sciendo

DOI: 10.2478/fv-2023-0014

FOLIA VETERINARIA, 67, 2: 24—32, 2023

DENDRIMERS AS ANTIMICROBIAL AGENTS IN THE CENTRAL NERVOUS SYSTEM INFECTIONS. A REVIEW

Katarína Kucková[1], Mangesh Bhide[1, 2]

[1]Laboratory of Biomedical Microbiology and Immunology, University of Veterinary Medicine and Pharmacy in Košice, Komenského 73, 041 81 Košice

[2]Institute of Neuroimmunology, Slovak Academy of Sciences v. v. i., Dúbravská cesta 9, 845 10 Bratislava Slovakia

mangesh.bhide@uvlf.sk

ABSTRACT

Bacterial meningitis is a serious infection of the central nervous system that affects people all over the world. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common pathogens causing meningeal inflammation in Europe. Treatment with standard antibiotics is becoming ineffective, not only due to their inability to cross the blood-brain barrier, but also due to rising antibiotic resistance. As a result, novel therapeutics to combat the infection are required. A promising solution could be therapeutic nanomolecules, such as dendrimers, some of which have antimicrobial properties due to their chemical structure. Additionally, they may be decorated with a suitable therapeutic and central nervous system homing peptides to construct nano-drug delivery systems, which can effectively cross the blood-brain barrier. To synthesize safe dendrimeric nano-drug delivery system it is necessary to select the best dendrimer candidates with antimicrobial activity and to understand pharmacosafety, pharmacokinetics and dynamics. This review provides a brief overview of dendrimers and their antimicrobial properties as they have been studied in relation to the blood-brain barrier and existing antibiotics.

Key words: bacterial meningitis; blood-brain barrier; central nervous system; dendrimer; drug delivery

INTRODUCTION

Bacterial meningitis

Among the central nervous system (CNS) infections caused by various pathogens (bacteria, viruses, fungi), bacterial meningitis is the most common life-threating infection often ending in death [20, 39]. Approximately half of survivors have cognitive impairments that put them at risk of permanent disability [4, 61]. Meningitis has been recognized for over a century as an inflammation of the membranes that cover the brain and spinal cord – the meninges, particularly the pia mater and arachnoid mater [16, 23]. The pathogens responsible for approximately 80% of bacterial meningitis are Gram negative meningococcus *Neisseria meningitidis* and Gram positive pneumococcus *Streptococcus pneumoniae* [22]. Other bacteria that can colonize different mucosal surfaces, penetrate protective barriers, and cause infection include *Haemophilus influenzae* type b, *Escherichia coli* K1, *Mycobacterium tuberculosis, Listeria monocytogenes, Staphylococcus aureus, Salmonella, Klebsiella* spp. [11,58] or some species of spi-

rochete *Borrelia burgdorferi sensu lato* complex [34, 64]. *Streptococcus suis* is a bacterium that originally infects pigs and pork and cause a major problem in swine industry worldwide. Moreover, it is also a zoonotic pathogen responsible for several infections in humans, including meningitis [15, 69].

The ability to survive in blood and successfully evade host immunity through a variety of mechanisms (e. g. encapsulation, complement resistance) is critical for spreading from the primary site of infection into the brain via the blood-brain barrier (BBB). Three major meningeal pathogens (*S. pneumoniae, N. meningitidis, H. influenzae*) share molecular mimicry called "innate invasion", which acts against innate immune system [11, 41]. Exact mechanism how they are able cross the BBB is still not fully explored. Extracellular bacteria may induce signalling events after adhesion to endothelial cells, which may lead to transcytosis or disruption of tight junctions between the cells. *E. coli, Streptococcus* or *S. pneumoniae* produce toxins, which also damage cells. Then, bacteria can cross the BBB via paracellular way as well. Moreover, *N. meningitidis* or *S. pneumoniae* may reach the brain through olfactory nerve [40]. Other pathogens, for example, intracellular *M. tuberculosis* and *L. monocytogenes* use macrophages to pass through various membranes. This phenomenon is known as "Trojan horse" [35].

Blood-brain barrier and antibiotics

Blood-brain barrier is anatomically formed by brain capillary endothelial cells, pericytes, astrocytes end foot and nerve cells (microglia), shown in the Fig. 1 [18, 71]. Between brain endothelial cells, on their apical side, are tight junctions (claudins, occludins, junctional adhesion molecules) and adherens junction proteins, which are responsible for creating literally tight connections between the cells [49, 54]. Thanks to these connections, BBB is a highly selective membrane and crossing of ions, oxygen, glucose [8, 49] and other molecules (such as therapeutics) from the blood vessels into brain parenchyma is limited [17].

Despite the fact that, as previously stated, bacteria can cross this barrier in a variety of ways. Due to low number of immune cells and complement proteins in the brain, they can multiply rapidly in cerebrospinal fluid, particularly in the subarachnoid area. Immediately after bacteria cross the barrier, they may cause extensive damage. After disruption of BBB, its permeability is higher [11, 12, 41], thus neutrophils and macrophages are able to passage through. Subsequent activation of brain cells (microglia, astrocytes) and strong immune response of local cells and leukocytes from the blood, presence of pro-inflammatory cytokines, chemokines, proteolytic enzymes, oxidants and bacterial toxins as well, lead to damage of epithelial cells of brain barriers, neurones and inflammation of meninges surrounding the subarachnoid space [23, 61].

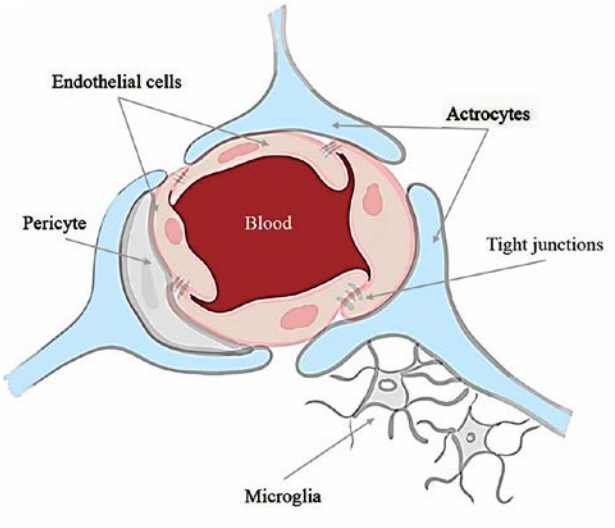

Fig. 1. Basic illustration of blood-brain barrier anatomy.
Original sketch, modified according to O m i d i et al. [49]

The use of antibiotics may decrease inflammation and restore balance of the BBB. However, using of β-lactam antibiotics may lead to cytokines and bacterial toxins release, which may dramatically increase inflammation response [12]. As a result, antibiotic treatment must be combined with other drugs that protect brain tissue by inhibiting several steps in the inflammatory cascade, such as dexamethasone [11]. The right choice of antimicrobial therapy depends on several factors that include mechanisms of antibiotic action, antimicrobial susceptibility, microbial growth rate, density and possible resistance to therapeutics. Patient age, status and type of infection are important as well. One of the most essential properties is the ability to cross the BBB into the subarachnoid space and act against bacteria. It is also affected by several physico-chemical factors, such as pH, structure of antibiotic, their protein binding ability or lipophilicity [12, 22]. Among the most used antibiotics to threaten meningococcal disease were sulfonamides, penicillin or chloramphenicol in the past [5]. D a v i s [9] published the list of

commonly used antibiotics for acute bacterial meningitis that included, for example, ciprofloxacin, cefepime, cefotaxime, gentamicin, meropenem, rifampin, vancomycin, also daptomycin and telavancin, but in high and long term dosages [9, 12]. Also, in the last few years, several new antibiotics have a potential to treat CNS infection, such as ceftriaxone, ceftobiprole, linezolid, moxifloxacin, trovafloxacin or tigecycline [46]. Additionally, thanks to synergistic effects of some of them, their appropriate combinations may be or are even desirable to be used [12].

Antimicrobial resistance is a natural phenomenon considering that several antibiotics are derived or naturally produced. Let us look at a few well-known examples: Actinomycetes produce secondary metabolites such as vancomycin, tetracycline, streptomycin and erythromycin [52], and, of course, mould *Penicilium notatum* produce penicillin [10]. History and mechanisms of antibiotic resistance are precisely described elsewhere [28, 31, 57, 70], discussion of those details would be beyond the scope of this mini-review. Antimicrobial resistance has also become a worldwide problem due to the overuse of antibiotics in therapy as well as feed supplements in husbandry or gain body weight [45]. *S. pneumoniae* has been resistant to penicillin for more than 60 years, and as a result, combination of two antibiotics (usually vancomycin and cephalosporin) is required instead of penicillin alone [22]. O p p e n h e i m published a brief overview in 1997 about increasing antibiotic resistance to drugs commonly used to treat meningococcal disease, which he saw as a future problem, particularly in the case of *N. meningitidis*. Therefore, more than 25 years ago, he suggested as a possible solution vaccination against meningococci and reducing of worldwide excessive using of antibiotics in the future [50]. Another report occurrence of multiresistant bacteria was emphasized in 1950s [36], and currently increasing multiresistant strains have been reported all over the world [60].

Nanomolecules in biomedicine

In biomedicine different types of nanomolecules can be used, for example, liposomes, micelles, metal nanoparticles, nanotubes, polymers or dendrimers [37]. Antimicrobial polymers in combination with other antimicrobial molecules, such as antibiotics, could be one of the most intriguing strategies for developing new nanotherapeutics [13]. More than 80 new nanoformulations are currently in preclinical testing and could be used as nano-drug delivery systems [27]. Dendrimers are among the nanoparticles that we are interested in.

Dendrimers

According to T o m a l i a et al. [68] their name consist of two Greek words: dendros (tree) and meros (part) [7]. Dendrimers are molecules with a regular geometrical structure [53] in size between 2 to 5 nm [17]. They have globular, radially symmetric, hyperbranched arrangement consisting of core, branching dendrones and various peripheral surface groups [38, 48], which defines their properties [37], as shown in the Fig. 2. In fact, polyamidoamine (PAMAM) dendrimer firstly synthesized by T o m a l i a et al. [68] is one of most studied, commercialized dendrimer from which many modification are constructed. The hydrophobic core of PAMAM is made of diamines (e. g. ethylene diamine), branches are made of ethylene diamine or methyl acrylate and on the surface are usually amide or carboxylic groups [67]. Unlike polymers synthesized by polymerization, dendrimers are synthetized differently, by two most commonly used methods. In divergent synthesis branches grows around the core layer by layer creating new "generation". On the contrary, in convergent synthesis they are made from periphery to the core [7, 48].

Polymer composition results in inner cavities containing one or more therapeutic agents [59]. Fig. 2 shows 3 possible basic interactions between dendrimer and drug: cleavable (ester, amid) bond (a), covalent bond (b) or as internal encapsulated part (c) part of structure. Therapeutic molecules (like antibiotics) could also be part of associated dendrimers. Covalent bond is very stable, thus the usage of dendrimers bounded with therapeutics by cleavable bond is more appropriate [7].

The physicochemical characteristic of nanomaterials (e. g. size, shape, surface properties, reactivity or biocompatibility) are crucial in stability, toxicity or biodistribution and drug delivery [37, 56]. Using dendrimers as a possible drug delivery system have a several advantages: safety, efficacy, regulated rate and location of drug release [2]. According to H u a n g and W u [26] the so-called "linkers" between drug and dendrimer may affect the activity and the drug release. Among these linkers are (1) ester bonds, which may be cleavable by ester enzymes in the cell, (2) groups unstable in acidic conditions of tumour or inflamed tissue (acetal/ketal, cis-aconityl, hydrazone groups) and (3) disulphide bond, which can be broken by glutathione

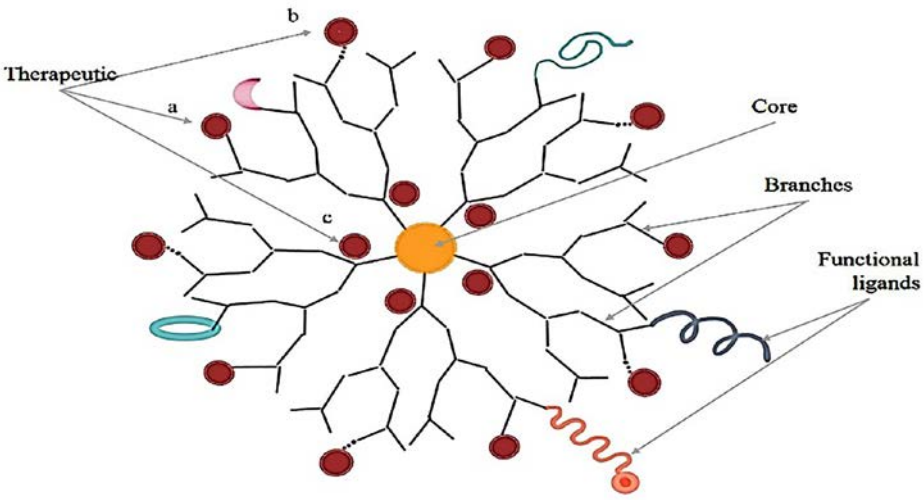

Fig. 2. Scheme of dendrimer structure and possible ways of therapeutics binding by a) cleavable (ester, amid) bond, b) covalent bond or as c) encapsulated therapeutic.
Original sketch, modified according to C a m i n a d e and T u r r i n [7].

in the cell [26]. Controlling dendrimer biodegradation into small fragments is also one of possible way to releasing drug at the specific target site. This intelligent delivery system may reduce the potential toxicity and side effects of drug-dendrimer molecule lower while increasing efficacy [26, 43].

In general, applying small molecules to the surface of nanoparticles opened up new avenues for potential applications because they determine their properties. These molecules can be antibodies, nanobodies, nucleic acids, aptamers, proteins or peptides, carbohydrates, signalling molecules etc. [63]. These functional ligands (Fig. 2) attached to branches influence the dendrimer`s reactivity to other receptor sites of cells, enzymes, peptides or pathogens, as well as the solubility of conjugated drug [59]. Nanobodies are small, single-domain and stable fragments of antibody with approximately 15 kDa weight [51]. Conjugation of specific nanobodies as one of functional group to the surface of dendrimer will allow active targeting of bacteria [21]. Similarly, using of aptamers, small oligonucleotides, is suitable option compared with antibody. They are able to penetrate through membranes, they have high specificity and stability in temperature and pH. Moreover, they have unlimited shelf life and may be diversified. Thus aptamers may be used as therapeutic agents or targeting component for drug delivery system [55]. Furthermore, several types of dendrimers are able to generate fluorescence under specific conditions (pH, oxidation). In order to improve this property and allow to study biodistribution and localization of nanoparticles in *in vitro* or *in vivo* systems by various imaging techniques, they can be associated with fluorescence dye [33, 42]. Dendrimers are used in a variety of medical applications, including tissue engineering, gene transfection, cancer treatment, drug delivery system, and as antiviral, antiparasitic, and antimicrobial agents [17, 48]. They have been used as therapeutics for about twenty years [53].

Despite extensive research into the functionality and safety of dendrimers, there is still the possibility of some negative effects. Among the negative properties of dendrimer is the possibility of toxicity not only to pathogens but also to human/animal cells. Another limitation is the inability to control drug`s incorporation and subsequent release [59]. Furthermore, structural changes – core, branches, surface – affect toxicity. Dendrimer of the third to fifth generation appears to be less harmful than the larger ones [67]. Often studied are polymers PEG (poly(ethylene)glycol) and PLGA (poly(lactic)-co-(glycolic) acid). They are biocompatible, biodegradable, low toxic and highly functionalized to using in drug delivery system to the brain [2]. PAMAM dendrimers conjugated with PEG showed lower toxicity while retaining antimicrobial activity [13].

They must be biodegradable, bio-pharmacologically safe, and highly selective in order to be effective as nano-drug delivery systems or therapeutics in clinical medicine. They should ensure low to no concentrations of captured therapeutics in non-targeted tissues while increasing concentration at the site of infection through precise drug

release, which could be accomplished using the methods described above [35]. They should also reduce treatment side effects and finally, avoid the development of antibiotic resistance [47, 63]. The advancement of nanobiotechnology should allow for the efficient use of targeted nano-drug delivery systems.

Antimicrobial effects of dendrimers

The use of dendrimers as antimicrobial agents has two effects. First, as previously stated, they can deliver a drug to the target site; second, they are therapeutics of themselves [56]. Dendrimer-drug conjugates are widely studied in many fields like cancer therapy, against inflammation, as antiviral or antimicrobial treatment [30, 32]. Choosing appropriate therapeutics to incorporate into dendrimer is a delicate issue. Aside from the chemical structure of the antibiotic and the dendrimer, the ability to fight effectively against G+ and G– bacteria is also important. For example, S v e n n i n g s e n et al. [66] synthesized PAMAM dendrimer-ciprofloxacin conjugate and observed synergic effect of this molecule against selected G+ or G– bacteria. It appears to be a beneficial solution, as drugs incorporation into dendrimers can increase solubility and bioavailability while decreasing dosage [59]. PAMAM or polypropylene imine (PPI) dendrimers with various terminal surface ligand modifications are the most studied dendrimers with positive effects against microbial or viral infection or inflammation [13, 14, 24]. Their biocidal effect is also determined by the size and generation of dendrimer branches. The main antibacterial mechanism is based on the cationic charge of dendrimer molecules, which can interact with negatively charged bacterial membranes. As a result, the membrane permeability increases, pores form, and bacteria lyse [17, 38]. G h o l a m i et al. synthesized a 7th generation PAMAM dendrimer and tested its antibacterial activity against a variety of G+ and G– bacteria (e. g. *E. coli, S. aureus, K. pneumonie, Acinetobacter baumannii*). They conclude, that this type of dendrimer is effective and tend to be a potential antimicrobial therapeutic [19]. C h e n et al. [29] also observed positive antibacterial effects of PPI dendrimers with quaternary ammonium groups. Not only cationic, but also modified anionic PAMAM dendrimers can be efficient against G+ bacteria [65].

Bacteria are able to recognize sugar on the surface of eukaryotic cells. Glycodendrimers decorated with various oligosaccharides on the surface remind eukaryotic cell, a result is bacteria binding to glycodendrimers instead their adhesion to the host cell [6]. Another type of effective dendrimeric nanomolecules are redox-active organometallic dendrimers. Antimicrobial properties of dendrimer conjugates with metal particles (e. g. silver, zinc or gold) enhance the stability and their bactericidal effect [2, 44]. They are able to produce free radicals and damage microbes. This mechanism with combination of positively charged molecule was successful against G+ bacteria (e. g. *S. aureus*) [1, 6]. Moreover, R i z v i et al. pointed out the possible usage of gold nanoparticles with combination of proper antibiotics, which could fight against pathogens causing bacterial meningitis (caused by in particular *S. pneumoniae* and *L. monocytogenes*) [58]. Interestingly, H o u et al. [25] and B a h a r et al. [3] observed positive antimicrobial effect of dendrimer against biofilm formed by *E. coli* or *Pseudomonas aeruginosa* respectively. The use of dendrimers may thus have a positive impact on the development of new antibiotic-resistant strains [6, 17], and it should be explored more.

Dendrimers ability to cross blood-brain

Drugs should be able to cross the BBB if pathogens can. Nonetheless, common therapeutics` passage and subsequent bioaccessibility are severely limited. This is one of the reasons why traditional antibiotics are almost ineffective in treatment CNS infections [59]. Thanks to nanostructure, dendrimers are able to cross various cell membranes and barriers, including BBB by paracellular or transcellular transport [17, 59]. The mechanism that was mentioned above also applies in this case. Molecules with positive charged surface may interact with negatively charged endothelial cell membrane and cross the barrier via adsorptive-mediated transcytosis (Fig. 3). Among other basic mechanisms of molecule transport, which are illustrated in the Fig. 3, belongs transcellular diffusion (1.), carrier-mediated transport (2.), passive or paracellular transport (3.) or receptor-mediated transport (4.) [54, 71, 72].

Receptor mediated transport, which is used for transmission of large molecules (e. g. proteins, hormones) is mostly utilized mechanism in bionanomedicine for the drug transport. Insulin, transferrin, low-density lipoprotein (LDL) receptors, and single domain llama antibodies are the most commonly studied [54]. The multifunctional receptors LRP1 and LRP2 are two of these LDL receptors. They can transport a variety of proteins, including lacto-

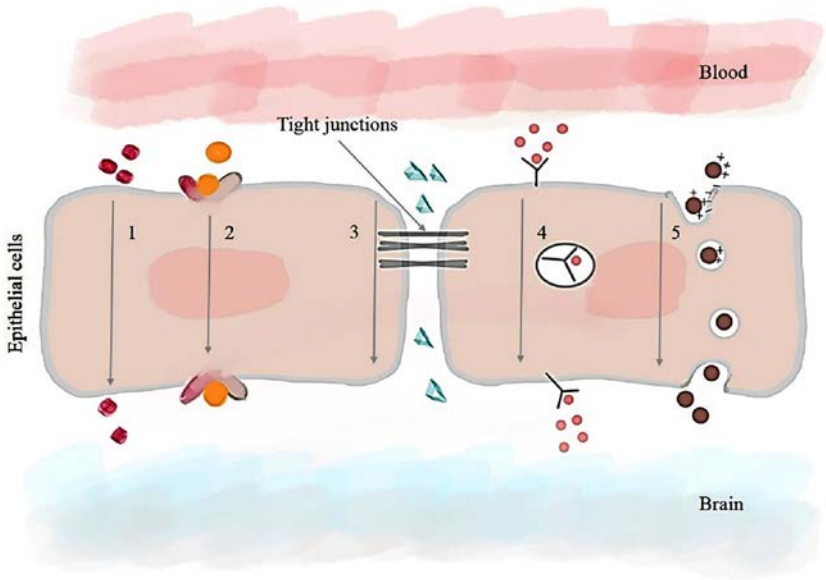

Fig. 3. Basic mechanisms of transport across blood-brain barrier. 1. Passive transcellular diffusion; 2. Carrier-mediated transport; 3. Paracellular transport; 4. Receptor-mediated transport; 5. Adsorptive-mediated transcytosis.
Original sketch, modified according to Velasco-Aguirre et al. [71]

ferrin, angiopep-2, and leptin peptide fragments [62]. Constructing nanoparticles, specifically dendrimers with these types of molecules on their surface as functional ligands, allows them to cross the BBB and have a direct effect on therapeutics at a target site. Furthermore, as previously stated, after pathogen entry into the CNS, tight junction proteins between endothelial cells are disrupted, increasing BBB permeability. As a result, dendrimers can more easily pass through the membrane via paracellular transport and attempt to fight the infection [72].

CONCLUSIONS

In conclusion, despite developed vaccines or antibiotics, bacterial meningitis poses a serious health risk. Pathogens adapt quickly, mutate and become resistant. To control meningitis globally, a new alternative antimicrobial strategy is required. We believe that using dendrimers as novel therapeutics is appropriate due to their advantageous structure as a nano-drug delivery agent to the central nervous system and health benefits. Given this information, a multidisciplinary approach is required to obtain stable, safe, and effective dendrimers for future treatment of bacterial meningitis in humans and animals.

ACKNOWLEDGEMENT

This study was supported by grants DSV-ITMS2014+ project code NFP313010V455, APVV-18-0259 and VEGA 1/0381/23.

REFERENCES

1. **Abd-El-Aziz, A. S., Agatemor, C., Etkin, N., Overy, D. P., Lanteigne, M., McQuillan, K., et al., 2015:** Antimicrobial organometallic dendrimers with tunable activity against multidrug-resistant bacteria. *Biomacromolecules*, 16, 11, 3694–3703. DOI: 10.1021/acs.biomac.5b01207.
2. **Ayub, A., Wettig, S., 2022:** An overview of nanotechnologies for drug delivery to the brain. *Pharmaceutics*, 14, 2. DOI: 10.3390/pharmaceutics14020224.
3. **Bahar, A. A., Liu, Z., Totsingan, F., Buitrago, C., Kallenbach, N., Ren, D., 2015:** Synthetic dendrimeric peptide active against biofilm and persister cells of Pseudomonas aeruginosa. *Appl. Microbiol. Biotechnol.*, 99, 19, 8125–8135. DOI: 10.1007/s00253-015-6645-7.
4. **Barichello, T., Generoso, J. S., Simoes, L. R. R., Goularte, J. S., Petronilho, F., Saigal, P., et al., 2016:** Role of microglial activation in the pathophysiology of bacterial meningitis. *Mol. Neurobiol.*, 53, 3, 1770–1781. DOI: 10.1007/s12035-015-9107-4.

5. **Bash, M. C., Matthias, K. A., 2017:** Antibiotic resistance in Neisseria. In **Mayers, D. L., Sobel, D. J., Ouellette, M., Kaye, K. S., Marchaim, D.:** *Antimicrobial Drug Resistance: Clinical and Epidemiological Aspects*, Volume 2. Springer Cham., 843–865.
6. **Borah, N., Gogoi, A., Saikia, J., 2022:** Dendrimeric entities as chemical alternatives toward antimicrobial therapy. In **Saha, T., Adhikari, M. D., Tiwary, B. K.:** *Alternatives to Antibiotics: Recent Trends and Future Prospects*. Springer, 379–400.
7. **Caminade, A. M.,Turrin, C. O., 2014:** Dendrimers for drug delivery. *J. Mater. Chem.*, 2, 26, 4055–4066. DOI: 10.1039/c4tb00171k.
8. **Coureuil, M., Lécuyer, H., Bourdoulous, S., Nassif, X., 2017:** A journey into the brain: insight into how bacterial pathogens cross blood-brain barriers. *Nat. Rev. Microbiol.*, 15, 3, 149–159. DOI: 10.1038/nrmicro.2016.178.
9. **Davis, L. E., 2018:** Acute bacterial meningitis. *Continuum* (Minneap. Minn.), 24, (5 Neuroinfectious Disease), 1264–1283. DOI: 10.1212/con.0000000000000660.
10. **Dodds, D. R., 2017:** Antibiotic resistance: A current epilogue. *Biochem. Pharmacol.*, 134, 139–146. DOI: 10.1016/j.bcp.2016.12.005.
11. **Doran, K. S., Fulde, M., Gratz, N., Kim, B. J., Nau, R., Prasadarao, N., et al., 2016**: Host-pathogen interactions in bacterial meningitis. *Acta Neuropathol.*, 131, 2, 185–209. DOI: 10.1007/s00401-015-1531-z.
12. **Ekizoğlu, M., 2017:** Infectious diseases of the brain. In **Gürsoy-Özdemir, Y., Bozdağ-Pehlivan, S., Sekerdag, E.:** *Nanotechnology Methods for Neurological Diseases and Brain Tumors*. Elsevier. 291–315.
13. **Falanga, A., Del Genio, V.,Galdiero, S., 2021:** Peptides and dendrimers: How to combat viral and bacterial infections. *Pharmaceutics*, 13, 1, 23. DOI: 10.3390/pharmaceutics13010101.
14. **Felczak, A., Wrońska, N., Janaszewska, A., Klajnert, B., Bryszewska, M., Appelhans, D., et al., 2012:** Antimicrobial activity of poly (propylene imine) dendrimers. *New J. Chem.*, 36, 11, 2215–2222.
15. **Feng, Y., Zhang, H., Wu, Z., Wang, S., Cao, M., Hu, D., et al., 2014:** *Streptococcus suis* infection: An emerging/reemerging challenge of bacterial infectious diseases? *Virulence*, 5, 4, 477–497. DOI: 10.4161/viru.28595.
16. **Flexner, S., 1907:** Experimental cerebro-spinal meningitis in monkeys. *J. Exp. Med.*, 9, 2, 142–167. DOI: 10.1084/jem.9.2.142.
17. **Garcia-Gallego, S., Franci, G., Falanga, A., Gomez, R., Folliero, V., Galdiero, S., et al., 2017:** Function oriented molecular design: Dendrimers as novel antimicrobials. *Molecules*, 22, 10. DOI: 10.3390/molecules22101581.
18. **Gauro, R., Nandave, M., Jain, V. K., Jain, K., 2021:** Advances in dendrimer-mediated targeted drug delivery to the brain. *J. Nanopart. Res.*, 23, 3, 76. DOI: 10.1007/s11051-021-05175-8.
19. **Gholami, M., Mohammadi, R., Arzanlou, M., Akbari Dourbash, F., Kouhsari, E., Majidi, G., et al., 2017:** *In vitro* antibacterial activity of poly (amidoamine)-G7 dendrimer. *BMC Infect. Dis.*, 17, 1, 395. DOI: 10.1186/s12879-017-2513-7.
20. **Giovan, R. A., Lavender, P. D., 2018:** Central nervous system infections. *Primary Care*, 45, 3, 505. DOI: 10.1016/j.pop.2018.05.007.
21. **He, Z. Y., Wei, X. W., Wei, Y. Q., 2017:** Recent advances of nanostructures in antimicrobial therapy. In **Grumezescu, A. M.:** *Antimicrobial Nanoarchitectonics: From Synthesis to Applications*. 167–194.
22. **Heckenberg, S. G., Brouwer, M. C., van de Beek, D., 2014:** Bacterial meningitis. *Handb. Clin. Neurol.*, 121, 1361–1375. DOI: 10.1016/b978-0-7020-4088-7.00093-6.
23. **Hoffman, O., Weber, R. J., 2009:** Pathophysiology and treatment of bacterial meningitis. *Ther. Adv. Neurol.*, 2, 6, 1–7. DOI: 10.1177/1756285609337975.
24. **Holmes, A. M., Heylings, J. R., Wan, K. W., Moss, G. P., 2019:** Antimicrobial efficacy and mechanism of action of poly(amidoamine) (PAMAM) dendrimers against opportunistic pathogens. *Int. J. Antimicrob. Agents*, 53, 4, 500–507. DOI: 10.1016/j.ijantimicag.2018.12.012.
25. **Hou, S., Zhou, C., Liu, Z., Young, A. W., Shi, Z., Ren, D., et al., 2009:** Antimicrobial dendrimer active against *Escherichia coli* biofilms. *Bioorg. Med. Chem. Lett.*, 19, 18, 5478–5481. DOI: 10.1016/j.bmcl.2009.07.077.
26. **Huang, D., Wu, D., 2018:** Biodegradable dendrimers for drug delivery. *Mater. Sci. Eng. C Mater. Biol. Appl.*, 90, 713–727. DOI: 10.1016/j.msec.2018.03.002.
27. **Huang, J., Li, Y. C., Orza, A., Lu, Q., Guo, P., Wang, L. Y., et al., 2016:** Magnetic nanoparticle facilitated drug delivery for cancer therapy with targeted and image-guided approaches. *Adv. Funct. Mater.*, 26, 22, 3818–3836. DOI: 10.1002/adfm.201504185.
28. **Chatterjee, A., Modarai, M., Naylor, N. R., Boyd, S. E., Atun, R., Barlow, J., et al., 2018:** Quantifying drivers of antibiotic resistance in humans: A systematic review. *Lan-*

cet Inf. Dis., 18, 12, E368–E378. DOI: 10.1016/s1473-3099(18)30296-2.

29. **Chen, C. Z., Beck-Tan, N. C., Dhurjati, P., van Dyk, T. K., LaRossa, R. A., Cooper, S. L., 2000:** Quaternary ammonium functionalized poly(propylene imine) dendrimers as effective antimicrobials: Structure-activity studies. *Biomacromolecules*, 1, 3, 473–480. DOI: 10.1021/bm0055495.
30. **Chis, A. A., Dobrea, C., Morgovan, C., Arseniu, A. M., Rus, L. L., Butuca, A., et al., 2020:** Applications and limitations of dendrimers in biomedicine. *Molecules*, 25, 17. DOI: 10.3390/molecules25173982.
31. **Christaki, E., Marcou, M., Tofarides, A., 2020:** Antimicrobial resistance in bacteria: Mechanisms, evolution, and persistence. *J. Mol. Evol.*, 88, 1, 26–40. DOI: 10.1007/s00239-019-09914-3.
32. **Kalhapure, R. S., Suleman, N., Mocktar, C., Seedat, N., Govender, T., 2015:** Nanoengineered drug delivery systems for enhancing antibiotic therapy. *J. Pharm. Sci.*, 104, 3, 872–905. DOI: 10.1002/jps.24298.
33. **Kimura, S., Harashima, H., 2020:** Current status and challenges associated with CNS-targeted gene delivery across the BBB. *Pharmaceutics*, 12, 12. DOI: 10.3390/pharmaceutics12121216.
34. **Kullberg, B. J., Vrijmoeth, H. D., van de Schoor, F., Hovius, J. W., 2020:** Lyme borreliosis: Diagnosis and management. *BMJ*, 369, m1041. DOI: 10.1136/bmj.m1041.
35. **Kumar, L., Verma, S., Vaidya, B., Mehra, N. K., 2017:** Nanocarrier-assisted antimicrobial therapy against intracellular pathogens. In **Ficai, A., Grumezescu, A. M.:** *Nanostructures for Antimicrobial Therapy*. Elsevier, 293–324.
36. **Kumar, M., Sarma, D. K., Shubham, S., Kumawat, M., Verma, V., Nina, P. B., et al., 2021:** Futuristic non-antibiotic the apies to combat antibiotic resistance: A review. *Front. Microbiol.*, 12. DOI: 10.3389/fmicb.2021.609459.
37. **Kumari, P., Luqman, S., Meena, A., 2020:** Nanomaterials: A promising tool for drug delivery. In **Daima, H. K., Navya, P. N., Ranjan, S., Dasgupta, N., Lichtfouse, E.:** *Nanoscience in Medicine*, 1, 39. 1–49.
38. **Ladd, E., Sheikhi, A., Li, N., van de Ven, T. G. M., Kakkar, A., 2017:** Design and synthesis of dendrimers with facile surface group functionalization, and an evaluation of their bactericidal efficacy. *Molecules*, 22, 6. DOI: 10.3390/molecules22060868.
39. **LaPenna, P. A., Roos, K. L., 2019:** Bacterial infections of the central nervous system. *Semin. Neurol.*, 39, 3, 334–342. DOI: 10.1055/s-0039-1693159.
40. **Le Guennec, L., Coureuil, M., Nassif, X., Bourdoulous, S., 2020:** Strategies used by bacterial pathogens to cross the blood-brain barrier. *Cell Microbiol.*, 22, 1, e13132. DOI: 10.1111/cmi.13132.
41. **Liechti, F. D., Grandgirard, D., Leib, S. L., 2015:** Bacterial meningitis: insights into pathogenesis and evaluation of new treatment options: a perspective from experimental studies. *Future Microbiol.*, 10, 7, 1195–1213. DOI: 10.2217/fmb.15.43.
42. **Longmire, M., Choyke, P. L., Kobayashi, H., 2008:** Dendrimer-based contrast agents for molecular imaging. *Curr. Top. Med. Chem.*, 8, 14, 1180–1186. DOI: 10.2174/156802608785849021.
43. **Mhlwatika, Z., Aderibigbe, B. A., 2018:** Application of dendrimers for the treatment of infectious diseases. *Molecules*, 23, 9. DOI: 10.3390/molecules23092205.
44. **Mintzer, M. A., Dane, E. L., O'Toole, G. A., Grinstaff, M. W., 2012**: Exploiting dendrimer multivalency to combat emerging and re-emerging infectious diseases. *Mol. Pharm.*, 9, 3, 342–354. DOI: 10.1021/mp2005033.
45. **Morrison, L., Zembower, T. R., 2020:** Antimicrobial resistance. *Gastrointest. Endosc. Clin. N. Am.*, 30, 4, 619–635. DOI: 10.1016/j.giec.2020.06.004.
46. **Nau, R., Djukic, M., Spreer, A., Ribes, S., Eiffert, H., 2015:** Bacterial meningitis: An update of new treatment options. *Expert Rev. Anti. Infect. Ther.*, 13, 11, 1401–1423. DOI: 10.1586/14787210.2015.1077700.
47. **Nazli, A., He, D. L., Liao, D., Khan, M. Z. I., Huang, C., He, Y., 2022:** Strategies and progresses for enhancing targeted antibiotic delivery. *Adv. Drug Deliv. Rev.*, 189, 114502. DOI: 10.1016/j.addr.2022.114502.
48. **Nikzamir, M., Hanifehpour, Y., Akbarzadeh, A., Panahi, Y., 2021:** Applications of dendrimers in nanomedicine and drug delivery: A review. *J. Inorg. Organomet. Polym. Mater.*, 31, 6, 2246–2261. DOI: 10.1007/s10904-021-01925-2.
49. **Omidi, Y., Kianinejad, N., Kwon, Y., Omidian, H., 2021:** Drug delivery and targeting to brain tumors: Considerations for crossing the blood-brain barrier. *Expert. Rev. Clin. Pharmacol.*, 14, 3, 357–381. DOI: 10.1080/17512433.2021.1887729.
50. **Oppenheim, B. A., 1997:** Antibiotic resistance in *Neisseria meningitidis*. *Clin. Infect. Dis.*, 24, S98–S101. DOI: 10.1093/clinids/24.Supplement_1.S98.
51. **Pardon, E., Laeremans, T., Triest, S., Rasmussen, S. G. F., Wohlkonig, A., Ruf, A., et al., 2014:** A general protocol for the generation of nanobodies for structural biology. *Nature Protocols*, 9, 3, 674–693. DOI: 10.1038/nprot.2014.039.

52. Perry, J., Waglechner, N., Wright, G., 2016: The prehistory of antibiotic resistance. *Cold Spring Harb. Perspect.*, 6, 6. DOI: 10.1101/cshperspect.a025197.

53. Pompilio, A., Geminiani, C., Mantini, P., Siriwardena, T. N., Di Bonaventura, I., Reymond, J. L., et al., 2018: Peptide dendrimers as "lead compounds" for the treatment of chronic lung infections by Pseudomonas aeruginosa in cystic fibrosis patients: *In vitro* and *in vivo* studies. *Infect. Drug Resist.*, 11, 1767–1782. DOI: 10.2147/idr.S168868.

54. Pulgar, V. M., 2018: Transcytosis to cross the blood brain barrier, new advancements and challenges. *Front. Neurosci.*, 12, 1019. DOI: 10.3389/fnins.2018.01019.

55. Rabiee, N., Ahmadi, S., Arab, Z., Bagherzadeh, M., Safarkhani, M., Nasseri, B., et al., 2020: Aptamer hybrid nanocomplexes as targeting components for antibiotic/gene delivery systems and diagnostics: A review. *Int. J. Nanomed.*, 15, 4237–4256. DOI: 10.2147/ijn.S248736.

56. Rajak, B. L., Kumar, R., Gogoi, M., Patra, S., 2020: Antimicrobial activity of nanomaterials. In **Daima, H. K., Navya, P. N., Ranjan, S., Dasgupta, N., Lichtfouse, E.:** *Nanoscience in Medicine*, 1, 39. 147–185.

57. Reygaert, W. C., 2018: An overview of the antimicrobial resistance mechanisms of bacteria. *Aims Microbiol.*, 4, 3, 482–501. DOI: 10.3934/microbiol.2018.3.482.

58. Rizvi, S. M. D., Hussain, T., Ahmed, A. B. F., Alshammari, T. M., Moin, A., Ahmed, M. Q., et al., 2018: Gold nanoparticles: A plausible tool to combat neurological bacterial infections in humans. *Biomed. Pharmacother.*, 107, 7–18. DOI: 10.1016/j.biopha.2018.07.130.

59. Santos, A., Veiga, F., Figueiras, A., 2020: Dendrimers as pharmaceutical excipients: Synthesis, properties, toxicity and biomedical applications. *Materials*, 13, 1. DOI: 10.3390/ma13010065.

60. Scorciapino, M. A., Serra, I., Manzo, G., Rinaldi, A. C., 2017: Antimicrobial dendrimeric peptides: Structure, activity and new therapeutic applications. *Int. J. Mol. Sci.*, 18, 3. DOI: 10.3390/ijms18030542.

61. Scheld, W. M., Koedel, U., Nathan, B., Pfister, H. W., 2002: Pathophysiology of bacterial meningitis: Mechanism(s) of neuronal injury. *J. Infect. Dis.*, 186, S225–S233. DOI: 10.1086/344939.

62. Somani, S., Dufes, C., 2014: Applications of dendrimers for brain delivery and cancer therapy. *Nanomedicine*, 9, 15, 2403–2414. DOI: 10.2217/nnm.14.130.

63. Spirescu, V. A., Chircov, C., Grumezescu, A. M., Andronescu, E., 2021: Polymeric nanoparticles for antimicrobial therapies: An up-to-date overview. *Polymers*, 13, 5. DOI: 10.3390/polym13050724.

64. Stanek, G., Wormser, G. P., Gray, J., Strle, F., 2012: Lyme borreliosis. *Lancet*, 379, 9814, 461–473. DOI: 10.1016/s0140-6736(11)60103-7.

65. Staneva, D., Angelova, S., Vasileva-Tonkova, E., Grozdanov, P., Nikolova, I., Grabchev, I., 2020: Synthesis, photophysical characterisation and antimicrobial activity of a new anionic PAMAM dendrimer. *J. Photochem. Photobiol.*, 403, 112878.

66. Svenningsen, S. W., Frederiksen, R. F., Counil, C., Ficker, M., Leisner, J. J., Christensen, J. B., 2020: Synthesis and antimicrobial properties of a ciprofloxacin and PAMAM-dendrimer conjugate. *Molecules*, 25, 6. DOI: 10.3390/molecules25061389.

67. Tarach, P., Janaszewska, A., 2021: Recent advances in preclinical research using PAMAM dendrimers for cancer gene therapy. *Int. J. Mol. Sci.*, 22, 6. DOI: 10.3390/ijms22062912.

68. Tomalia, D. A., Baker, H., Dewald, J., Hall, M., Kallos, G., Martin, S., et al., 1985: A new class of polymers – starbust-dendritic macromolecules. *Polymer J.*, 17, 1, 117–132. DOI: 10.1295/polymj.17.117.

69. van Samkar, A., Brouwer, M. C., Schultsz, C., van der Ende, A., van de Beek, D., 2015: *Streptococcus suis* meningitis: A systematic review and meta-analysis. *PLOS Negl. Trop. Dis.*, 9, 10, e0004191. DOI: 10.1371/journal.pntd.0004191.

70. Vega, N. M., Gore, J., 2014: Collective antibiotic resistance: mechanisms and implications. *Curr. Opin. Microbiol.*, 21, 28–34. DOI: 10.1016/j.mib.2014.09.003.

71. Velasco-Aguirre, C., Morales, F., Gallardo-Toledo, E., Guerrero, S., Giralt, E., Araya, E., et al., 2015: Peptides and proteins used to enhance gold nanoparticle delivery to the brain: preclinical approaches. *Int. J. Nanomed.*, 10, 4919–4936. DOI: 10.2147/ijn.S82310.

72. Zhu, Y. F., Liu, C. Y., Pang, Z. Q., 2019: Dendrimer-based drug delivery systems for brain targeting. *Biomolecules*, 9, 12. DOI: 10.3390/biom9120790.

Received February 27, 2023
Accepted March 30, 2023