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ANTIBIOTHERAPY IN NEUROSURGICAL PATIENTS AS A BLOOD-BRAIN BARRIER CHEATER – IS IT WORTH IT?

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Summary.
The blood-brain barrier (BBB) is a mandatory mechanism in the vascular dynamic of the central nervous system (CNS). It employs multiple processes to maintain homeostasis. A systematic literature review was conducted, encompassing 65 sources from different databases, that involved studies solely on humans. Potential routes, and barriers to pharmacotherapy were identified and described. In conclusion, antibiotherapy continues to be a relevant topic due to the diverse and sometimes conflicting pharmacodynamic properties exhibited by different antibiotic classes under varying pathological conditions.
Keywords: Antibiotherapy; infection; blood-brain barrier; neurosurgery.

Rezumat. Antibioterapia la pacienții neurochirurgicali în calitate de trișor al barierei hemato-encefalice – se merită?
Bariera hemato-encefalică (BHE) reprezintă un mecanism esențial pentru dinamica vasculară a sistemului nervos central (SNC). Aceasta implică multiple procese pentru a menține homeostazia. Un reviu sistematic al literaturii a fost realizat, utilizând 65 de surse din diferite baze de date, incluzând studii efectuate exclusiv pe subiecți umani. Au fost identificate și descrise căile potențiale de administrare, precum și obstacolele pentru farmacoterapie. În concluzie, antibioterapia rămâne un subiect de actualitate datorită proprietăților farmacodinamice variate și uneori conflictelor de interacțiune dintre antibioticele din diferite clase în cadrul diferitor stări patologice.
Cuvinte-cheie: antibioterapie; infecție; bariera hemato-encefalică; neurochirurgie.

Резюме. Антибиотикотерапия у нейрохирургических пациентов как средство обхода гематоэнцефалического барьера — оправдано ли это?
Гематоэнцефалический барьер (ГЭБ) является важным механизмом для сосудистой динамики центральной нервной системы (ЦНС). Он обладает множеством свойств, которые предотвращают дисбаланс гомеостаза. Проведен систематический обзор литературы, включавший 65 источников, основанных исключительно на исследованиях проведенных на людях. Были выявлены и описаны потенциальные пути введения препаратов а также препятствия для фармакотерапии. В заключение, антибиотикотерапия остается актуальной темой для обсуждения благодаря множеству различных и часто противоречивых фармакодинамических свойств, проявляемых антибиотиками в различных патологических состояниях.
Ключевые слова: антибиотерапия; инфекция; гематоэнцефалический барьер; нейрохирургия.

Introduction.

The blood-brain barrier (BBB) is a highly selective defensive system that protects the brain from potentially harmful substances, including pathogens, and certain drugs. Targeted antibiotic treatment, seeks to overcome the BBB, commonly through the use of specific antibiotics or innovative delivery methods that act as "BBB cheaters".

Currently, four primary mechanisms are emphasized for enhancing drug delivery across the blood-brain barrier: increasing lipophilicity, inhibiting P-glycoprotein function, loosening tight junctions using hyperosmolar agents, and bypassing the barrier through intrathecal, and intranasal routes [1].

The main ways that allow the drugs to pass through the BBB are: transmembrane diffusion, saturable transporters, adsorptive endocytosis, and extracellular pathways [2]. Approximately 98% of small molecules, as well as larger therapeutic agents are unable to cross the BBB [3]. Part of the efflux pumps are the ATP-binding cassette (ABC) transporter protein superfamily: P-glycoprotein, multidrug resistance-associated proteins (MRP), and

breast cancer resistance protein [4]. In humans, the organic cation transporter 2 (OCT2) and the organic cation/carnitine transporter (OCTN) can facilitate the transport of drugs across the BBB [5].

The aim of the study was to explore whether all the mentioned interventions justify the use of targeted antibiotic treatment in neurosurgical patients.

Material and methods.

A systematic literature review was conducted in October, 2024, utilizing the PubMed, Google Scholar, HINARY, MDPI, EMBASE, Cambridge Core, bioRxiv, Science Direct (Elsevier), and ResearchGate databases. Only studies involving human subjects were included. The keywords ‚antibiotics', ‚neurosurgery', and ‚blood-brain barrier' were used to identify relevant sources, resulting in the revision of 65 studies, from which only 30 were cited.

Results and discussions.

In order to avoid BBB disruption, the transcranial, and transnasal routes may be used. The hyperosmotic disruption of the BBB is the alternative to the less convenient nanoparticles (nanocarriers) [6]. Beta-lactam antibiotics, glycopeptides, polymyxins, metronidazole, clindamycin, rifamycins, daptomycin, fusidic acid, polipeptides, antituberculous drugs, antiretroviral drugs, and antifungals have a poor penetration through the BBB [6-9]. Cefotaxime has a higher BBB penetration compared to other antibiotics in the same class [10]. Fluoroquinolones, fosfomycin, sulfonamides, and trimethoprim have a slightly higher BBB penetration compared to the previously mentioned. Antiherpetic drugs, and antiparasitic drugs have a moderate BBB penetration. Chloramphenicol, tetracyclines, and oxazolidinones (such as linezolid) exhibit effective BBB penetration, with permeability increasing in the order they are listed [7, 11].

Previously, intravenous third-generation cephalosporins, and methicillin were employed to treat CNS infections [6]. Currently, intraventricular vancomycin and linezolid are preferred, especially for empiric therapy [6, 8, 12], with vancomycin often combined with meropenem for enhanced therapeutic effectiveness [13]. In contrast, kanamycin and penicillins are generally avoided for the intrathecal route [14]. Intrathecal, and intraventricular administration routes are considered for critically ill patients [14-16], with studies showing that these methods correlate with a shorter ICU/hospital stay, and reduced mortality, particularly with the use of intrathecal or intraventricular colistin in severe cases [15].

Post-neurosurgical infection is a common complication, that has its burden increased by the emerging resistance to the antibacterial drugs [17]. In clean neurosurgical procedures, intravenous cefuroxime (1.5 g preoperatively and 0.75 g at 8 hours postoperatively) effectively prevents potential infections [18], as does intravenous cefepime (2 g administered 0.5 hours postoperatively) [19]. Colistin may exhibit toxicity along with the possibility of inducing chemical meningitis [20], the last being mild and usually resolves spontaneously [15].

For shunt-related infections, recommended regimens include intravenous ceftazidime (2 g every 8 hours) [21], intravenous cefotaxime (2 g every 8 hours) [10], and intraventricular methicillin (25 mg/kg every 6 hours or a single 50 mg intraventricular dose during surgery) [22]. Heteroresistant Staphylococcus aureus shunt infections can be effectively treated with intravenous linezolid (10 mg/kg every 8 hours) [23].

Antibioresistance is an emerging threat in the contemporary field of antibiotic drugs management. Novel antibiotics are not suitable for the crossing of the BBB [24]. In common bacterial species, intrathecal options include glycopeptides, polipeptides, macrolides, amphenicols, beta-lactams, and rifamycins [14].

The proportion of the MRSA in the ICU is as high as 60%, this being a reason why vancomycin is often used in the neurosurgical postoperatory setting [25]. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) classifications apply rather to species like *Acinetobacter baumannii* [26].

Besides the BBB we describe the brain-tumor barrier (BTB) [27], and the blood-CSF barrier (BCSFB) [28], which imply different hydrodynamics compared to the BBB [27-28].

Neuroinflammation does not enhance colistin's penetration of the BBB [20]. Linezolid, however, has good BBB penetration, and conditions such as neuroinflammation can further increase its permeation, potentially leading to excessive accumulation in the cerebrospinal fluid (CSF) [11].

To properly evaluate a neurosurgical patient requiring antibiotic therapy, it is essential to prioritize the severity of the condition or disease. Mild to moderate cases can be managed with antibiotics that demonstrate better BBB penetration [29], especially in the context of potential shunt infections [10, 21-23].

Adverse reactions that may pose significant risks to the patient's survival should be carefully considered and minimized by using intrathecal and intraventricular routes in severe cases [14-16, 20].

Certain conditions can influence BBB permeability [4]. Adjustments in dosage calculations due to the potential accumulation of the drug in the

CSF [25], and consideration of BCSFB, and BTB should be prioritized [27, 28].

Understanding the different antibiotic administration regimens is crucial for selecting a safe, feasible, and effective approach [9, 20]. These regimens may involve preoperative, intraoperative, and postoperative administration [19-20, 20]. Many studies consider vancomycin [6, 8, 13, 30].

In conclusion, antibiotic therapy in neurosurgical patients is critical when addressing all types of infections. Each treatment approach should be individualized based on the infecting species, which may sometimes require the use of multiple antibiotic classes. Empirical therapy remains an essential strategy in emergency cases and should be employed judiciously.

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