcting the INR removes the only available prognostic indicator. Severe dietary restriction is not justified — the diet is adapted to

gastrointestinal tolerance, and the strict prohibition concerns alcohol and hepatotoxic drugs for at least three months.
Hepatitis A never becomes chronic, and its risk is confined to the acute phase: prolonged cholestatic forms in 5–10% of adults, relapsing biphasic forms in about 10%, and acute liver failure in less than 1%. The patient was discharged on day 22, with transaminases still four times the upper limit of normal; complete normalization occurs within 4–8 weeks. The patient was informed of the possibility of a biochemical relapse and scheduled for follow-up at 4 and 12 weeks. Family contacts were vaccinated, and the well was reported to the public health directorate. The vaccine, with over 95% protection after two doses, is recommended for patients with chronic liver disease, travelers to endemic areas and contacts; post-exposure, it protects immunocompetent persons under 40 years of age if given within the first 14 days, whereas above this age and in immunocompromised persons immunoglobulins are preferred.

QUESTIONS

1. Acute viral hepatitis A is characterized by: a. fecal-oral transmission; b. progression to chronicity in approximately 10% of cases; c. positive diagnosis by anti-HAV IgM; d. more severe forms in adults than in children; e. a chronic carrier state after recovery.
2. Factors associated with severe forms of acute hepatitis A are: a. age over 50 years; b. pre-existing chronic liver disease; c. female sex; d. use of hepatotoxic substances; e. coinfection with HBV or HCV.
3. Prophylaxis of acute hepatitis A includes: a. vaccination; b. post-exposure immunoglobulins in immunocompromised persons and those over 40 years of age; c. post-exposure vaccination within the first 14 days in immunocompetent persons; d. prophylactic antiviral treatment; e. water and food hygiene measures.

Answers. 1 — a, c, d. The infection does not become chronic and leaves no chronic carriers. In children it is often asymptomatic or anicteric, in adults icteric forms are the rule, and severity increases with age. 2 — a, b, d, e. Sex is not a recognized risk factor. 3 — a, b, c, e. There is no antiviral treatment for HAV, and hence no antiviral prophylaxis.

Case 3 — Acute hepatitis B or exacerbation of chronic hepatitis B?

PRESENTATION

A 64-year-old woman from a rural area, of modest socioeconomic status, presented with marked fatigue, loss of appetite, right upper

quadrant pain and intense scleral and skin jaundice. Symptoms had begun four days earlier with fatigue, loss of appetite and pain, the jaundice appearing subsequently — the classic sequence of acute hepatitis. The interval, however, is short: four days from the first symptoms to intense jaundice, with a bilirubin of 16 mg/dL at the first measurement, suggests an abrupt insult rather than an insidious course. The history identified no risk factors for parenteral transmission in recent months, no contact with a case of acute hepatitis and no use of hepatotoxic agents.

What is missing from the recent history is found in the past medical history. Diffuse large B-cell non-Hodgkin lymphoma, diagnosed 14 months earlier, treated with six cycles of R-CHOP — a regimen that includes rituximab, an anti-CD20 monoclonal antibody — and in complete remission; splenectomy in the same year for splenic involvement. No documented screening for HBsAg or total anti-HBc antibodies before chemotherapy. These lines radically change the interpretation of the case: acute hepatitis B appearing one year after rituximab in a splenectomized patient immediately raises the question of reactivation of chronic HBV infection, a scenario with completely different prognosis and management.

Physical examination and presumptive diagnosis

Weight 48 kg, height 1.58 m. Impaired general condition, afebrile, intensely jaundiced skin and sclerae, coated tongue, persistent skin fold, poorly developed subcutaneous tissue. BP 100/70 mmHg, HR 92/min. Abdomen painful spontaneously and on palpation in the right upper quadrant, liver palpable 1 cm below the costal margin, of increased consistency, post-splenectomy scar, no clinically detectable ascites on admission. Conscious, oriented, no flapping tremor.

Cytolysis of almost 70 times the upper limit of normal narrows the diagnosis to three possibilities — viral, toxic or ischemic hepatitis — and the last is ruled out in the absence of a hemodynamic event. Dehydration of approximately 7% requires correction before any interpretation of renal tests. The oncological history, however, changes the hierarchy: the profound and prolonged B-cell immunosuppression after rituximab means that the first hypothesis is no longer newly acquired acute infection but reactivation of a chronic infection. Hepatic involvement by lymphoma also enters the discussion, even though remission is documented.

Jaundice syndrome due to acute hepatitis of undetermined etiology, most likely viral, in a patient with non-Hodgkin lymphoma treated with R-CHOP and splenectomy. Acute dehydration syndrome, 7%.

LABORATORY DIAGNOSIS

HBsAg positive, HBeAg negative with anti-HBe positive, anti-HBc IgM positive at low titer, anti-HBc IgG positive at high titer, anti-HBs negative, HBV DNA 4,162,142 copies/mL (approximately 8.3 × 10□ IU/mL). Excluded serologically: HCV coinfection, delta superinfection, hepatitis A and E, CMV and EBV, HIV and autoimmune hepatitis. Electrophoresis showed albumin 49.6% (calculated albumin 2.85 g/dL) and γ-globulins 20.3%, with incipient beta-gamma bridging. Hypoalbuminemia with hypergammaglobulinemia cannot develop in a four-day acute hepatitis — the half-life of albumin is approximately 20 days. A cholinesterase of 5432 U/L, at the lower limit of normal, points the same way. Ultrasound on admission: liver of homogeneous structure, caudate lobe 24 mm, portal vein 9 mm, common bile duct 4 mm, gallbladder with markedly thickened walls, splenectomy.

It is the combination of negative HBeAg with positive anti-HBe, high-titer anti-HBc IgG and a viremia of millions of copies/mL that solves the case. This is not the pattern of a recent acute infection, in which HBeAg appears early and anti-HBe only in the resolution phase, as viremia declines — exactly the profile seen in the first case. Here we have the reverse, namely the pattern of a chronic infection with a precore mutant, in exacerbation. Anti-HBc IgM does not contradict this interpretation: its titer also rises in severe flares of reactivation, and the difference in titer between acute infection and exacerbation is indicative, not decisive.

Acute hepatitis B or reactivation of chronic infection?

Feature	Acute hepatitis B	Reactivation of chronic infection	In this patient
HBeAg / anti-HBe	HBeAg +, anti-HBe –	HBeAg –, anti-HBe + (precore mutant)	**HBeAg –, anti-HBe +**
Anti-HBc IgM	positive, high titer	positive, low titer or negative	**positive, low titer**
Anti-HBc IgG	positive, low titer	positive, high titer	**high titer**
Albumin	normal at onset	decreased	**2.85 g/dL**
Electrophoresis	normal	hypergammaglobulinemia	**γ 20,3%**
Cholinesterase	normal	decreased	**borderline, then 2787 U/L**
Immunosuppressive context	absent	present	**R-CHOP 14 months earlier**
Liver stiffness	< 7 kPa after remission	persistently increased	**44.3 kPa**

Elastography on day 26 showed 44.3 kPa, a value corresponding to stage F4, which cannot develop within four weeks. Measurement during a flare of cytolysis, however, overestimates stiffness because of edema and inflammation, so the value needed to be reassessed after normalization of the tests. In this patient, ascites appearing on day 16, the protein profile and the low cholinesterase supported cirrhosis independently of elastography. The Child-Pugh score on admission was 9 points (class B), with a MELD score of approximately 21.

FINAL DIAGNOSIS, TREATMENT AND COURSE

HBV-related liver cirrhosis with vascular decompensation (ascites). Post-chemotherapy HBV reactivation. Acute-on-chronic liver failure. Acute dehydration syndrome, 7%. Mixed anemia. Non-Hodgkin lymphoma in remission. Splenectomy.

Hepatic involvement by lymphoma remains unlikely, given the documented remission, the homogeneous liver structure and the absence of lymphadenopathy; a liver biopsy would have settled an equivocal picture but was contraindicated by coagulopathy. Post-chemotherapy drug-induced hepatitis would have occurred during cytostatic treatment, not a year later. Obstructive jaundice is ruled out by the non-dilated bile ducts, despite the thickened gallbladder walls, which here reflect edema due to hypoalbuminemia.

Fluid and electrolyte replacement corrected the dehydration within the first 48 hours. Treatment included empirical antibiotic coverage with amoxicillin and clavulanic acid, arginine, thioctic acid, L-ornithine-L-aspartate, rifaximin, hemostatics, lactulose and fresh frozen plasma on days 17–19. Ascites required spironolactone combined with furosemide, at a 100:40 mg ratio, with progressive tapering to monotherapy. Antiviral treatment was started with entecavir 0.5 mg daily.

Time course of laboratory tests and the relapse in month five

Parameter	Reference	Day 1	Day 16	Day 35	Month 5
ALT / AST (U/L)	< 41 / < 40	2570 / 2246	1089 / 1093	195 / 334	**1485 / 2089**
AST/ALT ratio	—	0,87	1,00	1,72	**1,41**
Total / direct bilirubin (mg/dL)	< 1,2 / < 0,3	19,99 / 15,02	21,9 / 18,8	4,06 / 2,4	10,8 / 6,8
Prothrombin index (%) / INR	> 70 / 0,8–1,2	64,7 / 1,32	49 / 1,60	68,3 / 1,28	**39,3 / 1,84**
Cholinesterase (U/L)	5300–12900	5432	**2787**	3487	—
Total protein (g/dL) / fibrinogen (g/L)	6,4–8,3 / 2–4	5,75 / 1,72	4,16 / 1,5	5,5 / 1,42	—
Hemoglobin (g/dL)	12–16	12,5	9,9	9,7	9,7
HBV DNA (copies/mL)	—	4,16 × 10□	—	—	**14,38 × 10□**

Cytolysis decreased steadily under treatment, but synthetic function did not recover — cholinesterase and total protein remained low at discharge, which is to be expected in cirrhosis, not in resolved acute hepatitis. The patient then discontinued lamivudine. The second episode was more severe than the first: viremia increased three-and-a-half-fold, ascites recurred, the prothrombin index fell to 39.3%, and the AST/ALT ratio reversed, the signature of cirrhosis. The Child-Pugh score reached 11 points, class C. Stopping the antiviral in a cirrhotic patient may trigger a reactivation flare with decompensation and death; in these patients treatment is indefinite, regardless of how long viremia has been undetectable.

The key teaching point of the case, however, lies in prophylaxis. Every patient undergoing chemotherapy or immunosuppressive treatment must be tested for HBsAg and total anti-HBc antibodies before initiation. Reactivation also occurs in occult infection, with negative HBsAg and positive anti-HBc, and the risk is highest with rituximab. Those who test positive receive prophylaxis with entecavir or tenofovir, started before the first course and continued for at least 12 months after the end of immunosuppression, or 18 months after rituximab. In this patient, two serological tests would have changed the outcome.

QUESTIONS

1. In a patient with positive HBsAg, positive anti-HBc IgM, negative HBeAg, positive anti-HBe and an HBV DNA of 4,000,000 copies/mL, the most likely diagnosis is: a. acute viral hepatitis B; b. HBeAg-

negative chronic hepatitis B with a precore mutant, in exacerbation; c. inactive chronic carrier; d. resolved infection; e. HBV reactivation.
2. Reactivation of HBV infection under immunosuppression: a. occurs only in HBsAg-positive patients; b. may also occur in those who are HBsAg negative and total anti-HBc positive; c. carries the highest risk with anti-CD20 monoclonal antibodies; d. is prevented by serological screening before starting therapy; e. requires prophylaxis with entecavir or tenofovir.
3. Discontinuation of antiviral treatment in a patient with hepatitis B cirrhosis: a. has no consequences if viremia was undetectable; b. may cause a reactivation flare; c. may precipitate hepatic decompensation; d. may be fatal; e. may be done after 12 months of undetectable viremia.

Answers. 1 — b, e. The combination of negative HBeAg and positive anti-HBe with a viremia of millions of copies/mL defines chronic infection with a precore mutant, which replicates intensely without producing HBeAg. Anti-HBc IgM also becomes positive in severe exacerbations, so it does not on its own support an acute infection. 2 — b, c, d, e. Reactivation also occurs in occult infection, especially with rituximab. 3 — b, c, d. In a cirrhotic patient treatment is not discontinued, regardless of the duration of undetectable viremia.

Case 4 – Chronic HBV and HDV hepatitis in a patient labeled as an inactive carrier

PRESENTATION

A 34-year-old man, known to be HBsAg positive for twelve years, discovered at a blood donation and followed intermittently as an inactive carrier on the basis of an HBV DNA consistently below 2,000 IU/mL. He presents with fatigue and with elevated transaminases at the last three check-ups, interpreted so far as unrelated to HBV infection. His mother is HBsAg positive, which makes vertical transmission likely. He has a tattoo done at the age of 19 in a studio without sanitary oversight. He denies alcohol, injection drug use and hepatotoxic drugs. He has never been tested for HDV.
Physical examination
Afebrile, good general condition, body mass index 24, anicteric, without spider angiomas or collateral circulation. Liver palpable 2 cm below the costal margin, of increased consistency and with a sharp

edge; spleen palpable 3 cm below the costal margin. No ascites, no flapping tremor.

PRESUMPTIVE DIAGNOSIS

Persistent cytolysis in an HBsAg-positive patient with low HBV viremia is not self-explanatory. A true inactive carrier has normal transaminases, and splenomegaly adds an argument for portal hypertension in someone considered to have no significant liver disease. Three hypotheses remain: HBeAg-negative chronic hepatitis B with a precore mutant, a non-viral cause of cytolysis and, most likely here, HDV coinfection, which inhibits HBV replication and keeps HBV DNA low despite active disease.

Chronic HBV hepatitis, active disease, with disproportionately low HBV viremia. Suspected HDV coinfection. Splenomegaly.

LABORATORY INVESTIGATIONS

Laboratory tests and viral markers

Parameter	Value	Reference / interpretation
ALT / AST	128 / 96 U/L	< 41 / < 40 — persistent cytolysis
GGT / alkaline phosphatase	112 / 138 U/L	< 60 / 40–130 — mild cholestasis
Albumin / INR	4.1 g/dL / 1.18	3.5–5.2 / 0.8–1.2 — preserved synthetic function
γ-globulins / platelets	21.4% / 94,000/µL	hypergammaglobulinemia, hypersplenism
HBsAg qualitative / quantitative	positive / 18,400 IU/mL	chronic HBV infection
HBeAg / anti-HBe / anti-HBc IgG	negative / positive / positive	HBe seroconversion, long-standing infection
HBV DNA	310 IU/mL	low viremia, disproportionate to cytolysis
Anti-HDV IgG / IgM	positive / positive	chronic HDV infection, highly active disease
HDV RNA	2.4 × 10□ copies/mL	intense HDV replication
Anti-HCV, HIV, ANA, ASMA	negative	exclude other causes of chronic hepatitis
FibroScan®	11.2 kPa	advanced fibrosis, METAVIR F3

Ultrasound showed a liver of heterogeneous structure with a slightly irregular contour, without nodules, portal vein 13 mm, spleen long

axis 15.4 cm. Upper gastrointestinal endoscopy showed no esophageal varices.

FINAL DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Chronic HBV and HDV hepatitis, active disease, advanced fibrosis (F3). Early portal hypertension with splenomegaly and thrombocytopenia.

Chronic hepatitis B with a precore mutant, the first competing hypothesis, would have been accompanied by high viremia, not 310 IU/mL. Hepatitis C is excluded serologically, autoimmune hepatitis by negative autoantibodies, and steatohepatitis and toxic hepatitis by the history and a normal body mass index. In a young patient with advanced fibrosis, Wilson disease and alpha-1 antitrypsin deficiency were ruled out.

TREATMENT, COURSE AND DISTINCTIVE FEATURES

Treatment was started with bulevirtide, an entry inhibitor that blocks the NTCP receptor, approved in the European Union for compensated hepatitis delta. Surveillance for hepatocellular carcinoma is performed every six months. Treatment may be continued for as long as the patient derives clinical, biochemical and virological benefit. Reassessment of HBV DNA every 6 months is recommended, and if viremia exceeds 2,000 IU/mL, treatment with nucleotide analogs must be added.

At 48 weeks ALT had normalized and HDV RNA had fallen by more than two logs — a favorable course, which nevertheless does not justify stopping treatment, because virological relapse is the rule. The distinctive feature of the case lies in the diagnostic delay: twelve years of follow-up as an inactive carrier, with cytolysis attributed to other causes, when the low HBV viremia was precisely the sign of HDV coinfection.

QUESTIONS

1. In a patient with positive HBsAg, persistent cytolysis and HBV DNA below 2,000 IU/mL: a. the diagnosis is inactive carrier; b. testing for HDV is mandatory; c. low viremia excludes active liver disease; d. HDV frequently inhibits HBV replication; e. assessment of the fibrosis stage is recommended.

2. HDV infection: a. requires the presence of HBsAg to infect the hepatocyte; b. can be transmitted independently of HBV; c. superinfection in a chronic HBV carrier becomes chronic in 80–90% of cases; d. is prevented by HBV vaccination; e. causes the most severe form of chronic viral hepatitis.

3. Treatment of chronic HBV and HDV hepatitis: a. is based on nucleoside analogs; b. is given with pegylated interferon alfa for at least 48 weeks; c. includes bulevirtide as an entry inhibitor; d. aims at sustained HDV RNA negativity; e. is stopped when transaminases normalize.

Answers. 1 — b, d, e. 2 — a, c, d, e; HDV is defective and is not transmitted without HBsAg, which is why HBV vaccination also prevents delta infection. 3 — b, c, d; nucleoside analogs have no effect on HDV, and normalization of transaminases is not a stopping criterion.

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CHAPTER 5

ACUTE DIARRHEAL DISEASE OF INFECTIOUS ETIOLOGY

Lecturer Talida-Georgiana Novăcescu, MD, PhD

5.1. DEFINITION AND TERMINOLOGY

Diarrhea is defined as the passage of **at least three unformed stools within 24 hours** or an increase in the number of bowel movements with a concomitant decrease in their consistency relative to the patient's usual bowel habit. In infants and young children, it is defined by a change in stool consistency relative to the age-specific norm, since an exclusively breastfed infant may physiologically pass frequent, semi-liquid stools of no pathological significance. The weight criterion — a fecal output exceeding 200 g/24 h in adults — is useful mainly in clinical research.

Duration distinguishes three entities with different etiological and therapeutic significance. **Acute diarrhea**, lasting less than 14 days, is in most cases infectious and self-limiting. **Persistent diarrhea**, lasting between 14 and 29 days, points to a parasitic infection, a protracted bacterial infection or post-infectious mucosal injury. **Chronic diarrhea**, lasting at least 30 days, primarily raises the question of differential diagnosis with inflammatory bowel disease, irritable bowel syndrome, malabsorption syndromes, gastrointestinal neoplasms and endocrine disorders, without, however, excluding an infectious etiology, especially in the immunocompromised host.

Acute diarrheal disease is therefore defined by **an increase in the volume, fluidity and frequency of bowel movements**, with a change in their macroscopic appearance — watery, mucoid, purulent, lumpy, mucopurulent and bloody, or steatorrheic. The picture is usually completed by accompanying gastrointestinal manifestations — abdominal pain, nausea, vomiting, borborygmi, bloating, tenesmus — and by systemic involvement: adynamia, loss of appetite and fever.

A second classification, useful in formulating the diagnosis, is based on **the predominantly involved digestive segment**. The following forms are thus distinguished: *acute gastritis*, dominated by nausea, vomiting and epigastric pain; *acute gastroenteritis*, in which diarrhea and diffuse colicky pain are added to these; *acute gastroenterocolitis*, in which colonic involvement is expressed by tenesmus and

mucosanguineous stools; and *acute enterocolitis*, in which gastric manifestations are absent.

The pathophysiological basis of fluid and electrolyte losses is multifactorial. Four mechanisms are involved: **increased intraluminal water content** through the formation of an inflammatory exudate, **reduced absorption** resulting from accelerated transit and shortened contact time with the mucosa, **reduced intake** due to vomiting and loss of appetite, and **increased extradigestive losses** due to fever and tachypnea. The summation of these mechanisms explains the rapid onset of dehydration even when the number of bowel movements is apparently modest.

In clinical practice, a syndromic terminology that promptly guides diagnostic reasoning is frequently used. *Food poisoning* implies the simultaneous illness of several persons who consumed the same food, with a short incubation period. *Dysenteric syndrome* comprises small-volume stools containing mucus, pus and blood, accompanied by tenesmus and colicky pain, and reflects inflammatory involvement of the colon. *Cholera-like syndrome* designates profuse, watery, "rice-water" stools, without fever, with rapid-onset and severe dehydration.

5.2. ROUTES OF TRANSMISSION AND RISK FACTORS

Transmission occurs by the fecal-oral route, directly from person to person or indirectly through contaminated water and food, hands, objects and surfaces. The infectious dose varies and accounts for differences in contagiousness: 10–100 organisms are sufficient for Shigella, Shiga toxin-producing Escherichia coli, Entamoeba histolytica and norovirus, whereas 10□–10□ organisms are required for Vibrio cholerae or enterotoxigenic Escherichia coli, which implies prior multiplication in food or water.

Risk factors for severe disease include extremes of age, protein-energy malnutrition, zinc and vitamin A deficiency, immunosuppression of any cause, hypochlorhydria (after gastrectomy or iatrogenic, due to long-term proton pump inhibitor therapy), achlorhydria, intestinal motility disorders, and occupational or behavioral exposures.

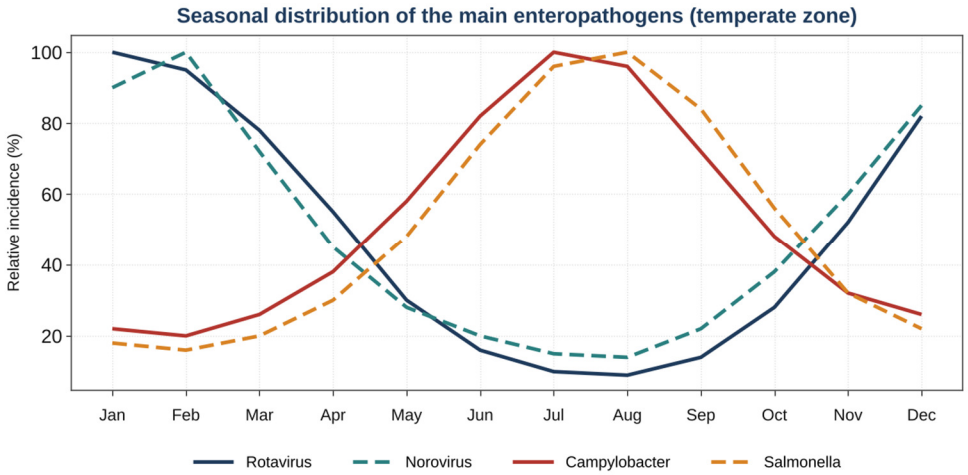


Figure 1. Seasonal distribution of the main enteropathogens in temperate regions.

Seasonality is a first-line etiological clue: viral infections predominate in the cold months, defining the "winter season" of rotavirus and norovirus, whereas infections with *Campylobacter* and *Salmonella* peak in the warm season, when food storage conditions are poorer and outdoor eating is more frequent.

In Romania, acute diarrheal diseases remain an important cause of morbidity, especially in young children and during the warm season, and food poisoning generates outbreaks reported every year to the public health directorates. The local determinants are the classic ones: unequal access to safe drinking water and sewerage in rural areas, deficiencies in food storage, and the absence of rotavirus vaccination from the national immunization program, a situation that maintains a significant burden of severe gastroenteritis in infants and young children.

Practical correlation. The epidemiological context — season, travel, foods consumed, community settings, hospitalization, recent antibiotic exposure — narrows the list of possible etiologies more effectively than the macroscopic appearance of the stools and must be systematically documented in every patient with acute diarrhea.

5.3. ETIOLOGY

The etiological agents of acute diarrheal disease are divided into viruses, bacteria and parasites, to which are added toxins preformed in food, responsible for syndromes with very early onset. In developed countries, **viral etiology clearly predominates**, accounting for 60–

70% of episodes of acute community-acquired gastroenteritis, whereas bacteria predominate in inflammatory forms, in travelers' diarrhea and in regions with poor sanitation.

Table 1. Main etiological agents of acute infectious diarrheal disease.

Category	Agents	Clinical and epidemiological features
Viruses	Rotavirus (group A), norovirus (GI, GII), sapovirus, enteric adenovirus (40, 41), astrovirus	Watery diarrhea, prominent vomiting, moderate fever; predominance in the cold season; rotavirus selectively affects infants aged 6–24 months, norovirus causes explosive outbreaks at all ages
Enterotoxigenic bacteria	Vibrio cholerae O1/O139, enterotoxigenic E. coli (ETEC), Aeromonas, Plesiomonas	Profuse watery diarrhea, without fever, with rapid dehydration; ETEC is the classic agent of travelers' diarrhea
Invasive bacteria	Shigella spp., non-typhoidal Salmonella, Campylobacter jejuni/coli, Yersinia enterocolitica, enteroinvasive E. coli	Febrile syndrome, bloody stools, tenesmus; Campylobacter is the most frequently isolated enteric bacterium in Europe
Cytotoxic bacteria	Shiga toxin-producing E. coli (STEC/EHEC, including O157:H7), Clostridioides difficile	Hemorrhagic colitis, with a risk of hemolytic uremic syndrome and toxic megacolon, respectively
Bacteria with systemic expression	Salmonella Typhi and Paratyphi, Yersinia spp.	Enteric fever: prolonged febrile syndrome, relative bradycardia, hepatosplenomegaly; diarrhea may be absent
Preformed toxins	Staphylococcus aureus, Bacillus cereus (emetic form), Clostridium botulinum	Incubation of 1–6 hours, predominantly emetic symptoms, course of a few hours, absence of fever
Parasites	Giardia duodenalis, Cryptosporidium spp., Entamoeba histolytica, Cyclospora cayetanensis, Cystoisospora belli	Prolonged incubation, protracted or recurrent course; Cryptosporidium resists standard chlorination, causing waterborne outbreaks; E. histolytica may cause amebic liver abscess
Etiologies to consider in particular settings	Vibrio parahaemolyticus, Listeria monocytogenes, Tropheryma whipplei, microsporidia	Seafood consumption, pregnancy, profound immunosuppression

In HIV-infected patients with CD4 T-lymphocyte counts below 100/mm³, the etiological spectrum widens considerably, including *Cryptosporidium*, *Cystoisospora belli*, *Cyclospora*, microsporidia, *Mycobacterium avium* complex, cytomegalovirus and non-typhoidal *Salmonella* with recurrent bacteremia. In neutropenic and transplant patients, neutropenic colitis, intestinal graft-versus-host disease and cytomegalovirus colitis must be considered.

5.4. PATHOLOGY AND PATHOPHYSIOLOGY

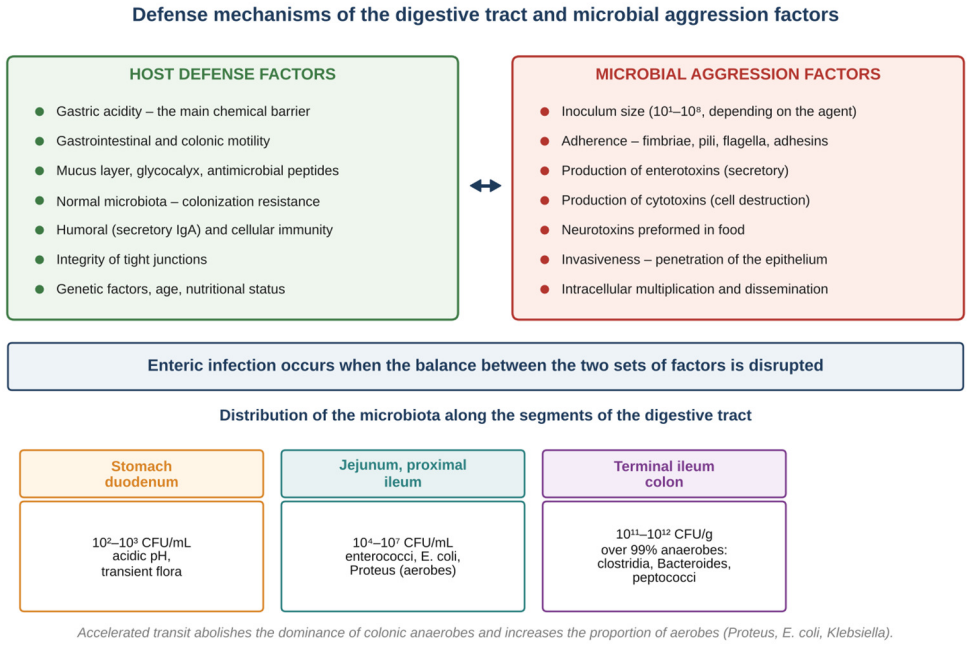


Figure 2. Balance between host defense factors and microbial aggression factors; distribution of the microbiota by segment.

5.4.1. Pathogenic classification of infectious diarrheas

From a pathogenic standpoint, three categories are distinguished, each with a characteristic clinical counterpart.

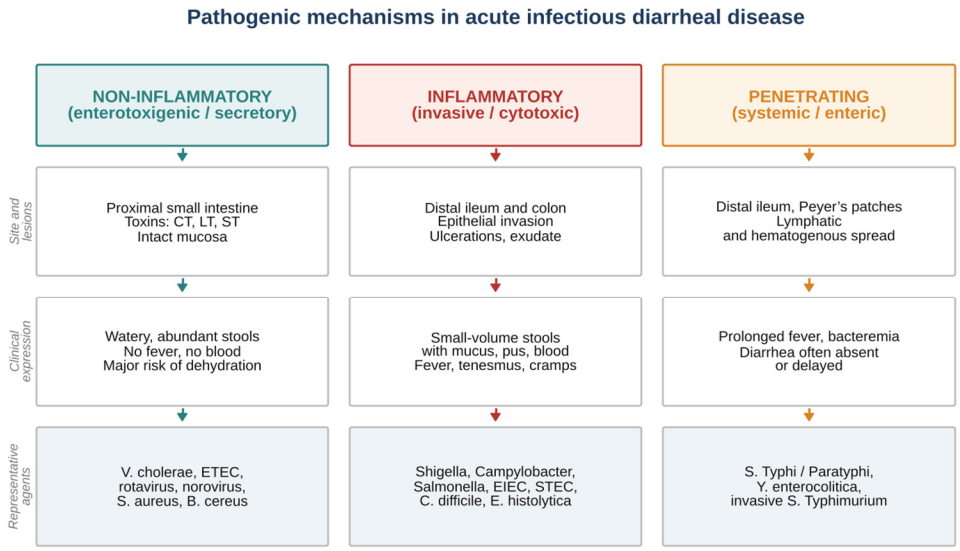


Figure 3. The three major pathogenic mechanisms and their clinical counterpart.

a) Non-inflammatory (enterotoxigenic, secretory) mechanism

The pathogen colonizes the proximal small intestine without invading the mucosa and produces enterotoxins that disrupt fluid and electrolyte transport. The prototype is *Vibrio cholerae*. Enteric viruses induce diarrhea through a mixed mechanism. Rotavirus infects mature enterocytes at the villus tips, causing villus shortening and loss of brush-border disaccharidases, with an osmotic component due to lactose malabsorption. The non-structural protein **NSP4** acts as a viral enterotoxin, mobilizing intracytoplasmic calcium and stimulating chloride secretion, while stimulation of the enteric nervous system contributes to accelerated transit.

b) Inflammatory (invasive and cytotoxic) mechanism

The pathogen invades the epithelium of the distal ileum and colon or produces cytotoxins with a lytic effect on enterocytes. *Shigella* enters through the M cells of Peyer's patches, is phagocytosed by macrophages, which it drives into apoptosis, then invades enterocytes from the basolateral side and spreads intracellularly by

actin polymerization. The result is colitis with superficial ulcerations, inflammatory exudate and hemorrhage, clinically expressed as dysenteric syndrome. *Campylobacter jejuni* and non-typhoidal *Salmonella* use partly similar invasion mechanisms, with type III secretion systems that translocate effectors into the host cell cytoplasm.

Shiga toxin-producing E. coli is a distinct entity. The bacterium does not invade the mucosa but adheres to enterocytes through "attaching and effacing" lesions and releases Shiga toxin, which binds to the globotriaosylceramide receptor Gb3, inhibits the 60S ribosomal subunit and suppresses protein synthesis, with consequent cell death. Once absorbed systemically, the same toxin damages the Gb3-rich glomerular endothelium and triggers hemolytic uremic syndrome.

Clostridioides difficile produces toxins A and B, which glucosylate and inactivate the Rho, Rac and Cdc42 proteins, leading to disorganization of the actin cytoskeleton, loss of tight junctions, apoptosis and an intense inflammatory response, morphologically expressed as pseudomembranes. The hypervirulent NAP1/BI/027 strain additionally produces binary toxin CDT and carries a deletion of the regulatory gene *tcdC*, resulting in toxin hyperproduction.

c) Penetrating (systemic) mechanism

Salmonella Typhi crosses the intestinal epithelium and is taken up by the macrophages of Peyer's patches, within which it survives and multiplies, subsequently disseminating via the lymphatic and hematogenous routes. The clinical picture is dominated by the systemic manifestations of enteric fever, diarrhea often being absent in the first week of illness or replaced by constipation.

Table 2. Main toxins involved in acute diarrheal disease and their mechanism of action.

Toxin	Agent	Molecular mechanism	Clinical consequence
Cholera toxin (CT)	V. cholerae	ADP-ribosylation of Gsα → ↑ cAMP → CFTR activation	Profuse "rice-water" watery diarrhea
Heat-labile toxin (LT)	ETEC	Mechanism identical to that of cholera toxin, of lower intensity	Travelers' diarrhea
Heat-stable toxin (ST)	ETEC	Guanylate cyclase activation → ↑ cGMP	Watery diarrhea
Shiga toxins 1 and 2	STEC, S. dysenteriae type 1	Binding to Gb3, inhibition of the 60S ribosomal subunit	Hemorrhagic colitis, hemolytic uremic syndrome
Toxins A and B	C. difficile	Glucosylation of Rho/Rac/Cdc42 proteins	Pseudomembranous colitis, toxic megacolon
NSP4	Rotavirus	Viral enterotoxin, mobilization of Ca^{2+} from intracellular stores	Secretory and osmotic diarrhea in infants
Staphylococcal enterotoxins	S. aureus	Superantigens, afferent vagal stimulation	Emetic symptoms 1–6 hours after ingestion
Cereulide	B. cereus	Preformed, heat-stable emetic toxin	Vomiting following consumption of reheated rice

Clinical correlation. The pathogenic mechanism determines the diagnostic and therapeutic approach. Secretory diarrhea occurs with an intact mucosa and results in fluid and electrolyte losses, dehydration and metabolic acidosis due to bicarbonate depletion, which are corrected by rehydration. Inflammatory diarrhea, a consequence of epithelial invasion and enterocyte cytolysis, requires etiological work-up (stool culture with antimicrobial susceptibility testing, multiplex PCR panel, Shiga toxin testing, blood cultures in febrile patients); antibiotic therapy is indicated according to the isolated agent and contraindicated in STEC infection.

5.5. CLINICAL PICTURE

5.5.1. Initial assessment

The history must systematically establish the time of onset and the course of the diarrhea, the number and appearance of stools, the presence of blood, mucus or pus, and the association of fever, vomiting, abdominal pain and tenesmus. The context is then documented: foods consumed in the preceding days and, in particular, meals shared with persons who developed similar symptoms; consumption of water from unsafe sources or of unpasteurized milk; recent travel and destination; exposure to animals, especially reptiles, poultry and farm animals; belonging to a community setting; recent hospitalization or antibiotic exposure in the last three months; presence of immunosuppression; sexual behavior.
The epidemiological criteria come down to three questions that must be asked of every patient: is this an isolated case or a collective outbreak? Has there been travel to an area endemic for diarrheal disease? Can an incriminating food or water source be identified? The source of infection may be human — the patient, the convalescent or the apparently healthy carrier — or non-human: water, food, contaminated surfaces, animal reservoirs. Transmission is predominantly digestive and indirect, through consumption of contaminated water or food, most often of animal origin, but may also be direct, from person to person, through hands and shared objects, or mediated by mechanical vectors — flies, cockroaches, rodents. Personal and food hygiene, crowding and natural disasters are the major determinants of risk.
The physical examination primarily looks for signs of severity: level of consciousness, signs of dehydration and hypoperfusion, temperature, heart rate and blood pressure measured supine and standing, and the appearance of the abdomen — distension, guarding, absent bowel sounds, suggestive of ileus or toxic megacolon. Inspection of the stool remains a simple and informative step. **Examination of the anal region and digital rectal examination are required in bloody and protracted diarrhea**, allowing identification of internal or external hemorrhoids, hemorrhoidal thrombophlebitis, anal fissures, perianal suppuration or a rectal mass, findings that may explain or complicate the picture.

The incubation period has considerable orienting value. Onset 1–6 hours after a meal, with predominantly emetic symptoms and no fever, points to a preformed toxin — staphylococcal enterotoxin or

cereulide. An interval of 8–16 hours suggests *Clostridium perfringens* or the diarrheal form of *Bacillus cereus*. An interval of 16–72 hours is compatible with most viral and bacterial infections.

Table 3. Correlation between incubation period, symptoms and food source.

Incubation period and organism	Predominant symptoms	Common food sources
1–6 hours — Staphylococcus aureus	Nausea, vomiting, diarrhea	Ham, poultry, potato or egg salad with mayonnaise, cream-filled products
1–6 hours — Bacillus cereus (emetic form)	Nausea, vomiting, diarrhea	Fried, reheated rice
8–16 hours — Clostridium perfringens	Abdominal cramps, diarrhea; vomiting is rare	Beef, poultry, legumes, gravies
8–16 hours — Bacillus cereus (diarrheal form)	Abdominal cramps, diarrhea; vomiting is rare	Meat, vegetables, dried beans, cereals
> 16 hours — Vibrio cholerae	Profuse watery diarrhea	Seafood, contaminated water
> 16 hours — enterotoxigenic E. coli	Watery diarrhea	Salad, cheese, meat, water
> 16 hours — enterohemorrhagic E. coli	Bloody diarrhea	Ground beef, grilled foods, cold cuts, unpasteurized milk, raw vegetables, apple juice
> 16 hours — Salmonella spp.	Inflammatory diarrhea, fever	Beef and poultry, eggs, dairy products
> 16 hours — Campylobacter jejuni	Inflammatory diarrhea	Poultry, unpasteurized milk
> 16 hours — Shigella spp.	Dysentery	Potato or egg salad, lettuce, raw vegetables

5.5.2. Clinical syndromes

Table 4. Clinical syndromes in acute diarrheal disease and etiological orientation.

Syndrome	Clinical features	Suggested agents	Management
Acute watery diarrhea	Abundant liquid stools, without blood, fever absent or moderate, vomiting	Rotavirus, norovirus, ETEC, V. cholerae, Cryptosporidium	Rehydration; stool culture, rotavirus and adenovirus stool antigen testing, multiplex PCR panel
Dysenteric syndrome	Small, frequent stools with mucus, pus and blood, tenesmus, colicky pain, fever	Shigella, Campylobacter, Salmonella, EIEC, E. histolytica	Stool culture with antimicrobial susceptibility testing and multiplex PCR panel, blood cultures in febrile patients; selective antibiotic therapy
Hemorrhagic colitis	Severe cramps, grossly bloody stools, often without fever	STEC/EHEC O157:H7 and non-O157	Shiga toxin testing; antibiotics and antimotility agents are contraindicated
Emetic syndrome	Vomiting 1–6 hours after a meal, mild diarrhea, no fever	S. aureus, emetic B. cereus	Symptomatic treatment; resolution within a few hours
Enteric fever	Prolonged febrile syndrome, headache, relative bradycardia, splenomegaly, rose spots	S. Typhi, S. Paratyphi	Blood cultures; systemic antibiotic therapy mandatory
Nosocomial diarrhea	Onset after ≥ 3 days of hospitalization, history of antibiotic therapy	C. difficile	C. difficile toxin A/B testing; standard stool culture is uninformative
Persistent diarrhea	Duration > 14 days, weight loss, bloating, steatorrhea	Giardia, Cryptosporidium, Cyclospora, secondary lactase deficiency	Stool ova and parasite examination on 3 samples, Giardia and Cryptosporidium antigens; reassessment of the diagnosis

5.5.3. Stool examination

Direct inspection of the stool is a classic semiological step, often neglected, yet it retains its orienting value. In infants, knowledge of what is normal is required beforehand: in the first four months of life, an exclusively breastfed infant passes 2–7 golden-yellow, acidic stools daily, with a pH of about 5, whereas an infant fed cow's milk-based formula passes 2–4 pasty stools with an alkaline pH. Consistency subsequently increases progressively, and after the age of one year the appearance approaches that of the adult.

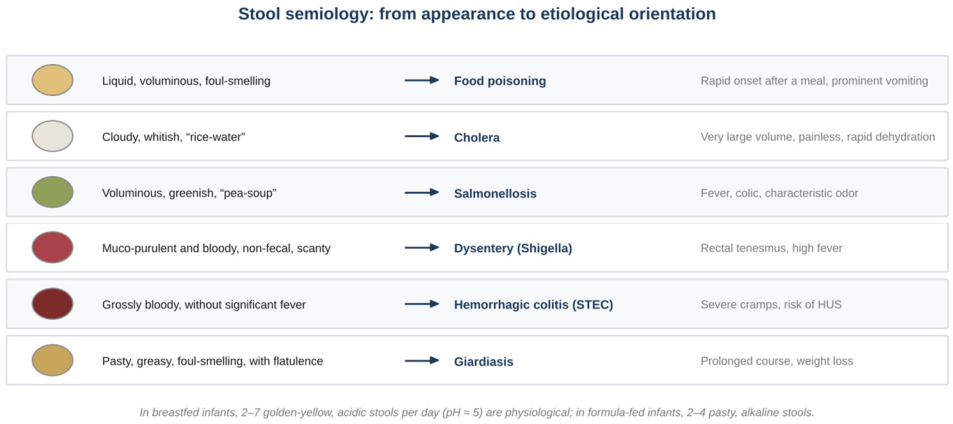


Figure 4. Stool appearance and the etiological orientation it suggests.

Several well-established correlations should be noted. A **liquid, voluminous and foul-smelling** stool suggests food poisoning. A **cloudy, whitish, "rice-water"** appearance, in large volume and painless, is characteristic of cholera. A **voluminous, greenish, "pea-soup"** stool points to salmonellosis. A **muco-purulent and bloody, non-fecal, small-volume stool accompanied by rectal tenesmus** defines dysenteric syndrome. A **pasty, greasy and foul-smelling appearance, with marked flatulence**, suggests giardiasis or a malabsorption syndrome.

5.5.4. Assessment of hydration status

Dehydration is the main determinant of immediate prognosis and must be quantified before any etiological concern. In children, the most reliable individual parameters are **prolonged capillary refill time, decreased skin turgor and an altered respiratory pattern** due to metabolic acidosis. No single sign is sufficient; a combination of several findings significantly increases accuracy. Acute weight loss, relative to the pre-illness weight, remains the reference standard.

Table 5. Clinical assessment of the degree of dehydration.

Parameter	None / minimal (< 3% adult, < 5% child)	Moderate (3–6% adult, 5–9% child)	Severe (> 6% adult, ≥ 10% child)
General condition	Alert, normal	Restless, irritable	Lethargic, obtunded, comatose
Thirst	Absent or mild	Intense, drinks eagerly	Drinks poorly or refuses fluids
Eyes	Normal	Slightly sunken	Deeply sunken, no tears
Mucous membranes	Moist	Dry	Very dry, "parchment-like"
Skin pinch	Returns immediately	Returns in less than 2 seconds	Returns in more than 2 seconds
Pulse	Normal	Tachycardic, low volume	Thready or impalpable
Blood pressure	Normal	Normal, with orthostatic hypotension	Hypotension, shock
Capillary refill	Under 2 seconds	2–3 seconds	Over 3 seconds, cold, mottled extremities
Urine output	Normal	Reduced, concentrated urine	Oliguria or anuria for more than 6 hours
Breathing	Normal	Slightly rapid	Deep, Kussmaul-type (acidosis)

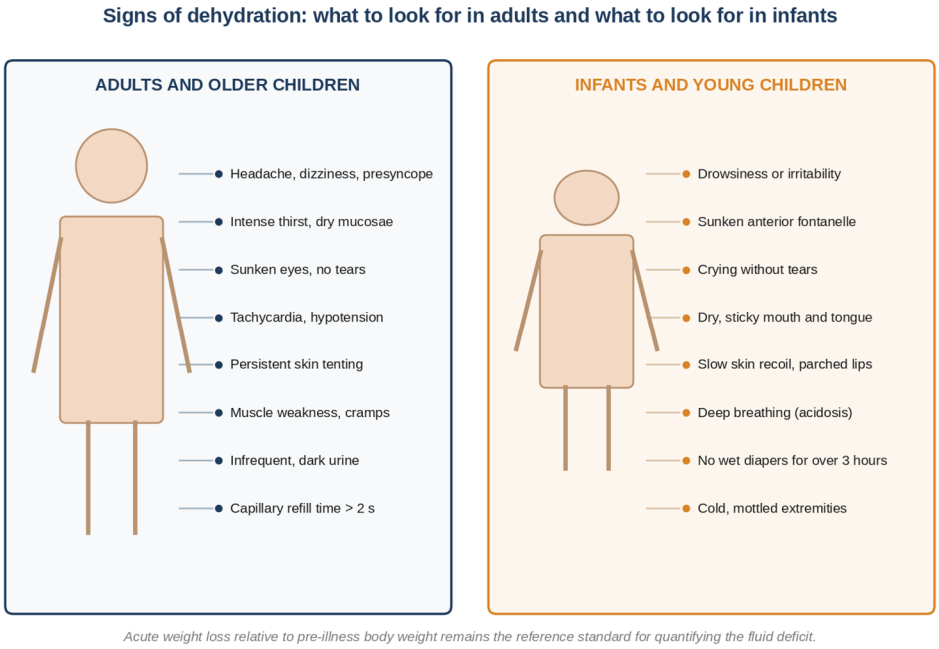


Figure 5. Signs of dehydration in adults and infants; the features to look for differ substantially with age.

Classic grading. The Romanian school frequently uses a three-step grading related to body weight: mild dehydration (≈ 5%) — thirst, dry mouth, dry skin and mucous membranes, reduced sweating and urine output, slight weight loss, normal blood pressure; moderate dehydration (≈ 8%) — intense thirst, orthostatic hypotension, persistent skin fold, enophthalmos, sunken fontanelle in infants, muscle cramps, tachycardia, without altered consciousness; severe dehydration (10–11%) — lethargy, obtundation, weak pulse, hypotension, shock. The thresholds differ slightly from those given in the previous table, but the therapeutic approach they require is identical.

5.6. SPECIFIC ETIOLOGICAL FORMS

5.6.1. VIRAL INFECTIONS

Table 6. Viral causes of gastroenteritis in humans (adapted from Harrison, 21st ed.).

Virus	Family	Genome	Age group at risk	Clinical severity	Detection tests
Group A rotavirus	Reoviridae	Double-stranded, segmented RNA	Children under 5 years	+++	Electron microscopy, enzyme immunoassay (commercial), PAGE, RT-PCR
Norovirus	Caliciviridae	Single-stranded, positive-sense RNA	All ages	++	Electron microscopy, enzyme immunoassay, RT-PCR
Sapovirus	Caliciviridae	Single-stranded, positive-sense RNA	Children under 5 years	+	Electron microscopy, enzyme immunoassay, RT-PCR
Astrovirus	Astroviridae	Single-stranded, positive-sense RNA	Children under 5 years	+	Electron microscopy, enzyme immunoassay, RT-PCR
Adenovirus (types 40 and 41)	Adenoviridae	Double-stranded DNA	Children under 5 years	+ / ++	Electron microscopy, enzyme immunoassay (commercial), PCR

Rotavirus, in the absence of vaccination, remains the leading cause of severe gastroenteritis in children aged 6 to 24 months. After an incubation of 1–3 days, onset is marked by fever and vomiting, followed within a few hours by profuse watery diarrhea lasting 5–7 days. The risk of dehydration is maximal, due to the combination of upper and lower gastrointestinal losses. Confirmation is obtained by

antigen detection in stool or by nucleic acid amplification. There is no specific antiviral therapy, management being exclusively supportive.

Norovirus affects all age groups and is the leading cause of gastroenteritis outbreaks in community settings. The incubation period is 12–48 hours, the picture is dominated by projectile vomiting, colicky pain and watery diarrhea, and the course is short, 24–72 hours. However, viral shedding persists for two to three weeks after clinical resolution, which explains the persistence of outbreaks. Resistance to common alcohol-based disinfectants requires handwashing with soap and water and disinfection of surfaces with chlorine-based solutions.
Enteric adenoviruses — serotypes 40 and 41 — cause diarrhea with a more prolonged course, of 5–12 days, in young children, whereas **astroviruses** and **sapoviruses** usually cause mild forms.

5.6.2. Cholera

Cholera, caused by *Vibrio cholerae* serogroups O1 and O139, remains a major public health problem in the context of armed conflicts, natural disasters and refugee camps. Approximately 75% of infected individuals remain asymptomatic, while continuing to shed the vibrio. The severe form, *cholera gravis*, presents with painless, watery, rice-water stools in volumes that may exceed one liter per hour, vomiting, muscle cramps secondary to hypokalemia and the onset of hypovolemic shock within a few hours. Mortality in untreated forms exceeds 50%, but falls below 1% with correct and prompt rehydration.
Treatment is primarily volume replacement, with lactated Ringer's solution administered in amounts guided by losses. Antibiotic therapy has an adjunctive role, shortening the duration of diarrhea and of vibrio shedding: doxycycline 300 mg as a single dose in adults, azithromycin 1 g as a single dose in pregnant women and children. Inactivated oral vaccines contribute to epidemic control.

5.6.3. Shigellosis

Shigella is the prototype of the dysenteric agent. The extremely low infectious dose, 10–100 bacteria, explains direct person-to-person transmission and the frequency of outbreaks in nurseries, schools and institutions. The course is biphasic: an initial phase of watery diarrhea, followed after 1–2 days by the dysenteric syndrome proper,

with small, frequent stools with mucus and blood, intense tenesmus and fever. Febrile seizures may occur in children, and *S. dysenteriae* type 1 may cause hemolytic uremic syndrome through Shiga toxin production. Antibiotic therapy is indicated, shortens the course and reduces transmission; azithromycin or ciprofloxacin is preferred, adjusted to susceptibility testing, given the spread of multidrug-resistant and fluoroquinolone-resistant strains.

5.6.4. Non-typhoidal salmonellosis

The established sources are eggs (especially duck eggs), undercooked poultry, unpasteurized milk and contact with reptiles. After an incubation of 6–72 hours, fever, colicky pain and diarrhea, sometimes bloody, occur, the course usually being self-limiting within 4–7 days. **Antibiotic therapy is indicated particularly in** infants under three months, persons over 50 years with atherosclerosis, immunocompromised patients, patients with hemoglobinopathies, vascular or valvular prostheses, and in bacteremic forms, given the risk of secondary localizations — endocarditis, mycotic aneurysm, osteomyelitis.

5.6.5. Campylobacteriosis

Campylobacter jejuni is the most frequently reported bacterial cause of gastroenteritis in the European Union. Transmission occurs through undercooked poultry, unpasteurized milk and contaminated water. The picture combines an influenza-like prodrome, followed by intense abdominal pain, sometimes mimicking appendicitis, and frequently bloody stools. Post-infectious complications are characteristic: **Guillain-Barré syndrome**, through molecular mimicry between bacterial lipooligosaccharide and nerve gangliosides, reactive arthritis and post-infectious irritable bowel syndrome. When treatment is chosen, azithromycin is the first-line agent, as fluoroquinolone resistance exceeds 60% in many European countries.

5.6.6. Escherichia coli infections

Five major pathotypes are distinguished, with distinct mechanisms and clinical expression: enterotoxigenic, enteropathogenic, enteroinvasive, enteroaggregative and Shiga toxin-producing. ETEC is the leading cause of travelers' diarrhea, EPEC affects infants in

resource-limited regions, EAEC is involved in persistent diarrhea, and STEC causes hemorrhagic colitis.
STEC infection requires particular attention. The sources are undercooked beef, unpasteurized milk, leafy greens and contact with ruminants. After an incubation of 3–4 days, severe abdominal cramps and initially watery diarrhea occur, which becomes grossly bloody, typically **in the absence of significant fever**. Hemolytic uremic syndrome complicates 5–15% of pediatric cases, 5–10 days after onset, with the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury.
Caution. When STEC infection is suspected, antibiotics and antimotility agents are contraindicated, as they increase Shiga toxin release and the risk of hemolytic uremic syndrome. Any afebrile bloody diarrhea requires Shiga toxin testing, including for non-O157 serotypes.

5.6.7. Yersiniosis

Yersinia enterocolitica is transmitted through undercooked pork and dairy products. In older children and adolescents it may mimic acute appendicitis through mesenteric adenitis and terminal ileitis, a picture known as Yersinia pseudoappendicitis, while in adults it frequently causes post-infectious manifestations (erythema nodosum, reactive arthritis), particularly in HLA-B27 carriers. Iron overload and hemochromatosis favor septicemic forms.

5.6.8. Intestinal parasitic infections

Giardia duodenalis causes, after an incubation of 1–2 weeks, diarrhea with pasty, foul-smelling stools, accompanied by bloating, flatulence, nausea and weight loss, with a prolonged course and possible malabsorption syndrome. Treatment uses metronidazole, tinidazole or nitazoxanide.

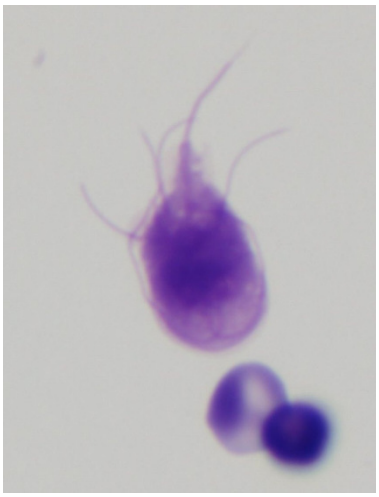


Figure 6. Giardia duodenalis trophozoite on microscopic stool examination.

Cryptosporidium spp. resists standard water chlorination and causes waterborne outbreaks, including in swimming pools. In immunocompetent individuals the course is self-limiting, within 1–2 weeks; in patients with advanced HIV infection it may cause devastating chronic diarrhea, sometimes with biliary involvement. Nitazoxanide has limited efficacy, the decisive therapeutic element being immune reconstitution through antiretroviral therapy.

Entamoeba histolytica causes amebic dysentery, with insidious onset, stools containing blood and mucus, but with a frequently preserved general condition and low-grade fever. The major complication is amebic liver abscess, presenting with fever, right upper quadrant pain and tender hepatomegaly. Treatment combines metronidazole for the invasive form with a luminal agent — paromomycin or iodoquinol — to eradicate cysts.

Cyclospora cayetanensis is associated with the consumption of imported berries and leafy greens, causing prolonged diarrhea with anorexia and marked fatigue, responsive to trimethoprim-sulfamethoxazole.

5.7. LABORATORY DIAGNOSIS

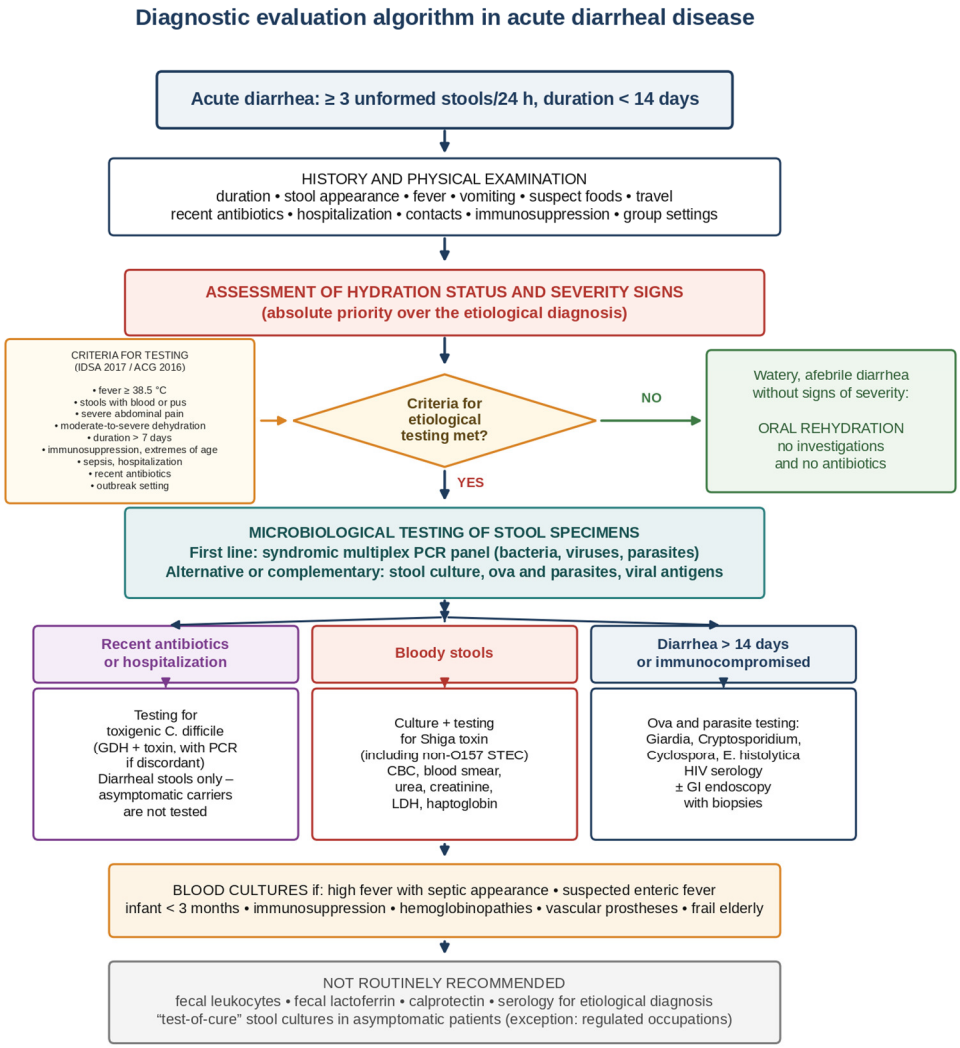


Figure 7. Diagnostic evaluation algorithm in acute diarrheal disease.

5.7.1. Diagnostic methods

Multiplex syndromic panels based on nucleic acid amplification have substantially changed practice, allowing simultaneous detection of 15–22 pathogens within 1–2 hours, with clearly higher sensitivity than conventional methods. Their limitations, however, must be known: they do not distinguish active infection from carriage or

prolonged post-infectious shedding, they frequently identify co-infections whose clinical significance remains uncertain, and they provide no isolate for susceptibility testing or strain for molecular typing in outbreak investigation. Consequently, **positive results for bacteria require culture to be performed in parallel**, both for susceptibility testing and for epidemiological surveillance.

Stool culture remains indispensable. The clinical context must be communicated to the laboratory, as standard media do not allow isolation of *Yersinia*, *Vibrio*, *Campylobacter* or *E. coli* O157:H7 without an explicit request. **Stool ova and parasite examination** requires three samples collected on different days to achieve acceptable sensitivity, and is progressively being replaced by antigen or molecular detection tests for *Giardia*, *Cryptosporidium* and *E. histolytica*.

Stool microscopy — direct microscopic examination of the stool — assesses the presence of leukocytes, intestinal parasites and undigested food particles; although it does not establish the etiology, it remains a simple and rapid investigation, useful for initial orientation. It may be supplemented by Sudan staining to detect fecal fat and eosin staining for undigested muscle fibers, both pointing to a maldigestion or malabsorption component.

General laboratory tests — complete blood count with differential, electrolytes, acid-base balance, urea, creatinine, blood glucose, transaminases, C-reactive protein, erythrocyte sedimentation rate — quantify the systemic impact and guide fluid and electrolyte replacement.

Blood cultures are obtained in febrile patients with sepsis, infants under three months, immunocompromised patients and when enteric fever is suspected. When STEC infection is suspected, hemoglobin, platelet count, renal function, lactate dehydrogenase, haptoglobin and the peripheral blood smear for schistocytes are monitored.

Lower gastrointestinal endoscopy is not indicated in uncomplicated acute diarrhea. It becomes useful in unexplained persistent diarrhea, in immunocompromised patients, when cytomegalovirus colitis is suspected, in differentiation from inflammatory bowel disease, or when pseudomembranous colitis is suspected and tests remain inconclusive.

Table 7. Microbiological diagnostic methods: advantages and limitations.

Method	Main indication	Advantages	Limitations
Multiplex PCR syndromic panel	First line when testing criteria are met	Speed (1–2 hours), high sensitivity, broad spectrum	Does not distinguish infection from carriage; provides no susceptibility testing; high cost
Stool culture	Inflammatory diarrhea, outbreaks, surveillance	Isolate available for susceptibility testing and typing	Yield of 2–5% with indiscriminate testing; 48–72 hours
Antigen detection (rotavirus, adenovirus, Giardia)	Rapid diagnosis in children	Low cost, speed, wide availability	Variable sensitivity, limited spectrum
C. difficile toxin A/B	Suspected C. difficile infection	Sequential algorithm, with good specificity	Use of PCR alone overdiagnoses carriage
Stool ova and parasite examination	Persistent diarrhea, epidemiological exposure	Covers a wide spectrum of parasites	Requires 3 samples; dependent on examiner experience
Blood cultures	Febrile syndrome with sepsis, enteric fever	Confirms bacteremia, guides therapy	Low yield in uncomplicated forms
Endoscopy with biopsies	Unexplained persistent diarrhea, immunosuppression	Histological and differential diagnosis	Invasive; reserved for selected cases

Common errors. Asymptomatic C. difficile carriers are not tested or treated; testing is not repeated to confirm cure; fecal leukocytes and calprotectin are not used to establish the etiology of acute diarrhea.

5.8. DIFFERENTIAL DIAGNOSIS

Differential diagnosis in acute diarrheal disease takes place on two distinct levels, which must not be confused. **The first** concerns etiological differentiation within infectious pathology: based on the epidemiological context, the incubation period and the characteristics of the stools, the clinician narrows the list of probable agents and decides whether investigation is warranted. **The second** aims to exclude non-infectious etiologies and becomes a priority when the course does not match expectations, when microbiological investigations are repeatedly negative or when warning signs appear.

5.8.1. ETIOLOGICAL DIFFERENTIAL DIAGNOSIS

In most situations, three elements allow a reasonable etiological orientation before laboratory results are available: **the interval between exposure and onset**, **the characteristics of the stools** and **the presence or absence of fever**. Abrupt onset a few hours after a meal, with predominantly emetic symptoms and no fever, indicates a preformed toxin. Abundant, watery stools without fever and with rapid dehydration suggest a secretory mechanism. Small-volume stools with mucus and blood, accompanied by fever and tenesmus, indicate invasive colitis. Grossly bloody stools without fever, with severe cramps, require STEC infection to be considered until proven otherwise.

Table 8. Clinical differentiation between the main infectious causes of acute diarrhea.

Feature	Watery (secretory) diarrhea	Food poisoning with preformed toxin	Inflammatory (dysenteric) diarrhea	Hemorrhagic colitis (STEC)
Incubation	12–72 hours	1–6 hours (S. aureus, B. cereus) 8–16 hours (C. perfringens)	1–5 days	3–4 days
Stools	Liquid, abundant, without blood	Mild diarrhea; emetic symptoms predominate	Small, frequent, with mucus, pus and blood	Initially watery, subsequently grossly bloody
Fever	Absent or moderate	Absent	Present, often above 38.5 °C	Absent or moderate
Abdominal pain	Diffuse, moderate colicky pain	Nausea, epigastric pain	Colicky pain, tenesmus, hypogastric pain	Severe cramps, sometimes mimicking a surgical abdomen
Site of lesions	Proximal small intestine	Stomach and small intestine	Distal ileum and colon	Colon, predominantly right-sided
Main risk	Dehydration	Self-limiting, a few hours	Sepsis, dehydration, local complications	Hemolytic uremic syndrome
Typical agents	Rotavirus, norovirus, ETEC, V. cholerae	S. aureus, B. cereus, C. perfringens	Shigella, Campylobacter, Salmonella, EIEC, E. histolytica	E. coli O157:H7 and non-O157
Management	Rehydration; stool culture and multiplex PCR panel when criteria are met	Symptomatic treatment	Stool culture with susceptibility testing, multiplex PCR panel, blood cultures in febrile patients; selective antibiotic therapy	Shiga toxin testing, including non-O157 serotypes; antibiotics are contraindicated

Table 9. Differential features of viral and bacterial gastroenteritis (adapted from Harrison, 21st ed.).

Feature	Viral gastroenteritis	Bacterial gastroenteritis
Geographic distribution	Similar incidence in developed and developing countries	More frequent in areas with poor hygiene and sanitation
Infectious dose	Low (10–100 viral particles) for most agents	High (> 10□ bacteria) for *E. coli*, *Salmonella*, *Vibrio*; intermediate (10^2–10□) for *Campylobacter jejuni*; low (10–100) for *Shigella*
Seasonality	In temperate climates, winter seasonality for most agents; uniform year-round distribution in tropical areas	More frequent in summer and in the rainy months, especially in developing countries
Incubation period	1–3 days for most agents; possibly shorter for norovirus	1–7 days for common agents (*Campylobacter*, *E. coli*, *Shigella*, *Salmonella*); a few hours for bacteria with preformed toxins (*S. aureus*, *B. cereus*)
Reservoir	Predominantly human	Variable: human (*Shigella*, *Salmonella*), animal (*Campylobacter*, *Salmonella*, *E. coli*) or water (*Vibrio*)
Fever	Common in rotavirus and norovirus infection; rare for the other agents	Common for agents causing inflammatory diarrhea (*Salmonella*, *Shigella*)
Vomiting	Predominant; may be the only manifestation, especially in children	Common in food poisoning with preformed toxins; less common in other situations
Diarrhea	Common, non-bloody in virtually all cases	Marked and frequently bloody for agents causing inflammatory diarrhea
Duration	1–3 days for norovirus and sapovirus; 2–8 days for the other viruses	1–2 days for bacteria with preformed toxins; 2–8 days for most others
Diagnosis	Clinically, often a diagnosis of exclusion; enzyme immune-assays are commercially available for rotavirus and adenovirus, identification of the other agents being limited to research and public health laboratories	Stool examination for leukocytes and blood is useful in the differential diagnosis; stool culture, sometimes on special media, can identify several pathogens; molecular techniques are epidemiologically useful but not routine
Treatment	Supportive therapy to maintain hydration and nutrition; antibiotics and antimotility agents are contraindicated	Hydration is sufficient in most patients; antibiotics are recommended in dysentery caused by *Shigella* or *Vibrio cholerae* and in some patients with colitis caused by *Clostridioides difficile*

Several situations prone to diagnostic error should be highlighted. Typhoid fever frequently runs its course **without diarrhea** in the first week, sometimes even with constipation, suspicion being raised by the prolonged febrile syndrome, relative bradycardia and splenomegaly. *Campylobacter* infection may mimic a surgical acute abdomen, as may yersiniosis, which causes mesenteric adenitis and terminal ileitis. *C. difficile* colitis may present with ileus even in the absence of diarrhea, abdominal distension and marked leukocytosis being the only clues. Intestinal amebiasis differs from shigellosis by its insidious onset, low-grade fever and relatively preserved general condition.

5.8.2. Differential diagnosis with non-infectious conditions

Although acute diarrheal disease has an infectious cause in most situations, a number of conditions may present with this picture and must be considered, especially when the course does not match expectations or when microbiological investigations remain repeatedly negative.

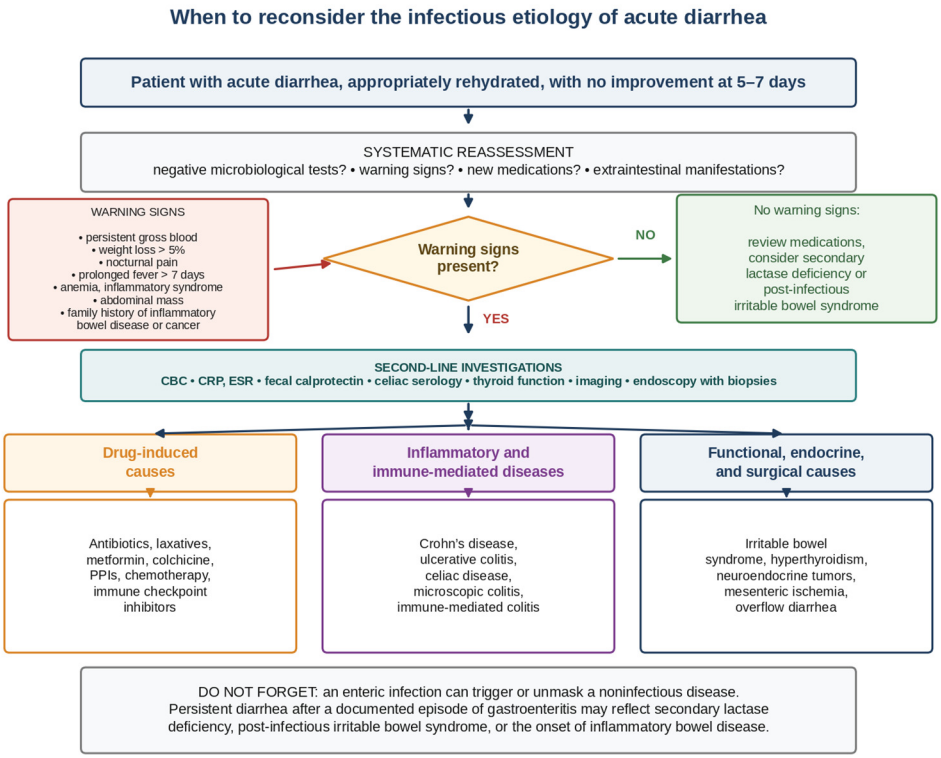


Figure 8. Reassessment of the patient with acute diarrhea not responding to supportive treatment.

Table 10. Main differential diagnoses of acute diarrhea.

Category	Entities	Clues
Drug-induced causes	Antibiotics, laxatives, metformin, colchicine, proton pump inhibitors, chemotherapeutic agents, immune checkpoint inhibitors	Temporal relationship with initiation of the drug; resolution upon discontinuation
Inflammatory bowel diseases	Crohn's disease, ulcerative colitis	Insidious onset, extraintestinal manifestations, persistent inflammatory syndrome, elevated calprotectin
Surgical acute abdomen	Appendicitis, diverticulitis, mesenteric ischemia, obstruction with paradoxical diarrhea	Localized pain, guarding, leukocytosis, imaging confirmation
Endocrine and metabolic disorders	Hyperthyroidism, adrenal insufficiency, neuroendocrine tumors	Associated systemic symptoms, prolonged course
Malabsorption and intolerances	Celiac disease, lactase deficiency, exocrine pancreatic insufficiency	Relationship with food intake, steatorrhea, nutritional deficiencies
Functional causes	Irritable bowel syndrome, including post-infectious	Absence of alarm signs, chronicity, relationship with psychosocial factors
Food intolerances	Lactose intolerance, cow's milk protein intolerance, fructose intolerance	Strict relationship with a specific food, resolution upon elimination, high frequency in infants and young children
Extradigestive infections	Viral exanthems, otitis, urinary tract infections, pneumonia in infants	Parainfectious diarrhea accompanies a clinically dominant infection at another site
Non-infectious poisonings	Mushrooms, ciguatera, histamine (scombroid poisoning), heavy metals	Suggestive dietary context, associated neurological or vasomotor manifestations

Reassessment of the diagnosis becomes imperative in the presence of **alarm signs**: persistent gross bleeding after resolution of the acute episode, unintentional weight loss of more than 5%, nocturnal

diarrhea, fever lasting longer than seven days, persistent anemia or inflammatory syndrome, a palpable abdominal mass, and a family history of inflammatory bowel disease or colorectal cancer. In these situations, second-line investigations include a complete blood count, inflammatory markers, fecal calprotectin (informative in this context, unlike in acute diarrhea), celiac disease serology, assessment of thyroid function, abdominal imaging and, as a last resort, digestive endoscopy with biopsy sampling.

Pitfall. A positive microbiological result does not exclude a concomitant non-infectious disorder. An enteric infection may trigger or unmask ulcerative colitis, and the identification of a pathogen in a patient with alarm signs should not halt further investigation

5.9. COMPLICATIONS

Immediate complications are dominated by dehydration and its consequences: hypovolemic shock, prerenal acute kidney injury, metabolic acidosis, hypokalemia with a risk of arrhythmia and ileus, hyponatremia or hypernatremia with neurological manifestations, and seizures in infants. These are preventable through correct and early rehydration.

Local complications include gastrointestinal bleeding, intestinal perforation (classically described in typhoid fever, in the third week of illness), toxic megacolon in *C. difficile* colitis or in shigellosis, and intussusception, reported in infants with adenovirus infections.

Prognosis depends primarily on the promptness of rehydration and on the patient's underlying condition. In the immunocompetent adult, the course is favorable within 3–7 days in most cases. Features that herald an unfavorable course and require urgent reassessment are fever persisting beyond 72 hours, the appearance of blood in the stools, worsening abdominal pain or the onset of guarding, decreased urine output, altered consciousness and lack of response to properly conducted oral rehydration. The child's caregivers must be explicitly instructed about these features before discharge or before being sent home.

Systemic and post-infectious complications are often underdiagnosed. Hemolytic uremic syndrome complicates STEC infection and is the leading cause of acute kidney injury in young children in developed countries. Reactive arthritis, sometimes as part of a complete Reiter's syndrome, follows infections with *Shigella*, *Salmonella*, *Campylobacter* or *Yersinia*, predominantly in HLA-B27 carriers. Guillain-Barré

syndrome follows *Campylobacter jejuni* infection with an incidence of approximately 1 per 1,000–3,000 cases. Erythema nodosum accompanies yersiniosis, and post-infectious irritable bowel syndrome affects 5–15% of patients some time after the acute episode. In children from resource-limited settings, repeated episodes of diarrhea contribute to malnutrition, stunting and environmental enteric dysfunction, in a vicious circle that is difficult to break.

5.10. TREATMENT

The treatment of acute diarrheal disease is structured on four levels, ranked by importance: **correction and maintenance of fluid and electrolyte balance**, **nutritional support**, **pathogenic and symptomatic therapy** and, only in well-defined situations, **antibiotic therapy**. The most common error in practice is the inversion of this hierarchy, by prescribing an antibiotic before the volume status has been properly assessed.

5.10.1. Rehydration

Oral rehydration solution relies on the preserved integrity of sodium-glucose cotransport and remains the intervention with the greatest impact on diarrhea-related mortality. The formula recommended by the World Health Organization and UNICEF since 2002 has a **reduced osmolarity of 245 mOsm/L**, with 75 mmol/L sodium and 75 mmol/L glucose. Compared with the classic 1975 formula, it reduces stool output by approximately 20%, the incidence of vomiting by about 30% and the need for unscheduled intravenous infusion by approximately one third. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommends for children in Europe a more hypotonic solution, with 60 mmol/L sodium and an osmolarity of 225 mOsm/L, suitable for non-cholera diarrhea.
Carbonated drinks, fruit juices and isotonic sports drinks **are not acceptable substitutes**: their sodium content is negligible, and the high osmotic load conferred by their sugar concentration may worsen diarrhea through an osmotic mechanism. Administration is fractionated, in small, repeated amounts (by teaspoon or syringe in infants); vomiting is not a contraindication: a ten-minute pause is required, followed by resumption with small volumes.

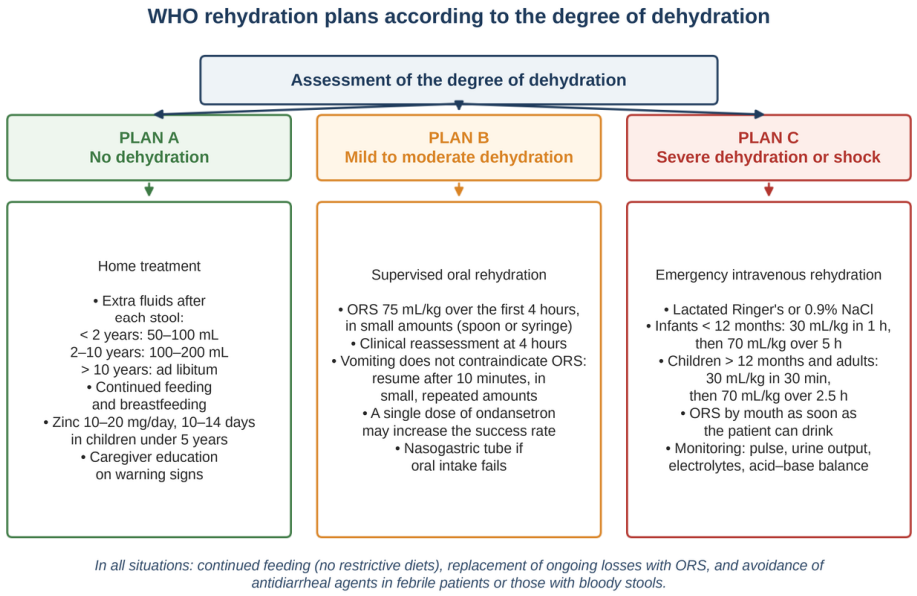


Figure 9. WHO rehydration plans according to the degree of dehydration.

Intravenous rehydration is reserved for severe dehydration, shock, ileus, intractable vomiting and failure of oral rehydration. The solution of choice is lactated Ringer's, or normal saline if it is unavailable. Switching to the oral route is done as soon as the patient regains the ability to drink fluids. Ultra-rapid intravenous rehydration regimens have not proven superior to standard regimens and are associated with higher readmission rates.

5.10.2. Adjunctive therapies

Table 11. Adjunctive therapies in acute diarrheal disease.

Class / agent	Usual dose	Indication and level of evidence	Precautions
Zinc	10 mg/day under 6 months; 20 mg/day over 6 months, for 10–14 days	Recommended by the WHO for children under 5 years in zinc-deficient regions; reduces duration and severity	Uncertain benefit in non-deficient populations; may induce vomiting
Racecadotril	1.5 mg/kg every 8 hours	Enkephalinase inhibitor with antisecretory effect; reduces stool output in children	Not to be combined with antiperistaltic agents
Loperamide	4 mg initially, then 2 mg after each loose stool, maximum 16 mg/day	Watery, afebrile diarrhea in adults; improves comfort and reduces the number of stools	**Contraindicated** in bloody or febrile diarrhea, when STEC or C. difficile is suspected; contraindicated under 2 years of age
Bismuth subsalicylate	524 mg every 30–60 minutes, maximum 8 doses/day	Alternative to loperamide in travelers' diarrhea	Turns stool and tongue black; to be avoided in children because of the risk of Reye syndrome
Ondansetron	0.15 mg/kg, single dose (children)	Facilitates oral rehydration by controlling vomiting, reduces the hospitalization rate	QT interval prolongation; repeated administration is avoided
Probiotics	Lactobacillus rhamnosus GG, Saccharomyces boulardii	Reduce the duration of diarrhea by approximately 12–24 hours in children; recent data are less conclusive	Caution in immunocompromised patients and in those with central venous catheters, because of the risk of fungemia
Diosmectite	3 g × 3/day (adults)	Adsorbent agent	Administered apart from other medications

5.10.3. Antibiotic therapy

Empirical antibiotic therapy **is not administered routinely**. It does not influence the course of viral diarrhea, increases the risk of hemolytic uremic syndrome in STEC infection, promotes *C. difficile* infection and contributes to the selection of resistance. Empirical therapy is justified in three situations: a patient with high fever and bloody stools, suggestive of shigellosis; a patient with signs of sepsis or who is immunocompromised; moderate or severe travelers' diarrhea.

Table 12. Targeted antibiotic therapy for the main bacterial and parasitic etiologies.

Etiological agent	First-line treatment (adults)	Alternatives	Remarks
Shigella spp.	Azithromycin 500 mg/day, 3 days or ciprofloxacin 500 mg × 2/day, 3 days	Ceftriaxone 2 g/day IV, 3–5 days	Indicated in all patients; beware of multidrug-resistant strains
Non-typhoidal Salmonella	Ciprofloxacin or ceftriaxone for 7–14 days	ampicillin	
Campylobacter spp.	Azithromycin 500 mg/day, 3 days	Ciprofloxacin, depending on susceptibility	Fluoroquinolone resistance exceeds 60% in many regions
STEC / E. coli O157:H7	**Antibiotics are contraindicated**	—	Antibiotics increase the risk of hemolytic uremic syndrome
Vibrio cholerae	Doxycycline 300 mg single dose	Azithromycin 1 g single dose; ciprofloxacin	Adjunct to rehydration, which remains essential
Salmonella Typhi	Ceftriaxone 2 g/day IV, 10–14 days	Azithromycin 1 g/day, 7 days	Widespread fluoroquinolone resistance in South Asia
Yersinia enterocolitica	Doxycycline	Doxycycline combined with an amino-glycoside, or co-trimoxazole, in severe forms	Indicated in immunocompromised patients and in bacteremia

Etiological agent	First-line treatment (adults)	Alternatives	Remarks
Giardia duodenalis	Metronidazole 250 mg × 3/day, 5–7 days	Tinidazole 2 g single dose; nitazoxanide	Symptomatic contacts are also treated
Entamoeba histolytica	Metronidazole 750 mg × 3/day, 7–10 days	Tinidazole	Must be followed by a luminal agent (paromomycin)
Cryptosporidium spp.	Nitazoxanide 500 mg × 2/day, 3 days	—	In HIV-infected patients, immune reconstitution is essential
Cyclospora cayetanensis	Trimethoprim-sulfamethoxazole 160/800 mg × 2/day, 7–10 days	Ciprofloxacin	Prolonged therapy in immunocompromised patients

5.10.4. Parenteral fluid and electrolyte replacement: principles of calculation

When the parenteral route is required (dehydration exceeding 10%, shock or vomiting that prevents oral tolerance), correction follows a stepwise principle. **In the first two hours, half of the estimated losses is administered**, the remaining half of the losses over the next six hours, and the daily maintenance requirement is completed by 24 hours. Bicarbonate and sodium chloride losses are corrected first, with potassium added **only after satisfactory urine output has resumed**, in order to prevent hyperkalemia in a patient with prerenal kidney injury. In shock, corticosteroid therapy may be added in the form of hydrocortisone hemisuccinate, 10 mg/kg intravenously.

Replacement uses Ringer's solution, normal saline and equimolar solutions (5.8% sodium chloride, 7.4% potassium chloride, 8.4% sodium bicarbonate), the advantage of the latter being the equivalence **1 mL of equimolar solution = 1 mEq**, which considerably simplifies the calculation. The daily maintenance requirement is approximately 1–2 mEq/kg sodium, 1 mEq/kg potassium, 2 mEq/kg calcium, 2–3 mEq/kg bicarbonate and about 80 mL/kg fluids.

Table 13. Calculation of fluid, electrolyte and acid-base deficits in parenteral replacement.

Parameter	Formula	Age-dependent coefficient
Sodium (mEq)	(ideal Na^+ – measured Na^+) × W (kg) × coefficient	0.2 in adults 0.3 in infants 0.5 in newborns
Potassium (mEq)	(ideal K^+ – measured K^+) × W (kg) × coefficient	0.2 in adults 0.3 in infants 0.5 in newborns
Bicarbonate (mEq)	(ideal HCO_3^- – measured HCO_3^-) × W (kg) × coefficient	0.2 in adults 0.3 in infants 0.5 in newborns
Daily maintenance requirement	Na^+ 1–2 mEq/kg • K^+ 1 mEq/kg • Ca^{2+} 2 mEq/kg HCO_3^- 2–3 mEq/kg • fluids 80 mL/kg	Ongoing losses through stools and vomiting are added

Caution. Correction of serum sodium should not exceed 10–12 mmol/L in 24 hours, particularly in hypernatremia, because of the risk of cerebral edema in children. Replacement is conducted under repeated clinical and laboratory monitoring, with a switch to the oral route as early as possible

5.10.5. Criteria for hospitalization and monitoring

Most patients with acute diarrheal disease can be treated as outpatients, with appropriate instruction of the patient or caregivers on the technique of oral rehydration and on the features that require reassessment. Hospitalization becomes necessary when oral rehydration is not possible or has failed, as well as in the presence of signs of severity.

- severe dehydration, signs of hypoperfusion or shock;
- intractable vomiting preventing oral fluid intake;
- altered consciousness, seizures or focal neurological signs;
- sepsis, suspected enteric fever or bacteremia;
- acute abdomen, marked distension, suspected ileus, toxic megacolon or perforation;

- confirmed or suspected hemolytic uremic syndrome;
- infant under three months, frail elderly patient, decompensated comorbidities, severe immunosuppression;
- inability to provide home supervision or failure of outpatient treatment after 48 hours.

In hospitalized patients, fluid balance, body weight, urine output, frequency and appearance of stools, hemodynamic parameters, serum electrolytes, renal function and acid-base balance are monitored. Discharge may take place after restoration of oral tolerance, correction of dehydration and resumption of feeding, with explicit recommendations on hygiene and, for persons working in food handling, in childcare settings or in patient care, on the period of temporary exclusion from work.

5.11. CLOSTRIDIOIDES DIFFICILE INFECTION

Infection with *Clostridioides difficile* is the leading cause of healthcare-associated diarrhea and a major patient safety concern. The key risk factors are antibiotic exposure (particularly clindamycin, third-generation cephalosporins, fluoroquinolones and amoxicillin-clavulanate), age over 65 years, prolonged hospitalization, immunosuppression, inflammatory bowel disease and, with a weaker association, the use of proton pump inhibitors. In recent years, community-acquired forms, occurring in patients without recent hospital exposure, have come to account for approximately half of cases.

The diagnosis is made **only in patients with diarrheal stools**, by detection of toxins A/B by immunoassay, with discordant results arbitrated by a molecular method. Stand-alone use of nucleic acid amplification leads to overdiagnosis, as it also identifies asymptomatic carriers, who account for 5–15% of hospitalized adults. Test of cure after treatment is of no value.

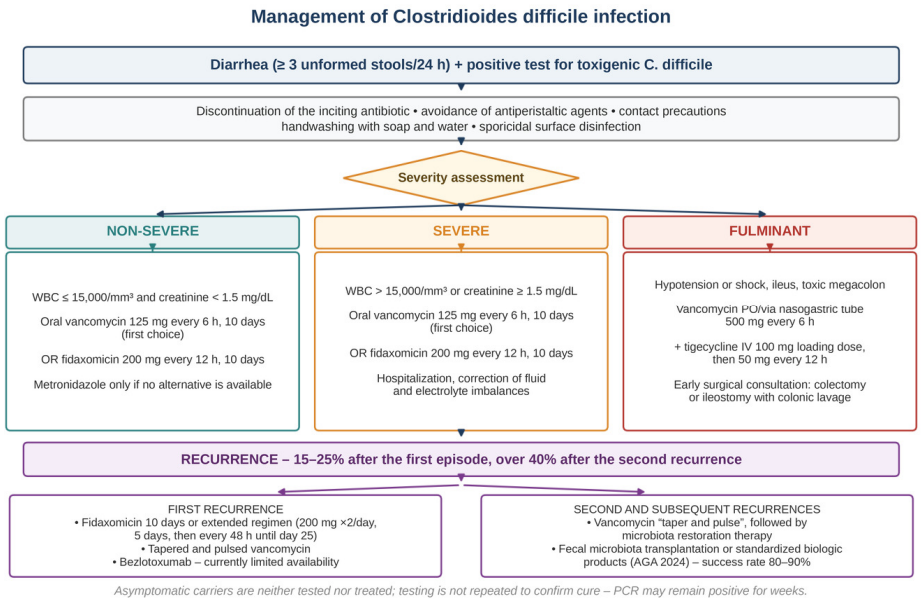


Figure 10. Management algorithm for Clostridioides difficile infection.

Oral vancomycin is the first therapeutic option in both non-severe and severe disease, at a dose of 125 mg every 6 hours for 10 days. Fidaxomicin, 200 mg every 12 hours for 10 days, is the alternative; the 2021 IDSA/SHEA guideline supports it on the basis of lower recurrence rates, whereas the American College of Gastroenterology guideline of the same year considers the two options equivalent, taking into account the high cost of fidaxomicin. Metronidazole is now recommended only when the other options are unavailable. In fulminant disease, vancomycin is administered orally or via nasogastric tube, 500 mg every 6 hours, combined with intravenous tigecycline (100 mg loading dose, then 50 mg every 12 hours), and surgical consultation is requested early.

Recurrence occurs in 15–25% of patients after the first episode and in more than 40% after the second recurrence, reflecting persistent dysbiosis. The 2024 American Gastroenterological Association guideline incorporated standardized fecal microbiota-derived biological products, approved by regulatory agencies, alongside conventional fecal microbiota transplantation, with success rates of 80–90% in multiple recurrences. Prevention is based on judicious antibiotic use, contact precautions, handwashing with soap and water (alcohol-based disinfectants do not inactivate spores) and sporicidal disinfection of surfaces.

5.12. TRAVELERS' DIARRHEA

Travelers' diarrhea affects 10–40% of persons traveling from high-resource regions to areas with poor sanitation in South and Southeast Asia, sub-Saharan Africa, and Central and South America. The most frequently involved agents are enterotoxigenic and enteroaggregative *E. coli*, followed by *Campylobacter*, *Shigella*, *Salmonella*, norovirus and, in prolonged forms, *Giardia*. Onset typically occurs within the first days after arrival, and the course is self-limiting within 3–5 days.

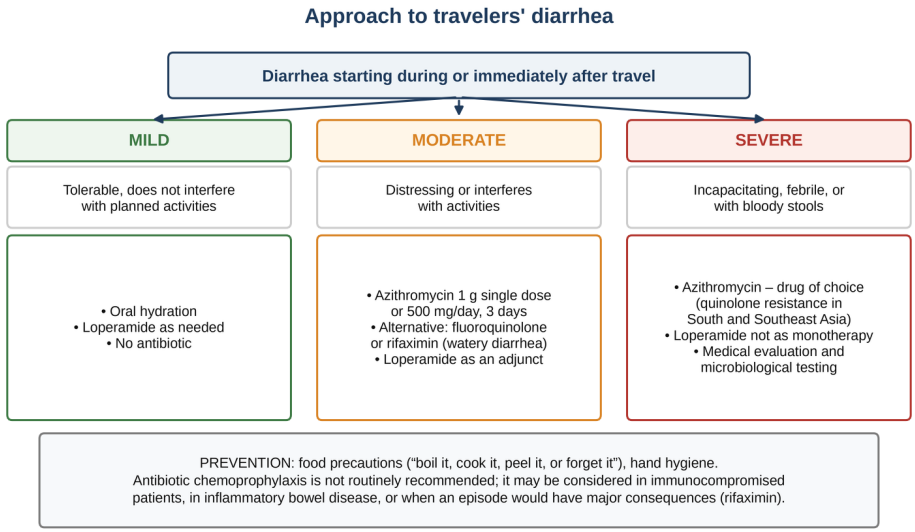


Figure 11. Approach to travelers' diarrhea according to severity.

Management is stratified according to the functional impact of the illness. Azithromycin has become the first-line antibiotic for most destinations, given the high fluoroquinolone resistance of *Campylobacter* in Southeast Asia. Rifaximin, a non-absorbable antibiotic, is effective in uncomplicated watery diarrhea but not in invasive forms. Loperamide may be combined with the antibiotic in moderate and severe forms, but should not be given as monotherapy in the presence of fever or blood in the stools. Antibiotic chemoprophylaxis is not routinely recommended and is reserved for particular situations.

Persistent diarrhea after travel. When diarrhea lasts longer than two weeks after return, Giardia, Cyclospora and Cryptosporidium should be sought first, without overlooking secondary lactase deficiency, post-infectious irritable bowel syndrome and, more rarely, the onset of inflammatory bowel disease

5.13. PROPHYLAXIS AND PUBLIC HEALTH MEASURES

5.13.1. General measures

Prevention of diarrheal disease is based on simple interventions with demonstrated impact: access to safe drinking water, adequate sanitation, hand hygiene, food safety from production to consumption, exclusive breastfeeding during the first six months of life and correction of nutritional deficiencies. Handwashing with soap and water reduces the incidence of diarrheal disease by approximately 30%, ranking among the most cost-effective public health interventions.

In healthcare facilities, infection control measures include contact precautions for patients with infectious diarrhea, cohorting during outbreaks, use of personal protective equipment, rigorous surface disinfection and, for *C. difficile* and norovirus, the use of chlorine-based sporicidal and virucidal agents. Healthcare personnel and food handlers with gastrointestinal symptoms do not return to work until 48 hours after resolution of symptoms and, in certain regulated situations, only after negative microbiological tests.

5.13.2. Vaccination

Rotavirus vaccination is the most important achievement in this field. The live attenuated oral vaccines are given in two or three doses, the first necessarily before 15 weeks of age and the last by 8 months, in order to limit the risk of intussusception, estimated at 1–6 additional cases per 100,000 vaccinated infants, a risk clearly outweighed by the benefits. The impact of vaccination programs is remarkable: a 70–90% reduction in hospitalizations for rotavirus gastroenteritis, a 40–50% reduction in hospitalizations for all-cause gastroenteritis and a reduction of more than one third in diarrheal mortality among children under five years, in addition to the indirect protection of unvaccinated children.

Table 14. Vaccines available for the prevention of diarrheal diseases.

Vaccine	Composition and schedule	Indications	Remarks
Monovalent rotavirus	Live attenuated, human, 2 oral doses (2 and 4 months)	All infants; first dose before 15 weeks of age	85–98% efficacy against severe forms
Pentavalent rotavirus	Bovine-human reassortant, 3 oral doses (2, 4, 6 months)	Idem	Last dose by 8 months of age
Inactivated oral cholera	Whole cells ± toxin B subunit, 2 doses	Travelers to endemic areas, epidemic control campaigns	Partial, short-term protection against ETEC
Vi polysaccharide typhoid	Injectable, single dose, revaccination every 3 years	Travelers to endemic areas, over 2 years of age	50–70% efficacy
Typhoid conjugate (TCV)	Vi-tetanus toxoid conjugate, single dose	Recommended by the WHO for introduction into national programs in endemic areas	Superior immunogenicity, usable from 6 months of age
Live oral typhoid (Ty21a)	Capsules, 3–4 doses given every other day	Alternative to the Vi vaccine	Contraindicated in immunocompromised patients

In Romania, rotavirus vaccination **is not included in the National Immunization Program**; it is available optionally, at the patient's expense, on the recommendation of the family physician or pediatrician, although it is recommended by the World Health Organization and by the National Institute of Public Health (INSP). Its inclusion in the routine schedule remains a public health objective.

5.13.3. Surveillance and reporting

Acute diarrheal diseases are subject to epidemiological surveillance. In Romania, foodborne illnesses, cholera, typhoid and paratyphoid fever, bacillary dysentery, botulism and hemolytic uremic syndrome are reported nominally, in accordance with current regulations on

notifiable communicable diseases. Any suspected outbreak (two or more epidemiologically linked cases) requires notification of the public health directorate, initiation of an epidemiological investigation, collection of food samples and samples from contacts, and implementation of containment measures. Persons working in food handling, in childcare settings or in patient care are subject to specific regulations on temporary exclusion from work.

5.14. CLINICAL CASE

5.14.1. Case presentation

General data. Male patient, aged 1 year and 2 months. Ill for two days, with fever (38.5 °C) and poor appetite at onset. On the second day of illness, he had two episodes of post-prandial vomiting and one loose stool. He was assessed in the pediatric emergency department and referred to the infectious diseases clinic with a diagnosis of diarrheal syndrome.

Physical examination on admission. Drowsy patient, low-grade fever (37.8 °C). Pale skin, slow skin pinch retraction, dry lips. Heart rate 113 beats/minute, respiratory rate 30/minute, oxygen saturation 99% on room air. Soft, depressible abdomen, no guarding. Large-volume, watery, yellow-green stools, without blood, mucus or pus.



Figure 12. Appearance of the stool in the presented patient: watery, abundant, yellow-green, with no macroscopic pathological elements, suggestive of viral gastroenteritis.

5.14.2. Multiple-answer multiple-choice questions

Question 1. Which of the following must necessarily be established in the history of this patient?

A. The number of wet diapers in the last 24 hours

B. Vaccination status, including rotavirus vaccination

C. The existence of similar cases in the family or in the community

D. The mother's rotavirus antibody titer

E. Determination of the child's blood group and Rh type

Question 2. Which of the following statements regarding the diagnostic classification of the case are correct?

A. The slow skin pinch retraction, dry mucous membranes and drowsiness support an acute dehydration syndrome

B. The absence of blood, mucus and pus argues for a non-inflammatory mechanism

C. The age, season and association of vomiting with watery diarrhea suggest rotavirus infection

D. The low-grade fever on admission excludes an infectious etiology

E. The clinical picture requires classification as dysenteric syndrome

Question 3. Which of the following investigations are justified in this patient?

A. Rotavirus fecal antigen testing

B. Serum electrolytes and acid-base balance

C. Complete blood count with differential

D. Colonoscopy with biopsy sampling

E. Celiac disease serology

Question 4. Which of the following statements regarding the differential diagnosis, complications and management are correct?

A. Intussusception must be considered in the differential diagnosis

B. Feeding is continued, and restrictive diets are abandoned

C. Febrile seizures and hypoglycemia are possible complications at this age

D. Antibiotic therapy is started empirically on admission

E. Loperamide is indicated to reduce the number of stools

5.15. SELF-ASSESSMENT QUESTIONS

5.15.1. Single-answer multiple-choice questions

Question 1. A 42-year-old man and his 12-year-old son present with diarrhea persisting for two weeks. Both describe watery, non-bloody, foul-smelling, greasy stools, accompanied by abdominal pain and cramps. Two weeks earlier they had gone on a camping trip in the mountains, where they ate wild edible plants and fish caught from the river and cooked over a fire, and drank water from a stream. What is the most likely etiological agent?

A. *Bacillus cereus*
B. *Campylobacter jejuni*
C. *Clostridioides difficile*
D. *Giardia duodenalis (lamblia)*
E. *Yersinia enterocolitica*

Question 2. A 4-year-old girl is brought to the doctor with diarrhea of 12 hours' duration. Her mother reports that she came home from nursery and developed fever, abdominal pain and stools containing streaks of bright red blood and pus. The child did not eat at the nursery, and her diet has not changed in the past week. What is the most likely agent?

A. *Campylobacter jejuni*
B. Enterotoxigenic *Escherichia coli*
C. *Vibrio cholerae*
D. *Shigella dysenteriae*
E. *Yersinia enterocolitica*

Question 3. A 2-year-old girl presents with vomiting and diarrhea for two days. Her mother describes the stools as non-bloody and free of mucus. The child appears unwell and is lethargic. What is the most likely agent?

A. Enterotoxigenic *Escherichia coli*
B. Enterohemorrhagic *Escherichia coli*
C. Norovirus
D. *Ascaris lumbricoides*
E. *Giardia duodenalis*

5.15.2. Multiple-answer clinical cases

Case 1. A 34-year-old man presents with profuse, watery, non-bloody diarrhea that began 36 hours after returning from a trip to Southeast Asia. He is afebrile, has five to six stools per day and moderate abdominal cramps, but is able to continue his activities. Which of the following statements regarding management are correct?

A. Oral hydration is the mainstay of treatment

B. Azithromycin 1 g as a single dose is justified if the symptoms interfere with activities

C. An urgent stool culture is required before any therapy

D. Ciprofloxacin is started for 7 days

E. The patient requires hospitalization for parenteral rehydration

Case 2. A 4-year-old child has had severe abdominal cramps for three days and stools that have become frankly bloody, without significant fever. One week earlier he ate a hamburger at an outdoor event. Which of the following statements are correct?

A. The stools are tested for Shiga toxin, including for non-O157 serotypes

B. Hemoglobin, platelet count and creatinine are monitored

C. Antibiotics and antiperistaltic agents are contraindicated

D. Ciprofloxacin is administered to shorten the course

E. High fever is the defining feature of the clinical picture

Case 3. A 72-year-old female patient, hospitalized for ten days for pneumonia treated with ceftriaxone, develops six diarrheal stools per day, fever of 38.3 °C, a leukocyte count of 18,000/mm³ and a creatinine level of 1.7 mg/dL. Which of the following statements are correct?

A. The laboratory criteria classify the case as severe

B. Oral vancomycin 125 mg every 6 hours for 10 days is the first therapeutic option

C. Ceftriaxone is discontinued whenever possible

D. Testing is repeated at the end of treatment to confirm cure

E. Loperamide is added to reduce the number of stools

Case 4. An 8-month-old infant has had vomiting and frequent watery stools for two days. He is lethargic, with sunken eyes, a skin pinch

persisting for more than two seconds and a capillary refill time of four seconds. Which of the following statements are correct?

A. Intravenous rehydration with lactated Ringer's is started urgently

B. 30 mL/kg is administered in the first hour, followed by 70 mL/kg over the next five hours

C. Exclusively oral rehydration is sufficient in this case

D. Breastfeeding is interrupted during rehydration

E. Zinc is contraindicated at this age

Case 5. A 27-year-old woman had an episode of acute gastroenteritis three weeks ago, with a stool culture positive for Campylobacter jejuni, treated with azithromycin. The diarrhea persists, with 4–5 stools per day, some with streaks of blood; the patient has lost four kilograms and complains of nocturnal abdominal pain. Follow-up microbiological investigations are negative. Which of the following statements are correct?

A. Weight loss, bleeding and nocturnal pain are alarm signs

B. Fecal calprotectin and inflammatory markers are measured

C. Lower gastrointestinal endoscopy with biopsy sampling is indicated

D. The persistence of symptoms is explained by Campylobacter resistance to azithromycin

E. The azithromycin course is repeated, for twice the duration

5.16. CORRECT ANSWERS AND COMMENTS

This section brings together the answers to the questions in this chapter. It is recommended that you consult it only after formulating your own answers.

5.16.1. Clinical case (section 5.14)

Question 1. Correct answers: A, B, C. Urine output, assessed in infants by the number of wet diapers, is the most reliable indicator of volume status and must be quantified every time. Vaccination status guides the etiological probability, since rotavirus vaccination reduces severe forms by 85–98%, and in Romania it is not part of the national program, being optional. Identification of similar cases among

contacts supports person-to-person transmission and calls for containment measures. The history is completed with the course of the fever and the antipyretic given, fluid tolerance, the number and appearance of vomiting episodes and stools, and any seizures. Maternal antibody titer and blood group have no diagnostic or therapeutic relevance in this context.

Question 2. Correct answers: A, B, C. The findings noted (fever at onset, pale skin with dry mucous membranes, slow skin pinch retraction, drowsiness and watery, abundant, yellow-green stools) define an acute moderate dehydration syndrome occurring in the setting of acute gastroenteritis. The absence of inflammatory elements in the stools indicates a non-inflammatory mechanism, while the patient's age, the season and the association of vomiting with watery diarrhea support the suspicion of rotavirus infection. Low-grade fever by no means excludes an infectious etiology, and dysenteric syndrome implies small-volume stools with mucus and blood, which are absent in this patient.

Question 3. Correct answers: A, B, C. Etiological confirmation is obtained by rotavirus fecal antigen testing, a rapid, low-cost and widely available investigation; the alternative is a multiplex molecular panel. Serum electrolytes and acid-base balance reveal the metabolic acidosis and electrolyte imbalances that guide replacement, and the complete blood count may show hemoconcentration and, possibly, moderate leukocytosis with lymphocytosis. Urea, creatinine and blood glucose complete the workup. Colonoscopy has no indication in uncomplicated acute diarrhea, and celiac disease serology belongs to the workup of chronic diarrhea.

Question 4. Correct answers: A, B, C. The differential diagnosis includes foodborne illnesses, other viral gastroenteritides (norovirus, enteric adenovirus, astrovirus), bacterial gastroenteritis, food intolerances, viral exanthems and, necessarily, surgical abdominal conditions, among them intussusception, which at this age may have an insidious onset. The complications to monitor are febrile seizures, progression of dehydration to hypovolemic shock, metabolic acidosis and hypoglycemia due to lack of intake. Treatment consists of fluid, electrolyte and acid-base replacement, continued feeding, antipyretics and zinc supplementation; an antibiotic is given only in the event of documented bacterial superinfection, and loperamide is contraindicated under two years of age.

5.16.2. Single-answer multiple-choice questions (section 5.15.1)

Question 1. Correct answer: D. Giardiasis should be suspected in any patient with greasy, foul-smelling, non-bloody stools following exposure to surface water. Transmission occurs through ingestion of cysts from fecally contaminated water or food; chlorination is not cysticidal, but cysts can be removed by filtration. The clinical picture combines nausea, loss of appetite, flatulence and cramps, with a course of weeks or months, typically **without fever**. The diagnosis is traditionally made by identifying trophozoites or cysts on microscopic stool examination, with a sensitivity of 50–70% after a single sample and over 90% after three samples collected on different days. If results are negative, antigen detection by enzyme immunoassay or molecular testing is used and, in selected cases, upper gastrointestinal endoscopy with biopsy sampling and duodenal aspirate.

Question 2. Correct answer: D. The decisive element is **person-to-person, fecal-oral and hand-borne transmission** in a childcare setting, in the absence of an incriminated food. *Shigella* has humans as its only host, and its very low infectious dose explains its rapid spread in nurseries. The typical picture combines fever above 38.5 °C, abdominal cramps, tenesmus and small-volume stools mixed with blood and mucus, present in approximately half of children with shigellosis. *Campylobacter* also causes bloody diarrhea, but is transmitted through contaminated food or water, with an animal reservoir. Enterotoxigenic *E. coli* and *V. cholerae* cause watery diarrhea, not dysenteric syndrome. Yersiniosis also affects young children in group settings, but has a much lower incidence and a longer incubation period of 4–7 days.

Question 3. Correct answer: C. The association of vomiting with acute-onset, watery, non-bloody diarrhea in a young child is characteristic of viral gastroenteritis. In populations with rotavirus vaccine coverage, norovirus is the main agent at this age. Enterohemorrhagic *E. coli* causes bloody stools, *Ascaris* does not produce acute diarrhea, and giardiasis has an insidious onset and a prolonged course, without prominent vomiting.

5.16.3. Multiple-answer clinical cases (section 5.15.2)

Case 1. Correct answers: A, B. The picture corresponds to mild to moderate travelers' diarrhea. Oral hydration remains the essential measure, and loperamide may be added if needed. Single-dose

azithromycin is justified when symptoms interfere with activities, being preferred to fluoroquinolones because of the high resistance of Campylobacter in Southeast Asia. Microbiological investigations are not necessary in the absence of fever, blood in the stools or signs of severity, and hospitalization is not indicated in a patient who is able to continue his activities.

Case 2. Correct answers: A, B, C. The combination of severe cramps, frankly bloody stools and absence of fever, following consumption of undercooked ground meat, suggests hemorrhagic colitis due to Shiga toxin-producing E. coli. Testing must also cover non-O157 serotypes. Monitoring of hemoglobin, platelets, creatinine, lactate dehydrogenase and the peripheral blood smear allows early detection of hemolytic uremic syndrome, which occurs in 5–15% of infected children, 5–10 days after onset. Antibiotics and antiperistaltic agents increase toxin release and the risk of this complication.

Case 3. Correct answers: A, B, C. A leukocyte count above 15,000/mm^3 and a creatinine level of at least 1.5 mg/dL define severe Clostridioides difficile infection. The first therapeutic option is oral vancomycin, with fidaxomicin as the alternative. Discontinuation of the offending antibiotic, contact precautions and handwashing with soap and water complete the management. Test of cure after treatment is of no value, since nucleic acid amplification may remain positive for weeks, and antiperistaltic agents are contraindicated.

Case 4. Correct answers: A, B. Lethargy, sunken eyes, a persistent skin pinch and a capillary refill time of more than three seconds define severe dehydration, which requires rehydration Plan C. In infants under 12 months, 30 mL/kg is administered in the first hour, followed by 70 mL/kg over the next five hours, with frequent reassessment. Oral rehydration solution is started as soon as the child regains the ability to drink fluids. Breastfeeding is continued without interruption, and zinc, 20 mg daily for 10–14 days, is recommended.

Case 5. Correct answers: A, B, C. Persistence of symptoms beyond two weeks, bleeding, weight loss of more than 5% and nocturnal pain are alarm features that require looking beyond an infectious cause. Fecal calprotectin, which is informative in this setting, unlike in acute diarrhea, and inflammatory markers point toward organic disease, while endoscopy with biopsy sampling establishes the diagnosis. An enteric infection may unmask or trigger inflammatory bowel disease; a previous positive microbiological result is not an argument for postponing investigation or for repeating antibiotic therapy.

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CHAPTER 6

Diseases of the Respiratory System

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6.1. INFLUENZA

6.1.1. Definition and Terminology

An acute, highly contagious viral infection affecting the upper and/or lower respiratory tract, frequently accompanied by systemic manifestations (fever, headache, myalgia, arthralgia, fatigue).
Epizootic: An epidemic affecting various animal species.
Zoonosis: An infectious disease specific to animals that can also affect humans.
Epidemic: An infectious disease affecting a large proportion of the population at the same time and in the same geographic area.

Table 1. Epidemiological features of seasonal vs. pandemic influenza.

EPIDEMIC	PANDEMIC
An infectious disease affecting a large proportion of the population at the same time and in the same geographic area.	An epidemic affecting a large proportion of the population in all regions of the world.
• caused by influenza viruses A and B. • triggered by "antigenic drift" (minor antigenic variation), consisting of minor mutations in the genes encoding the surface antigens hemagglutinin (HA) and neuraminidase (NA). This results in insufficient recognition of the virus by the immune system (affects types A and B). • occurs at intervals of 2-3 years for influenza A virus and 4-5 years for influenza B virus. • confined to one geographic region or continent. • affects 5-15% of the population, with a mortality of 0.1%. • mainly affects the elderly and persons with underlying diseases.	• caused only by influenza virus A. • triggered by "antigenic shift" (major antigenic variation), consisting of major mutations in the genes encoding HA and NA (or HA/NA alone), giving rise to new viral subtypes against which the population has no antibodies. • occurs at intervals of 10-40 years (3-4 pandemics per century). • spreads rapidly worldwide, affecting all continents (25-50% of the world population). • affects healthy adults and causes high case fatality.
Differential diagnosis note: Seasonal human influenza should not be confused with the *common cold*, caused by *rhinoviruses*, which affects only the rhinopharyngeal mucosa and has a self-limiting course without major complications.	

6.1.2. Etiology and Viral Structure

- Family: *Orthomyxoviridae* (spherical RNA viruses with a complex antigenic structure).
- External and internal components:
    - Viral envelope: Derived from the membrane of the infected cell, it bears prominent spikes (the glycoproteins hemagglutinin - HA and neuraminidase - NA).
    - Hemagglutinin (HA): Mediates binding of the virus to sialic acid receptors on the host cell. There are 16 HA subtypes.
    - Neuraminidase (NA) or sialidase: An enzyme involved in the release and detachment of newly formed virions, preventing reinfection deep in the respiratory tract. There are 9 NA subtypes.
    - M proteins (M1 and M2): M2 has ion channel activity, specific to influenza A viruses.
    - Viral nucleocapsid: Composed of 8 segments of single-stranded RNA encoding 11 viral proteins, associated with the nucleoprotein (NP) and three polymerase proteins (P).

6.1.3. Epidemiology

- Seasonality: In the Northern Hemisphere, epidemics occur between November and February (in the Southern Hemisphere, between June and August).
- Mortality and morbidity: Worldwide, influenza affects 5-10% of adults and 20-30% of children each year. It is responsible for 3-5 million cases of severe illness and 250,000–500,000 deaths/year.
- Natural reservoir of infection:
    - Birds are the main natural reservoir of influenza A viruses and can host all subtypes.
    - Mammals such as pigs and horses can be infected (the pig being regarded as a genetic "mixing vessel" essential for the emergence of pandemic strains).
- Routes of transmission:
    - Direct: Person-to-person via the respiratory route (through droplets of nasopharyngeal secretions expelled by sneezing, coughing, talking) – the most common route.

    - Indirect: Via contaminated objects (handkerchiefs, personal items) – less frequently involved.
- Contagiousness and susceptibility:
    - Contagiousness index of over 90% (similar to measles and varicella).
    - Period of contagiousness: from 1-2 days before clinical onset until 6 days after symptom onset.
    - There is no cross-immunity between influenza A and B viruses.

6.1.4. Pathogenesis

The clinical and pathogenic course in the respiratory tract (in uncomplicated infection) proceeds in 3 phases:

1. Initial phase (intense viral replication): Lasts approximately 72 hours; the virus replicates in the surface epithelium and gradually spreads to the lower airways (bronchioles), facilitated by neuraminidase.
2. Immuno-inflammatory phase: Lasts 7-10 days; consists of massive destruction of the respiratory epithelium, bronchial wall edema, bronchial hypersecretion and the appearance of cytokine-mediated systemic signs (TNF-α, IFN-α, IL-6, IL-8).
3. Repair phase: Lasts up to 3 weeks; regeneration of the respiratory mucosa (possible bronchial instability or hyperreactivity / late-onset bronchial asthma).

6.1.5. Clinical Manifestations

- Common (seasonal) clinical form:
    - Incubation: Short, between 24-72 hours (mean 48 hours).
    - Invasion phase: Lasts 2-3 days. Abrupt onset with an infectious syndrome (high fever of 39-40°C, chills, intense retro-orbital headache, diffuse and lumbosacral myalgia and arthralgia).
    - Full-blown phase: Cough becomes constant and appears early (initially dry, then productive due to bronchial hypersecretion), accompanied by odyno-phagia. Fever lasts 3-5 days (complete remission within 5-7 days in the absence of complications).

- Population groups at risk of severe disease:
    - Young children (especially under 2 years) and the elderly (≥ 65 years)
    - Patients with chronic diseases (pulmonary, cardiovascular, metabolic/diabetes, renal, hemoglobinopathies).
    - Immunocompromised patients (including HIV, chemotherapy) and pregnant women (second and third trimesters).
- Hospitalization criteria in adults:
    - Altered consciousness; temperature < 35°C or > 40°C.
    - Dyspnea with a respiratory rate > 30/min.
    - Arterial hypotension (systolic < 90 mmHg or a drop of 40 mmHg from the usual value).
    - Tachycardia with a heart rate > 120/min.

6.1.6. Complications

1. Pulmonary:
    - Primary influenza viral pneumonia ("malignant influenza"): Rare but extremely severe; dyspnea, cyanosis, refractory hypoxemia, acute lesional (non-cardiogenic) pulmonary edema.
    - Secondary bacterial pneumonia: Occurs after a transient improvement of 2-3 days and is dominated by recurrence of fever and purulent sputum. Commonly involved pathogens: *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, S. pyogenes*.
    - Mixed (viral and bacterial) pneumonia, exacerbations of COPD / bronchial asthma, laryngeal croup (in children), otitis media and acute sinusitis.
2. Extrarespiratory:
    - Acute myositis: Predominantly affects the lower limb muscles and is accompanied by elevated serum levels of creatine phosphokinase.
    - Cardiac complications: Myocarditis (the most common; occurs 4-8 days after fever onset; sinus bradycardia, atrial fibrillation, ventricular extrasystoles, elevated CK-MB).
    - Neurological complications (encephalitis, myelitis, Guillain-Barré syndrome, Reye syndrome associated with aspirin administration in children).

6.1.7. Laboratory Diagnosis

- Specific etiological diagnosis:
  - Rapid tests: Detection of viral antigens in nasopharyngeal swabs by enzyme immunoassays (rapid result, moderate sensitivity of 70-75%).
  - RT-PCR (reverse transcriptase PCR): The molecular gold standard for detection of viral RNA in nasopharyngeal swabs; maximal sensitivity and specificity (essential in pandemics, e.g., H1N1).
  - Viral isolation in cell culture (MDCK): Isolation of the virus within the first 3 days of onset (historically considered the gold standard, but not used in current routine practice).
  - Serological diagnosis: A fourfold or greater rise in antibody titer (by hemagglutination inhibition - HI or ELISA) between the acute and convalescent phases (retrospective value).
- Nonspecific laboratory changes: Leukopenia with neutropenia at onset; leukocytosis $> 15.000/\mu$l suggests bacterial superinfection.

6.1.8. Treatment

- Etiological (antiviral) treatment:
  - Maximal efficacy if started early (within the first 48 hours of symptom onset).

Table 2: Antiviral treatment and chemoprophylaxis for influenza A and B

Antiviral agent	Use	Recommended for	Not recommended for use in	Adverse reactions
Oral oseltamivir	Treatment	Any age	N/A	• nausea • vomiting • headache *Post-marketing reports of serious skin reactions and sporadic transient neuro-psychiatric events[1].*
	Chemo-prophylaxis	3 months and older	N/A	

Inhaled zanamivir	Treatment	7 years and older	Persons with underlying respiratory disease (asthma, COPD)	• risk of bronchospasm • sinusitis • dizziness *Post-marketing reports of serious skin reactions and sporadic transient neuro-psychiatric events[1].*
	Chemo-prophylaxis	5 years and older	Persons with underlying respiratory disease (asthma, COPD)	
Intravenous peramivir	Treatment	6 months and older	N/A	• diarrhea *Post-marketing reports of serious skin reactions and sporadic transient neuro-psychiatric events[1].*
	Chemo-prophylaxis	Not recom-mended	N/A	
Oral baloxavir	Treatment	5 years and older	N/A	No more frequent than with placebo in clinical trials.
	Chemo-prophylaxis	Approved for post-exposure chemo-prophylaxis in persons aged 5 years and older		

- Symptomatic treatment:
    - Adequate hydration, bed rest, antipyretics/analgesics (paracetamol).
    - CAUTION: Avoid salicylates (aspirin) in children under 18 years because of the major risk of Reye syndrome.
- Antibiotic therapy: Reserved exclusively for the treatment of secondary bacterial complications (guided by Gram stain and urine/sputum cultures).

Table 3. Antiviral treatment in influenza (doses in children and adults)

ANTIVIRAL AGENT	***CHILDREN***	***ADULTS***
OSELTAMIVIR	A: 0-1 month: 2 mg/kg x 2/day, 5 days, PO A: 1-3 months: 2.5 mg/kg x 2/day, 5 days, PO A: 3-12 months: 3 mg/kg x 2/day, 5 days, PO A > 12 months, the dose depends on weight: • W < 15 kg: 30 mg x 2/day, 5 days, PO • W: 15-23 kg: 45 mg x 2/day, 5 days, PO • W: 23-40 kg: 60 mg x 2/day, 5 days, PO • W: > 40 kg: 75 mg x 2/day, 5 days, PO	75 mg x 2/day, 5 days, PO **IN SEVERE CASES REQUIRING ICU ADMISSION, DOUBLING THE DOSE IS RECOMMENDED (150 MG X 2/DAY, PO)**
ZANAMIVIR	10 mg (2 inhalations of 5 mg each) x 2/day, 5 days, from the age of 5 years **INHALATIONS ARE TAKEN BY MOUTH, USING A SPECIAL MOUTHPIECE DEVICE SUPPLIED BY THE MANUFACTURER.**	**10 MG (2 INHALATIONS OF 5 MG EACH) X 2/DAY, 5 DAYS** **INHALATIONS ARE TAKEN BY MOUTH, USING A SPECIAL MOUTHPIECE DEVICE SUPPLIED BY THE MANUFACTURER.**
PERAMIVIR	> 2 years and W < 50 kg: 12 mg/kg, slow IV infusion, single dose. > 2 years and W > 50 kg: 600 mg, slow IV infusion, single dose. **1 VIAL CONTAINS 20 ML OF PERAMIVIR CONCENTRATE, CONTAINING 200 MG PERAMIVIR. IT IS DILUTED IN NORMAL SALINE, 5% GLUCOSE OR RINGER'S SOLUTION.**	Single dose of 600 mg as a slow intravenous infusion (15-30 min). 1 vial contains 20 mL of peramivir concentrate, containing 200 mg peramivir. It is diluted in normal saline, 5% glucose or Ringer's solution.
BALOXAVIR	***W < 20 KG: ORAL SUSPENSION ONLY*** 10-20 kg: 2 mg/kg body weight (or the exact equivalent measured with the oral dosing syringe for the suspension). W: 20-80 kg: 40 mg single dose.	**W *< 80 KG: 40 MG SINGLE DOSE*** **W > 80 KG: 80 MG SINGLE DOSE**
W = WEIGHT; A = AGE; PO = PER OS (BY MOUTH); IV INFUSION = INTRAVENOUS INFUSION.		

6.1.9. Prophylaxis

- Specific prophylaxis (influenza vaccination):
  - The most effective preventive measure.
  - Types of vaccines:
    - *Inactivated and split vaccines* (injectable, containing 3 or 4 strains – trivalent or quadrivalent).
    - *Live attenuated vaccine* (administered intranasally, e.g., FluMist/Fluenz).
  - Administered annually, preferably in early autumn (October-November), before the influenza season.
  - Currently recommended for the entire population older than 6 months, with emphasis on high-risk groups.
- Antiviral chemoprophylaxis:
  - Use of oseltamivir for prophylactic purposes (e.g., after recent exposure to confirmed cases in persons at high risk of complications, or in a nosocomial outbreak).

6.1.10. Knowledge Assessment

1*. What is the mean incubation period of seasonal influenza?
A) 24–72 hours (mean 48 hours)
B) 5–10 days
C) 14–30 days
D) Exactly 3 weeks
E) 1–2 days in total

2*. Which of the following types of influenza virus is solely responsible for causing pandemics?
A) Influenza B virus only
B) Influenza C virus
C) Influenza A virus only
D) Both A and B viruses
E) Rhinoviruses

3*. What is the optimal time window for early initiation of etiological antiviral treatment in influenza?
A) Within the first 12 hours of onset
B) Within the first 48 hours of symptom onset
C) Within the first 7 days of onset
D) At any time during convalescence
E) Only after pulmonary complications have developed

4*. Which nonspecific hematological change is characteristic at the onset of uncomplicated influenza infection?
A) Marked leukocytosis with neutrophilia
B) Severe eosinophilia
C) Leukopenia with neutropenia
D) Reactive thrombocytosis
E) Secondary polycythemia

5*. What is the correct dose of oral oseltamivir recommended in adults with standard forms of influenza?
A) 30 mg twice daily for 5 days
B) 75 mg twice daily for 5 days
C) 150 mg once daily for 7 days
D) 60 mg three times daily for 3 days
E) A single dose of 600 mg

6*. Which antiviral agent is contraindicated for chemoprophylaxis?
A) Oral oseltamivir
B) Inhaled zanamivir
C) Intravenous peramivir
D) Oral baloxavir
E) All of the above options are recommended

7*. What is the main natural reservoir of influenza A viruses, able to host all subtypes?
A) Small rodents
B) Birds
C) Reptiles
D) Amphibians
E) Insects

8*. How long does the initial phase (intense viral replication) last in the clinical and pathogenic course in the respiratory tract?
A) Approximately 72 hours
B) 7–10 days
C) Up to 3 weeks
D) Exactly 24 hours
E) 5–6 hours

9*. What is the recommended period for administering the annual influenza vaccine?
A) In early spring (March-April)

B) In early autumn (October-November)
C) In midsummer (July-August)
D) At any time during winter
E) Once every 5 years

10*. What is the specific indication of oral baloxavir with regard to chemoprophylaxis?
A) It is completely prohibited at any age
B) It is approved for post-exposure chemoprophylaxis in persons aged 5 years and older
C) It is recommended exclusively for newborns
D) It is administered only to patients admitted to the ICU
E) It is used exclusively as curative treatment in animals

11. What are the characteristics of seasonal influenza epidemics, as opposed to pandemics?
A) They are caused by influenza A and B viruses
B) They are triggered by "antigenic drift" (minor antigenic variation)
C) They occur at intervals of 2-3 years for influenza A virus and 4-5 years for influenza B virus
D) They affect 5-15% of the population, with a mortality of 0.1%
E) They are caused only by influenza A virus through "antigenic shift"

12. What are the external and internal structural components of the influenza virus?
A) The viral envelope, derived from the membrane of the infected cell, bearing HA and NA spikes
B) Hemagglutinin (HA), with 16 subtypes, which mediates binding to sialic acid receptors
C) Neuraminidase (NA), with 9 subtypes, which mediates the release of new virions
D) The M proteins (M1 and M2), M2 having ion channel activity specific to influenza A viruses
E) A complex bacterial capsule composed of 4 peptidoglycan layers

13. Which elements are part of the routes of transmission and contagiousness of influenza?
A) Direct person-to-person transmission via the respiratory route (through droplets of nasopharyngeal secretions)

B) Indirect transmission via contaminated objects (handkerchiefs, personal items)
C) A contagiousness index of over 90% (similar to measles and varicella)
D) A period of contagiousness from 1-2 days before clinical onset until 6 days after onset
E) The existence of complete cross-immunity between A and B viruses

14. What are the 3 phases of the clinical and pathogenic course in the respiratory tract in uncomplicated infection?
A) The initial phase (intense viral replication, lasting approximately 72 hours)
B) The immuno-inflammatory phase (lasting 7-10 days, with destruction and edema)
C) The repair phase (lasting up to 3 weeks, with mucosal regeneration)
D) An obligatory chronic phase in all patients
E) A long-lasting asymptomatic viral latency phase of 5 years

15. Which population groups are mentioned as being at increased risk of severe influenza?
A) Young children (especially under 2 years) and the elderly
B) Patients with chronic diseases (pulmonary, cardiovascular, metabolic/diabetes, renal, hemoglobinopathies)
C) Immunocompromised patients (including HIV, chemotherapy)
D) Pregnant women (second and third trimesters)
E) Young competitive athletes with no other disease

16. What are the hospitalization criteria in adults?
A) Altered consciousness
B) Dyspnea with an increased respiratory rate
C) Arterial hypotension (low systolic pressure or a significant drop from the usual value)
D) Tachycardia with an increased heart rate
E) The presence of a mild sore throat alone

17. Which pulmonary and extrarespiratory complications can occur in the course of influenza?
A) Primary influenza viral pneumonia ("malignant influenza")

B) Secondary bacterial pneumonia with pathogens such as Streptococcus pneumoniae or Staphylococcus aureus
C) Acute myositis predominantly affecting the lower limb muscles, with elevated creatine phosphokinase
D) Myocarditis (the most common cardiac complication, occurring after 4-8 days)
E) Neurological complications (encephalitis, myelitis, Guillain-Barré syndrome, aspirin-associated Reye syndrome)

18. What are the methods of specific etiological laboratory diagnosis?
A) Rapid tests for the detection of viral antigens in nasopharyngeal swabs
B) RT-PCR (reverse transcriptase PCR) as the molecular gold standard
C) Viral isolation in cell culture (MDCK) within the first 3 days of onset
D) Serological diagnosis by a fourfold or greater rise in antibody titer (HI or ELISA)
E) Mandatory stool culture to identify the respiratory strain

19. Which adverse reactions or other features are associated with oral oseltamivir?
A) Nausea
B) Vomiting
C) Headache
D) Post-marketing reports of serious skin reactions and sporadic transient neuropsychiatric events
E) Obligatory irreversible chronic kidney failure at the first administration

20. Which adverse effects or precautions are associated with inhaled zanamivir?
A) Risk of bronchospasm
B) Sinusitis
C) Dizziness
D) It is not recommended for persons with underlying respiratory disease (asthma, COPD)
E) It is administered exclusively intravenously as a slow infusion

21. Which elements are part of symptomatic treatment and precautionary measures in influenza?
    A) Adequate hydration, bed rest, antipyretics/analgesics (paracetamol)
    B) Avoidance of salicylates (aspirin) in children under 18 years because of the risk of Reye syndrome
    C) Antibiotic therapy reserved exclusively for the treatment of secondary bacterial complications
    D) Routine use of antibiotics from the first day of illness in every patient with uncomplicated influenza
    E) Mandatory administration of aspirin to 1-month-old infants for fever

22. What are the dosing rules for oseltamivir in children according to weight or age?
    A) Age 0-1 month: 2 mg/kg x 2/day, 5 days, PO
    B) Age 1-3 months: 2.5 mg/kg x 2/day, 5 days, PO
    C) Age 3-12 months: 3 mg/kg x 2/day, 5 days, PO
    D) Weight 15-23 kg: 45 mg x 2/day, 5 days, PO
    E) Weight under 15 kg: 300 mg x 2/day, 5 days, PO

23. What are the indications and special features of intravenous peramivir?
    A) For > 2 years and W < 50 kg, 12 mg/kg is given as a slow IV infusion, single dose
    B) For > 2 years and W > 50 kg, 600 mg is given as a slow IV infusion, single dose
    C) One vial contains 20 mL of peramivir concentrate containing 200 mg peramivir and is diluted in normal saline, 5% glucose or Ringer's solution
    D) It is fully recommended as first-line chemoprophylaxis
    E) It is administered exclusively orally as 75 mg tablets

24. Which statements about oral baloxavir are true?
    A) It is approved for treatment in persons aged 5 years and older
    B) Adverse effects are no more frequent than with placebo in clinical trials
    C) It is approved for post-exposure chemoprophylaxis in persons aged 5 years and older
    D) For W between 20-80 kg, the dose is 40 mg as a single dose

E) It is administered exclusively by oral inhalation with a special device

25. What are the measures of specific prophylaxis and chemoprophylaxis?
    A) Influenza vaccination is considered the most effective preventive measure
    B) Inactivated and split vaccines are used (injectable, trivalent or quadrivalent)
    C) A live attenuated vaccine administered intranasally is used (e.g., FluMist/Fluenz)
    D) Vaccination is currently recommended for the entire population older than 6 months
    E) Antiviral chemoprophylaxis uses oseltamivir for prophylactic purposes after recent exposure

Correct answers: 1. A; 2. C; 3. B; 4. C; 5. B; 6. C; 7. B; 8. A; 9. B; 10. B; 11. A, B, C, D; 12. A, B, C, D; 13. A, B, C, D; 14. A, B, C; 15. A, B, C, D; 16. A, B, C, D; 17. A, B, C, D, E; 18. A, B, C, D; 19. A, B, C, D; 20. A, B, C, D; 21. A, B, C; 22. A, B, C, D; 23. A, B, C; 24. A, B, C, D; 25. A, B, C, D, E.

6.1.11. CLINICAL CASES

Case 1:

History of present illness: A 3-year-old child is brought by his mother to the emergency department for sudden fever (39.6°C), loss of appetite, agitation and marked right ear pain. Approximately 30 hours earlier, the illness began with high fever, chills, sneezing and a simple febrile seizure during the rapid rise in temperature. Over the last few hours he has become drowsy and complains of pain in the right ear.

The family and social history reveals that he has not received influenza vaccination and that there are several cases of respiratory viral infections in the nursery he attends.

Physical examination on admission: Moderately to severely impaired general condition, febrile ($39,1$°C), warm extremities, diffusely congested pharynx, abundant serous nasal discharge. Otoscopy: intense congestion of the right tympanic membrane, which is slightly bulging. Respiratory system: harsh vesicular breath sounds, no added crackles, respiratory rate 32 breaths/min, oxygen saturation

(SpO_2): 97% on room air. Cardiovascular system: regular heart sounds, tachycardia ($AV: 135$ beats/min), BP 90/50 mm Hg. Abdomen soft, unremarkable.

Questions:

1. What is the most likely presumptive diagnosis in this 3-year-old child?
2. How can the occurrence of the seizure in the first hours of the illness be explained?
3. Which common local complication in children is suggested by the ear pain and the otoscopic findings?
4. What minimum laboratory and ancillary investigations are needed to assess this pediatric patient?
5. What antiviral and symptomatic treatment is indicated, given the age of 3 years?

Case 2:

History of present illness: A 26-year-old man, a computer programmer, with no known chronic medical history and no drug allergies, presents to his family physician's office with an acute febrile syndrome that began approximately 48 hours earlier. He reports an abrupt onset with fever ($38,9$°C), intense frontal headache, generalized myalgia ("aching all over"), marked fatigue, odynophagia and an irritating dry cough.

The patient reports that he has not been vaccinated against influenza in the current season and that he has been in direct contact with an office colleague with confirmed influenza. At home he took paracetamol (2 grams/day), with transient improvement of the fever.

Physical examination on admission: Good general condition, patient oriented to time and place, febrile ($38,3$°C), mildly hyperemic conjunctivae. Congested pharynx without purulent exudate. Respiratory system: vesicular breath sounds present bilaterally, no crackles, respiratory rate 16 breaths/min, SpO_2: 98% on room air. Cardiovascular system: regular heart sounds, $AV: 82$ beats/min, BP 120/75 mm Hg. Abdomen soft, non-tender on palpation.

Questions:

1. What positive diagnosis is established for this young adult?
2. Why does this clinical presentation fall into the category of uncomplicated forms?

3. Which epidemiological and clinical criteria support the diagnosis at the height of the epidemic season, without necessarily requiring complex laboratory tests?
4. Is it necessary to initiate specific antiviral therapy (such as oseltamivir) in this case, and within what optimal time window?
5. What general recommendations regarding symptomatic treatment, lifestyle and diet will be given to the patient for the convalescent period?

Case 3:

History of present illness: A 78-year-old man with a personal history of chronic obstructive pulmonary disease (COPD), NYHA class III chronic heart failure and mild chronic kidney disease is brought by ambulance to the Infectious Diseases Clinic with high fever ($39,0$°C), chills, distressing cough with mucopurulent sputum, severe dyspnea at rest and deterioration of his general condition. The symptoms began abruptly 4 days earlier, initially with a typical influenza-like presentation, followed over the last 24 hours by sudden worsening, marked by tachypnea and peripheral cyanosis. He has not received seasonal influenza vaccination.

Physical examination on admission: Severely impaired general condition, mild drowsiness, pallor, perioral and perinasal cyanosis. Respiratory system: tachypnea (28 breaths/min), SpO_2: 87% on room air, bilateral basal subcrepitant crackles and diffuse wheezing. Cardiovascular system: regular, tachycardic heart sounds (AV: 110 beats/min), BP 100/60 mm Hg. Moderate chronic lower leg edema. No meningeal signs.

Questions:

1. What complex presumptive diagnosis is established for this elderly patient?
2. What are the major factors in the patient's history that place him in the category at increased risk of complicated forms?
3. Which type of post-influenza pulmonary complication is most likely responsible for the sudden worsening 24 hours ago?
4. Which emergency investigations (laboratory, imaging and etiological) are mandatory on admission?
5. What emergency therapeutic management is required in this case (including respiratory support and antiviral/antibiotic therapy)?
6.

6.1.12. CLINICAL CASE SOLUTIONS

Case 1: Influenza in a young child, with an ear complication and febrile seizures

1. Presumptive diagnosis: Seasonal influenza infection (moderate form), complicated by acute otitis media and an episode of simple febrile seizures.
2. Explanation of the seizures: The sudden, rapid rise in body temperature in the onset phase of the viral infection may trigger febrile seizures in young children with an immature seizure threshold.
3. Ear complication: Acute otitis media, i.e., inflammation of the middle ear mucosa due to the extension of edema from the upper respiratory tract.
4. Mandatory investigations: Nasopharyngeal swab for a rapid influenza test or RT-PCR, complete blood count (to rule out a concomitant severe bacterial infection) and a detailed ENT examination.
5. Therapeutic management: Since the symptoms began approximately 30 hours earlier, the child is within the optimal therapeutic window of less than 48 hours for antiviral administration. For a 3-year-old child, the dose of oseltamivir is calculated strictly according to body weight, as per the guideline:
    - If weight is under 15 kg: 30 mg twice daily for 5 days, orally.
    - If weight is between 15–23 kg: 45 mg twice daily for 5 days, orally.
    - If weight is between 23–40 kg: 60 mg twice daily for 5 days, orally.

Symptomatic treatment is added with antipyretics (paracetamol or ibuprofen, strictly avoiding aspirin because of the major risk of Reye syndrome), adequate oral hydration and an ENT consultation for targeted antibiotic therapy of the acute otitis media.

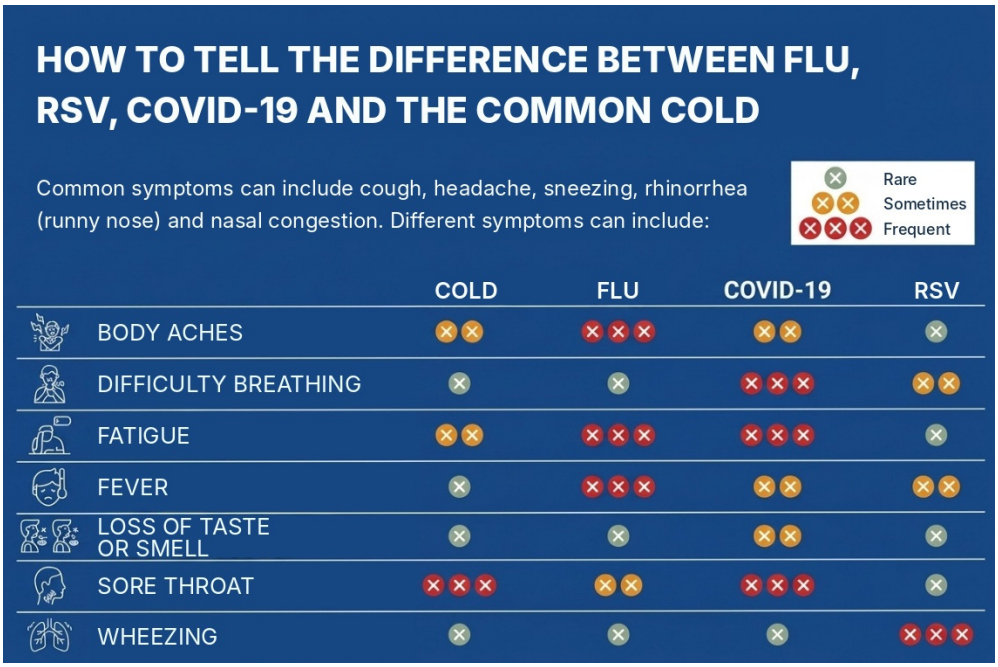
Case 2: Influenza – moderate form in a young adult without comorbidities

1. Positive diagnosis: Uncomplicated seasonal influenza.
2. Definition of the uncomplicated form: Absence of signs of respiratory failure, pneumonia, decompensation of chronic diseases or need for hospitalization; symptoms limited to a systemic infectious syndrome and upper respiratory tract signs.

3. Epidemiological/clinical criteria: Abrupt onset with high fever, severe myalgia, headache and cough at the height of the epidemic season, together with a contact within an outbreak. Since the patient presents approximately 48 hours after onset, the antiviral is administered within the optimal window, in which it can shorten the duration of symptoms by 1–1.5 days. The standard dose of oseltamivir for adults is 75 mg twice daily for 5 days, orally.
4. Convalescence recommendations: Rest at home, rigorous oral hydration, paracetamol for fever/myalgia, avoidance of strenuous physical exertion and gradual resumption of activities after the fever has resolved.

Case 3: Influenza – severe form in an elderly patient with multiple comorbidities

1. Presumptive diagnosis: Seasonal influenza (severe form) complicated by secondary bacterial pneumonia, acute respiratory failure and exacerbation of chronic conditions (COPD and heart failure).
2. Major risk factors: Advanced age (≥ 65 years) and multiple chronic comorbidities (pulmonary, cardiac, renal).
3. Pulmonary complication: Secondary bacterial pneumonia (suggested by the biphasic course: apparent improvement or stagnation followed by sudden worsening with purulent sputum, tachypnea and hypoxemia).
4. Mandatory investigations: RT-PCR / rapid influenza test, complete blood count, ESR, CRP, renal function tests (urea, creatinine), arterial blood gases (Astrup), emergency chest X-ray, sputum for bacteriological examination, and blood cultures.
5. Therapeutic management: Emergency admission to the Intensive Care Unit or the Infectious Diseases Department, provision of respiratory support and oxygen therapy guided by blood gas analysis. Prompt administration of oseltamivir; although 4 days have passed since onset, the antiviral is beneficial in severe hospitalized cases. The usual dose is 75 mg twice daily, orally, but the guideline specifies that in severe cases requiring ICU admission doubling the dose to 150 mg twice daily is recommended. Broad-spectrum empirical antibiotic therapy targeting the pathogens involved in superinfections (such as *Streptococcus pneumoniae* or *Staphylococcus aureus*) must be added.



Symptoms	Seasonal allergy	Influenza	COVID-19
Fever	✗	✓	✓
Chills	✗	✓	✓
Sneezing	✓	✓	✗
Itching (itchy sensation of the face)	✓	✗	✗
Cough	✓	✓	✓
Nasal congestion (stuffy nose)	✓	✓	✓
Rhinorrhea	✓	✓	sometimes
Loss of smell	✗	✗	✓
Sore throat	✗	✓	✓
Watery eyes	✓	✓	✗
Muscle aches	✗	✓	✓
Headache	sometimes	✓	sometimes
Difficulty breathing	sometimes	sometimes	✓
Vomiting and diarrhea	✗	✗	sometimes
Fatigue	✗	✓	✓
Incubation period	Gradual onset	1-4 days	2-14 days
Duration	Allergy season	5-7 days	Varies from case to case

6.2. SARS-COV-2 INFECTION (COVID-19)

6.2.1. Introduction and Definition

The coronavirus *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2) was first identified in December 2019 in Wuhan, China, causing the disease named COVID-19. It was declared a pandemic by the World Health Organization on March 11, 2020.

Before the discovery of SARS-CoV-2, six coronaviruses pathogenic to humans were known, all of animal origin.

6.2.2. Etiology and Viral Structure

SARS-CoV-2 belongs to the family *Coronaviridae*; it is a betacoronavirus whose genome consists of positive-sense single-stranded RNA. The name derives from Latin, in which *corona* means crown, reflecting the appearance of the viral envelope on electron microscopy, where small needle-like projections formed by the *spike* (S) protein can be seen.

In addition to the *S* protein, SARS-CoV-2 contains three other structural proteins: the *E* (envelope) protein, the *M* (membrane) protein and the *N* (nucleocapsid) protein, as well as 16 non-structural proteins (nsp1-16), which play various roles in the pathogenesis of the disease. The *spike* protein is an essential protein on the surface of the virus that mediates receptor recognition, viral attachment and entry into the host cell. It is the main target of COVID-19 vaccines and antiviral therapies. Subunit S_1 (Attachment): Contains the N-terminal domain and the receptor-binding domain. Its main role is to bind to the human cell receptor, called angiotensin-converting enzyme 2 (ACE-2). Subunit S_2 (Fusion): Fuses the viral envelope with the host cell membrane through irreversible conformational changes. It contains several structural components: the fusion peptide, the heptad repeat regions (HR1 and HR2), the receptor-binding domain, the transmembrane domain and the cytoplasmic tail. Activation by cleavage: host cell proteins (proteases), such as transmembrane serine protease 2, cleave the S protein at a specific cleavage site (S_1/S_2), activating the mechanism by which the virus enters the cell.

6.2.3. Epidemiology and Viral Variants

Natural reservoir: Bats of the species *Rhinolophus affinis*; SARS-CoV-2 shares 96% genetic similarity with Bat-CoV RaTG13, but transmission to humans is thought to have involved an intermediate host that is still unknown, possibly the pangolin (91%

genetic similarity with Pangolin-CoV). The source of infection consists of asymptomatic or symptomatic patients with SARS-CoV-2 infection.

Route of transmission: Human-to-human transmission of SARS-CoV-2 is predominantly respiratory, via Flügge droplets. Aerosol transmission is well documented only in hospital settings where aerosol-generating medical procedures are performed: advanced cardiopulmonary resuscitation, high-flow oxygen therapy, nebulization of medications, invasive/non-invasive mechanical ventilation, bronchial suction and bronchoscopy. Transmission through direct contact with contaminated objects is not a determining factor in the epidemiological chain, and fecal-oral transmission has not been clearly documented.

Contagiousness: It begins 1-2 days before symptom onset and lasts on average 6-8 days after disease onset. In severe forms of the disease and in immunocompromised patients, the contagious period may extend to 14-20 days, owing to prolonged viral shedding.

Susceptibility: Susceptibility is universal; COVID-19 can affect any person not immunized either naturally or by vaccination.

Post-infection immunity: The duration of immunity after disease is not clearly defined and is still under evaluation. Based on the humoral immune response, quantified by the titer of SARS-CoV-2 neutralizing antibodies (anti-RBD IgG), and on the cellular immune response provided by RBD-specific memory B lymphocytes, a degree of protection is estimated to persist for 6-12 months after disease.

Viral variants: They are classified according to their impact on transmissibility, disease severity and immunity: variants of concern, variants of interest and variants under monitoring. Important variants include:

- *Alpha variant* (501Y.V1, lineage B.1.1.7, UK, November 2020) — approximately 70% higher transmission rate, higher risk of hospitalization and death.
- *Beta variant* (501Y.V2, lineage B.1.351, South Africa, December 2020) — 50% higher transmission rate, 3-4 times higher risk of hospitalization and ICU admission.
- *Gamma variant* (501Y.V3, lineage B.1.1.28 - P1, Brazil, January 2021) — 2.6 times higher transmission rate, 2-3 times higher risk of hospitalization and ICU admission.
- *Delta variant* (double-mutant variant, lineage B.1.617.2, India, April-May 2021) — 40-60% more transmissible than the Alpha variant, with an impact on disease severity and evidence of a reduced antiviral humoral immune response in convalescent and vaccinated individuals.

6.2.4. Pathogenesis

From a pathogenic standpoint, SARS-CoV-2 infection is divided into three stages, which correspond to the clinical phases of disease progression:

Stage 1 or the asymptomatic phase (first few days): SARS-CoV-2 binds to the epithelial cells of the nasal mucosa through the interaction between the cellular ACE-2 receptor and subunit S_1 of the viral S protein. The virus then enters the host cell by endocytosis, replicates intracellularly and spreads along the respiratory tract, in the setting of a limited innate immune response. RT-PCR tests become positive during this phase.

Stage 2 or the mild symptomatic phase (80% of cases): It corresponds to the viral replicative phase and to the first week of illness. The virus propagates along the upper airways and migrates toward the lower respiratory tract. This stage correlates with mild clinical symptoms of acute upper respiratory tract infection and with the triggering of a more robust innate immune response.

Stage 3 or the immune phase of the disease: It corresponds to the second week of illness and is characterized by the onset of acute respiratory failure with hypoxia, which progresses to ARDS in 20% of cases. The course is marked by the appearance of pulmonary infiltrates (ground-glass opacities). SARS-CoV-2 replicates intensely in the lower airways, where it infects cells expressing the ACE-2 receptor, especially type II pneumocytes. Their invasion leads to aberrant activation of the immune response, with the release of numerous pro-inflammatory molecules. This "cytokine storm" leads to the recruitment of neutrophils, B lymphocytes and T CD_4+ and CD_8+ lymphocytes, which attempt to contain the infectious process, but the "orchestration" of diffuse alveolar damage progresses to ARDS. There is a positive feedback loop in which the attempt at *viral clearance* through exaggerated cell-mediated cytotoxicity leads to the destruction of type I and type II pneumocytes and to the release of viral particles that infect neighboring cells. In addition to alveolar damage, there is formation of cellular syncytia through the fusion of type II pneumocytes, intra-alveolar fibrin deposition, and numerous intrapulmonary microthromboses, with disruption of the microvascular architecture, extensive endothelial injury and angiogenesis. These vascular lesions are also found in the multiple organ dysfunction of critical forms.

6.2.5. Clinical Picture

SARS-CoV-2 infection has a wide range of clinical forms, from asymptomatic forms (20-40% of all cases) to critical forms that progress to ARDS and multiple organ dysfunction. Asymptomatic patients can transmit the virus, but less than symptomatic patients, because the intensity and duration of viral shedding are significantly lower.

The incubation period averages 5-6 days, ranging from 2 to 14 days.

The clinical picture includes:

- *Systemic symptoms:* fever, myalgia, arthralgia, headache, marked physical fatigue.
- *Symptoms of upper (URTI) and lower (LRTI) respiratory tract involvement:* anosmia, rhinorrhea, dysgeusia, odynophagia, dysphonia, dry cough $\pm$ hemoptysis, diffuse chest pain, dyspnea.
- *Gastrointestinal symptoms (especially in children):* nausea, vomiting, diarrhea, abdominal pain.
- *Silent hypoxemia or happy hypoxemia:* a clinical entity described in COVID-19. Some patients with acute respiratory failure do not report dyspnea, which on the one hand suggests a pathophysiological paradox and on the other may considerably delay presentation to a physician, diagnosis and initiation of treatment. Silent hypoxemia may involve a central mechanism, which could explain the absence of the compensatory mechanisms for hypoxemia.

Physical examination is usually unremarkable, except in cases of LRTI, in which diffuse bronchial rales (tracheobronchitis) and bilateral crepitant or subcrepitant crackles may be detected.

Clinical forms of the disease:

- *Mild forms:* The symptoms described above, defined by the absence of (radiological) SARS-CoV-2 pneumonia.
- *Moderate form:* Characterized by the presence of SARS-CoV-2 pneumonia.
- *Severe forms:* Defined by any of the following: respiratory rate $\geq$ 30/min, $SpO_2 \leq 93\%$ (at rest), $P_aO_2/F_iO_2 \leq 300$ mmHg, rapid progression (> 50%) of CT changes within 24-48 hours.
- *Critical forms:* Defined by respiratory distress syndrome requiring orotracheal intubation and mechanical ventilation, or by multiple organ dysfunction.

6.2.6. Positive Diagnosis

Diagnosis is based on epidemiological, clinical and paraclinical criteria.

6.2.6.1. Nonspecific laboratory diagnosis

Complete blood count: It may be normal or may show leukopenia with lymphopenia, or even leukocytosis with neutrophilia (in the absence of bacterial superinfection), mild anemia and infection-related thrombocytopenia. In severe and critical forms the following may occur: severe lymphopenia, coagulation disorders (significant increase in D-dimers, prolonged aPTT), elevated LDH, elevated inflammatory markers (C-reactive protein, fibrinogen, ferritin, IL-6, IL-1), elevated troponin, hepatic cytolysis (elevated ALT and AST), azotemia (acute kidney injury), and other changes depending on complications.

6.2.6.2. Specific (etiological) laboratory diagnosis

Virological diagnosis by molecular biology tests: Tests based on viral nucleic acid amplification are used, the usual technique being reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA performed on nasopharyngeal specimens. A positive PCR test confirms the diagnosis and does not require reconfirmation by another test. A negative PCR test does not rule out infection, since a false-negative result is possible depending on the timing of testing and the quality of sampling.
Virological diagnosis by detection of SARS-CoV-2 antigen: Rapid antigen testing identifies the viral antigen; it is less sensitive than RT-PCR but has the advantage of a faster result.
Serological diagnosis: It should not be used to diagnose the acute phase, as antibodies are absent in the first days. It is useful for documenting late complications or for retrospective diagnosis. Anti-N antibodies do not appear after vaccination, unlike anti-S antibodies.

6.2.6.3. Imaging studies

Chest radiography: It remains the first-line investigation in non-severe forms. In mild forms it may be normal. Most commonly it shows *ground-glass opacities* with a peripheral, bilateral distribution at the lung bases.

Non-contrast computed tomography (CT): It is much more sensitive than radiography. Ground-glass opacities may be associated with consolidation, pleural thickening, interlobular septal thickening and air bronchograms. Other frequently described lesions: ground-glass opacities associated with a *crazy paving pattern*, bronchiectasis, pleural effusion, pericarditis, lymphadenopathy. CT pulmonary angiography is indicated when associated PE is suspected.
Other paraclinical investigations: ECG (for suspected acute coronary syndrome, myocarditis or arrhythmias), arterial blood gas analysis (to quantify respiratory failure).

6.2.7. Differential Diagnosis and Prognosis

The differential diagnosis includes: other viral respiratory diseases (influenza viruses, parainfluenza viruses, RSV, rhinoviruses, enteroviruses, metapneumoviruses, adenoviruses, other coronaviruses), bacterial respiratory diseases (typical bacteria and atypical bacteria such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Coxiella burnetii*, *Legionella pneumophila*), immunocompromised patients (acute bacterial pneumonia, influenza, pneumonia caused by specific pathogens such as *Pneumocystis carinii*, *Nocardia sp.*, *Mycobacterium tuberculosis*, *CMV*, *Aspergillus sp.*, *Candida sp.*), fever with pulmonary infiltrates in patients with bacterial sepsis, and acute gastrointestinal symptoms.

6.2.8. Course and prognosis

Most cases have a favorable course, self-limiting within 1-2 weeks without specific treatment. However, 15-20% require hospitalization and 2-3% require intensive care.
Risk factors for severe forms: Older age (>65 years), male sex, comorbidities (cardiovascular disease, diabetes mellitus, obesity, chronic respiratory disease, chronic kidney disease, malignancies).
Special patient categories: In children under 1 year of age most cases are asymptomatic or mild; pregnant women are at increased risk of severe forms, preeclampsia, preterm birth or miscarriage (vertical transmission is rare, at 2%).

6.2.9. Complications

Short-term complications:
- *Cardiovascular:* Prothrombotic state (deep vein thrombosis, acute coronary syndromes STEMI/non-STEMI), myocarditis, cardiac arrhythmias, pericarditis.
- *Pulmonary:* PE, pneumothorax.

- *Neurological and neuropsychiatric:* Stroke, encephalopathy, encephalitis, Guillain-Barré syndrome.
- *Renal and hepatic:* Acute kidney injury, acute liver injury.
- *Hematological:* COVID-19-associated coagulopathy, autoimmune hemolytic anemia, immune thrombocytopenia.
- *Other:* Multisystem inflammatory syndrome with manifestations similar to Kawasaki disease, described in children (MIS-C).

Long-term complications (> 3 months): Pulmonary fibrosis with chronic respiratory failure, persistence of multiorgan symptoms (post-COVID-19 syndrome or *Long COVID*).

6.2.10. Etiological treatment of SARS-CoV-2 infection

Antiviral treatment	***Indication***	***Optimal timing of initiation***	***Route of administration and dosage***	***Clinical aspects***
Nirmatrelvir + Ritonavir (Paxlovid) (Preferred first-line option)	*Adults and children aged >12 years (and weighing > 40 kg)*	*Within the first 5 days of symptom onset*	*Oral, at home* 300 mg nirmatrelvir plus 100 mg ritonavir twice daily for 5 days	Carries a risk of significant drug-drug interactions and requires review of long-term medications. Requires dose adjustment according to renal function.
Remdesivir (Veklury) ***(Preferred second-line option)***	*Adults and children aged > 28 days (and weighing > 3 kg)*	Within the first 7 days of symptom onset	Intravenous infusion for 3 consecutive days	Requires assessment of liver function and prothrombin time before initiation Safe and approved, including in renal failure.
Molnupiravir (Lagevrio) (Alternative option / second line)	*Adults (when the other options are unavailable or contraindicated)*	Within the first 5 days of symptom onset	Oral, at home 800 mg twice daily for 5 days.	<u>Contraindicated in pregnancy.</u> Lower overall clinical efficacy compared with Paxlovid or remdesivir.

Symptomatic management (for all mild/moderate forms)

Symptomatic treatment: Antipyretics (paracetamol), analgesics or antitussives are given to control fever, headache, myalgia and cough. Hydration and rest: Adequate fluid intake to prevent dehydration and physical rest adapted to tolerance.

6.2.11. Knowledge assessment

1*. What is the mean incubation period of SARS-CoV-2 infection?

A) 1–2 days

B) 5–6 days

C) 14–21 days

D) 30 days

E) 48 hours

2*. What is the main cellular receptor used by SARS-CoV-2 for attachment to and entry into the host cell?

A) Angiotensin-converting enzyme 2 (ACE-2)

B) The acetylcholine receptor

C) CD4

D) Sialyllactose

E) CD8

3*. What oxygen saturation value (SpO_2) on room air defines, together with other criteria, a severe form of COVID-19?

A) $\leq 98\%$

B) $\leq 95\%$

C) $\leq 93\%$

D) $\leq 85\%$

E) $\leq 90\%$

4*. Which of the following oral antiviral options is the preferred first-line treatment for mild-to-moderate disease in high-risk patients?

A) Remdesivir

B) Molnupiravir

C) Nirmatrelvir + ritonavir (Paxlovid)

D) Oseltamivir

E) Zanamivir

5*. What is the main recognized natural reservoir of SARS-CoV-2?

A) Pigs

B) Migratory birds

C) Field rodents

D) Bats of the species *Rhinolophus affinis*

E) Domestic rodents

6*. Which laboratory technique is the molecular gold standard for the specific etiological diagnosis of the acute phase of COVID-19?

A) ELISA serological testing for IgG

B) Hemagglutination inhibition assay

C) Reverse-transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal specimen

D) Stool culture

E) Simple direct microscopic examination

7*. Which of the following viral variants was designated lineage B.1.1.7 (initially detected in the UK)?

A) Alpha

B) Beta

C) Gamma

D) Delta

E) Omicron

8*. What is the optimal recommended window, from symptom onset, for initiating oral antiviral treatment with nirmatrelvir + ritonavir (Paxlovid)?

A) Within the first 14 days

B) Within the first 5 days

C) At any time during ICU stay

D) Only after day 10

E) Within the first 24 hours, necessarily intravenously

9*. Which nonspecific hematological abnormality is most frequently associated with severe and critical forms of COVID-19?

A) Marked eosinophilia

B) Leukocytosis with basophilia

C) Severe lymphopenia

D) Secondary polycythemia

E) Massive reactive thrombocytosis

10*. What is the recommended duration of intravenous remdesivir treatment according to current guidelines?

A) 1 day, single dose

B) 3 consecutive days

C) 14 days

D) 30 days

E) A mandatory fixed 7 days

11. Which of the following structural proteins are components of the SARS-CoV-2 virus?

A) Spike protein (S)

B) Envelope protein (E)

C) Membrane protein (M)

D) Nucleocapsid protein (N)

E) Influenza A-type hemagglutinin-neuraminidase

12. What are the main documented routes of transmission of SARS-CoV-2?

A) The respiratory route via Flügge droplets

B) Aerosols generated during medical procedures in hospital settings (e.g., bronchoscopy, orotracheal intubation)

C) Transmission through direct contact with contaminated objects as the main determining factor in the epidemiological chain

D) Human-to-human transmission predominantly via respiratory secretions

E) Fecal-oral transmission, clearly documented as the main route of infection

13. Which features define stage 3 (the immune/hyperinflammatory phase) of SARS-CoV-2 infection?

A) Onset of acute respiratory failure and hypoxia, progressing to ARDS in some cases

B) Triggering of a "cytokine storm" through massive release of pro-inflammatory molecules

C) Formation of cellular syncytia and intrapulmonary microthromboses

D) Intense viral replication in the lower respiratory tract, with infection of type II pneumocytes

E) Complete absence of any imaging or laboratory abnormalities

14. Which clinical signs and entities are described in the clinical picture of COVID-19?

A) Anosmia and dysgeusia

B) Silent hypoxemia ("happy hypoxemia"), in which patients have severe hypoxemia without reporting dyspnea

C) Gastrointestinal symptoms such as diarrhea, nausea or vomiting, especially in children

D) Fever, myalgia, marked physical fatigue

E) Symmetrical acute flaccid paralysis confined to the lower limbs from the first day

15. Which paraclinical and imaging criteria are used to define severe forms of COVID-19?

A) Respiratory rate ≥ 30/min

B) $SpO_2 \leq 93\%$ at rest

C) The ratio $PaO_2/FiO_2 \leq 300$ mmHg

D) Rapid progression of CT changes > 50% within 24-48 hours

E) Exclusively the absence of any pulmonary opacity on radiography

16. Which nonspecific laboratory abnormalities may occur in severe and critical forms of COVID-19?

    A) A significant decrease in D-dimers and prolonged aPTT

    B) Markedly elevated C-reactive protein (CRP), ferritin and IL-6

    C) Hepatic cytolysis reflected by elevated ALT and AST

    D) Azotemia and acute kidney injury

    E) Elevated troponin in the setting of myocardial involvement

17. Which statements about imaging investigations in COVID-19 are true?

    A) Chest radiography remains the first-line investigation in non-severe forms

    B) The most common typical imaging appearance is bilateral, peripheral ground-glass opacities

    C) Non-contrast computed tomography (CT) is much more sensitive than chest radiography

    D) CT may show ground-glass opacities associated with a mosaic paving pattern (*crazy paving pattern*)

    E) CT pulmonary angiography is indicated when associated pulmonary embolism (PE) is suspected

18. Which of the following conditions are included in the differential diagnosis of SARS-CoV-2 infection?

    A) Other viral respiratory infections (influenza, RSV, adenoviruses, rhinoviruses)

    B) Typical and atypical bacterial pneumonias (*Mycoplasma pneumoniae*, *Legionella pneumophila*)

    C) Pneumonias in immunocompromised patients caused by specific pathogens (*Pneumocystis carinii*, *Aspergillus sp.*)

    D) Bacterial sepsis with fever and pulmonary infiltrates

    E) Rabies virus infections acquired by direct cutaneous transmission

19. Which population groups have been identified as having major risk factors for severe forms of COVID-19?

    A) Older adults over 65 years of age

    B) Males

C) Patients with obesity or diabetes mellitus

D) Patients with cardiovascular or chronic respiratory disease

E) Malignancies and chronic kidney disease

20. Which short-term complications may occur in the course of COVID-19?

A) Deep vein thrombosis and acute coronary syndromes (prothrombotic state)

B) Pulmonary embolism (PE) and pneumothorax

C) Neurological complications such as stroke, encephalitis or Guillain-Barré syndrome

D) Multisystem inflammatory syndrome in children

E) Chronic pulmonary fibrosis permanently established within the first 24 hours of fever onset

21. Which clinical and epidemiological features are characteristic of pregnant women infected with SARS-CoV-2?

A) They are at increased risk of severe forms of disease

B) They are at risk of preeclampsia, preterm birth or miscarriage

C) Vertical transmission is considered rare (approximately 2%)

D) They are naturally and completely immune to any form of coronavirus infection

E) They require automatic exclusion from any form of ultrasound evaluation

22. Which features and precautions are associated with the use of the antiviral nirmatrelvir + ritonavir (Paxlovid)?

A) It is administered orally at home

B) It carries a risk of significant drug-drug interactions due to the presence of ritonavir

C) It requires careful review of the patient's long-term medications before administration

D) It requires dose adjustment according to the patient's renal function

E) It is completely contraindicated exclusively in renal failure, any other form of dose evaluation being prohibited

23. Which statements apply to remdesivir in the treatment of COVID-19?

A) It is given as an intravenous infusion for 3 consecutive days

B) It is the preferred second-line antiviral option in current guidelines

C) It requires assessment of liver function and prothrombin time before initiation

D) It is safe and approved, including in renal failure

E) It is a drug administered exclusively orally at home for 30 days

24. Which features are associated with the antiviral molnupiravir (Lagevrio)?

A) It is an alternative / second-line option

B) It is administered orally, at home, 800 mg twice daily for 5 days

C) It is strictly contraindicated in pregnancy

D) It has lower overall clinical efficacy compared with Paxlovid or remdesivir

E) It is the preferred first-line option for infants under 1 month of age

25. Which general measures are part of symptomatic and lifestyle/ dietary management of mild/moderate forms of COVID-19?

A) Administration of antipyretics (paracetamol), analgesics or antitussives

B) Adequate fluid intake to prevent dehydration

C) Physical rest adapted to the patient's tolerance

D) Monitoring of symptoms and general condition

E) Routine administration of broad-spectrum antibiotics within the first hour of onset to absolutely every asymptomatic patient.

Correct answers: 1. B; 2. A; 3. C; 4. C; 5. D; 6. C; 7. A; 8. B; 9. C; 10. B; 11. A, B, C, D; 12. A, B, D; 13. A, B, C, D; 14. A, B, C, D; 15. A, B, C, D; 16. B, C, D, E; 17. A, B, C, D, E; 18. A, B, C, D; 19. A, B, C, D, E; 20. A, B, C, D; 21. A, B, C; 22. A, B, C, D; 23. A, B, C, D; 24. A, B, C, D; 25. A, B, C, D.

6.2.12. CLINICAL CASES

CASE 1:

History of present illness: A 55-year-old male engineer living in an urban area is admitted as an emergency via the Ambulance Service for persistent fever ($> 38,5°$C) for 6 days, distressing dry cough, profound fatigue and progressive dyspnea that has become disabling over the last 24 hours, occurring even on minimal exertion (personal hygiene). Symptoms began gradually, with moderate fever, myalgia and anosmia appearing on the third day. Over the past 48 hours, dyspnea has worsened dramatically. Past medical history: grade II obesity (BMI > 35 kg/m^2), recently diagnosed type 2 diabetes mellitus and essential hypertension. He has not received the recommended COVID-19 booster doses.

Physical examination on admission: Obese patient, severely ill, perioral cyanosis, tachypneic (respiratory rate 32 breaths/minute), thoracoabdominal paradoxical (see-saw) breathing. SpO_2: 83% on room air (rising to 92% with oxygen via non-rebreather mask at 15 L/min). Lung auscultation: bilaterally diminished vesicular breath sounds, crackles over all lung fields ("Velcro" crackles). Regular, tachycardic heart sounds (HR 118 beats/minute), BP 155/90 mm Hg.

Questions

1. What presumptive diagnosis would you make given the clinical picture and the epidemiological context?
2. What imaging (chest CT) and laboratory (inflammatory/coagulation markers) changes are characteristic and expected in this case?
3. Which major factors in the patient's history place him in the high-risk category for severe forms?
4. What respiratory support measures and emergency pharmacological therapy are required in this critical case?
5. What short-term complications may occur in a critically ill patient with COVID-19 and metabolic comorbidities?

CASE 2:
History of present illness: A 74-year-old retired woman presents with the chief complaint of moderate fever ($38,0$°C) of gradual onset 5 days earlier, dry irritative cough, marked loss of appetite, diffuse myalgia and pronounced weakness (severe physical fatigue). She reports contact 7 days earlier with a grandchild confirmed positive for SARS-CoV-2 infection. Past medical history: paroxysmal atrial fibrillation (on direct oral anticoagulants), osteoporosis and chronic venous insufficiency. She has not been vaccinated against COVID-19 in the last 12 months.

Physical examination on admission: Normosthenic patient, moderately impaired general condition, afebrile at the time of examination ($37,1$°C), oriented to time and place. Normal pharynx. Respiratory system: occasional cough, harsh vesicular breath sounds at the lung bases, no clinically evident crackles; respiratory rate 20 breaths/minute, SpO_2: 93% on room air. Cardiovascular system: irregular heart rhythm, HR ~80 beats/minute, BP 130/75 mm Hg. No peripheral edema.

Questions

1. What is the presumptive diagnosis for this patient?
2. Which antiviral and supportive therapeutic options are indicated according to current guidelines, given her age and comorbidities?
3. Which clinical criteria differentiate a moderate form from a severe form in the course of the infection?
4. Why is particular caution needed when prescribing the oral antiviral (Paxlovid) to this patient?
5. What monitoring recommendations are required for this patient in home or hospital care?

6.2.13. ANSWERS

Case 1: COVID-19 – Severe form with ARDS in a patient with obesity and diabetes.

1. **Presumptive diagnosis:** Acute SARS-CoV-2 infection, critical form; acute respiratory distress syndrome; severe acute hypoxemic respiratory failure; grade II obesity and newly diagnosed type 2 diabetes mellitus. The diagnosis is based on the clinical picture of severe respiratory distress, marked hypoxemia and the history of epidemiological exposure.
2. **Imaging and laboratory changes:**
    - *Imaging:* Non-contrast chest CT shows extensive pulmonary lesions, with bilateral *ground-glass opacities*, areas of consolidation and a mosaic paving pattern (*crazy paving*), involving more than 50% of the parenchyma ("white lung").
    - *Laboratory:* Severe lymphopenia and markedly elevated inflammatory markers (CRP, ESR, ferritin, IL-6) reflecting the cytokine storm, as well as elevated D-dimers and fibrinogen, indicating a procoagulant state with a high risk of thromboembolic events.
3. **Major risk factors:** Age 55 combined with grade II obesity, recently diagnosed type 2 diabetes mellitus, essential hypertension and the absence of COVID-19 booster doses.
4. **Emergency management (respiratory support and therapy):** Emergency admission to the Intensive Care Unit (ICU), with advanced respiratory support (high-flow oxygen therapy or mechanical ventilation depending on blood gas results). Pharmacological therapy includes remdesivir, systemic corticosteroids to modulate the hyperinflammatory phase, and anticoagulants at prophylactic/therapeutic doses.
5. **Short-term complications:** Pulmonary embolism, deep vein thrombosis, acute coronary syndromes, myocarditis, acute kidney injury, secondary bacterial superinfections and multiple organ dysfunction.

Case 2: COVID-19 – Moderate form with interstitial pneumonia in an older adult

1. **Presumptive diagnosis:** SARS-CoV-2 infection, moderate form, complicated by SARS-CoV-2 interstitial pneumonia, with a relevant history of paroxysmal atrial fibrillation. The diagnosis is supported by the epidemiological criterion (direct contact

within a cluster), the clinical picture of respiratory infection and the presence of interstitial pneumonia.

2. **Therapeutic options and management:** Advanced age (74 years) and comorbidities place the patient in the high-risk category for progression to severe forms. Early specific oral antiviral therapy is indicated (e.g., *Paxlovid*, with extreme caution and the necessary alternatives because of major interactions with direct oral anticoagulants) or intravenous *remdesivir* , initiated within the first 5 days of onset. Management is completed by monitoring oxygen saturation with pulse oximetry, oxygen therapy if needed, and avoidance of early systemic corticosteroids in non-hypoxemic forms.
3. **Clinical criteria for differentiation:** The moderate form shows clinical or imaging signs of pneumonia but maintains respiratory parameters within safe limits (respiratory rate < 30/min and $SpO_2 > 93\%$ on room air), unlike the severe form, which develops tachypnea (≥ 30/min), desaturation ($\leq 93\%$) or rapid progression of lesions.
4. **Caution when administering the oral antiviral (Paxlovid):** Because the patient is on long-term direct oral anticoagulants for paroxysmal atrial fibrillation, Paxlovid (which contains ritonavir, a potent enzyme inhibitor) can significantly increase the plasma concentration of the anticoagulant and the risk of major bleeding, requiring careful evaluation of interactions, dose adjustment or a switch to remdesivir.
5. **Monitoring recommendations:** Strict monitoring of oxygen saturation by pulse oximetry 2-3 times daily, close follow-up of fever and of the onset or worsening of dyspnea, maintenance of adequate hydration, and reassessment of heart rhythm in view of the history of atrial fibrillation.

6.3. PERTUSSIS (WHOOPING COUGH)

Whooping cough (*pertussis*) is an acute, highly contagious infectious disease of the respiratory tract, caused mainly by *Bordetella pertussis*. The term pertussis comes from Latin and means "violent cough"; the popular name "whooping cough" refers to the paroxysmal inspiratory noise (the whoop, which is rare in infants under 6 months and frequently absent in adults), and the disease is also known as the "100-day cough" because of its long duration.

6.3.1. Etiological spectrum (genus Bordetella)

Of the 10 known species, only three are medically relevant:

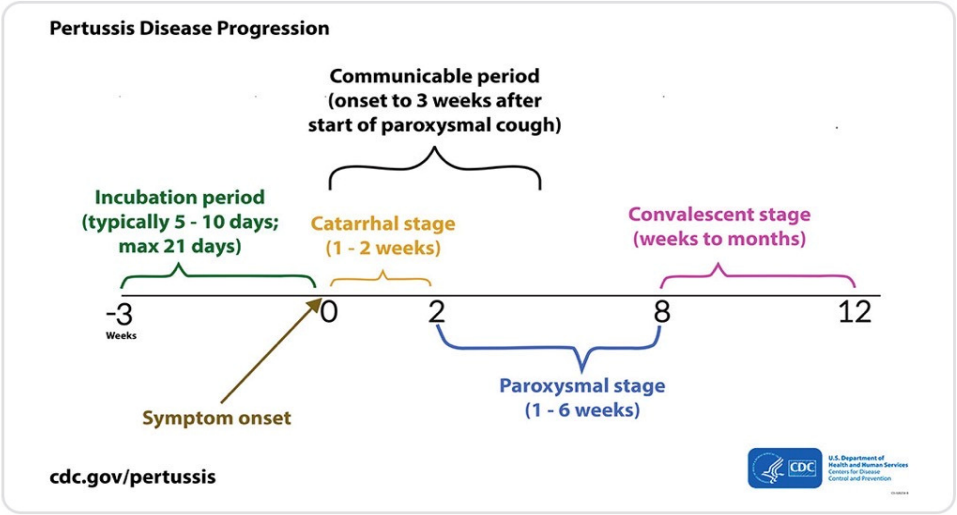
- *B. pertussis:* Infects humans exclusively and is the main agent.
- *B. parapertussis:* Causes a similar but milder illness, as it does not express pertussis toxin. *B. pertussis – B. parapertussis* coinfections have been described.
- *B. bronchiseptica:* An animal pathogen (kennel cough, atrophic rhinitis in pigs), rarely involved in opportunistic respiratory infections in humans. Other species such as *B. holmesii* may cause sepsis in immunocompromised patients.

6.3.2. Major virulence factors

- *Pertussis toxin (PT):* A binding B subunit and an enzymatic A protomer that ADP-ribosylates G proteins in target cells. It stimulates mitogenesis, alters lymphocyte trafficking and acts as an adhesin.
- *Surface adhesins:* Filamentous hemagglutinin (FHA) and pertactin (an outer membrane protein), which bind to cellular integrins.
- *Fimbriae:* Important role in adhesion; the main antigens for agglutinating antibodies.
- *Other factors:* Tracheal cytotoxin (damage to the ciliated epithelium), adenylate cyclase (inhibits local immunity), dermonecrotic toxin and lipooligosaccharide.

6.3.3. Clinical course by stage

Stage	Estimated duration	Main clinical manifestations and characteristic signs
Incubation	7–10 days, ranging between 5 and 21 days	Clinically silent period, without overt symptoms.
Catarrhal stage	1–2 weeks	• coryza • excessive lacrimation • mild cough • low-grade fever Picture difficult to distinguish from a common viral infection.
Paroxysmal stage	2–4 weeks	• paroxysms of spasmodic cough (5–10 coughs in a single expiration), frequently followed by vomiting (emesis) and expulsion of a mucus plug. • whooping inspiration (the "whoop") caused by rapid inspiration against a closed glottis. • Transient exophthalmos, cyanosis and jugular venous distension may occur.
Convalescent stage	2–8 weeks or 1–3 months	Gradual resolution of the cough, with a risk of paroxysmal recurrence during subsequent intercurrent viral infections (at 6–12 months).



6.3.4. Criteria for positive diagnosis

- Epidemiological criterion: History of contact with a confirmed case within the last 21 days, absence of vaccination or an incomplete vaccination schedule.
- Clinical criterion: Cough lasting at least two weeks, accompanied by at least one of the following: paroxysms of coughing, noisy inspiration (*whooping*) or post-tussive vomiting, or episodes of apnea in children under 1 year of age. Caution is required with atypical forms in adults, adolescents or vaccinated individuals, characterized by paroxysmal cough that worsens at night in the absence of fever.

- Laboratory criterion:
    - *Complete blood count:* Marked leukocytosis with absolute lymphocytosis (> 10-20 x 10□/L or 80–90%) in young children; rarely seen in adults.
    - *Gold standard (culture):* Nasopharyngeal swab or aspirate (collected with a flexible catheter or a Dacron/Rayon swab) inoculated immediately onto Bordet-Gengou or Regan-Lowe selective media. Only swabs with a polyester tip (Dacron or Rayon) and a flexible shaft are used for sampling (cotton or calcium alginate swabs, which inhibit the reactions, must not be used). Cultures are positive during the first 3 weeks in the absence of treatment and become negative within 5 days of starting antibiotic therapy.
    - *Molecular biology (PCR):* Higher sensitivity and speed (results within a few hours), but requires rigorous standardization to avoid false-positive results.
    - *Serology:* ELISA tests using highly purified pertussis toxin (PT) and WHO reference sera.
      The anti-PT IgG titer is interpreted as follows:

      ≥ 100 UI/ml indicates acute/recent infection (in the absence of recent vaccination);

      < 40 UI/ml is negative;

      40–99 IU/mL represents a *borderline* zone, requiring repeat testing or collection of a second sample after 7–10 days to capture a rising titer.

Cautionary note: If the patient has been vaccinated within the last 12 months, a high titer may be a consequence of vaccination, in which case detection by PCR is preferred.

6.3.5. Diagnostic particularities

- Standard clinical criterion: Cough lasting at least two weeks, accompanied by at least one of the following: paroxysms of coughing, noisy inspiration (*whooping*) or post-tussive vomiting (in infants under 1 year, episodes of apnea are defining).
- Beware of atypical forms: Adults, adolescents or vaccinated individuals may present with attenuated clinical pictures; any paroxysmal cough that worsens at night and occurs in the absence of fever warrants diagnostic suspicion and investigation.

6.3.6. Case classification

Possible: any person meeting the clinical criteria

Probable: any person meeting the clinical criteria and having an epidemiological link to a confirmed case.

Confirmed: any person meeting the clinical and laboratory criteria.

6.3.7. Therapeutic management protocol

According to WHO guidelines and the specialist literature, management aims at eradicating the infection, reducing contagiousness and providing supportive care.

Patient isolation:

- Respiratory isolation (droplet precautions) until at least 48 hours after initiation of appropriate antimicrobial therapy or for 21 days from onset in the absence of treatment.
- Etiological antibiotic therapy (macrolides – first line):
    - Aim: Eradication of nasopharyngeal infection; it alters the clinical course only if given early, in the catarrhal stage.
    - Erythromycin (estolate): 1–2 g/day in adults divided into 3 doses (40–50 mg/kg/day in children, with the possibility of doubling the dose in severe infections), for 7–14 days. Comment: Gastrointestinal adverse reactions are frequent.

    - Clarithromycin: 500 mg/day in adults divided into 2 doses (15 mg/kg/day in children), for 7 days. In neonates under 1 month of age, the preferred regimen is 7,5 mg/kg × 2/zi for 7 days.
    - Azithromycin: 500 mg on day 1, then 250 mg/day as a single daily dose for 5 days (or 10 mg/kg/day for 3 days in infants/children).
- Therapeutic alternative (in case of macrolide allergy):
    - Trimethoprim-sulfamethoxazole (co-trimoxazole): 160 mg trimethoprim / 800 mg sulfamethoxazole divided into 2 doses in adults, for 14 days. Efficacy data are limited. It is absolutely contraindicated in neonates/infants under 6 weeks of age because of the risk of hypertrophic pyloric stenosis.
- Supportive treatment and complications:
    - Hospitalization is mandatory for infants and severe cases (risk of apnea in 27.1% of infants, pneumonia in 9.4%, seizures in 2.6%, and death).
    - Providing a quiet environment to prevent paroxysms triggered by external stimuli.
    - Beta-adrenergic agonists, glucocorticoids and antitussives have not proven effective and are not recommended.
    - Mechanical complications include subconjunctival hemorrhages, petechiae, hernias (inguinal/abdominal), pneumothorax and rib fractures secondary to increased intrathoracic pressure during coughing paroxysms.

Table 1. Recommended treatment and post-exposure prophylaxis by age and risk category.

Age group	Clarithromycin	Azithromycin	Erythromycin*	Co-trimoxazole**
Newborns (under 1 month)	**Preferred** in newborns 7.5 mg/kg × 2/day, 7 days	10 mg/kg, 1/day, 3 days	Not recommended due to its association with hypertrophic pyloric stenosis	Not licensed for infants under 6 weeks of age
Infants (1–12 months) and children > 12 months	**1 month – 11 years:**	**1–6 months:** 10 mg/kg, 1/day, 3 days	**1–23 months:** 125 mg every 6 hours, 7 days	**6 weeks–5 months:** 120 mg × 2/day, 7 days
	Under 8 kg: 7.5 mg/kg × 2/day, 7 days	**>6 months:** 10 mg/kg (max 500 mg), 1/day, 3 days	**2–7 years:** 250 mg every 6 hours, 7 days	**6 months–5 years:** 240 mg × 2/day, 7 days
	8–11 kg: 62.5 mg × 2/day, 7 days		**8–17 years:** 500 mg every 6 hours, 7 days	**6–11 years:** 480 mg × 2/day, 7 days
	12–19 kg: 125 mg × 2/day, 7 days			**12–17 years:** 960 mg × 2/day, 7 days
	20–29 kg: 187.5 mg × 2/day, 7 days			
	30–40 kg: 250 mg × 2/day, 7 days			
	12–17 years: 500 mg × 2/day, 7 days			
Adults	500 mg × 2/day, 7 days	500 mg/day, 1/day, 3 days	500 mg every 6 hours, 7 days	960 mg × 2/day, 7 days
Pregnancy	Not recommended	Not recommended	**Preferred**	**Contraindicated**

* doses may be doubled in severe infections

** if macrolides are contraindicated or not tolerated

Source: PHE – Guidelines for the Public Health Management of Pertussis in England

6.3.8. Management of contacts

The priority groups for public health intervention are the following:

Group 1: Persons at increased risk of developing severe complications ("vulnerable"):

- unvaccinated infants (aged under 2 months), regardless of the mother's vaccination status
- infants aged at least 2 months who are unvaccinated or partially vaccinated

(fewer than 3 doses of DTaP by 1 year of age), regardless of the mother's vaccination status.

Group 2: Persons at increased risk of transmitting the bacterium to persons in Group 1

- pregnant women (>32 weeks of gestation);

• healthcare workers who work with infants and/or pregnant women;
• persons whose activity involves regular, close or prolonged contact with infants too young to be fully vaccinated;
• persons living in the same household as an infant too young to be fully vaccinated.
Significant healthcare-associated exposure involves direct, unprotected contact within 2 meters, for a cumulative period of more than 1 hour, with an infectious case OR direct contact with respiratory secretions from an infectious case, for example during a procedure or examination of the nose/throat, without wearing appropriate protective equipment.

6.3.9. Prophylaxis and vaccination protocol

- Post-exposure chemoprophylaxis:
    - It targets the priority groups: Group 1 (unvaccinated infants under 2 months or infants partially vaccinated with < 3 doses of DTaP) and Group 2 (pregnant women in the third trimester, healthcare workers and household contacts of vulnerable infants).
    - Recommended for household members and high-risk contacts (infants under 1 year, pregnant women), regardless of vaccination history, preferably using macrolides (e.g., erythromycin or azithromycin) to reduce the transmission rate.
- Active immunization (vaccination):
    - Whole-cell vaccines (wP): Prepared by heat and chemical inactivation; highly effective (mean efficacy ~85%), but with increased reactogenicity (fever, local reactions, rarely febrile seizures or hypotonic-hyporesponsive episodes). Widely used in developing countries.
    - Acellular vaccines (aP): Contain pertussis toxoid, filamentous hemagglutinin, pertactin and, optionally, fimbriae. Preferred in industrialized countries because of their favorable safety profile. Protection correlates best with the levels of anti-pertactin, anti-fimbrial and anti-pertussis toxin antibodies.
    - WHO and national schedule:
        - Primary vaccination: 3 doses in the first year of life (at 2, 4 and 6 months, with boosters at 15–18 months and 4–6 years). In unvaccinated or

partially vaccinated contacts under 10 years of age, rapid completion of the schedule is recommended, while those over 10 years of age who have not received a booster in the last 5 years are given one dose of a pertussis-containing vaccine (Tdap).

- Boosters in adolescents and adults: One dose of a Tdap-type combined vaccine (with reduced diphtheria and acellular pertussis antigen content) is recommended in preadolescence, in unvaccinated adults and, mandatorily, in healthcare workers, in order to reduce the infectious reservoir and protect young unimmunized infants.
- Vaccination of pregnant women: Recommended after 32 weeks of gestation (in the third trimester of pregnancy) or at any gestational age if they are at risk of transmitting the bacterium to infants, in order to ensure transplacental transfer of protective antibodies to the newborn.

6.3.10. Knowledge assessment: multiple-choice tests

1*. What is the mean incubation period of pertussis according to the text?

A) 1–3 days

B) 7–10 days, with a range of 5 to 21 days

C) 14–30 days

D) A fixed 3 weeks

E) 2–4 weeks

2*. Which of the following species of the genus *Bordetella* does not express pertussis toxin, yet causes a similar disease?

A) *Bordetella pertussis*

B) *Bordetella bronchiseptica*

C) *Bordetella holmesii*

D) *Bordetella parapertussis*

E) *Bordetella bronchiseptica* and *Bordetella holmesii*

3*. What is the main virulence factor of *Bordetella pertussis*?

A) Pertactin

B) Filamentous hemagglutinin

C) Pertussis toxin (PT)

D) Tracheal cytotoxin

E) Lipooligosaccharide

4*. What characteristic hematological change is found in the complete blood count of young children with pertussis?

A) Marked neutrophilia with eosinophilia

B) Severe leukopenia with lymphopenia

C) Marked leukocytosis with absolute lymphocytosis (80–90%)

D) Severe thrombocytopenia with hemolytic anemia

E) Transient pancytopenia

5*. What must be used to collect a nasopharyngeal swab for bacteriological culture, according to the gold standard?

A) Ordinary cotton swabs

B) Calcium alginate swabs

C) Exclusively polyester-tipped swabs (Dacron or rayon) with a flexible shaft

D) A sterile wooden tongue depressor

E) A sterile absorbent cotton swab

6*. What is the minimum duration of respiratory isolation (droplet precautions) in a patient with pertussis who is not receiving antibiotic treatment?

A) 48 hours from onset

B) 5 days from onset

C) 10 days from onset

D) 21 days from onset

E) 30 days from onset

7*. Which macrolide antibiotic is given to infants under 1 month of age (newborns) as the first-line option for treatment/prophylaxis, according to the data provided?

A) Azithromycin as a single lifetime dose

B) Clarithromycin (7,5 mg/kg × 2/zi for 7 days)

C) Erythromycin estolate at a maximum dose of 2 g/day for one month

D) Co-trimoxazole as a single dose

E) No macrolide is permitted in newborns

8*. Which of the following substances or drug classes has **not** proven effective and is not recommended in the supportive treatment of pertussis?

A) Oxygen therapy

B) Beta-adrenergic agonists, glucocorticoids and antitussives

C) Intravenous rehydration solutions

D) Macrolide antibiotics

E) Small, frequent feedings

9*. What is the WHO and national recommended age for administering a dose of Tdap-type combined vaccine to adolescents/adults, or for boosters aimed at preventing an infectious reservoir?

A) Only at 1 year of age

B) Every 6 months, mandatorily, in institutional settings

C) In preadolescence, in unvaccinated adults and in healthcare workers (as well as a booster at over 10 years of age for those who have not received one in the last 5 years)

D) Exclusively in elderly persons over 65 years of age

E) Only during the first trimester of pregnancy

10*. According to the case definition, how is any patient who meets the clinical criteria and has an epidemiological link to a confirmed case classified?

A) Possible case

B) Randomly proven case

C) Probable case

D) Laboratory-confirmed case

E) Discarded case

11. What are the clinical manifestations characteristic of the paroxysmal stage of pertussis?

A) Bouts of spasmodic coughing (5–10 coughs on a single expiration)

B) Persistent high fever above 39.5°C every afternoon

C) Post-tussive vomiting (emesis) and expulsion of a mucus plug

D) Whooping inspiration (*"reprise"* / *whoop*) caused by rapid inspiration against a closed glottis

E) Transient exophthalmos, cyanosis and jugular venous distension

12. Which species of the genus *Bordetella* are recognized as medically relevant?

A) *Bordetella pertussis*

B) *Bordetella parapertussis*

C) *Bordetella bronchiseptica*

D) *Bordetella avium*

E) *Bordetella holmesii*

13. What are the major virulence factors of *Bordetella pertussis*?

A) Pertussis toxin (PT)

B) Filamentous hemagglutinin (FHA) and pertactin

C) Fimbriae

D) Tracheal cytotoxin and adenylate cyclase

E) Heat-labile Shiga-type enterotoxin

14. Which elements are part of the standard clinical criteria established for the case definition of pertussis?

    A) Cough lasting at least two weeks

    B) Paroxysms of coughing

    C) Inspiratory whoop (*whooping*) or post-tussive vomiting

    D) Apneic episodes in a child under 1 year of age

    E) Moderate generalized jaundice and skin pruritus

15. Which methods are included in the laboratory criteria for the positive diagnosis of pertussis?

    A) Isolation of *Bordetella pertussis* from a clinical specimen (culture - the gold standard)

    B) Detection of *Bordetella pertussis* nucleic acid in a clinical specimen (PCR)

    C) Specific serological response (ELISA tests using purified pertussis toxin)

    D) Parasitological stool examination by stool culture

    E) PPD intradermal skin test

16. How are anti-PT IgG titer values (by ELISA) interpreted in the absence of vaccination in the previous 12 months?

    A) A titer ≥ 100 UI/ml indicates acute or recent infection

    B) A titer < 40 UI/ml is a negative result

    C) Values between 40 and 99 IU/mL represent a *borderline* (indeterminate) zone

    D) Any value above 10 IU/mL is considered chronic invasive infection

    E) A titer of 50 IU/mL automatically rules out any suspicion of disease

17. Which etiological antibiotic regimens (first line - macrolides) are mentioned for adults or children?

    A) Erythromycin (estolate): 1–2 g/day in adults (40–50 mg/kg/day in children), for 7–14 days

B) Clarithromycin: 500 mg/day in adults divided into 2 doses (15 mg/kg/day in children), for 7 days

C) Azithromycin: 500 mg on day 1, then 250 mg/day as a single daily dose for 5 days (or 10 mg/kg/dayfor 3 days in infants/children)

D) Aqueous penicillin G IV as a single dose of 10 million IU

E) Tetracycline hydrochloride 2 g per day in newborns

18. Which mechanical or clinical complications may occur during the course of pertussis?

A) Subconjunctival hemorrhages and petechiae on the face/trunk

B) Abdominal or inguinal hernias and pneumothorax

C) Rib fractures secondary to increased intrathoracic pressure during coughing

D) Mandatory hospitalization for infants and severe cases (risk of apnea, pneumonia, seizures)

E) Post-infectious atrophic liver cirrhosis

19. Which categories of persons belong to Group 1 (persons at increased risk of developing severe complications / "vulnerable")?

A) Unvaccinated infants under 2 months of age, regardless of the mother's vaccination status

B) Infants aged at least 2 months who are unvaccinated or partially vaccinated (fewer than 3 doses of DTaP by 1 year of age), regardless of the mother's status

C) Young adult elite athletes

D) Persons over 80 years of age with no respiratory history

E) Patients with minor orthopedic limb injuries

20. Which categories of persons belong to Group 2 (persons at increased risk of transmitting the bacterium to persons in Group 1)?

A) Pregnant women in the third trimester of pregnancy (> 32 weeks)

B) Healthcare workers who work with infants and/or pregnant women

C) Persons whose activity involves regular, close or prolonged contact with infants too young to be fully vaccinated

D) Persons living in the same household as an infant too young to be fully vaccinated

E) Veterinarians specializing exclusively in the diseases of large farm animals

21. What characterizes a significant healthcare-associated exposure?

A) Direct, unprotected contact within 2 meters, for a cumulative period of more than 1 hour, with an infectious case

B) Direct contact with respiratory secretions from an infectious case (e.g., during a procedure or examination of the nose/throat without appropriate protective equipment)

C) Mere presence in the same hospital building on different floors, without visual or direct contact

D) Exchange of medical documents by e-mail

E) The conditions mentioned are not mandatory if the exposed persons are unvaccinated or partially vaccinated infants

22. What characteristics are attributed to whole-cell pertussis vaccines (*wP*)?

A) They are prepared by heat and chemical inactivation

B) They have a high mean efficacy (approximately 85%)

C) They have increased reactogenicity (fever, local reactions, rarely febrile seizures or hypotonic-hyporesponsive episodes)

D) They are completely free of any local adverse reactions

E) They are widely used in developing countries

23. Which elements define acellular pertussis vaccines (*aP*) and the protection they confer?

A) They contain pertussis toxoid, filamentous hemagglutinin, pertactin and, optionally, fimbriae

B) They are preferred in industrialized countries because of their favorable safety profile

C) Protection correlates best with the levels of anti-pertactin, anti-fimbrial and anti-pertussis toxin antibodies

D) They contain whole live bacteria carefully attenuated by serial passage in embryonated eggs

E) They are prohibited by international protocol in the pediatric population

24. What recommendations regarding vaccination of pregnant women against pertussis are mentioned in the text?

A) It is recommended after 32 weeks of gestation (in the third trimester of pregnancy)

B) It may be given at any gestational age if the pregnant woman is at risk of transmitting the bacterium to infants

C) Its main purpose is to ensure transplacental transfer of protective antibodies to the newborn

D) It is given exclusively in the first week of pregnancy

E) It is strictly contraindicated at any stage of pregnancy

25. Which statements are true regarding post-exposure chemoprophylaxis and the established control measures?

A) It targets the priority groups (Group 1 and Group 2)

B) It is recommended for household members and high-risk contacts (infants under 1 year, pregnant women), regardless of vaccination history, preferably using macrolides to reduce the transmission rate

C) In unvaccinated or partially vaccinated contacts under 10 years of age, rapid completion of the vaccination schedule is recommended

D) Contacts over 10 years of age who have not received a booster in the last 5 years are given one dose of a pertussis-containing vaccine (Tdap)

E) It is carried out exclusively by administering injectable beta-lactam antibiotics for 30 days.

Correct answers:

1. B; 2. D; 3. C; 4. C; 5. C; 6. D; 7. B; 8. B; 9. C; 10. C; 11. A, C, D, E; 12. A, B, C, E; 13. A, B, C, D; 14. A, B, C, D; 15. A, B, C; 16. A, B, C; 17. A, B, C; 18. A, B, C, D; 19. A, B; 20. A, B, C, D; 21. A, B, E; 22. A, B, C, E; 23. A, B, C; 24. A, B, C; 25. A, B, C, D

6.3.11. CLINICAL CASES

Case 1:

History of present illness

A 2-month-old male infant from an urban area is admitted urgently to the Infectious Diseases Department for paroxysms of distressing cough, perioral cyanosis and repeated episodes of respiratory arrest (apnea) during the paroxysms, followed by respiratory distress and physical exhaustion. Symptoms began approximately 10 days earlier with serous rhinorrhea, sneezing and a mild, irritative cough, without fever. Over the last 48 hours, the cough has changed in character, becoming paroxysmal (bouts with apnea and cyanosis), frequently triggered by feeding or handling.

Relevant personal medical and epidemiological history: born at term by cesarean section, breastfed. The infant has not received any vaccine dose under the National Immunization Program (the primary vaccination schedule was not started because of temporary refusal by the family). For about 2 weeks the mother has had a persistent, dry, hacking cough, which has not been diagnosed.

Physical examination on admission

Severely ill general condition, transient perioral cyanosis, respiratory rate 58 breaths/minute, apneic episodes observed on the ward. Oxygen saturation (SpO_2): 84% on room air (corrected to 96% with an oxygen mask). Respiratory system: harsh vesicular breath sounds, no focal crackles. Cardiovascular system: regular heart sounds, sinus tachycardia (HR: 160 beats/minute). No focal neurological signs, but marked fatigue after the paroxysms.

Questions

1. What is the presumptive diagnosis, what is the epidemiological classification of the case, and to which risk group does this infant belong?

2. Which specific laboratory investigations and sampling methods are mandatory for the etiological confirmation of *Bordetella pertussis* infection in a young infant?
3. What are the major risks and main clinical complications described in infants under 1 year of age who develop this form of the disease?
4. Which emergency and supportive therapeutic measures are indicated for monitoring and treating a hospitalized infant with severe paroxysms of apnea and cyanosis?
5. Which etiological antibiotic regimen and duration of administration are recommended for a newborn or a 2-month-old infant?

Case 2:
History of present illness

A 7-year-old schoolchild presents to the infectious diseases outpatient clinic with a chief complaint of persistent spasmodic cough of almost 3 weeks' duration, which has not improved with symptomatic treatment and common antitussive syrups. The cough began insidiously as an ordinary viral respiratory infection, but over the last week it has become noisy, with frequent paroxysms, predominantly at night, during which the child has bouts of staccato coughing on a single expiration, followed by a deep, crowing inspiration (inspiratory whoop / *whooping*) and post-tussive vomiting (emesis).

The vaccination history shows that the patient received only the first doses of the primary series in the first months of life, with the subsequent preschool boosters missing. Several cases of prolonged cough have been reported among other classmates at his school.

Physical examination on admission

Moderately affected general condition, afebrile, oriented, normal build. Mildly hyperemic pharynx. Respiratory system: normal vesicular breath sounds, no adventitious sounds; respiratory rate 22 breaths/minute, SpO_2: 97% on room air. Cardiovascular system: regular heart sounds, HR 84 beats/minute, BP 100/60 mm Hg. No neurological or abdominal abnormalities; a few mild petechiae on the face and conjunctivae, which appeared after intense coughing bouts.

Questions
1. How does the clinical picture presented (prolonged spasmodic cough, inspiratory whoop and emesis) correlate with the 4 stages of pertussis?

2. Which hematological changes (complete blood count) and which serological or direct tests are expected in this case?
3. How should anti-PT IgG titer results obtained by ELISA be correctly interpreted, and what interference may occur depending on the vaccination history?
4. What are the main possible mechanical complications associated with intense coughing bouts in a 7-year-old child?
5. Which public health measures and post-exposure prophylaxis are required for contacts in the child's school?

Case 3:
History of present illness

A 34-year-old female patient, a healthcare worker (nurse in a pediatric ward), presents to the infectious diseases physician complaining of a hacking, dry, irritative cough lasting approximately 18 days. She reports that the cough has gradually worsened, being very troublesome at night and causing episodes of mild choking, but without the typical inspiratory whoop (*whooping*) or vomiting. She has had no fever throughout the illness.

The epidemiological history reveals that she lives with her husband and their 6-week-old son (who is completely unvaccinated because of his age). The patient has not received any booster dose of a pertussis-containing combined vaccine in recent years.

Physical examination on admission

Good general condition, afebrile, oriented to time and place. Visible mucous membranes clear. Respiratory system: diffusely harsh vesicular breath sounds, no pulmonary crackles; respiratory rate 16 breaths/minute, SpO_2: 98% on room air. Cardiovascular system: regular heart sounds, HR 76 beats/minute, BP 120/75 mm Hg. Abdomen soft, non-tender.

Questions

1. What clinical features characterize *Bordetella pertussis* infection in the adult population and in healthcare workers compared with infants?

2. To which priority risk category (Group 1 or Group 2) does the patient's household contact belong, and what is the epidemiological risk for the 6-week-old child?

3. Which clinical and epidemiological criteria mandate suspicion of pertussis in an adult with prolonged cough in the absence of fever?
4. Which strict respiratory isolation measures and period of exclusion from work apply to a healthcare worker with confirmed or suspected pertussis?
5. Which post-exposure chemoprophylaxis regimens are recommended for a 6-week-old infant in direct contact with an infectious case?

6.3.12. Clinical case solutions

Case 1: Pertussis – Severe form with apnea in an unvaccinated infant

1. Presumptive diagnosis, classification and risk group assignment:
    - Presumptive diagnosis: Pertussis syndrome (whooping cough), severe form, complicated by apneic episodes, cyanosis and acute respiratory distress.
    - Case classification: Case confirmed (based on the characteristic clinical picture of paroxysmal coughing bouts with apnea in an infant with a definite epidemiological link to an index case - the mother with persistent cough) or initially classified as a probable/confirmed case after specimen collection.
    - Risk group assignment: The infant belongs to Group 1 (persons at increased risk of developing severe complications / "vulnerable"), being an unvaccinated infant under 2 months of age, regardless of the mother's vaccination status.
2. Specific laboratory investigations and sampling methods:
    - Direct diagnosis: Collection of a nasopharyngeal swab or nasopharyngeal aspirate is recommended.
    - Mandatory technical requirements: For nasopharyngeal swabs, only polyester-tipped swabs (Dacron or rayon) with a flexible plastic or aluminum shaft are used; cotton or calcium alginate swabs are prohibited, because their residues inhibit microbiological reactions and PCR. Specimens are collected in the acute phase and immediately inoculated onto selective media (Bordet-Gengou with 15% sheep blood and cephalexin) or into suitable transport media (Regan-Lowe or Amies) so that processing is completed within a maximum of 24 hours.

- Molecular biology: Nucleic acid detection by PCR from a nasopharyngeal swab offers superior sensitivity and speed.

3. Major risks and main clinical complications:
   - Young infants have high rates of complications and death.
   - Common complications in this age group include apnea, pneumonia (primary, due to *B. pertussis* , or secondary bacterial), seizures, acute hypoxic encephalopathy, and a risk of death from exhaustion or refractory pulmonary hypertension.
4. Emergency and supportive therapeutic measures:
   - Mandatory hospitalization: All young infants with severe forms require emergency admission to a ward, preferably the ICU, or close monitoring.
   - Respiratory support: Continuous monitoring of oxygen saturation (SpO_2) and prompt initiation of oxygen therapy or assisted ventilation in case of apnea and cyanosis.
   - Provision of a quiet environment to prevent excessive sensory stimulation, which may trigger new paroxysmal coughing bouts.
5. Etiological antibiotic regimen and duration:
   - Antibiotics stop contagiousness, but alter the clinical course only if given early, in the catarrhal stage.
   - Treatment consists of clarithromycin ($7{,}5$ mg/kg $\times$ 2/zi for 7 days) or azithromycin (10 mg/kg once daily for 3 days).
   - *Caution in infants under 1 month of age:* Erythromycin and azithromycin are used with caution because of the risk of infantile hypertrophic pyloric stenosis, but the benefit outweighs the risk; co-trimoxazole is absolutely contraindicated in infants under 6 weeks of age.

Case 2: Pertussis – Classic form in a schoolchild with an incomplete vaccination history

1. Correlation of the clinical picture with the stages of the disease:
   - The clinical picture described (persistent spasmodic cough for 3 weeks, nocturnal paroxysmal bouts on a single expiration, inspiratory whoop – *whooping*, and post-tussive vomiting – emesis) corresponds classically to the paroxysmal stage (convulsive stage), which

usually lasts 2–4 weeks. It was preceded by the incubation period (7–10 days) and the catarrhal stage (1–2 weeks with signs of a mild viral infection), and will be followed by the convalescent stage (2–8 weeks).

2. Hematological changes and laboratory tests:
    - Complete blood count: May show marked leukocytosis accompanied by absolute lymphocytosis ($> 10 - 20 \times 10^9$/L or 80–90% of the differential count), specific to the pediatric age group in pertussis.
    - Laboratory diagnosis: A PCR test on a nasopharyngeal swab (owing to its high sensitivity in weeks 2–3 of illness) or serological evaluation by ELISA (measurement of IgG against pertussis toxin - anti-PT) is indicated.
3. Interpretation of ELISA results and vaccine interference:
    - Interpretation thresholds (no vaccination in the previous 12 months): An anti-PT IgG titer ≥ 100 UI/ml indicates acute/recent infection; below 40 UI/ml is considered negative; values between 40 and 99 IU/mL represent a *borderline* (indeterminate) zone, requiring repeat testing or collection of a second sample after 7–10 days to capture a rising trend.
    - Interference: If the patient has received vaccine doses in the previous 12 months, an elevated antibody titer may simply be a direct consequence of vaccination, in which case the serological test becomes inconclusive and direct detection by PCR is preferred.
4. Possible mechanical complications:
    - Owing to the sudden rise in intrathoracic and intra-abdominal pressure during violent coughing bouts, the following may occur: subconjunctival hemorrhages, petechiae on the face and trunk, abdominal or inguinal hernias, pneumothorax and rib fractures.
5. Public health measures and prophylaxis for school contacts:
    - Isolation of the case: The child will be isolated at home or in hospital for at least 48 hours after the start of appropriate antibiotic treatment (or 21 days from onset in the absence of treatment).
    - Measures in the community setting: An epidemiological investigation is launched by the Public Health Directorate within a maximum of 24 hours. In unvaccinated or partially vaccinated contacts under 10

years of age in the community setting (school), rapid completion of the vaccination schedule is recommended, while those over 10 years of age who have not received a booster in the last 5 years are given one dose of a pertussis-containing vaccine (Tdap).

Case 3: Pertussis – Atypical form in an adult with a risk of intrafamilial transmission

1. Clinical features in adults and healthcare workers:
    - In adolescents and adults, *Bordetella pertussis* infection frequently has an atypical presentation: the classic noisy coughing bouts are usually absent, the inspiratory whoop (*whooping*) is rare and fever is absent. The disease manifests as a prolonged (over 2 weeks), hacking, dry, irritative cough, often markedly nocturnal, and is easily mistaken for acute bronchitis or an ordinary viral infection. Healthcare workers may constitute a silent reservoir for nosocomial or household transmission.
2. Priority risk categories and assessment of the infant:
    - The household includes a 6-week-old infant. He belongs to Group 1 (persons at increased risk of developing severe complications) - an unvaccinated infant under 2 months of age.
    - The patient (mother/healthcare worker) belongs to Group 2 (persons at increased risk of transmitting the bacterium to persons in Group 1), being a person who lives in the same household as an infant too young to be fully vaccinated. The risk of intrafamilial transmission is extremely high (the attack rate among household contacts reaches 70-100%), placing the infant's life in imminent danger.
3. Criteria for suspicion in prolonged cough in adults:
    - Any adult patient presenting with a cough lasting at least 2 weeks that does not improve, paroxysmal cough, cough accompanied by vomiting (emesis), or cough that worsens at night in the absence of fever, or who has been in direct contact with a confirmed case of pertussis, must be suspected of having pertussis and must be investigated for it.

4. Strict isolation and occupational exclusion rules:
    - As a healthcare worker and a suspected/confirmed case, the patient will be mandatorily excluded from the workplace (exclusion from the pediatric ward, where she comes into contact with infants) and from the community until at least 48 hours have elapsed since the start of appropriate antibiotic therapy (or 21 days from onset in the absence of treatment).
5. Post-exposure chemoprophylaxis for the young infant:
    - For the 6-week-old infant (newborn / infant under 6 weeks/1 month) in direct contact with an infectious household case, post-exposure chemoprophylaxis is initiated urgently within the first 21 days after onset in the index case.
    - The preferred agents are clarithromycin (7,5 mg/kg × 2/zi for 7 days) or azithromycin (10 mg/kg once daily for 3 days); erythromycin and co-trimoxazole are avoided or contraindicated at this young age because of the risk of pyloric stenosis or major adverse effects.

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