

Chemotherapy of *Listeria* infections

Abstract

The combination of amoxicillin or ampicillin, respectively, with an aminoglycoside remains still the standard therapy of infections with *Listeria monocytogenes*, although it has been questioned in clinical studies as well as in animal experiments whether the addition of an aminoglycoside really improves the outcome. There are some alternatives for example cotrimoxazole. Several microbiological and experimental evidences vote for the use of quinolones, in particular of moxifloxacin, against these facultative intracellular bacteria; clinical experiences with these agents are, however, limited. In addition to these drugs a large number of antimicrobials can be used for therapy of listeriosis in certain situations. Cephalosporins should be avoided. Resistance development is not a major problem.

Keywords: *Listeria*, antibiotics, in vitro activities, intracellular action, animal experiments, clinical activities

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Microbiology of *Listeria* spp.

The genus *Listeria* comprises of at least 10 different species [1], [2], [3], [4]. Most of these are, however, non-pathogenic bacteria; yet they have to be differentiated from each other when *Listeriae* are isolated from the environment for example from various food items. In human cases of listeriosis almost exclusively *Listeria monocytogenes* is found. The individual isolates of this major pathogen can differ in their virulence [5] as well as in their antigenic surface composition. Serovars 1 and 4 represent by far the most frequent variants. A striking difference between non-pathogenic and pathogenic strains is the presence of a series of virulence factors most of which are located in a pathogenicity island on the chromosome encoding a haemolysin (listeriolysin), phospholipases and an actin polymerizing protein [6]. In principle, *Listeriae* are geophilic, i.e. they reside in the soil, since they are non-fastidious. They are able to adapt to various challenges by multiple changes in bacterial metabolism and gene expression and therefore can grow at many quite different sites; hence, vegetables are contaminated and even milk and meat and fish products can get polluted secondarily. This means that various food items, especially soft-cheese, salami, gravled salmon, ready-to-eat food and salads, are the source of infections of men and animals [7].

Pathogenesis: Intracellular growth is a relevant process

Whereas the exposition to *Listeriae* via various food items is rather frequent, listeriosis is rare. One reason is, that the innate immune system generally protects the hosts to some extent. For example there are some antimicrobial peptides, such as defensins. In principle *L. monocyto-*

genes is susceptible to a large range of human as well as non-human antimicrobial peptides [8], [9]. It can be anticipated that these natural products might reduce the bacterial load of the ingested food. Hence, the chance for pathogenic bacteria to come into contact with the mucosal epithelium is lessened and the risk of infection is lowered.

Surface proteins of *L. monocytogenes* such as Inl A und B, which are leucine-rich repeat-containing proteins, bind to special receptors on the host cell membrane and trigger the uptake of *L. monocytogenes* by clathrin-dependant mechanisms [10]. Once inside a host cell, i.e. in a membrane bound vacuole, the bacterium is confronted to unfavorable growth conditions such as low pH, kationic antimicrobial compounds, cytokines and lytic enzymes [11]. By means of several virulence factors, such as hemolysin (listeriolysin O) and phospholipases, the pathogenic bacteria produce a hole in the vacuolar membrane through which the bacteria may rapidly escape into the cytosol [6] a privileged site, where the bacterium is largely protected against host's defense mechanisms as well as most antibiotics. There, they are able to multiply. By means of a cell wall protein, i.e. Act A, they can actively polymerize actin filaments of the host cell just on one pole of the bacterial cell, so that the bacterium is pushed forward. By this type of intracellular motility they migrate through the host cell and by chance the bacteria may arrive at the inner front of the host cell membrane. This situation triggers the extrusion of long filaments of the host cell containing a bacterium, which penetrate into adjacent host cells and at last are integrated in this second host cell [6]. By this way, *L. monocytogenes* is thought to be able to spread from one host cell to another without an extracellular stage and to cross anatomical barriers such as the intestinal mucosa, the blood-brain-barrier or the placenta [12]. Indeed, during listeriosis the

bacteria are found within the cytosol and even within the nucleus of various host cells for example in neurons [13]. Within the host cells, several bacterial components are processed and typically presented together with MHC class I-receptors at the cell surface to CD8 T-lymphocytes [14]. Indeed, the intracellular habitat of *L. monocytogenes* calls for a cell-mediated immune response, which is histologically characterized by a granulomatous inflammatory reaction developing after a few days of infection [15]. On the other hand, *L. monocytogenes* is quite able to grow extracellularly, too. Like other pyogenic bacteria they induce an acute granulocytic inflammatory response; typically in the CSF in patients with *Listeria* meningitis the majority of visible bacteria are extracellular surrounded by polymorphonuclear granulocytes [7].

Epidemiology of listeriosis

Exposure of humans to *L. monocytogenes* is quite frequent, but infections are rare. In most instances these infections occur sporadically, but sometimes small outbreaks have been reported. In some countries such as USA the incidence has decreased [16] whereas in others such as England, Wales, the Netherlands and Germany, the incidence of listeriosis has grown up in the last few years [17]. Food-borne infections with *L. monocytogenes* predominantly occur in immunocompromised patients. Less than 30% of infections develop in otherwise healthy subjects. Advanced age, acute myeloid leukemia as well as iatrogenic immunosuppression by steroids and lymphotoxic agents (mycophenolic acid, cyclosporine A, azathioprin, etanercept) in organtransplant recipients, in cancer patients, in individuals with severe rheumatic diseases and in auto-immune disorders are the most common predisposing factors. In recent times immunomodulating monoclonal antibodies directed against TNF α or IL 1 such as retuximab, infliximab or adalimumab [18] are of special concern. In addition debilitating diseases such as HIV infection, diabetes and liver cirrhosis as well as conditions resulting in high iron load will facilitate the manifestation of listeriosis [16].

In rare cases a contact of farmers and veterinaries with infected animals may lead to a direct inoculation of *Listeriae* into the skin or the conjunctival mucosa inducing localized infections. Furthermore, nosocomial infections, particularly of newborns, have been described [19].

Clinical manifestations

Whereas intestinal symptoms of an infection with *L. monocytogenes* such as enteritis are outlined by a few patients, in most instances the prominent clinical manifestations are sepsis, meningitis and encephalitis, sometimes in combinations. Obviously, *L. monocytogenes* is one of those bacterial pathogens able to cross first the intestinal mucosa and then the blood brain barrier and other anatomical structures. In only few instances other

organs may be involved; endocarditis, arthritis, cholecystitis etc. have been reported. Overt disease develops primarily – but not exclusively – in immunocompromised adult patients especially in the very old. Pyogenic local infections of the skin and the conjunctival mucosa are rather uncommon [20].

A particular situation exists, when a pregnant women being about 12 times more prone to listeriosis than normal population will be infected; during a short episode of septic spreading of bacteria which will be anticipated as a flu-like disease a colonization of the placenta may happen, and in some cases a transition of bacteria through the anatomical barrier may result in an intrauterine infection of the fetus [21]. While most pregnancy-related infections of the fetus occur during the third trimester, listeriosis can develop at any time during pregnancy and, in some instances, asymptomatic pregnant women may pass on infection to the fetus.

Diagnostics

L. monocytogenes are non-fastidious and can easily be grown in various nutrient media. Since bacteremia is often only transient, blood cultures can, however, remain negative. Meningitis can be approved by microscopy and culture of CSF. During encephalitis, however, the bacteria may reside entrapped in infective foci and cannot be detected in CSF in every case. Consequently, in some cases *Listeria* infections are undiagnosed. In these cases, imaging methods such as CT scan [22] can help to make a presumptive diagnosis. Pyogenic infections of other organs can be diagnosed by biopsies.

Therapy

Antibiotic activities against *Listeria* spp.

Susceptibility of *Listeria* spp. in vitro

In case of testing susceptibility of *L. monocytogenes* special conditions and break-points have been proposed by CLSI for penicillin, ampicillin as well as cotrimoxazole [23]. All other antibiotics are not recommended for routine testing, since generally, clinical isolates of *L. monocytogenes* are susceptible in vitro to a wide range of antibiotics except to older quinolones, cephalosporins, aztreonam and fosfomycin; it is noteworthy that only a narrow range of MICs is found [7], [24] (Table 1). The susceptibility of clinical isolates can be predicted with a high probability even without a laboratory testing [7]. In particular resistance to penicillins does not have any practical impact in medicine! Conclusively, microbial resistance does not play a major role in the therapy of listeriosis [25]. Amoxicillin is slightly more active than ampicillin against *L. monocytogenes*, since the MIC values are marginally lower and the time to kill is somewhat lower.

Table 1: Activities of some antibiotics on *Listeria monocytogenes* in vitro, in cell cultures and in animal experiments [7]

	in vitro	on intracellular bacteria	in experimental infections
ampicillin/amoxicillin	+++	++	++
cephalosporins	–	–	–
aminoglycosides	+++	–	–
tetracyclines	+++	+	++
macrolides	+++	+++	+++
cotrimoxazole	+++	+	+++
linezolid	++	++	++
fluoroquinolones	+++	+++	+++
glycopeptides	+++	–	–
rifampicin	–	++	++

Occasionally, resistance or at least reduced susceptibility to a few antibiotics, such as tetracyclines, aminoglycosides and chloramphenicol have been found in food isolates [26]. Indeed, a horizontal transfer of antimicrobial resistance from other gram-positive bacteria to *Listeria* by means of conjugative genetic elements such as transposons and plasmids has been observed [27]. The meaning of a report on penicillin resistance in all 9 *Listeria* isolates from chickens in East Africa [28] remains unclear.

The role of Penicillin Binding Proteins

L. monocytogenes produces 5 vital penicillin binding proteins (PBP) [29] as well as some additional PBP-like structures [30]. About 80 up to 600 copies of each protein are present in one bacterial cells; it is obvious not necessary to neutralize absolutely all of these targets by penicillin molecules but only a majority of them. The activity of PBP3 is essential whereas neutralization of the other targets can be partially compensated.

Cephalosporins, in particular those of the 3rd generation, as well as mecillinam and aztreonam, have a rather low affinity for the PBP3. Hence, *L. monocytogenes* is generally resistant to these betalactam antibiotics except of a very few isolates [31]. Penicillins, especially ampicillin and amoxicillin, are active as well as imipenem disposing even of lower MIC values than ampicillin [32].

The effect of betalactams is, however, only bacteriostatic in vitro for *L. monocytogenes* [7], [32], which is a definite disadvantage in a compromised patient. Only at rather high concentrations, i.e. 16 fold above the MIC, killing is achieved within 6 hours [30]. On the other hand, the production of essential virulence factors such as hemolysin, is reduced already at low, subinhibitory concentrations [33].

Resistance mechanisms of *Listeria* spp. to quinolones

L. monocytogenes is inherently resistant to quinolones of the first generation such as nalidixic acid [34], most

probably due to an inherited mutation in the active center of subunit A of the DNA gyrase [35]. At positions 88 and 84 two amino acids, namely Phe and Tyr, are found in *L. monocytogenes* instead of Asp/Glu and Ser residues in quinolone susceptible bacteria. Newer quinolones such as norfloxacin, ciprofloxacin [34], ofloxacin [36] and clinafloxacin [37], however, are rather active exerting a rapid and strong concentration dependant bactericidal effect. Especially moxifloxacin exerts excellent concentration-dependent bactericidal activities against a lot of different strains of *L. monocytogenes* exceeding definitely that of ampicillin [38].

Coumermycin, a substance which is not used in clinical medicine because of possible side-effects on blood coagulation, inhibits the subunit B of the bacterial gyrase. This agent is extremely active in vitro showing a bacteriostatic effect at quite low MIC values [39], [40].

Bactericidal activity of aminoglycosides and synergy with betalactams

Gentamicin is bactericidal against clinical isolates of *L. monocytogenes* [41]. In combination with betalactams a synergistic effect can be observed [25], [41]. In particular the killing of *Listeriae* can be definitely augmented, presumably because the penetration of aminoglycoside molecules through the compact network of the cell wall of the grampositive bacteria can be facilitated by the softening of the peptidoglycan layers by ampicillin. Furthermore, it has to be kept in mind that even at subinhibitory concentrations gentamicin is able to inhibit the production of essential bacterial virulence factors such as listeriolysin [42].

The impact of intracellular habitat of *L. monocytogenes* on activities of antibiotics

The basic structure of the host cell membrane is a lipid bilayer that acts as a definite barrier for free, passive diffusion of most but not all antibiotics [43]. Hence, most

antibiotics have only poor access to intracellular sites [44].

a) **Fosfomycin:** *L. monocytogenes* is naturally resistant in vitro to fosfomycin, because under the chosen conditions the drug is not taken up by the bacteria [45]. Additionally, some strains may possess target mutations as well as enzymes hydrating the compound rendering the bacterium highly resistant [46]. Paradoxically, in vivo *L. monocytogenes* appears to be susceptible, which is due to the fact that once in an cytosolic compartment certain virulence factors such as listeriolysin O, phospholipases and ActA are produced and coexpressed with an hexose-phosphate inward transporter transporting also fosfomycin into the bacterial cells, where it can exert its antibacterial effect [45].

b) **β -lactams:** Penicillin derivatives at least in their ionized form, reacting as weak organic acids, are able to diffuse slowly across the host membrane. The absolute amounts transported by this mechanism remains, however, is rather low. Storage takes place in the cytosol. Once the extracellular concentrations gets lower, the intracellular penicillin molecules can move in the opposite direction [43].

Amoxicillin is able to reduce the intracellular counts in infected cells at least when high extracellular concentrations are present [44].

In spite of the relatively low intracellular concentrations the efficiency of ampicillin, amoxicillin and meropenem against intracellular *Listeriae* is higher than against extracellular ones. In fact time dependant killing is achieved at least after 24 hours [44], [47], whereas azlocillin, mezlocillin and cephalosporins were ineffective [38]. One reason could be the fact that ampicillin in contrast to several other antibiotics was able to inhibit even in subinhibitory concentrations the production of hemolysin [31], a virulence factor which is essential for the intracellular life cycle of *L. monocytogenes* [6].

In experimental infections the effect of ampicillin was dependant on the dose and the time of the beginning of treatment. If treatment started rather early, the containment of bacteria was so effective, that an induction of an immune response to the bacteria could be prevented. Even in nude, athymic mice which are devoid of T lymphocytes a marked reduction of the bacterial load was achieved but complete eradication was not be enforced. Obviously, without the cooperation of the host's own immune system, a few bacteria survived and an exacerbation was observed in the immunocompromised mice few days after [48]. Another process contributing to the curing effect of ampicillin is a host defense strategy against intracellular pathogens, i.e. the induction of cell death, thereby eliminating the pathogen's intracellular niche. Pyroptosis, one such form of cell death, is triggered, when intracellular *Listeriae* are lysed by ampicillin [49].

c) **Gyrase inhibitors (quinolones/coumermycin):** The uptake of quinolones in eukaryotic cells takes place by passive diffusion, since these agents are amphiphilic; at least no carrier has been identified up to now. Whereas

ciprofloxacin is a subject of active efflux mechanisms, moxifloxacin obviously remains unaffected [50].

Moxifloxacin is concentration dependant rapidly bactericidal in vitro and active against intracellular *Listeria* in cultured cells [36], [47], [51]. Moxifloxacin has a rapid bactericidal effect against intracellular reservoirs of bacteria, whereas amoxicillin is only bacteriostatic [51]. Whereas ciprofloxacin is a substrate for efflux pumps, so that *Listeriae* residing in host cells expressing these transporters, moxifloxacin is not and remains active [52]. In experimental infections with infestation of internal organs where *Listeriae* reside mostly intracellular, moxifloxacin was superior to ciprofloxacin as well as to ampicillin [36]. Also in experimental models of *Listeria* meningitis, where bacteria predominantly multiply extracellularly, moxifloxacin was highly effective [53], [54].

The most active agent in the experimental setting was coumermycin, a gyrase B inhibitor. In experimental infections of the mouse coumermycin exerting a strong bactericidal activity in vitro could eliminate the bacteria even in immunocompromised nude mice [37]. This duty was accomplished so efficiently that the mice were not compelled to mount an immune reaction. In comparison to all other antibiotics tested it was by far the most active drug [55].

d) **Macrolides:** Erythromycin as well as other macrolides are bacteriostatic against *L. monocytogenes* in vitro [56]. The activity on intracellular bacteria is depending on the extracellular concentration [7]. Since it is known, that macrolides loose activity at low pH [57], it can be anticipated that it does not act on bacteria lying in the phagocytic vacuole. But once *Listeriae* have escaped into the cytoplasm, it can work. There is, however, a risk that the host cell has overexpressed efflux pumps due to genetic or environmental conditions; in such cases the macrolide antibiotic cannot reach the intracellular bacteria and is unable to cure the infection of those host cells [7].

In experimental infections of normal mice erythromycin is able to inhibit bacterial multiplication. In immunocompromised animals without the aid of the body's own defense system the protective effect was rather low [56].

e) **Tetracyclines:** In vitro tetracycline is bacteriostatic for *L. monocytogenes* [58]. In various mouse models (normal adult mice, nude, macrophage deprived animals, baby mice) this antibiotic was able to reduce the bacteria multiplication [58].

f) **Cotrimoxazole:** Trimethoprim is rather active in vitro against *L. monocytogenes*, whereas the sulfonamide component alone is rather inactive. In combination there is a synergistic effect [59].

This lipophilic drug is taken up by host cells via diffusion [43] and is active against intracellular *Listeriae* [38]. In experimental infections of normal and immunocompromised mice a definite therapeutic effect was observed [59].

g) **Aminoglycosides:** Aminoglycosides are taken up actively into host cells by fluid-phase pinocytosis. Thereby, substances dissolved in the extracellular fluid are internalized. The rate at which vesicles are transported varies from cell type to cell type but is in general relatively high.

Thus, after a few minutes and even hours the absolute amounts of intracellular drug is still low but can be remarkable after several days. After penetration the agents are not distributed evenly in the cytosol but are avidly trapped into the lysosomes. Within these longlasting reservoirs characterized by a low pH, aminoglycosides are stored in their cationic, i.e. microbiologically inactive forms, and are released only very slowly over a period of several days [43].

Consequently, aminoglycosides can only be active against extracellular bacteria. Indeed, no activity against intracellular *Listeriae* in host cells was detected [38], [44], [47]. Furthermore, a lack of synergism with ampicillin was also observed in experimental listeriosis when bacteria reside mainly intracellularly [60].

h) **Rifampicin:** Rifampicin is bactericidal for *L. monocytogenes* in vitro [61]. This lipophilic drug easily penetrates through the lipid bilayer of the host cell membrane [43], and it acts on intracellular *L. monocytogenes* about 200 times more effectively than ampicillin [62]. Furthermore, in experimental infection, when *Listeriae* multiply mainly in the reticuloendothelial organs such as spleen and liver, it is highly effective [62] and even in compromised hosts, such as nude mice, deprived of T-lymphocytes, rifampicin is able to reduce the bacterial load although a complete eradication was not achieved [63]. When bacteria multiply extracellularly, like in a meningitis model, it is, however less active than ampicillin [64].

i) **Glycopeptides (vancomycin/teicoplanin/daptomycin):** *Listeria monocytogenes* is susceptible in vitro to vancomycin and teicoplanin [65] as well as to daptomycin [66]. According to a recent report *Listeria grayi* is resistant to vancomycin [67].

In experimental infections of normal mice only a poor therapeutic activity of both vancomycin and teicoplanin [65] was seen and daptomycin was completely ineffective [66]. In athymic nude mice, which are immunocompromised, no activity of teicoplanin was seen [65].

One explanation for this discrepancy between in vitro and in vivo activities could be that these compounds are inactive against intracellular bacteria, because they may remain adherent to the cytoplasmic membrane of host cells after penetration, so that finally they do not come into contact with the microbe in the phagocytic vacuole or in the cytoplasm, respectively [43].

j) **Linezolid:** This oxazolidinone is active against all gram-positive bacteria including *Listeria monocytogenes* exerting a bacteriostatic effect [68]. In addition the growth of bacteria within host cells was inhibited [68]. Mice infected intravenously or intracerebrally were protected, although linezolid was less efficient than ampicillin [68]. Clinical experience with linezolid is limited but promising [69] possibly, because linezolid is found in high concentrations in CSF [70].

k) **Combinations:** Although in vitro a definite synergistic effect between β -lactams and aminoglycosides can be seen [23], [39], there is no such phenomenon observed on intracellular *Listeriae* [44]. Furthermore, a lack of synergism of gentamicin with ampicillin was also re-

gistered in experimental listeriosis [60], when bacteria reside mainly intracellularly.

Combination of antibiotics are better than single drugs not only because of a possible in vitro synergism; in case of a combination of ampicillin and rifampicin it could be argued that both agents would penetrate into the host cells as well as into different compartments of a host in different degrees and pathways and may exert additive effects.

Combinations of antibiotics with anti-inflammatory agents such as diclofenac may be synergistic [71].

The impact of the site of Listeria infection. Location at remote sites hardly accesible for antibiotics and the microenvironment on efficacy of antimicrobial therapy

CSF

Because of the blood brain barrier the entry of antibiotics into the CNS is restricted [72]. Whereas linezolid [70], rifampicin and quinolones [72] and especially moxifloxacin [73] are found in high concentrations in the cerebrospinal fluid, β -lactam antibiotics including ampicillin as well as amoxycillin penetrate the blood brain barrier only poorly [72]. Furthermore, in an inflammatory CSF the pH is rather low due to massive lactate production (>3.5 nmol/l) so that there is a risk that the labile β -lactam ring will be cleaved catalytically [74]. Ampicillin as well as amoxycillin, however, are relatively acid stable [75]. Macrolides also lose activity at low pH [57].

Granuloma

After a few days of infection with *L. monocytogenes* a granulomatous reaction is created by the host [13], [76], so the cells infected with *Listeriae* are surrounded by a dense wall of lymphocytes. Lipophilic compounds such as rifampicin and quinolones generally penetrate better such anatomic barriers than hydrophilic, ionized drugs [72]. Thus, complete eradication can only hardly be achieved by ampicillin.

Placental barrier

A few antibiotics only cross the placenta rapidly; among these is ampicillin. Other antibiotics such as piperacillin, cefoxitin, gentamicin, fosfomycin and vancomycin show incomplete transfer to the placenta where concentrations are lower in the cord than maternal plasma [77]. The placental transfer of macrolides is generally low; among them clarithromycin achieves the relatively highest concentrations [78].

Therapeutic options

Current therapeutic approaches

The local inoculation of *L. monocytogenes* in the skin or in the conjunctiva may induce localized infections in otherwise healthy people. In general, these superficial infections as well as the gastrointestinal manifestations are self-limited. Occasionally, however, such local infections need appropriate systemic therapy to resolve [79]. Antibiotics given to a patient are seldom able to overcome an infection without the contribution of the defense system [80]. Since systemic listeriosis occurs mainly in immunocompromised patients, it is quite conceivable that curing is not always possible, even if the best antibiotics have been chosen. Bactericidal activity of an antibiotic seems to be an advantage. Furthermore, in most cases, the infection happens in the CNS, which remains hardly accessible for most antibiotics due to the blood-brain-barrier. Consequently, the mortality remains high, i.e. up to 25%, and sequelae are frequent instead of rational antibiotic treatment.

Drug of primary choice remains ampicillin or even more so amoxicillin. Ureidopenicillins and carbapenems are also active but not superior to aminopenicillins. High doses, for example 2–3 g ampicillin given 3–4 times a day, are recommended. This regimen should be given at least for 2–3 weeks, even if the clinical conditions have improved in the meantime, to prevent a relapse. Because a total eradication is difficult to achieve without the body's own defense system, it is even prudent especially in cases of encephalitis in strongly immunocompromised patients to continue the regimen for about 2–6 weeks to avoid exacerbation; in this case an oral application of aminopenicillin could be advised to eliminate reservoirs of bacteria. In case of relapse the same regimen can be given, since this is not due to resistance, since until now the clinical isolates are unanimously susceptible to ampicillin. A poor response to rational antimicrobial therapy rather results from the remote place of infection hardly accessible for antibiotics or from the weak host's defense as a natural consequence of the underlying disease.

Because there is a synergistic effect *in vitro* of combinations of β -lactams with aminoglycosides against *L. monocytogenes* [25], [41], it has been widely accepted that this combination would be the therapy of choice especially for the treatment of CNS infections and endocarditis [25]. In cell cultures and animal experiments, however, this effect is lacking. A review of a large number of cases of CNS infections has shown a superiority of this combination [81]. But there is growing evidence that this combination does not provide a definite advantage over an aminopenicillin alone [82], [83]. But the debate is still ongoing [84]. In any case the aminoglycoside has to be omitted after 2 weeks, because of potential nephrotoxicity, especially in the elderly.

In case of allergy to penicillins parenteral application of cotrimoxazole (for example 80 mg trimethoprim and

400 mg sulfamethoxazole q.i.d for six weeks), is recommended as therapy of second choice, since this drug combination is bactericidal for *L. monocytogenes* *in vitro* and is accumulated within host cells and finds access to the CNS as well as to the placenta. This drug or trimethoprim alone can also be used for oral follow-up treatment after an initial parenteral application also after initial therapy with amoxicillin [7], [25], when the predisposing factors are still persisting so that an endogenous exacerbation could take place. Even a combination of amoxicillin and cotrimoxazole could be advised [85]. Because of a possible risk for the fetus – at least shown by animal experiments – cotrimoxazole should be avoided during pregnancy.

On the other hand a combination of amoxicillin with rifampicin in the therapy of cerebral listeriosis gives sense, since rifampicin can penetrate quite well into the CSF and can act on intracellular bacteria [25]. A final view, however, is impossible, because the clinical experience is limited.

Macrolides and tetracyclines are no more recommended today for the therapy of human listeriosis [86].

Unfortunately, in some guidelines it has been recommended to start calculated therapy of presumptive bacterial meningitis with ceftriaxone as monotherapy [16]. This cephalosporine is, however, inherently inactive against *L. monocytogenes*. Hence, the beginning of an effective antimicrobial therapy of listeric meningitis is delayed which implicates a worse outcome. Therefore, ampicillin should be added according to the German Society of Neurology [87], in particular in those individuals prone to *Listeria* infections, namely in aged people and in immunocompromised patients.

Future trends (including novel agents/ approaches)

There is ample evidence that moxifloxacin is qualified to replace ampicillin as therapy of the first choice. It is rapidly bactericidal at low concentrations [36], [47], [51], it is accumulated in host cells and remains active under such special conditions [47]. In animal experiments it is able to reduce the bacterial load – even in immunocompromised animals [36], [53], [54]. Furthermore, it is highly active in CSF [73]. Since large clinical experience is still lacking, it cannot be unanimously recommended for therapy of listeriosis yet. Successful clinical experience exists at least with another, similar quinolone namely levofloxacin [88]. It should be kept in mind, however, that quinolones are not allowed during pregnancy.

Adjunctive therapy

Some authorities have proposed a treatment with dexamethasone to reduce an excessive inflammatory response during bacterial meningitis [16], [87], which otherwise may have deleterious effects. On the other hand this co-medication may have some influence on the pharmaco-

dynamics of some antibiotics, especially vancomycin [16], [72], [89].

Combinations of antibiotics with other anti-inflammatory agents such as diclofenac may have synergistic effects with antibiotics [71].

Unconventional approaches

In spite of a rational antibiotic therapy the prognosis of *Listeria* infections remains poor. Therefore, it is quite logic to look for other even unconventional approaches. Lactoferrin has several interesting effects on *L. monocytogenes* in vitro [90], on *Listeriae* in cell cultures [91] as well as on experimental listeriosis [92]. Obviously, it exerts not only a direct antibacterial activity but also modulates the host defense. This aspect seems to be of special importance in the therapy of listeriosis occurring predominantly in patients with a compromised immune system. In general it is difficult yet to direct the immune system in the desired way without triggering an opposite effect. Vaccination strategies to prevent or to fight against listeriosis are not yet clinically available but experimental evidence is promising [93].

Notes

Competing interests

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