Gram-Positive Bacterial Infections

Gram-positive bacteria like Bacillus anthracis and Listeria monocytogenes are of high clinical significance but are often barely regarded despite their ubiquitous occurrence and high resistance towards infaust conditions. But also diseases from atypical mycobacteria increase nowadays. Therefore, this article creates an overview over the symptoms and diagnostics of the different clinical pictures and their therapy.

Corynebacteria

The most important pathogen in corynebacteria group is C. diphtheria which produce diphtheria toxin, and cause serious, life threatening disease called diphtheria. C. ulcerans and C. pseudotuberculosis are two other important species which are potentially toxigenic which can cause diptheria. Recently many non-toxigenic corynebacterial infections have been implicated as opportunistic infections in immunosuppressed patients.

Morphology of corynebacteria

Corynebacteria are small procaryotes that owe their name to the swollen end of the cell. Observed by microscope, this swollen end lets them look like a club (coryne = old greek for club). Nevertheless, Corynebacteria are pleomorph which means that they can take on other shapes during their growth and appear more coccoid then.
A further succinct attribute of Corynebacteria is a V-shaped connection between mother and daughter cell after cell division. This form appears due to the so-called snapping postfission movement. This snap division occurs due to the fact that only the inner cell wall of Corynebacteria participates in the cell division.

The outer wall surrounds mother and daughter cell afterwards and cracks on one side due to cell growth. Both cells drift apart there but are still connected on one side so that the V-shape appears. In the Anglophone area, this is also known as an array taking the shape of Chinese letters.

**Lab Diagnosis of corynebacteria**

Corynebacteria are aerobe, amastigote and, for this reason, immobile rod cells which are not able to form spores or capsules. In the cell plasm of the bacteria, so called polar bodies that include polyphosphate and calcium can be found. These polar bodies can barely be displayed with Gram stain so **Neisser stain** is used for this purpose.

After staining, the bacteria are colored yellow to rosé, the polar bodies, by contrast, are dark blue to black. This kind of staining is still widely used in the diagnostics of Corynebacterium diphtheriae and pseudodiphteriticum nowadays. The cultivation takes place on blood agar and can be made with sputum, gastric juice, laryngeal smear, urine and even ejaculate or menstrual blood.

By putting a fosfomycine platelet onto the blood agar, the standard pharyngeal flora can be inhibited in growth. Corynebacteria are visible as greyish colonies with slight flare of hemolysis. **Tinsdale agar** (natriumtellurite agar or Clauberg agar) works as indicator medium. Due to reduction of the included tellurium, Corynebacteria grow black with a blue flare on this medium. The tellurite also suppresses the growth of some bacteria of the pharyngeal flora.

Before macroscopic colonies become visible, the growth period amounts to circa 18 – 24 hours. Afterwards, the differentiation between pathogenic and apathogenic
Corynebacteria happens through biochemical reactions. Pathogenic species are characterized by their positive catalase reaction, negative urease reaction, the fermentative breakdown of glucose (but not of saccharose) and nitrate reduction.

By their different colony morphology, hemolysis behavior and ability to break down dextrin and glucose, the 3 biovarces of Corynebacterium diphtheriae mitis, intermedius and gravis can be distinguished. To detect diphtheria toxin, different in vitro methods like gel immunodiffusion or PCR and in vivo tests like the Draize test where serum of the patient or culture solution are put onto the shaved skin of a rabbit, are used.

The Elek test is a particular type of the gel immunodiffusion tests. In this test, a stripe of filtering paper drained with antitoxin is applied. Additionally, the stem to be analyzed is applied crosswise. If the stem includes diphtheria toxin, antigen-antibody complexes occur which can be seen as S-shaped lines. Nevertheless, the diagnosis diphtheria has to be found primarily clinically, the laboratory diagnosis is only of proving character.

Epidemiology and incidence of corynebacteria

The transfer of Corynebacterium diphtheriae exclusively takes place from human to human by droplet infection, other secretions or direct contact. Due to the good vaccination coverage in Germany, a contamination often takes place in subtropical areas where diphtheria is endemic. The incidence in Middle Europe is about 0.001/100,000 per year. Dogs and cats are a natural reservoir for toxigenous stems of Corynebacterium ulcerans. Apathogenic species belong to the normal flora of the skin and mucosa.

Pathomechanism of corynebacteria

Only Corynebacteria that are infected with a specific phage trigger the disease. This phage carries genes for the exotoxin that inhibits the translation during the phase of elongation in the protein biosynthesis. First, the B-part of the bacterium docks to the host cell, afterwards the A-toxin is absorbed into the cell in a vacuole. The diphtheria toxin A inhibits the elongation factor 2 by ADP ribosylation of a specific amino acid residue with the name diphthamide.

Also, some stems of the Corynebacterium ulcerans carry these phages and are, consequently, pathogenic. By destruction of the infected cells, the typical pseudomembrane appears, consisting of necrotic cell components.

Clinical pictures at infections with corynebacteria
Two to six days after the infection, first symptoms like fatigue, sickness and swallowing pain occur. With the typical pharyngeal diphtheria, a yellowish-white fur and musty-sweet mouth odor emerge. Nurselings and toddlers are often effected with diphtheria up to the nose so that a saniopurulent nose leak occurs.

The laryngeal diphtheria where a stridor or even asphyxiation can occur, is feared. Symptom triad of this real croup are barking cough, hoarseness and aphonia.

With other Corynebacteria, clinical pictures like wound infections, otitis and urinary tract infections can also be caused.

**Therapy of corynebacteria**

The early administration of antitoxin has priority at diphtheria. Simultaneously, an antibiotic therapy with penicillin G should be started. Contact persons or asymptomatic carriers should get penicillin V or clarithromycin prophylactically. Other Corynebacteria are often multi-resistant and only sensitive to vancomycin, teicoplanin and linezolid. The vaccination also takes place by immunization with diphtheria toxin. There is a namely reporting obligation for disease suspicion, affection and death by diphtheria.

**Listeria**

Listeria monocytogenes is an opportunistic pathogen which causes foodborne infectious disease, mostly seen in immunocompromised individuals, and vulnerable groups, such as pregnant women, neonates and elderly, with a high mortality rate up to 20–30% of clinical cases. It may cause mild and self-limiting febrile gastroenteritis in healthy people.

**Attributes of listeria**

Listeria are gram-positive rod cells that are mastigote at low temperatures under 20°C and form a typical end-to-end movement. The fermentative catalase positive listeria can grow aerobically and anaerobically but do not form spores.
Listeria monocytogenes secretes a pore-forming toxin called listeriolysin O. On blood containing agars, this toxin causes ß-hemolysis that virulent and avirulent stems can be differentiated with. This toxin is analogous to streptolysin O from A-streptococci and pneumolysin from Pneumococci.

Listeria are very resistant to outer influences, they can even survive pasteurizing of milk. This special attribute is used in diagnostics in the form of cold enrichment. Also, in the body, listeria protect themselves from the host’s immune defense by intracellular stay.

In infected cells, listeria causes an evagination of the host cell by actin increase. Due to this evagination, the bacteria can enter neighbor cells without any contact to the extracellular defense.

Incidence and epidemiology of listeria

Listeria can be found in the intestine of domestic and wild animals as well as humans. They also occur in samples of soil, water and waste. Very often they can be isolated out of milk and milk products.

Typically, jobwise exposed persons like butchers, farmers or veterinary medicals are infected. Also, immunosuppressive pregnant women and unborn children have a higher risk to fall ill with Listeria. Circa 1/3 of listerioses affect pregnant women and newborns. Next to rubella and toxoplasmosis, it therefore belongs to the most frequent prenatal infections in Germany. Due to contaminated food, local outbreaks with several infected persons can occur. In Germany, the prevalence is at 1-4 cases per 1,000,000 inhabitants and year.

Pathomechanism of listeriosis

Listeria monocytogenes mostly finds its way into the host organism from the intestine over the M-cells of the Peyer plaques and from there into local lymph nodes. From there, further spread takes place over the thoracic duct into the blood. Afterwards, they are absorbed from macrophages and leave the phagosome by use of the pore-forming listeriolysin.
In the cytoplasm of the macrophages they can reproduce unimpededly and lead to a release of chemotactic factors. The **monocytosis** associated with the infection owes Listeria monocytogenes its name. The specific immune defense leads to the formation of granulomas.

In pregnant women, usually a symptom-poor bacteremia occurs that causes a severe sepsis by diaplacental transmission to the unborn child, the so called **granulomatosis infantiseptica**. Typical symptoms of the fetus are infections of the liver, lungs, kidneys and brain. Infections with Listeria can occur in every stage of the pregnancy but are most common in the 3rd trimester.

**Laboratory diagnosis of listeria**

As testing material, liquor, blood, forewaters and tissue samples can be used. The cold resistance of listeria is useful for isolation because only a few other bacteria can grow at 4°C (so called cold enrichment). The propagation takes place on blood agar or in **trypticase-soy-bouillon**.

The colonies are small and white, in virulent stems they are additionally surrounded by a flare of β-hemolysis. In liquid culture mediums, they show a typical somersault-like movement. In microscopy, they often appear to be coccoid.

**Therapy of listeriosis**

Therapeutics of choice are **ampicillin** in combination with an **aminoglycoside** because a synergism is found here.
Bacilli

Attributes of bacilli

Bacteria of the genus Bacilli are big aerobic, immobile, spore-forming rod cells that are mostly gram-positive but also slightly gram-variable. The species *Bacillus anthracis*, *cereus* and *subtilis* are of relevance for humans.

*Bacillus anthracis*

The bacillus anthracis rod cells are stringed together like a chain and feature a capsule made of D-glutamic acid. This capsule is only formed on nutrient agar if increased CO\(_2\) tension is present. Under infaust culture conditions, endospores are formed which are extremely environmentally resistant.

During the Second World War, some islands in the Atlantic were infested with anthrax in B-weapon tests and, therefore, are still uninhabitable. *Bacillus anthracis* is a biological agents that can be used in bioterrorism attacks. The distribution is ubiquitous in the ground. The plasmid-coded exotoxin, also *anthratoxin*, consists of three parts, the edema factor, the protective antigen and the lethal factor.

Anthrax is a zoonosis. The human is infected by direct contact to sick or deceased grazers or indirectly by animal products like wool, bone meal or saddle cloth. That is why anthrax is also called *Woolsorter's disease*. Through skin lesions, the spores enter the human body and pass into the vegetative, toxin-building form.

**Pathomechanism of bacillus anthracis**

The *edema factor* and the *lethal factor* invade leucocytes under protection by their *protective antigen*. In the leucocytes, they increase the concentration of cAMP which inhibits the phagocytosis of the infected cells. Since leucocytes are infested, the infected tissue typically seems indifferent. The lethal factor induces the necrosis of granulocytes and masses of Anthrax bacteria are released. An uninhibited reproduction of the Bacilli and a proliferation over lymph vessels and bloodstream follows.
Clinical picture at infections with bacillus anthracis

- **skin anthrax**: Most common localization are hands, forearms and face. After an incubation time of 2-5 days, the so-called pustula maligna appears at the infection site. This is a painless but itchy papule with edematous edge. After a short period of time, necrosis of the center with black coloration occurs. At the edge, serous cysts emerge. Without treatment, the infection is fatal in about 20% of the cases due to toxemia and bacteremia. After survived infection, a humoral immunity of unknown duration occurs.

- **pulmonary anthrax**: After initial grip symptoms, massive edemas appear in the area of neck and thorax. The patients suffer from dyspnea and fever. Pulmonary anthrax is the most dangerous clinical form and is extremely difficult to treat.

- **intestinal anthrax**: By ingestion of anthrax spores, a severe enteritis can appear. This ends lethal in most cases due to the toxemia.

All three forms of anthrax can lead to a sepsis with lethal outcome.

**Laboratory diagnosis of anthrax**

Depending on the kind of infection, the content of serous cysts in skin anthrax, **sputum** in pulmonary anthrax and **feces** in intestinal anthrax can be used as test material. The propagation must only take place in S3 laboratories. Simple culture mediums with aerobic conditions are being used.
The colony morphology of Bacillus anthrax taking the form of harsh colonies with curly branches at the edges which is also called head of Medusa is typical. In microscopy, the bacteria appear as box-like rod cells with central endospores which are arranged in long chains, the so called bamboo stick.

Suspicion of illness, affection and death by anthrax are subject to mandatory reporting. Also, reporting is mandatory in case of detection of Bacillus anthrax.

**Therapy of anthrax infections**

Already upon suspicion of anthrax, a **highly dosed antibiotic therapy with penicillin G, ciprofloxacin or tetracyclines** should be started. In bioterroristic assaults, ciprofloxacin should be favored because resistances can be transferred from Bacillus cereus to anthrax in the laboratory.

New antibiotics found to be effective against anthrax include levofloxacin, daptomycin, gatifloxacin and dalbavancin. Newer therapies like peptides, bacteriophages enzymes, monoclonal antibodies etc. are being evaluated.

Farm animals should be vaccinated against anthrax. Exposed persons can profit from new **vaccines** that base on the blockade of the protective antigen. Carcasses have to be burned.

**Bacillus cereus**
In humans, Bacillus cereus causes invasive local infections and self-limiting food intoxications.

**Food intoxications from bacillus cereus**

Bacillus cereus produces three toxins, the **emetic toxin** and two enterotoxins. While the enterotoxins are heat-labile and proteolytically inactivatable, the emetic toxin is heat-stable and cannot be inactivated by proteolysis.

The enterotoxins are often absorbed in form of cooked rice or meat. 1-6 hours after the intake of contaminated food, vomiting occurs, after 10-12 hours stomachache and watery diarrhea with tenesmuses and vomiting appear. The symptoms last for circa 24 hours. The intoxication is self-limiting. Two forms of intestinal illness, diarrheal and emetic have been described which are attributed to different toxins. Treatment is symptomatic and most patients recover within 24 hours after symptom onset.

**Local infections with bacillus cereus**

Since Bacillus cereus produces numerous tissue-destructing virulence factors, the wound infection leads to gas gangrene-like myonecroses that are only of superficial character. The therapy takes place surgically and with antibiotics. In contrast to Bacillus anthracis, Bacillus cereus often forms ß-lactamases wherefore an antibiosis with vancomycin or clindamycin is preferable.

**Laboratory diagnosis of bacillus cereus**

The propagation can be made of feces and food. The most important differential attribute of Bacillus anthracis is the motility of Bacillus cereus.
Propionibacteria

Attributes of propionibacteria

Propionibacteria are anaerobic, oxygen-tolerant, non-spore-forming, immobile, gram-positive rod cells. They stand out by their slow growth and high requirements for breeding ground. They owe their name to propionic acid fermentation where especially carbohydrates like glucose and fructose serve as substrate for the main product propionic acid. On blood agar, ß-hemolysis can be detected. Some propionibacteria have probiotic properties and are being use in dairy probiotic products.

Clinical picture of pathogen propionibacteria

A pathogen Propionibacteria mostly live on the skin as normal flora and commensal. The Propionibacterium acnes can be found primarily in the sebum of hair follicles where it can cause an inflammation by induction of chemokine and cytokine production. The leucocytes attracted by this lead to the formation of pus-filled pustules.

In the hair follicles, optimal conditions for propagation of the acne causer are provided because there is an anaerobic milieu and the Propionibacteria have a lipase available which they can use to harvest the fat contained in the sebum for energy production.

Furthermore, Propionibacteria have been described as the cause of endocarditis and spondylodiscitis. Propionybacaterium acnes can additionally lead to the development of circulating immune complexes which can deposit on bones and joints. This clinical picture especially appears on young adults and is called SAPHO syndrome which stands for synovitis, acne, pustolosis, hyperostosis and osteitis.
Attributes and detection of actinomycetes

For humans, the anaerobic, fermentative Actinomycetes are of particular importance. They are characterized by a positive behavior in the Gram stain and their elongated, branched form. They are immobile and do not form spores. Actinomycetes can often be found as pathogens or commensals on the mucosa of endotherms and metabolize carbohydrates and organic acids there.
The radial-filamentous branches of Actinomycetes visible under the microscope, which are called ray fungus and owe their name to their appearance (Greek aktis for ray and mykes for fungus), are characteristic. Also, macroscopically, a radial structure shows in the druses formed by the Actinomycetes. Druses are nodular conglomerates surrounded by a wall of lymphocytes where the bacteria hyphas spread radially on the inner side.

The propagation should take place on Columbia agar but usually takes several days or weeks. The colonies appear yellowish, dry with small runners.

**Actinomycosis**

The main cause of the actinomycosis is *actinomyces israelii*. This bacterium belongs to the normal oral flora but can intrude into deeper layers in mucosal injuries and lead to the formation of fistulas and granulation tissue there. By these chronically emerging fistulas, Actinomycetes can reach the blood circulation. Actinomycosis may mimic the malignancy process in various anatomical sites.
In 95% of the cases, only a **cervico-facial actinomycosis occurs** where inviscid pus with sulfur-yellow druses drains from the fistulas. Hormonal factors are likely to play a role in the emergence of actinomycosis because men are distinctly more often affected, in contrast to children who are never affected.

The therapy should be a combination of **surgical intervention and antibiosis**. Because of the β-lactamase-forming collateral flora, a combination of amoxicillin and clavulanic acid has been established as standard therapy.

**Other clinical pictures from actinomycetes**

An important ophthalmologic differential diagnosis portrays the **canaliculitis lacrimalis** causes by Actinomyces israelii.

Furthermore, Actinomycetes can appear sensitizing and, by formation of immune complexes, can cause a 3rd grade allergy. In this context, they are a typical cause of the so-called **farmer’s lung**, a form of exogenous-allergic alveolitis.

**Clostridia**
Clostridia belong to the **obligate anaerobic, spore-forming rod cells**. This species is ubiquitously represented in nature and can often be found in the intestinal tract of humans. The endospores formed under infaust living conditions are resistant against heat and exsiccosis and are able to survive in an aerobic milieu.

**Clostridium perfringens**

This bacterium is the main cause (but not the only one) of gas gangrene, also called **clostridial myonecrosis**. Especially in times of war, this infection frequently occurs because Clostridium perfringens spores ubiquitously exist in the ground and can get into wounds from there.

**Attributes of clostridium perfringens**

They are box-shaped, gram-positive, immobile rod cells without granulocytes. It is frequently referred to as a claybrick-shape. Additionally, in most of the isolates, a polysaccharide capsule can be found. Due to their formed toxins, C. perfringens is divided into the types A-E.

**Pathomechanism of gas gangrene**

Clostridium perfringens stems of the type A are mostly causing gas gangrene. The **alpha-toxin** is a lecithinase that destroys cell membranes by splitting lecithin.
A decrease of the redox potential of the infected tissue is **required** for **sprouting of Clostridia spores**. For example, this is the case in circulatory disorders or necroses. This is why the cell destruction and emergence of edemas by further occurring toxins from *C. perfringens* can be seen as a vicious cycle because it facilitates its own growth. Due to fermentation, the eponymous gas is formed.

**Clinical picture of gas gangrene**

After an incubation time of circa 2 days, a swelling and brownish-livid discoloration of the extremely painful infection area occurs. Crepitations due to the CO2 gasification can be detected by palpation. A serous and, due to volatile fatty acids, stinky fluid drains from the wounds. The muscles are necrotically decomposed. A toxin-induced shock in gas gangrene can lead to death within hours.
The suspicion of illness and the illness of gastroenteritis caused by Clostridium perfringens is subject to mandatory reporting.

![Image: "gram stained clostridium perfringens". License: Public Domain](image)

**Therapy of infections with clostridium perfringens**

A **surgical wound revision** with eventual amputation of the infected extremity is essential because the antibiosis often does not reach the necrotic tissue. A combination of **penicillin G** and **metronidazole** is often used because in most cases, it is a combined infection with other anaerobic bacteria.

Furthermore, the **hyperbaric oxygenation** in form of oxygen hyperbaric chambers is the standard solution for gas gangrene infections to eliminate the basis of existence of the obligate anaerobic bacteria.

**Clostridium tetani**
Attributes of clostridium tetani

The structure of Clostridium tetani corresponds to other Clostridia. The tennis racket shape is characteristic.

Clinical picture of tetanus

Newborns where Clostridium tetani leads to the so called disease of the 8th day (or tetanus neonatorum) are most likely to be affected. This is an infection of the umbilicus since this provides an optimal anaerobic milieu.

At the portal of entry, C. tetani propagates and forms tetanospasmin which is released by autolysis and retrogradely spreads down the nerves up to the anterior horn cells in the spinal cord. There, it proteolytically divides synaptobrevins. The synaptobrevins are involved in the release of GABA into the synaptic cleft. So a neutralization of the inhibitory effect takes place.

Due to an excessive activity of the spinal motoneurons, a spasticity with strychnine-like, tonic-clonic convulsions occurs.

The first symptoms appear after an incubation time of few days to 3 weeks. The so-called trismus, a tension of the masticatory muscles, and a permanent contraction of the mimic muscles that is called risus sardonicus, are typical.
Laboratory diagnosis of clostridium tetani

Since propagation often fails, toxin detection is important. For this detection, an animal experiment is necessary. In most cases, mice or guinea pigs are vaccinated with different amounts of the patient’s serum. The experiment is rated as positive when the animals die in seal position, that means with catalepsy of the rear legs.

Control animals are simultaneously vaccinated with the patient’s serum and antitoxin. These animals should survive for a **positive mice protection experiment**.

Therapy of tetanus infections

Next to the administration of **anti-tetanustoxin-antibodies**, the therapy consists of anticonvulsant drugs and artificial respiration to work against a paralyzation of the respiratory muscles.

Due to the high lethality, an **active vaccination** with formalinized toxins (toxoid) is of great importance.

Atypical mycobacteria

The atypical mycobacteria which are potentially pathogenic for humans are often summarized as **MOTT** (mycobacteria other than tuberculosis).

Attributes of atypical mycobacteria

The structure of MOTT does **not differ from other mycobacteria**. They also have an acid-proof capsule and are extremely resistant against environmental influences, heat and many disinfectants. They ubiquitously occur in the ground and in water samples, some of them only in particular areas like M. ulcerans for example which is only prevalent...
in Africa.

The classification is made in **4 groups**. Slowly growing mycobacteria that only produce a pigment during light exposure, belong to group I. The so-called scotochromogenic mycobacteria of group II also produce a pigment in the dark. Slowly growing MOTT that do not produce a pigment, belong to group III, whereas all fast-growing ones belong to group IV.

**Diseases from atypical mycobacteria**

As an opportunistic pathogen, the atypical mycobacteria especially cause infections at immunosuppressive patients.

*Pulmonary infections* that, clinically, do not differ from Tbc frequently occur. Also, *granulomatous infections of the skin* and *lymphangitis of the cervical lymph nodes* are frequent. M. scrofulaceum causes ‘scrofula’, a granulomatous cervical adenitis which is usually seen in children.

M. marinum is the cause of the so-called *swimming pool granuloma*. After bathing in contaminated water and an incubation time of 2-3 weeks, granulomas that ulcerate after some time appear at entry portals like elbows and knees. M. ulcerans causes ‘Buruli ulcer’, primarily affecting the lower extremities.

**Laboratory diagnosis of atypical mycobacteria**

As with M. tuberculosis, the propagation usually succeeds on **Löwenstein-Jensen agar**. Fast growing mycobacteria already build colonies after 3-4 days, other ones only after an incubation time of several days to weeks. The differentiation especially takes place based on growth rate, culture morphology and pigment incurrence. The differentiation is complemented with **restriction fragment length polymorphism**.
In contrast to tuberculosis, the disease is not obliged to register.

Therapy of atypical mycobacteria

Most MOTT are highly resistant against tuberculostatics which is why the therapy turns out to be very difficult. In an infection with M. avium or M. intracellulare, a combination of clarithromycin, ethambutol and rifabutin is recommended. In other atypical mycobacterioses, up to 6 antibiotics can be necessary.

Popular exam question about bacterial infectious diseases

The answers can be found below the references.

1. Which statement does not apply for skin anthrax?

   A. The cause is Bacillus anthracis.
   B. Risk groups are farmers and graziers.
   C. The macroscopic appearance is called Pustula maligna.
   D. Basic module of the therapy is surgical wound debridement next to antibiosis
   E. The edema factor, the lethal factor and the protective antigen conduce to the pathomechanism.

2. Which statement does not apply for Clostridium perfringens?

   A. It is the only cause of gas gangrene.
   B. It is an anaerobic, ubiquitously present rod cell.
   C. Detection of the alpha-toxin takes place with Nagler’s test.
   D. The bacterium appears plump, clay brisk-like in microscopy.
   E. The alpha-toxin releases by the bacterium is lecithinase.
3. What applies for Corynebacterium diphtheria?

A. It is an anaerobic, mobile rod cell.
B. It is the cause of pseudo croup.
C. Tinsdale agar is used as indicator medium
D. It does not have polar bodies.
E. It is negative with catalase and positive with oxidase.

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Correct answers: 1D, 2A, 3C

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