



---

International Journal of Infection 2022, Vol.6, ISSUE 3, September-December

CONTENTS

<b>THE ROLE OF INTERLEUKIN-1 IN BACTERIAL INFECTIONS.</b> E. Chiappini and G. Bazzocchi .....	68-71
<b>MINIMUM INHIBITIVE AND BACTERICIDAL CONCENTRATION OF ANTIBIOTICS.</b> Franco Pandolfi .....	72-75
<b>BACTERIAL MENINGITIS CAUSES NEUROLOGICAL DAMAGE WITH A HIGH RISK OF MORBIDITY AND MORTALITY.</b> L. Lobefalo .....	76-79
<b>AIDS DEMENTIA COMPLEX: PATHOGENESIS AND SYMPTOMS.</b> S. Di Michele and C. D'Aurizio .....	80-85
<b>SOME KEY BIOMARKERS IN ACUTE RESPIRATORY DISTRESS SYNDROME.</b> E. Mazzon .....	86-87
<b>OBESITY, INFLAMMATION, AND INFECTION.</b> R. Pellegrino .....	88-89
<b>ENTEROBACTERIACEAE AND ANTIBIOTIC RESISTANCE.</b> A. Perrella, G. Martinotti, A. Lauri and P. Romualdi .....	90-93



# THE ROLE OF INTERLEUKIN-1 IN BACTERIAL INFECTIONS

Elena Chiappini<sup>1\*</sup> and Gabriele Bazzocchi<sup>2</sup>

<sup>1</sup> Department of Health Sciences, Section of Pediatrics, University of Florence, Florence, Italy;

<sup>2</sup> Montecatone Rehabilitation Institute, University of Bologna, Imola, Italy.

\*Correspondence to:

Prof. Elena Chiappini,  
Department of Health Sciences,  
Section of Pediatrics,  
University of Florence,  
Florence, Italy.  
e-mail: [elena.chiappini@unifi.it](mailto:elena.chiappini@unifi.it)

## ABSTRACT

Cytokines are small, numerous immunoregulatory molecules that play an important role in immune and inflammatory responses. Interleukin-1 (IL-1) is an important cytokine in the body's defense against foreign agents, including bacteria, but when overproduced, it is a highly inflammatory molecule. Targeting IL-1 may be a relevant strategy in many inflammatory diseases including those caused by microorganisms. IL-1 exists in two main forms, IL-1 $\alpha$  and IL-1 $\beta$ , and both are activated after maturation of their precursors. IL-1 $\beta$  is produced mainly by macrophage cells and plays an inflammatory role in many diseases, including infectious ones. IL-1 $\beta$  generates the inactive precursor pro-IL-1 $\beta$  that is cleaved by the caspase-1 enzyme and then becomes active. IL-1 $\beta$  binds to the receptor and triggers a signaling cascade involving the adaptor protein MyD88 and leads to activation of nuclear factor kappa B (NF- $\kappa$ B). Targeting IL-1 in infections reduces inflammation and improves the course of the disease.

**KEYWORDS:** *Cytokine, IL-1, bacteria, infection, immune response*

## INTRODUCTION

Cytokines are small proteins that play crucial roles in cell signaling, particularly in immune responses (1). Among these, Interleukin-1 (IL-1) stands out due to its significant involvement in inflammatory processes and immune defense mechanisms (2). This paper explores the functions of IL-1 in the context of bacterial infections, highlighting its dual roles in promoting and regulating inflammation, as well as its potential as a therapeutic target.

## DISCUSSION

Cytokines are a broad category of signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis (3). They include interleukins (ILs), interferons, tumor necrosis factors, chemokines, and growth factors (4). ILs are a group of cytokines that were first seen to be expressed by leukocytes (5). IL-1 is one of the most studied cytokines within this group and is known for its role in the inflammatory response (6).

IL-1 exists in two primary forms as IL-1 $\alpha$  and IL-1 $\beta$ , and both are produced after activation of their precursors (7). IL-1 $\beta$  is particularly significant in bacterial infections due to its potent inflammatory effects (8). It is primarily produced by macrophages, monocytes, and dendritic cells in response to microbial stimuli (9).

IL-1 $\beta$  is synthesized as an inactive precursor (pro-IL-1 $\beta$ ) that is cleaved by the enzyme caspase-1 to become active (10). This cleavage occurs within a complex known as the inflammasome, which is activated by various pathogen-

Received: 21 February, 2022  
Accepted: 08 September, 2022

1972-6945 (2022)

Copyright © by Biolife-Publisher

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

associated molecular patterns (PAMPs) found on bacteria (10). The most well-characterized inflammasome in this context is the NLRP3 inflammasome, which responds to a variety of bacterial components and stress signals (11).

Once activated, IL-1 $\beta$  binds to the IL-1 receptor type 1 (IL-1R1) on target cells, initiating a signaling cascade that involves the adaptor protein MyD88 and leads to the activation of nuclear factor-kappa B (NF- $\kappa$ B) and mitogen-activated protein kinases (MAPKs) which results in the transcription of pro-inflammatory genes and leads to the production of other cytokines, chemokines, and adhesion molecules that recruit and activate additional immune cells (12).

The primary function of IL-1 in bacterial infections is to coordinate the inflammatory response, which is crucial for controlling and eliminating pathogens (13). IL-1 $\beta$  enhances the migration of neutrophils to the site of infection, promotes phagocytosis, and stimulates the production of antimicrobial peptides (14). Additionally, it induces fever by acting on the hypothalamus, creating an environment less favorable for bacterial growth (15). However, the powerful inflammatory response driven by IL-1 $\beta$  must be tightly regulated to prevent tissue damage (16). Excessive or prolonged IL-1 $\beta$  production can lead to chronic inflammation and tissue injury, contributing to diseases such as sepsis, chronic obstructive pulmonary disease (COPD), and inflammatory bowel disease (IBD) (17,18).

IL-1 is important for the immune defense against bacterial infections. *Staphylococcus aureus* is a bacterium that can cause severe infections such as sepsis and endocarditis (19). IL-1 $\beta$  plays a crucial role in recruiting neutrophils to sites of infection, which is essential for controlling *S. aureus* (20). However, the bacterium can evade immune responses by producing factors that inhibit IL-1 $\beta$  production or signaling. In *Mycobacterium tuberculosis* infection, IL-1 $\beta$  is involved in the formation of granulomas, which are structures that contain the infection (21). While beneficial in containing the bacteria, excessive IL-1 $\beta$  can lead to tissue damage and exacerbate disease symptoms (22). IL-1 $\beta$  contributes to the inflammatory response that clears the bacteria *Escherichia coli*, responsible for urinary tract infections (UTIs). However, excessive IL-1 $\beta$  can lead to discomfort and tissue damage in the urinary tract (23).

Given the potent effects of IL-1 $\beta$ , its activity is subject to multiple levels of regulation. The production of IL-1 $\beta$  is controlled at the transcriptional level by NF- $\kappa$ B and other transcription factors (24). Additionally, the activation of pro-IL-1 $\beta$  by caspase-1 is a tightly regulated process, requiring the assembly of the inflammasome.

Once secreted, IL-1 $\beta$  activity is further regulated by natural inhibitors such as IL-1 receptor antagonist (IL-1Ra), which binds to IL-1R1 without inducing signaling, thus blocking IL-1 $\beta$  from exerting its effects (25). Soluble IL-1 receptors can also act as decoys, sequestering IL-1 $\beta$  and preventing it from binding to cell surface receptors (26).

Given the central role of IL-1 $\beta$  in inflammation and its contribution to tissue damage in bacterial infections, targeting IL-1 $\beta$  signaling represents a promising therapeutic strategy (27,28). IL-1Ra (anakinra) is already used in the treatment of various inflammatory diseases such as rheumatoid arthritis. In bacterial infections, modulating IL-1 $\beta$  activity could help control excessive inflammation and reduce tissue damage (29). For instance, in sepsis, blocking IL-1 $\beta$  could mitigate the overwhelming inflammatory response that leads to organ failure. However, such interventions must be carefully balanced to avoid impairing the host's ability to control the infection.

## CONCLUSIONS

IL-1 $\beta$  is a pivotal cytokine in the immune response to bacterial infections and helps to orchestrate inflammation and control pathogen spread. Its potent effects on immune cell recruitment and activation are crucial for effective defense against bacteria but also pose risks of excessive inflammation and tissue damage. Understanding the precise mechanisms of IL-1 $\beta$  regulation and signaling provides valuable insights for developing targeted therapies to manage bacterial infections and their associated inflammatory responses. As research progresses, the potential for therapeutic modulation of IL-1 $\beta$  activity holds promise for improving outcomes in bacterial diseases.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

## REFERENCES

1. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Seminars in Immunopathology*. 2017;39(5):517-528. doi:<https://doi.org/10.1007/s00281-017-0639-8>
2. Mantovani A, Dinarello CA, Molgora M, Garlanda C. IL-1 and related cytokines in innate and adaptive immunity in health and disease. *Immunity*. 2019;50(4):778-795. doi:<https://doi.org/10.1016/j.immuni.2019.03.012>

3. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews*. 2017;281(1):8-27. doi:<https://doi.org/10.1111/imr.12621>
4. Dinarello CA. Historical insights into cytokines. *European Journal of Immunology*. 2007;37(S1):S34-S45. doi:<https://doi.org/10.1002/eji.200737772>
5. Strober W, James SP. The Interleukins. *Pediatric Research*. 1988;24(5):549-557. doi:<https://doi.org/10.1203/00006450-198811000-00001>
6. Tetè S, Tripodi D, Rosati M, et al. IL-37 (IL-1F7) the Newest Anti-Inflammatory Cytokine Which Suppresses Immune Responses and Inflammation. *International Journal of Immunopathology and Pharmacology*. 2012;25(1):31-38. doi:<https://doi.org/10.1177/039463201202500105>
7. Arend WP, Palmer G, Gabay C. IL-1, IL-18, and IL-33 families of cytokines. *Immunological Reviews*. 2008;223(1):20-38. doi:<https://doi.org/10.1111/j.1600-065x.2008.00624.x>
8. Man SM. Inflammasomes in the gastrointestinal tract: infection, cancer and gut microbiota homeostasis. *Nature Reviews Gastroenterology & Hepatology*. 2018;15(12):721-737. doi:<https://doi.org/10.1038/s41575-018-0054-1>
9. Cho MH, Ahn HJ, Ha HJ, et al. *Bacillus anthracis* Capsule Activates Caspase-1 and Induces Interleukin-1 $\beta$  Release from Differentiated THP-1 and Human Monocyte-Derived Dendritic Cells. *Infection and Immunity*. 2010;78(1):387-392. doi:<https://doi.org/10.1128/iai.00956-09>
10. van de Veerdonk FL, Joosten LA, Devesa I, et al. Bypassing Pathogen-Induced Inflammasome Activation for the Regulation of Interleukin-1 $\beta$  Production by the Fungal Pathogen *Candida albicans*. *The Journal of Infectious Diseases*. 2009;199(7):1087-1096. doi:<https://doi.org/10.1086/597274>
11. Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. *Cellular & Molecular Immunology*. 2021;18(5):1141-1160. doi:<https://doi.org/10.1038/s41423-021-00670-3>
12. Ge H, Farris CM, Tong M, Maina A, Richards AL. Transcriptional profiles of cytokines and chemokines reveal important pro-inflammatory response from endothelial cells during *Orientia tsutsugamushi* infection. *Microbes and Infection*. 2019;21(7):313-320. doi:<https://doi.org/10.1016/j.micinf.2019.01.002>
13. Slaats J, ten Oever J, van de Veerdonk FL, Netea MG. IL-1 $\beta$ /IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections. Bliska JB, ed. *PLOS Pathogens*. 2016;12(12):e1005973. doi:<https://doi.org/10.1371/journal.ppat.1005973>
14. Shanmugham LN, Petrarca C, Castellani ML, et al. IL-1 $\beta$  Induces Alkaline Phosphatase in Human Phagocytes. *Archives of Medical Research*. 2006;38(1):39-44. doi:<https://doi.org/10.1016/j.arcmed.2006.05.016>
15. Alheim K, Chai Z, Fantuzzi G, et al. Hyperresponsive febrile reactions to interleukin (IL) 1 and IL-1, and altered brain cytokine mRNA and serum cytokine levels, in IL-1-deficient mice. *Proceedings of the National Academy of Sciences*. 1997;94(6):2681-2686. doi:<https://doi.org/10.1073/pnas.94.6.2681>
16. Zahid A, Li B, Kombe AJK, Jin T, Tao J. Pharmacological Inhibitors of the NLRP3 Inflammasome. *Frontiers in Immunology*. 2019;10. doi:<https://doi.org/10.3389/fimmu.2019.02538>
17. Lopez-Castejon G, Brough D. Understanding the mechanism of IL-1 $\beta$  secretion. *Cytokine & Growth Factor Reviews*. 2011;22(4):189-195. doi:<https://doi.org/10.1016/j.cytogfr.2011.10.001>
18. Zhen Y, Zhang H. NLRP3 Inflammasome and Inflammatory Bowel Disease. *Frontiers in Immunology*. 2019;10. doi:<https://doi.org/10.3389/fimmu.2019.00276>
19. Brauweiler AM, Goleva E, Leung DYM. Staphylococcus aureus Lipoteichoic Acid Damages the Skin Barrier through an IL-1-Mediated Pathway. *Journal of Investigative Dermatology*. 2019;139(8):1753-1761.e4. doi:<https://doi.org/10.1016/j.jid.2019.02.006>
20. Constanza Giaì, Gonzalez CD, Sabbione F, et al. *Staphylococcus aureus* Induces Shedding of IL-1RII in Monocytes and Neutrophils. *Journal of Innate Immunity*. 2016;8(3):284-298. doi:<https://doi.org/10.1159/000443663>
21. Moorlag SJCFM, Khan N, Novakovic B, et al.  $\beta$ -Glucan Induces Protective Trained Immunity against Mycobacterium tuberculosis Infection: A Key Role for IL-1. *Cell Reports*. 2020;31(7):107634. doi:<https://doi.org/10.1016/j.celrep.2020.107634>

22. Conti P, Pregliasco FE, Bellomo RG, et al. Mast Cell Cytokines IL-1, IL-33, and IL-36 Mediate Skin Inflammation in Psoriasis: A Novel Therapeutic Approach with the Anti-Inflammatory Cytokines IL-37, IL-38, and IL-1Ra. *International Journal of Molecular Sciences*. 2021;22(15):8076. doi:<https://doi.org/10.3390/ijms22158076>
23. Jung JH, Hong HJ, Aziz Ghaderpour, et al. Differential interleukin-1 $\beta$  induction by uropathogenic *Escherichia coli* correlates with its phylotype and serum C-reactive protein levels in Korean infants. *Scientific Reports*. 2019;9(1). doi:<https://doi.org/10.1038/s41598-019-52070-3>
24. Karin M, Ben-Neriah Y. Phosphorylation Meets Ubiquitination: The Control of NF- $\kappa$ B Activity. *Annual Review of Immunology*. 2000;18(1):621-663. doi:<https://doi.org/10.1146/annurev.immunol.18.1.621>
25. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117(14):3720-3732. doi:<https://doi.org/10.1182/blood-2010-07-273417>
26. Kondera-Anasz Z, Sikora J, Mielczarek-Palacz A, Jońca M. Concentrations of interleukin (IL)-1 $\alpha$ , IL-1 soluble receptor type II (IL-1 sRII) and IL-1 receptor antagonist (IL-1 Ra) in the peritoneal fluid and serum of infertile women with endometriosis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2005;123(2):198-203. doi:<https://doi.org/10.1016/j.ejogrb.2005.04.019>
27. Schauer AE, Klassert TE, Lachner C von, et al. IL-37 Causes Excessive Inflammation and Tissue Damage in Murine Pneumococcal Pneumonia. *Journal of Innate Immunity*. 2017;9(4):403-418. doi:<https://doi.org/10.1159/000469661>
28. Dinarello CA. Anti-cytokine therapeutics and infections. *Vaccine*. 2003;21:S24-S34. doi:[https://doi.org/10.1016/s0264-410x\(03\)00196-8](https://doi.org/10.1016/s0264-410x(03)00196-8)
29. Labzin LI, Lauterbach MAR, Latz E. Interferons and inflammasomes: Cooperation and counterregulation in disease. *Journal of Allergy and Clinical Immunology*. 2016;138(1):37-46. doi:<https://doi.org/10.1016/j.jaci.2016.05.010>



# MINIMUM INHIBITIVE AND BACTERICIDAL CONCENTRATION OF ANTIBIOTICS

Franco Pandolfi\*

Department of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Roma, Italy.

\*Correspondence to:

Prof. Franco Pandolfi,  
Department of Internal Medicine,  
Fondazione Policlinico Universitario A. Gemelli IRCCS,  
Università Cattolica del Sacro Cuore,  
Roma, Italy.  
e-mail: [pandolfi@rm.unicatt.it](mailto:pandolfi@rm.unicatt.it)

## ABSTRACT

The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of an antibiotic are two important parameters. The MIC is the lowest concentration of antibiotic that can completely inhibit bacterial growth after 18-24 hours at 37 °C *in vitro*, while the MBC represents the lowest concentration of antibiotic that can reduce the initial bacterial population by 99.99% after 24 hours of incubation. However, for bactericidal antibiotics such as beta-lactams and fluoroquinolones, the MIC and MBC are comparable. To evaluate the sensitivity of a bacterial species to the antibiotic, the MIC50 and MIC90 must be taken into account. The maximum plasma concentration (C<sub>max</sub>) of an antibiotic in 24 hours is the concentration reached at the end of absorption of the drug, which is a function of the dose, the route of administration, and the galenic form, while the minimum plasma concentration (C<sub>min</sub>) is the minimum concentration reached at the end of the dosing interval, before the next dose of the drug. The therapeutic efficacy of an antibiotic depends on the relationship between pharmacokinetic and pharmacodynamic (PK/PD) parameters. In choosing an antibiotic, the dose, the therapeutic efficacy of the drug, the pharmacologically active plasma concentration, and the post-antibiotic effect (PAE) are very important. Plasma concentration is directly proportional to the therapeutic efficacy. All these considerations have therapeutic value and are also useful for preventing bacterial resistance.

**KEYWORDS:** *Antibiotic, minimum inhibitory concentration, minimum bactericidal concentration, pharmacodynamic, bacterial sensitivity*

## INTRODUCTION

The efficacy of an antibiotic can be evaluated through two pharmacodynamic parameters: the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) (1). The chemosensitivity of a microorganism to the antibiotic is estimated *in vitro* by determining the MIC which represents the lowest concentration of antibiotic capable of completely inhibiting bacterial growth after 18-24 hours of incubation at 37°C (2). The distinction of antibiotics into bactericides and bacteriostatics instead exploits the determination of the MBC which represents the lowest concentration of antibiotic capable of reducing the initial bacterial population by 99.99% after 24 hours of incubation at 37°C (3).

A bactericidal antibiotic lowers the bacterial population by 1000 times compared to that of the initial inoculum (4). For bactericidal antibiotics, such as beta-lactams and fluoroquinolones, the MICs and MBCs are comparable (5). The MICs therefore provide a good approximation of the bactericidal activity of the antibiotic (6). However, in the same

Received: 16 June, 2022  
Accepted: 14 September, 2022

1972-6945 (2022)

Copyright © by Biolife-Publisher

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

bacterial species, not all strains have the same sensitivity, so the evaluation of the sensitivity of a bacterial species towards an antibiotic must be based on MIC<sub>50</sub> and MIC<sub>90</sub>, which respectively represent the sensitivity of 50% and 90% of the population of the bacterial species under examination towards that antibiotic (7). The MIC<sub>90</sub>s are considered the more reliable benchmark of the two (8).

## DISCUSSION

The clinical efficacy of an antibiotic is correlated not only to the level of chemosensitivity of the microorganism but also to the following pharmacokinetic parameters: the patient's exposure to the drug, which is determined by its maximum plasma concentration (C<sub>max</sub>), area under the curve in 24 hours (AUC<sub>24</sub>), minimum plasma concentration (C<sub>min</sub>), and bioavailability and plasma elimination half-life (9,10).

The C<sub>max</sub> represents the peak concentration reached at the end of the absorption of the drug, and is a function of the dose, the route of administration, and the galenic form (11). Sodium or potassium penicillin G reaches the highest serum peaks only with intermittent and discontinuous perfusions, while third generation cephalosporins always reach high plasma peaks because they are strongly bound to plasma proteins (12). For macrolides, serum peaks increase with repeated intakes, reaching levels in the equilibrium phase that are even double those obtained with the first intake. From the comparison of T<sub>max</sub> values (time necessary to reach C<sub>max</sub>) in third generation cephalosporins administered intramuscularly and in some oral antibiotics, there is a substantial similarity, and therefore, oral administration is preferable. AUC<sub>24</sub> indicates the extent of systemic exposure to the drug that is indirectly proportional to clearance and C<sub>min</sub> is the minimum concentration reached at the end of the dosing interval, before the next dose of the drug (13).

Bioavailability indicates the percentage share of drug that is absorbed and reaches the systemic circulation in an unchanged form after administration by a route other than the intravenous one (14). The oral bioavailability of beta-lactams is almost zero as they are highly water-soluble antibiotics that cannot passively diffuse through the membranes of the gastrointestinal tract and disappear quickly in the gastric acid environment. Penicillin G is only used parenterally (15). Among beta-lactams, however, amoxicillin and clavulanic acid are exceptions as, although they are highly hydrophilic, they resist the gastric acid environment and are absorbed from the gastrointestinal tract via specific transporters (16). Several authors have stated that the kinetics of amoxicillin and clavulanic acid administered orally and parenterally are almost comparable. Fluoroquinolones and linezolid are moderately lipophilic but have an oral bioavailability greater than 80-90%, while macrolides are strongly dipophilic and, therefore, are easily absorbed (17).

The plasma elimination half-life of a drug is equivalent to the time necessary for its plasma concentration to reach t/2 and is equal to 4/5 of the t/2 itself (18). This parameter is indirectly related to the clearance of the drug and, therefore, to its mode of elimination (19). Hydrophilic beta-lactam antibiotics are eliminated via the kidneys by glomerular filtration and active secretion, while lipophilic antibiotics such as fluoroquinolones and macrolides are predominantly eliminated via the liver by oxidation-reduction or conjugation (20). Penicillin has a short plasma elimination half-life of <1.5 h, and third-generation cephalosporins have a medium or long half-life depending on the molecular characteristics. For example, ceftriaxone has a very long half-life of >7 h, macrolides have a variable half-life, such as erythromycin with 2-3 hours, while azithromycin has a half-life of 15-20 hours (21).

### *Therapeutic efficacy: pharmacokinetics and pharmacodynamics*

The therapeutic efficacy of an antibiotic is related to the relationship between pharmacokinetic parameters and pharmacodynamic parameters (PK/PD) (22). First, antibiotics must be distinguished based on their antibacterial mode of action into two classes: time-dependent and concentration-dependent (23). Time-dependent antibiotics, including beta-lactams and macrolides, have a correlated action *in vivo* and t>MIC (the time during which concentrations remain above the MIC of the pathogen) (24). To guarantee the therapeutic efficacy of the drug, the pharmacologically active plasma concentration must be maintained for most of the 50/70% dosing range. Thus, increasing the dose has little effect on the bactericidal action, provided that the concentration is already above the threshold and effectiveness. This condition is achieved through a multi-fractionation of the daily dose which also takes into account the plasma elimination half-life of the drug.

Another parameter that must be considered when choosing the most effective antibiotic is the post-antibiotic effect (PAE) (25). Most time-dependent antibiotics have no PAE effect, and so, the elimination of bacterial growth after the disappearance of the antibiotic is zero (24). The administration of these antibiotics in particular requires careful fractionation of the dose. Some antibiotics with time-dependent action, such as azithromycin, are distinguished from others by a prolonged PAE against many bacterial species. For these drugs, the therapeutic efficacy correlates more with the ratio between the daily plasma exposure to the antibiotic and the MIC than t>MIC and AUC>MIC (26).

According to some authors, the AUC/MIC to be maintained for azithromycin, frequently used in the treatment of atypical pneumonia and pertussis, must be 20-30 h (27). For this reason, azithromycin is used in single daily administrations rather than in multiple administrations, unlike other time-dependent antibiotics. However, since 2007, azithromycin has not been widely used for streptococcal infections that cause the most common bacterial pneumonia, as it is resistant (less in Europe than in the United States) (28).

For concentration-dependent antibiotics including fluoroquinolones and aminoglycosides, the indicator of efficacy is  $C_{max} > MIC$ , the ratio between the maximum plasma concentration and the MIC (23). As the plasma concentration of these antibiotics increases, the therapeutic efficacy also progressively increases, and the  $C_{max}/MIC$  must be greater than or equal to 10 to achieve eradication of the infection and resolution of the clinical picture in at least 80% of cases (29). The drugs belonging to this class also have a prolonged post-antibiotic effect, and for this reason and the intrinsic concentration-dependent action, they are administered once a day (30). It is estimated that fluoroquinolones used as second-choice antibiotics in community-acquired pneumonia must have an AUC/MIC ratio greater than 25-35 hours in infections caused by Gram positives and greater than 125 hours in those caused by Gram negatives to ensure safe clinical efficacy. The parameters listed above not only have a high clinical value but also an epidemiological value, as they allow to prevent the selection of resistant strains during antibiotic therapy.

## CONCLUSIONS

MIC and MBC are important parameters to obtain effective antibiotic therapy. In antibiotics such as beta-lactams and fluoroquinolones, these two parameters are comparable. The plasma concentration of the antibiotic is related to the absorption of the drug, depending on the dose and route of administration. The observations on these topics reported here are vital considerations for targeted and effective therapy.

### *Conflict of interest*

The author declares that they have no conflict of interest.

## REFERENCES

1. Santos NC de S, Scodro RB de L, Sampiron EG, et al. Minimum Bactericidal Concentration Techniques in Mycobacterium tuberculosis: A Systematic Review. *Microbial Drug Resistance (Larchmont, NY)*. 2020;26(7):752-765. doi:<https://doi.org/10.1089/mdr.2019.0191>
2. Dhariwal NS, Hugar SM, Harakuni S, Sogi S, Assudani HG, Mistry LN. A comparative evaluation of antibacterial effectiveness of sodium hypochlorite, Curcuma longa, and Camellia sinensis as irrigating solutions on isolated anaerobic bacteria from infected primary teeth. *Journal of Indian Society of Pedodontics and Preventive Dentistry*. 2016;34(2):165-165. doi:<https://doi.org/10.4103/0970-4388.180447>
3. Abushaheen MA, Muzahed, Fatani AJ, et al. Antimicrobial resistance, mechanisms and its clinical significance. *Disease-a-Month*. 2020;66(6):100971. doi:<https://doi.org/10.1016/j.disamonth.2020.100971>
4. Clavijo V, Flórez MJV. The gastrointestinal microbiome and its association with the control of pathogens in broiler chicken production: A review. *Poultry Science*. 2018;97(3):1006-1021. doi:<https://doi.org/10.3382/ps/pex359>
5. Kohanski MA, Dwyer DJ, Hayete B, Lawrence CA, Collins JJ. A common mechanism of cellular death induced by bactericidal antibiotics. *Cell*. 2007;130(5):797-810. doi:<https://doi.org/10.1016/j.cell.2007.06.049>
6. Roy R, Tiwari M, Donelli G, Tiwari V. Strategies for combating bacterial biofilms: A focus on anti-biofilm agents and their mechanisms of action. *Virulence*. 2017;9(1):522-554. doi:<https://doi.org/10.1080/21505594.2017.1313372>
7. Lehtinen S, Blanquart F, Lipsitch M, Fraser C. On the evolutionary ecology of multidrug resistance in bacteria. Schurr E, ed. *PLOS Pathogens*. 2019;15(5):e1007763. doi:<https://doi.org/10.1371/journal.ppat.1007763>
8. Wang J, Jing W, Shi J, et al. Bipolar Distribution of Minimum Inhibitory Concentration of Q203 Across Mycobacterial Species. *Microbial Drug Resistance*. 2021;27(8):1013-1017. doi:<https://doi.org/10.1089/mdr.2020.0239>
9. Xie B, Jiang SQ, Shen XL, Wu HQ, Hu YJ. Pharmacokinetics, plasma protein binding, and metabolism of a potential natural chemosensitizer from Marsdenia tenacissima in rats. *Journal of Ethnopharmacology*. 2021;281:114544. doi:<https://doi.org/10.1016/j.jep.2021.114544>

10. Li Y, Theuretzbacher U, Clancy CJ, Nguyen MH, Derendorf H. Pharmacokinetic/Pharmacodynamic Profile of Posaconazole. *Clinical Pharmacokinetics*. 2010;49(6):379-396. doi:<https://doi.org/10.2165/11319340-000000000-00000>
11. Grotenhermen F. Pharmacokinetics and Pharmacodynamics of Cannabinoids. *Clinical Pharmacokinetics*. 2003;42(4):327-360. doi:<https://doi.org/10.2165/00003088-200342040-00003>
12. Panaphut T, Domrongkitchaiporn S, Vibhagool A, Thinkamrop B, Susaengrat W. Ceftriaxone Compared with Sodium Penicillin G for Treatment of Severe Leptospirosis. *Clinical Infectious Diseases*. 2003;36(12):1507-1513. doi:<https://doi.org/10.1086/375226>
13. Matsumoto K, Shigemi A, Takeshita A, et al. Analysis of thrombocytopenic effects and population pharmacokinetics of linezolid: a dosage strategy according to the trough concentration target and renal function in adult patients. *International journal of antimicrobial agents*. 2014;44(3):242-247. doi:<https://doi.org/10.1016/j.ijantimicag.2014.05.010>
14. McRose DL, Newman DK. Redox-active antibiotics enhance phosphorus bioavailability. *Science*. 2021;371(6533):1033-1037. doi:<https://doi.org/10.1126/science.abd1515>
15. Amyes SGB. Resistance to  $\beta$ -Lactams - The Permutations. *Journal of Chemotherapy*. 2003;15(6):525-535. doi:<https://doi.org/10.1179/joc.2003.15.6.525>
16. Huttner A, Bielicki J, Clements MN, et al. Oral amoxicillin and amoxicillin-clavulanic acid: properties, indications and usage. *Clinical Microbiology and Infection*. 2020;26(7):871-879. doi:<https://doi.org/10.1016/j.cmi.2019.11.028>
17. Levison ME, Levison JH. Pharmacokinetics and Pharmacodynamics of Antibacterial Agents. *Infectious Disease Clinics of North America*. 2009;23(4):791-815. doi:<https://doi.org/10.1016/j.idc.2009.06.008>
18. Bailey JM. Context-Sensitive Half-Times. *Clinical Pharmacokinetics*. 2002;41(11):793-799. doi:<https://doi.org/10.2165/00003088-200241110-00001>
19. Raemsch KD, Sommer J. Pharmacokinetics and metabolism of nifedipine. *Hypertension*. 1983;5(4\_pt\_2). doi:[https://doi.org/10.1161/01.hyp.5.4\\_pt\\_2.ii18](https://doi.org/10.1161/01.hyp.5.4_pt_2.ii18)
20. Inui KI, Masuda S, Saito H. Cellular and molecular aspects of drug transport in the kidney. *Kidney International*. 2000;58(3):944-958. doi:<https://doi.org/10.1046/j.1523-1755.2000.00251.x>
21. Cunningham RF, Israili ZH, Dayton PG. Clinical pharmacokinetics of probenecid. *Clinical pharmacokinetics*. 1981;6(2):135-151. doi:<https://doi.org/10.2165/00003088-198106020-00004>
22. Craig WA. State-of-the-Art Clinical Article: Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men. *Clinical Infectious Diseases*. 1998;26(1):1-10. doi:<https://doi.org/10.1086/516284>
23. Eyer RF, Shvets K. Clinical Pharmacology of Antibiotics. *Clinical Journal of the American Society of Nephrology*. 2019;14(7):1080-1090. doi:<https://doi.org/10.2215/CJN.08140718>
24. McKenzie C. Antibiotic dosing in critical illness. *Journal of Antimicrobial Chemotherapy*. 2011;66(Supplement 2):ii25-ii31. doi:<https://doi.org/10.1093/jac/dkq516>
25. Bowker KE, Holt HA, Reeves DS, MacGowan AP. Bactericidal activity, post antibiotic effect and modified controlled effective regrowth time of meropenem at high concentrations. *Journal of Antimicrobial Chemotherapy*. 1996;38(6):1055-1060. doi:<https://doi.org/10.1093/jac/38.6.1055>
26. Krickler JA, Page CP, Gardarsson FR, Baldursson O, Gudjonsson T, Parnham MJ. Nonantimicrobial Actions of Macrolides: Overview and Perspectives for Future Development. *Pharmacological Reviews*. 2021;73(4):1404-1433. doi:<https://doi.org/10.1124/pharmrev.121.000300>
27. Woodhead M. Guidelines for the management of adult lower respiratory tract infections. *European Respiratory Journal*. 2005;26(6):1138-1180. doi:<https://doi.org/10.1183/09031936.05.00055705>
28. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clinical Infectious Diseases*. 2019;44(Supplement\_2):S27-S72. doi:<https://doi.org/10.1086/511159>
29. Rybak MJ. Pharmacodynamics: Relation to antimicrobial resistance. *American Journal of Infection Control*. 2006;34(5):S38-S45. doi:<https://doi.org/10.1016/j.ajic.2006.05.227>
30. Reed MD. Optimal Antibiotic Dosing: The pharmacokinetic-pharmacodynamic. *Postgraduate Medicine*. 2000;108(7 Suppl Contemporary):17-24. doi:<https://doi.org/10.3810/pgm.12.2000.suppl10.52>



# BACTERIAL MENINGITIS CAUSES NEUROLOGICAL DAMAGE WITH A HIGH RISK OF MORBIDITY AND MORTALITY

Lucio Lobefalo\*

Department of Medical and Oral Sciences and Biotechnologies, University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy.

\*Correspondence to:

Lucio Lobefalo, MD,

Department of Medical and Oral Sciences and Biotechnologies,

University "G. d'Annunzio" of Chieti-Pescara,

Chieti, Italy.

e-mail: [lobefalo@gmail.com](mailto:lobefalo@gmail.com)

## ABSTRACT

Bacterial meningitis is characterized by inflammation of the brain and has a mortality rate of approximately 50% in low-income countries. Meningitis can be caused by bacterial or viral agents, with the bacterium *Streptococcus pneumoniae* (group B) responsible for about 70% of cases. In bacterial meningitis, there is an increase in neutrophil granulocytes in the cerebrospinal fluid (CSF), increased intracranial pressure, cerebral edema, and neuronal lesions, which all contribute to neurological damage. Pneumolysin, produced by *S. pneumoniae*, forms pores in cell membranes, causing cell lysis and inflammation, while bacterial lipooligosaccharide (LOS) induces an immune reaction which aggravates the disease. Neuroinflammation increases the permeability of the blood-brain barrier (BBB), facilitating the entry of immune cells that produce inflammatory mediators. These reactions induce coagulation with vasculitis and the release of inflammatory mediators which are activated by bacterial toxins to induce apoptosis and necrosis, with the death of neurons and glial cells. Bacteria such as *Neisseria meningitidis*, *S. pneumoniae*, and *Haemophilus influenzae* use different strategies to cross the BBB.

**KEYWORDS:** *Bacterial meningitis, neuroinflammation, neurological damage, immune, inflammation*

## INTRODUCTION

Bacterial meningitis is a serious disease that causes over 300,000 deaths every year across the globe with a mortality rate that can reach up to 54% in low-income countries (1). Bacterial meningitis can have high rates of complications, especially in children, the elderly, and immunocompromised individuals. In fact, in low-income countries, many survivors are left with chronic neurological sequelae, including hearing loss or focal neurological deficits.

Bacterial meningitis infection is characterized by inflammation of the protective membranes covering the brain and spinal cord, known as the meninges (2). The disease is associated with high morbidity and mortality rates if not treated promptly (3). The most common complications are cognitive deficits, hearing loss, seizures, hydrocephalus, and motor deficits.

*Streptococcus pneumoniae* causes over 70% of meningitis cases, while *Neisseria meningitidis* causes approximately 10% (4). The mortality rate due to *S. pneumoniae* is 10-30%, but this can vary depending on the type of pathogen, the age of the patient, and the site of infection. The bacteria first colonize the nose, pharynx, and upper respiratory tract, and then infect the bloodstream. Patients with bacterial meningitis are treated with intravenous antibiotics, often in combination with cortisone (if the pathogen is not *Listeria*) which inhibits inflammation and gives better results (5).

Received: 12 December, 2022

Accepted: 30 December, 2022

1972-6945 (2022)

Copyright © by Biolife-Publisher

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

Meningitis can be caused by bacterial or viral agents that induce increased protein and leukocyte counts in the cerebrospinal fluid (CSF) (6). Bacterial meningitis increases neutrophilic granulocytes in the CSF, while viral meningitis does not (7). Pregnant women should be screened for the presence of group B streptococcus and, if positive, treated with intravenous penicillin to avoid neonatal streptococcal meningitis.

## DISCUSSION

Complications of bacterial meningitis include neurological damage resulting from increased intracranial pressure, cerebral edema, and direct bacterial toxin effects, that results in serious neuronal injury, and systemic complications such as septicemia, disseminated intravascular coagulation (DIC), and multi-organ failure (8). For this, it is particularly important to control the infection rapidly (9).

Bacterial toxins include pneumolysin produced by *S. pneumoniae* and lipooligosaccharide (LOS), which is found in *N. meningitidis* (10). Pneumolysin induces pores in cell membranes, leading to cell lysis and further inflammation (11). LOS causes strong immune responses and contributes to the pathology (12) (Table I,II).

**Table I. Immune Response.**

Innate Immunity:	<ul style="list-style-type: none"> <li>• <i>Recognition:</i> Pattern recognition receptors (PRRs) on innate immune cells detect pathogen-associated molecular patterns (PAMPs). Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NOD-like receptors) are crucial in recognizing bacterial components.</li> <li>• <i>Cytokine release:</i> Activation of PRRs leads to the release of pro-inflammatory cytokines (e.g., IL-1<math>\beta</math>, TNF-<math>\alpha</math>, IL-6), chemokines, and other mediators, which recruit and activate immune cells.</li> </ul>
Adaptive Immunity:	<ul style="list-style-type: none"> <li>• <i>B cells and antibody production:</i> Antigen-presenting cells (APCs) present bacterial antigens to B cells, leading to the production of specific antibodies that neutralize bacteria and facilitate phagocytosis.</li> <li>• <i>T cells:</i> Helper T cells (CD4+) assist in the activation of B cells and cytotoxic T cells (CD8+) which kill infected cells.</li> </ul>

**Table II. Immune evasion and bacterial toxins.**

<ul style="list-style-type: none"> <li>• <i>Capsular polysaccharides:</i> The bacterial capsule prevents phagocytosis and inhibits complement activation.</li> </ul>
<ul style="list-style-type: none"> <li>• <i>Molecular mimicry:</i> Bacteria can mimic host molecules to evade the immune system, as seen with <i>N. meningitidis</i>'s sialic acid capsule.</li> </ul>
<ul style="list-style-type: none"> <li>• <i>Pneumolysin (Toxin):</i> Produced by <i>S. pneumoniae</i>, this toxin can damage host cells and induce inflammation.</li> </ul>
<ul style="list-style-type: none"> <li>• <i>Lipooligosaccharide (LOS) (Toxin):</i> A component of the outer membrane of <i>N. meningitidis</i> that triggers strong inflammatory responses.</li> </ul>

In bacterial meningitis, an edematous state can occur with increased permeability of the blood-brain barrier (BBB) and inflammation that can lead to accumulation of fluid in the brain and increased intracranial pressure.

Bacteria such as *N. meningitidis*, *S. pneumoniae*, and *Haemophilus influenzae* can invade and survive in the bloodstream (13). They use various strategies to cross the BBB, including transcellular traversal, paracellular passage, and the "trojan horse" mechanism via infected leukocytes. Surface adhesins and pili help bacteria adhere to and invade endothelial cells. For example, *N. meningitidis* uses outer membrane proteins like Opc and Opa to bind to host cell receptors. Bacterial components bind to epithelial cells via adhesins and activate Toll-like receptors (TLRs) on microglia and endothelial cells.

Immune cells are activated, including neutrophils and macrophages. These cells are recruited to the infection site, where they phagocytose bacteria and release more inflammatory mediators (14). The inflammatory response increases BBB permeability, facilitating the entry of immune cells and further bacteria into the CSF.

Neuroinflammation may occur due to glial cell activation, when microglia and astrocytes in the brain become activated and produce inflammatory mediators (15). Oxidative stress is interconnected with neuroinflammation and plays a major role in the development and progression of many neurological disorders, such as Alzheimer's, Parkinson's, multiple sclerosis, and stroke. Inflammation-induced reactive oxygen species (ROS) can damage neurons and other cells in the brain (16). Bacteria and bacterial toxins can activate the coagulation cascade with the release of inflammatory cytokines

(17), which in turn, can cause micro-thrombosis and impair blood flow. These phenomena can lead to vasculitis, which is the inflammation of the blood vessels, further contributing to brain damage (18). Damage to the meninges, neuronal death, and apoptosis are then mediated by inflammatory mediators and bacterial toxins (19).

Pro-inflammatory cytokines increase the permeability of the BBB, allowing immune cells and more bacteria to enter the central nervous system (CNS), which exacerbates inflammation. An overproduction of cytokines can lead to a “cytokine storm” that can cause severe tissue damage, edema, and increased intracranial pressure (20).

Neuroinflammation is the response of the CNS and involves the activation of glial cells such as microglia and astrocytes (21). It can be induced by infections, toxins, traumatic injuries, and neurodegeneration. Bacterial meningitis is mediated by the release of inflammatory cytokines (e.g. IL-1, TNF, IL-6, and IL-18) and chemokines (15). Activated microglia release more ROS and cytokines, creating a vicious cycle (22). The activation of microglia and astrocytes in the CNS leads to the production of inflammatory mediators that contribute to neuronal damage and apoptosis (23). Matrix metalloproteinases (MMPs) are upregulated and break down the extracellular matrix, further disrupting the BBB (24). ROS can activate microglia and promote inflammatory signaling. However, prolonged oxidative stress supports inflammation (25).

Treatment for bacterial meningitis typically involves the prompt administration of broad-spectrum antibiotics and supportive care to manage symptoms and complications. In neuroinflammation, treatment for oxidative stress with antioxidants such as N-acetylcysteine and/or vitamin E has shown moderate therapeutic effects, suggesting that more studies should be performed investigating these (26). It is important to understand the molecular mechanisms, immune response, and inflammatory processes involved in bacterial meningitis in order to better address the disease both pathologically and therapeutically.

## CONCLUSIONS

Bacterial meningitis involves complex interactions between bacterial virulence factors and host immune responses. The bacteria must evade the immune system, cross the BBB, and survive in the hostile environment of the CNS. The host's immune response, while aimed at controlling the infection, often contributes to the pathology through inflammation and oxidative stress. Bacterial meningitis causes neurological damage due to increased intracranial pressure, cerebral edema, and direct bacterial toxin effects, and there can be significant neuronal injury, and systemic complications such as septicemia, DIC, and multi-organ failure.

Bacterial meningitis involves a complex interplay of pathogen invasion, immune response, and inflammatory processes. Understanding these mechanisms is critical for developing effective treatments and interventions to reduce the high morbidity and mortality associated with this disease.

### *Conflict of interest*

The author declares that they have no conflict of interest.

## REFERENCES

1. Hasbun R. Progress and Challenges in Bacterial Meningitis. *JAMA*. 2022;328(21):2147-2154. doi:<https://doi.org/10.1001/jama.2022.20521>
2. Sharma N, Zahoor I, Sachdeva M, et al. Deciphering the role of nanoparticles for management of bacterial meningitis: an update on recent studies. *Environmental Science and Pollution Research*. 2021;28(43):60459-60476. doi:<https://doi.org/10.1007/s11356-021-16570-y>
3. McGill F, Heyderman RS, Panagiotou S, Tunkel AR, Solomon T. Acute bacterial meningitis in adults. *The Lancet*. 2016;388(10063):3036-3047. doi:[https://doi.org/10.1016/s0140-6736\(16\)30654-7](https://doi.org/10.1016/s0140-6736(16)30654-7)
4. Soest van, Chekrouni N, Nina, Brouwer MC, van. Community-acquired bacterial meningitis in patients of 80 years and older. *Journal of the American Geriatrics Society*. 2022;70(7):2060-2069. doi:<https://doi.org/10.1111/jgs.17766>
5. Swanson D. Meningitis. *Pediatrics in Review*. 2015;36(12):514-526. doi:<https://doi.org/10.1542/pir.36-12-514>
6. Wall EC, Chan JM, Gil E, Heyderman RS. Acute bacterial meningitis. *Current Opinion in Neurology*. 2021;34(3):386-395. doi:<https://doi.org/10.1097/WCO.0000000000000934>
7. Rahimi J, Woehrer A. Overview of cerebrospinal fluid cytology. *Handbook of Clinical Neurology*. 2017;145:563-571. doi:<https://doi.org/10.1016/B978-0-12-802395-2.00035-3>

8. Cook AM, Morgan Jones G, Hawryluk GWJ, et al. Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients. *Neurocritical Care*. 2020;32(3):647-666. doi:<https://doi.org/10.1007/s12028-020-00959-7>
9. Wen S, Feng D, Chen D, Yang L, Xu Z. Molecular epidemiology and evolution of Haemophilus influenzae. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases*. 2020;80:104205. doi:<https://doi.org/10.1016/j.meegid.2020.104205>
10. Gerber J, Nau R. Mechanisms of injury in bacterial meningitis. *Current Opinion in Neurology*. 2010;23(3):312-318. doi:<https://doi.org/10.1097/wco.0b013e32833950dd>
11. El-Rachkidy RG, Davies NW, Andrew PW. Pneumolysin generates multiple conductance pores in the membrane of nucleated cells. *Biochemical and Biophysical Research Communications*. 2008;368(3):786-792. doi:<https://doi.org/10.1016/j.bbrc.2008.01.151>
12. Koedel U. Toll-Like Receptors in Bacterial Meningitis. *Current topics in microbiology and immunology*. 2009;336:15-40. doi:[https://doi.org/10.1007/978-3-642-00549-7\\_2](https://doi.org/10.1007/978-3-642-00549-7_2)
13. Tuomanen EI. The Biology of Pneumococcal Infection. *Pediatric Research*. 1997;42(3):253-258. doi:<https://doi.org/10.1203/00006450-199709000-00001>
14. Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. *Physiological Reviews*. 2019;99(3):1325-1380. doi:<https://doi.org/10.1152/physrev.00010.2018>
15. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice Guidelines for the Management of Bacterial Meningitis. *Clinical Infectious Diseases*. 2004;39(9):1267-1284. doi:<https://doi.org/10.1086/425368>
16. Koedel U, Pfister HW. Oxidative Stress in Bacterial Meningitis. *Brain Pathology*. 2006;9(1):57-67. doi:<https://doi.org/10.1111/j.1750-3639.1999.tb00211.x>
17. Teske. The role of plasminogen activator inhibitor-2 in pneumococcal meningitis. *Acta neuropathologica communications*. 2022;10(1). doi:<https://doi.org/10.1186/s40478-022-01461-1>
18. Javier F. Clinical management of infectious cerebral vasculitides. *Expert review of neurotherapeutics*. 2016;16(2):205-221. doi:<https://doi.org/10.1586/14737175.2015.1134321>
19. Grandgirard D, Leib SL. Strategies to prevent neuronal damage in paediatric bacterial meningitis. *Current Opinion in Pediatrics*. 2006;18(2):112-118. doi:<https://doi.org/10.1097/01.mop.0000193292.09894.b7>
20. Pasa S, Abdullah Altintas, Timucin Cil, et al. Two cases of bacterial meningitis accompanied by thalidomide therapy in patients with multiple myeloma: is thalidomide associated with bacterial meningitis? *International Journal of Infectious Diseases*. 2008;13(1):e19-e22. doi:<https://doi.org/10.1016/j.ijid.2008.04.003>
21. Putz K, Hayani K, Zar FA. Meningitis. *Primary Care: Clinics in Office Practice*. 2013;40(3):707-726. doi:<https://doi.org/10.1016/j.pop.2013.06.001>
22. Wang G, Zhang C, Jiang F, Zhao M, Xie S, Liu X. NOD2-RIP2 signaling alleviates microglial ROS damage and pyroptosis via ULK1-mediated autophagy during Streptococcus pneumonia infection. *Neuroscience Letters*. 2022;783:136743-136743. doi:<https://doi.org/10.1016/j.neulet.2022.136743>
23. Liu P, Wang X, Yang Q, et al. Collaborative Action of Microglia and Astrocytes Mediates Neutrophil Recruitment to the CNS to Defend against Escherichia coli K1 Infection. *International journal of molecular sciences*. 2022;23(12):6540-6540. doi:<https://doi.org/10.3390/ijms23126540>
24. Nau R, Djukic M, Spreer A, Ribes S, Eiffert H. Bacterial meningitis: an update of new treatment options. *Expert Review of Anti-infective Therapy*. 2015;13(11):1401-1423. doi:<https://doi.org/10.1586/14787210.2015.1077700>
25. Yang C, Yuk J, Shin D, Kang J, Lee SJ, Jo E. Secretory phospholipase A2 plays an essential role in microglial inflammatory responses to Mycobacterium tuberculosis. *Glia*. 2008;57(10):1091-1103. doi:<https://doi.org/10.1002/glia.20832>
26. Christen S, Schaper M, Jens Lykkesfeldt, et al. Oxidative stress in brain during experimental bacterial meningitis: differential effects of  $\alpha$ -phenyl-tert-butyl nitron and N-acetylcysteine treatment. *Free Radical Biology and Medicine*. 2001;31(6):754-762. doi:[https://doi.org/10.1016/s0891-5849\(01\)00642-6](https://doi.org/10.1016/s0891-5849(01)00642-6)



# AIDS DEMENTIA COMPLEX: PATHOGENESIS AND SYMPTOMS

Stefano Di Michele<sup>1\*</sup> and Carlo D'Aurizio<sup>2</sup>

<sup>1</sup> Division of Gynecology and Obstetrics, Department of Surgical Sciences, University of Cagliari, Cagliari, Italy;

<sup>2</sup> Department of Neurorehabilitation, Popoli Hospital, Popoli, Italy.

\*Correspondence to:

Stefano Di Michele,

Division of Gynecology and Obstetrics,

Department of Surgical Sciences,

University of Cagliari,

Cagliari, Italy.

e-mail: [dr.dimichelestefano@gmail.com](mailto:dr.dimichelestefano@gmail.com)

## ABSTRACT

AIDS Dementia Complex (ADC) is a frequent pathology caused by HIV infection that can affect cognitive, motor, and behavioral functions with a mechanism that is still unclear. HIV infection is often known before the onset of dementia, but ADC can sometimes appear before other clinical signs. The onset is usually abrupt in the more advanced stages of HIV infection and begins with apathy, psychomotor slowing, memory problems, and loss of interest in usual activities. ADC is characterized by disturbances in recent memory, the slowing down of mental processes, personality changes, headaches, aphasia, and hemiparesis. Antiretroviral therapy (ART) can reduce the incidence and severity of ADC by controlling viral replication. HIV infection is associated with inflammation and the production of reactive oxygen species (ROS), resulting in neuronal damage. It is likely that HIV causes damage to the central nervous system (CNS) through indirect mechanisms, such as inducing the production of inflammatory cytokines or neuropeptides. In fact, neuronal cells and oligodendrocytes incubated *in vitro* are damaged by exogenous TNF. In the brain, HIV can cause diffuse paleness of the white matter, reduction in the number of neurons, and atrophy in the frontotemporal regions. HIV can induce the chemokines and pro-inflammatory cytokines causing sympathetic damage and cell death.

**KEYWORDS:** *HIV, infection, AIDS dementia complex, central nervous system*

## INTRODUCTION

Some pathologies affecting the central nervous system (CNS) are attributable to the primary action of the human immunodeficiency virus (HIV) and not to opportunistic infections (1). Broad neurological and cognitive impairments can occur in people with HIV, including a range of symptoms from mild cognitive issues to severe dementia. Acquired immunodeficiency syndrome (AIDS) Dementia Complex (ADC), also known as HIV-associated dementia (HAD), and sometimes referred to as subacute encephalitis, AIDS encephalopathy, or HIV encephalitis (2), is considered the most frequent neurological complication of HIV infections (3). This severe neurological pathology results in significant cognitive and motor dysfunction that interferes with daily life and functioning.

In most patients, HIV infection is already known before the onset of dementia, but ADC can sometimes appear before other signs or symptoms of the infection (2). In this last case, the onset of the disease is usually insidious and one of the first signs is psychomotor slowing which can be confused with depression (4). The onset is usually more abrupt in the more advanced stages of HIV infection.

ADC begins with apathy, psychomotor slowing, memory problems, and loss of interest in usual activities (2). Sometimes, however, the onset can be characterized by psychomotor agitation. This is followed by disturbances in

Received: 01 July, 2022  
Accepted: 14 October, 2022

1972-6945 (2022)

Copyright © by Biolife-Publisher

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

recent memory, the slowing down of mental processes, and personality changes. There may be headaches, alteration disorders, aphasia, hemiparesis, more rarely, compulsive seizures and ocular disorders such as nystagmus and gaze paralysis (5). As the disease progresses, there is a further slowing down of mental processes which can lead to a state of confusion, disorientation, hallucinations, stupor, and coma. Microcephaly and progressive psychomotor disorders may be present in children (6). In the absence of therapy, the decline is rapid, and an average survival period of less than 6 months is generally reported (7).

The therapeutic implications for ADC involve antiretroviral therapy (ART). Effective ART can reduce the incidence and severity of ADC by controlling viral replication (8). Anti-inflammatory treatments target neuroinflammation and may offer additional benefits (9). Neuroprotective agents that reduce oxidative stress and excitotoxicity are potential therapeutic avenues (10) (Table I).

**Table I.** *Therapeutic Approaches to treating AIDS dementia complex (ADC).*

Optimization of antiretroviral therapy (ART):	<ul style="list-style-type: none"> <li>• Developing ART drugs that effectively penetrate the central nervous system (CNS).</li> <li>• Combination therapies target both viral replication and neuroinflammation.</li> </ul>
Anti-inflammatory and neuroprotective agents:	<ul style="list-style-type: none"> <li>• Use of anti-inflammatory drugs to reduce CNS inflammation.</li> <li>• Neuroprotective agents to prevent neuronal damage and promote repair.</li> </ul>
Biomarkers and imaging:	<ul style="list-style-type: none"> <li>• Identifying biomarkers for early detection and monitoring of ADC.</li> <li>• Advanced neuroimaging techniques to assess brain structure and function.</li> </ul>
Gene therapy:	<ul style="list-style-type: none"> <li>• Exploring gene editing technologies (e.g., CRISPR) to eliminate HIV reservoirs in the CNS.</li> <li>• Developing therapeutic strategies to modulate gene expression related to neuroinflammation and repair.</li> </ul>
Cognitive rehabilitation:	<ul style="list-style-type: none"> <li>• Implementing cognitive training and rehabilitation programs for ADC patients.</li> <li>• Behavioral therapies to improve quality of life and cognitive function.</li> </ul>

## DISCUSSION

ADC alone represents more than 15% of all neurological complications in HIV infection, and even in children, ADC is more frequent than opportunistic infections (11). ADC can be defined as a subcortical dementia that affects cognitive, motor, and behavioral functions and can be considered the direct result of the action of the HIV virus, although the mechanism of action is not yet perfectly known (12). HIV has been isolated in the brain and cerebrospinal fluid (CSF) of patients with ADC (13). In particular, the virus has been found in macrophage cells, astrocytes, and microglial cells, as well as in multinucleated giant cells within the CNS (14). Oligodendrocytes and neurons have also been found infected, although on rare occasions (15). The pathogenesis of ADC involves multiple complex mechanisms at the molecular level (Table II).

**Table II.** *The molecular mechanisms and inflammatory responses involved in AIDS dementia complex (ADC).*

HIV neuroinvasion:	<ul style="list-style-type: none"> <li>• HIV can cross the blood-brain barrier (BBB) through infected monocytes/macrophages.</li> <li>• These cells release viral particles and inflammatory cytokines, causing neuronal injury.</li> </ul>
Inflammatory response:	<ul style="list-style-type: none"> <li>• Chronic activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines (e.g., TNF, IL-1<math>\beta</math>).</li> <li>• This inflammatory milieu contributes to neurotoxicity and synaptic dysfunction.</li> </ul>
Viral proteins:	<ul style="list-style-type: none"> <li>• HIV proteins, such as gp120 and transactivator of transcription (Tat), are neurotoxic.</li> <li>• gp120 can bind to neuronal receptors and induce apoptosis.</li> <li>• Tat can disrupt calcium homeostasis and mitochondrial function.</li> </ul>
Oxidative stress:	<ul style="list-style-type: none"> <li>• Increased production of reactive oxygen species (ROS) damages neuronal cells.</li> <li>• HIV infection disrupts antioxidant defense mechanisms.</li> </ul>
Synaptic dysfunction:	<ul style="list-style-type: none"> <li>• HIV disrupts synaptic signaling and plasticity, leading to cognitive deficits.</li> <li>• Altered neurotransmitter levels and receptor function are observed in ADC.</li> </ul>

In the early stages of infection, HIV can enter the CNS through infected monocytes and CD4 T cells by crossing the blood-brain barrier (BBB). Within the CNS, HIV primarily infects microglia and macrophages, while astrocytes can also be infected but generally do not produce new virions. The transactivator of transcription (Tat) protein can be secreted by infected cells and can be taken up by neurons, causing oxidative stress and mitochondrial dysfunction (16). The viral gp120 protein is an envelope protein that can bind to neurons and cause direct toxicity, leading to apoptosis (17).

Infected glial cells can release excess glutamate, leading to excitotoxicity through overactivation of NMDA receptors on neurons, with an increase in intracellular calcium, which can trigger cell death pathways (18). HIV infection associated with the inflammatory process causes an increase in the production of reactive oxygen species (ROS), leading to oxidative damage to neurons (19,20).

HIV and its proteins can disrupt synaptic signaling and plasticity, cause chronic inflammation and neurotoxic environments that promote neuronal apoptosis, and lead to cognitive deficits (21) (Table III). Therefore, opportunistic infections and other co-morbidities in HIV-infected individuals can further impair CNS function (22).

**Table III.** *The immune response in AIDS dementia complex (ADC).*

Immune activation:	<ul style="list-style-type: none"> <li>• Persistent immune activation despite antiretroviral therapy (ART) contributes to ADC.</li> <li>• Elevated levels of activated monocytes and macrophages are associated with neurocognitive impairment.</li> </ul>
Immune cells in the central nervous system (CNS):	<ul style="list-style-type: none"> <li>• Microglia and astrocytes become chronically activated, perpetuating a state of neuroinflammation.</li> <li>• This activation results in the release of neurotoxic substances and contributes to neuronal damage.</li> </ul>
Blood-brain barrier (BBB):	<ul style="list-style-type: none"> <li>• HIV infection and chronic inflammation can compromise the integrity of the BBB.</li> <li>• This allows further infiltration of infected cells and inflammatory mediators into the CNS.</li> </ul>

The presence of the virus in the CNS has been demonstrated with various techniques including direct isolation, morphological identification, and *in situ* hybridization. HIV probably penetrates the CNS through macrophages which must be considered primary targets of the infection (23). However, the mechanisms through which neurological

complications arise are still uncertain. Perhaps HIV induces damage to the CNS through indirect mechanisms, one of which could be the release of substances, such as cytokines, which would be able to act on the functioning of nerve cells or on neuromodulators (24). Myelin damage has been demonstrated in oligodendrocyte *in vitro* in cultures incubated with TNF. Furthermore, mononuclear phagocytes infected by HIV can release toxic substances capable of destroying isolated rat or chicken neurons *in vitro* (25). On the other hand, TNF can increase HIV replication. Another possible mechanism of damage is represented by the release of gp120, which could increase the quantity of free calcium within neurons with subsequent irreversible damage (26).

Macroscopically, cerebral atrophy is frequently noted primarily in the frontotemporal regions (27). A diffuse pallor of the white matter may also be present; this occurs mainly in frontal and temporal areas but sometimes the results of the clinical investigation are normal. Histologically, alterations of white matter can be observed such as demyelization, vaporization, and astrocytosis. Inflammatory elements consisting mainly of lymphocytic and mononuclear cells are observable in the vicinity of the cerebral vessels (28). The most characteristic picture is the presence of multinucleated giant cells with several elongated and basophilic nuclei generally arranged at the periphery of the cells (29). The cytoplasm of these cells appears eosinophilic, densely colored in the center, and vaporized. Giant cells are more frequent in vascular spaces (30). Microglial nodules, which are mainly composed of mononuclear cells, are not specific to infection with HIV as they are also observed during cytomegalovirus encephalitis or toxoplasmosis (31). Electron microscopic studies have demonstrated the presence of retroviral particles in the cytoplasm of giant cells, which could therefore represent the major reservoir of the virus (32). Morphometric analysis has noted a reduction in the number of neurons (particularly of cells in the frontal and temporal regions), the loss of dendritic arborizations, and synaptic simplifications (33). HIV proteins such as gp120, Tat, and Vpr, have neurotoxic effects (34). gp120 is an envelope protein that interacts with chemokine receptors (e.g., CCR5, CXCR4) on neurons and glial cells, inducing apoptosis and synaptic damage (35). Tat can be secreted by infected cells and taken up by neurons, where it disrupts cellular functions, promotes inflammation, and increases oxidative stress (36). This viral protein induces cell cycle arrest and apoptosis in neurons.

## CONCLUSIONS

The molecular mechanisms underlying ADC are crucial for developing targeted therapies to prevent and treat this debilitating condition in HIV-infected individuals. With further research focusing on these molecular aspects, it is hoped that the cognitive and functional decline associated with ADC can be further mitigated.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

## REFERENCES

1. Balcom E, Roda W, Cohen E, Li M, Power C. HIV-1 persistence in the central nervous system: viral and host determinants during antiretroviral therapy. *Current Opinion in Virology*. 2019;38:54-62. doi:<https://doi.org/10.1016/j.coviro.2019.06.004>
2. Eggers C, Arendt G, Hahn K, et al. HIV-1-associated neurocognitive disorder: epidemiology, pathogenesis, diagnosis, and treatment. *Journal of Neurology*. 2017;264(8):1715-1727. doi:<https://doi.org/10.1007/s00415-017-8503-2>
3. Rahimian P, He JJ. HIV/neuroAIDS biomarkers. *Progress in Neurobiology*. 2017;157:117-132. doi:<https://doi.org/10.1016/j.pneurobio.2016.04.003>
4. Sacktor NC, H Bacellar, Hoover DR, et al. Psychomotor slowing in HIV infection: A predictor of dementia, AIDS and death. *Journal of NeuroVirology*. 1996;2(6):404-410. doi:<https://doi.org/10.3109/13550289609146906>
5. Hedges TR. Ophthalmoplegia associated with AIDS. *Survey of Ophthalmology*. 1994;39(1):43-51. doi:[https://doi.org/10.1016/s0039-6257\(05\)80043-8](https://doi.org/10.1016/s0039-6257(05)80043-8)
6. Boivin MJ, Green SDR, Davies AG, Giordani B, et al. A preliminary evaluation of the cognitive and motor effects on pediatric HIV infection in Zairian children. *Health Psychology*. 1995;14(1):13-21. doi:<https://doi.org/10.1037//0278-6133.14.1.13>
7. Innes S, Laughton B, van Toorn R, et al. Recovery of HIV encephalopathy in perinatally infected children on antiretroviral therapy. *Developmental medicine and child neurology*. 2020;62(11):1309-1316. doi:<https://doi.org/10.1111/dmcn.14639>
8. Brew BJ. AIDS DEMENTIA COMPLEX. *Neurologic Clinics*. 1999;17(4):861-881. doi:[https://doi.org/10.1016/s0733-8619\(05\)70170-5](https://doi.org/10.1016/s0733-8619(05)70170-5)

9. Rizzo MD, Henriquez JE, Blevins LK, Bach A, Crawford RB, Kaminski NE. Targeting Cannabinoid Receptor 2 on Peripheral Leukocytes to Attenuate Inflammatory Mechanisms Implicated in HIV-Associated Neurocognitive Disorder. *Journal of Neuroimmune Pharmacology*. 2020;15(4):780-793. doi:<https://doi.org/10.1007/s11481-020-09918-7>
10. Steiner J, Haughey N, Li W, et al. Oxidative Stress and Therapeutic Approaches in HIV Dementia. *Antioxidants & Redox Signaling*. 2006;8(11-12):2089-2100. doi:<https://doi.org/10.1089/ars.2006.8.2089>
11. Thakur KT, Boubour A, Saylor D, Das M, Bearden DR, Birbeck GL. Global HIV neurology. *AIDS*. 2019;33(2):163-184. doi:<https://doi.org/10.1097/qad.0000000000001796>
12. Price RW, Sidtis JJ, Brew BJ. AIDS Dementia Complex and HIV-1 Infection: A View From the Clinic. *Brain Pathology*. 1991;1(3):155-162. doi:<https://doi.org/10.1111/j.1750-3639.1991.tb00655.x>
13. Williams ME, Stein DJ, Joska JA, Naudé PJW. Cerebrospinal fluid immune markers and HIV-associated neurocognitive impairments: A systematic review. *Journal of Neuroimmunology*. 2021;358:577649. doi:<https://doi.org/10.1016/j.jneuroim.2021.577649>
14. Wang T, Gong N, Liu J, et al. HIV-1-Infected Astrocytes and the Microglial Proteome. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology*. 2008;3(3):173-186. doi:<https://doi.org/10.1007/s11481-008-9110-x>
15. Jadhav S, Nema V. HIV-Associated Neurotoxicity: The Interplay of Host and Viral Proteins. Nilsen N, ed. *Mediators of Inflammation*. 2021;2021:1-11. doi:<https://doi.org/10.1155/2021/1267041>
16. Thangaraj A, Periyasamy P, Liao K, et al. HIV-1 TAT-mediated microglial activation: role of mitochondrial dysfunction and defective mitophagy. *Autophagy*. 2018;14(9):1596-1619. doi:<https://doi.org/10.1080/15548627.2018.1476810>
17. He X, Yang W, Zeng Z, et al. NLRP3-dependent pyroptosis is required for HIV-1 gp120-induced neuropathology. *Cellular & Molecular Immunology*. 2019;17(3):283-299. doi:<https://doi.org/10.1038/s41423-019-0260-y>
18. Haughey NJ, Holden CP, Nath A, Geiger JD. Involvement of Inositol 1,4,5-Trisphosphate-Regulated Stores of Intracellular Calcium in Calcium Dysregulation and Neuron Cell Death Caused by HIV-1 Protein Tat. *Journal of Neurochemistry*. 2002;73(4):1363-1374. doi:<https://doi.org/10.1046/j.1471-4159.1999.0731363.x>
19. Shiu C, Barbier E, Cello FD, Choi HJ, Stins M. HIV-1 gp120 as Well as Alcohol Affect Blood?Brain Barrier Permeability and Stress Fiber Formation: Involvement of Reactive Oxygen Species. *Alcoholism: Clinical and Experimental Research*. 2007;31(1):130-137. doi:<https://doi.org/10.1111/j.1530-0277.2006.00271.x>
20. Mishra R, Singh SK. HIV-1 Tat C phosphorylates VE-cadherin complex and increases human brain microvascular endothelial cell permeability. *BMC Neuroscience*. 2014;15(1). doi:<https://doi.org/10.1186/1471-2202-15-80>
21. Boska MD, Dash PK, Knibbe J, et al. Associations between brain microstructures, metabolites, and cognitive deficits during chronic HIV-1 infection of humanized mice. *Molecular neurodegeneration*. 2014;9(1). doi:<https://doi.org/10.1186/1750-1326-9-58>
22. Roulet E. Opportunistic infections of the central nervous system during HIV-1 infection (emphasis on cytomegalovirus disease). *Journal of Neurology*. 1999;246(4):237-243. doi:<https://doi.org/10.1007/s004150050341>
23. Bagasra O, Lavi E, Bobroski L, et al. Cellular reservoirs of HIV-1 in the central nervous system of infected individuals: identification by the combination of in situ polymerase chain reaction and immunohistochemistry. *AIDS (London, England)*. 1996;10(6):573-585. doi:<https://doi.org/10.1097/00002030-199606000-00002>
24. Abergel C, Robertson DL, Jean Michel Claverie. "Hidden" dUTPase Sequence in Human Immunodeficiency Virus Type 1 gp120. *Journal of Virology*. 1999;73(1):751-753. doi:<https://doi.org/10.1128/jvi.73.1.751-753.1999>
25. Peng H, Sun L, Jia B, et al. HIV-1-Infected and Immune-Activated Macrophages Induce Astrocytic Differentiation of Human Cortical Neural Progenitor Cells via the STAT3 Pathway. Proost P, ed. *PLoS ONE*. 2011;6(5):e19439. doi:<https://doi.org/10.1371/journal.pone.0019439>
26. Pasquereau S, Kumar A, Herbein G. Targeting TNF and TNF Receptor Pathway in HIV-1 Infection: from Immune Activation to Viral Reservoirs. *Viruses*. 2017;9(4):64. doi:<https://doi.org/10.3390/v9040064>
27. Ferrell D, Giunta B. The impact of HIV-1 on neurogenesis: implications for HAND. *Cellular and Molecular Life Sciences*. 2014;71(22):4387-4392. doi:<https://doi.org/10.1007/s00018-014-1702-4>

28. Minagar A, Shapshak P, Fujimura R, Ownby R, Heyes M, Eisdorfer C. The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. *Journal of the Neurological Sciences*. 2002;202(1-2):13-23. doi:[https://doi.org/10.1016/s0022-510x\(02\)00207-1](https://doi.org/10.1016/s0022-510x(02)00207-1)
29. Dahal S, Chitti SVP, Nair MPN, Saxena SK. Interactive effects of cocaine on HIV infection: implication in HIV-associated neurocognitive disorder and neuroAIDS. *Frontiers in Microbiology*. 2015;6. doi:<https://doi.org/10.3389/fmicb.2015.00931>
30. Hurwitz AA, Berman JW, Lyman WD. The role of the blood-brain barrier in HIV infection of the central nervous system. *Advances in Neuroimmunology*. 1994;4(3):249-256. doi:[https://doi.org/10.1016/s0960-5428\(06\)80263-9](https://doi.org/10.1016/s0960-5428(06)80263-9)
31. Ho DD. The Acquired Immunodeficiency Syndrome (AIDS) Dementia Complex. *Annals of Internal Medicine*. 1989;111(5):400. doi:<https://doi.org/10.7326/0003-4819-111-5-400>
32. Hatch WC, Pousada E, Losev L, Rashbaum WK, Lyman WD. Neural Cell Targets of Human Immunodeficiency Virus Type 1 in Human Fetal Organotypic Cultures. *AIDS Research and Human Retroviruses*. 1994;10(12):1597-1607. doi:<https://doi.org/10.1089/aid.1994.10.1597>
33. Abe H, Parviz Mehraein, Weis S. Degeneration of the cerebellar dentate nucleus and the inferior olivary nuclei in HIV-1-infected brains: a morphometric analysis. *Acta Neuropathologica*. 1996;92(2):150-155. doi:<https://doi.org/10.1007/s004010050502>
34. Patel CA, Mukhtar M, Harley S, Kulkosky J, Pomerantz RJ. Lentiviral expression of HIV-1 Vpr induces apoptosis in human neurons. *Journal of NeuroVirology*. 2002;8(2):86-99. doi:<https://doi.org/10.1080/13550280290049552>
35. Wang S, Lin C, Li Y, et al. Distinct chemokines selectively induce HIV-1 gp120-integrin  $\alpha 4\beta 7$  binding via triggering conformer-specific activation of  $\alpha 4\beta 7$ . *Signal Transduction and Targeted Therapy*. 2021;6(1). doi:<https://doi.org/10.1038/s41392-021-00582-8>
36. Marino J, Maubert ME, Mele AR, Spector C, Wigdahl B, Nonnemacher MR. Functional impact of HIV-1 Tat on cells of the CNS and its role in HAND. *Cellular and molecular life sciences : CMLS*. 2020;77(24):5079-5099. doi:<https://doi.org/10.1007/s00018-020-03561-4>



Letter to the Editor...

## SOME KEY BIOMARKERS IN ACUTE RESPIRATORY DISTRESS SYNDROME

Emanuela Mazzon\*

IRCCS Neurolesi Center "Bonino-Pulejo", Messina, Italy.

\*Correspondence to:

Dr. Emanuela Mazzon,

IRCCS Centro Neurolesi "Bonino-Pulejo",

Contrada Casazza,

98124 Messina, Italy.

e-mail: [emanuela.mazzon@ircsme.it](mailto:emanuela.mazzon@ircsme.it)

**KEYWORDS:** *Acute respiratory distress syndrome, infection, alveoli, lung, biomarker*

### INTRODUCTION

The inflammation that is caused by infection induced by foreign microorganisms increases the permeability of the alveolar-capillary barrier, allowing fluid to enter the alveoli. Infection results in the activation of immune cells, such as neutrophils, which increase in number and release proteases and reactive oxygen species (ROS) that damage tissue. The onset of edema in the lung alveoli causes reduced oxygen flow and reduced lung compliance and activated inflammatory cells release various cytokines that participate in inflammation and activation of endothelial cells.

Infection can cause acute respiratory distress syndrome (ARDS) that results in damage to type II pneumocytes with reduced surfactants, increased surface tension, and alveolar collapse. The discovery of biomarkers in ARDS has helped to improve the diagnosis and therapy for this disease. The primary biomarkers are soluble decoy receptors for advanced glycation end products (sRAGE), angiotensin-2 (Ang-2), and pulmonary immune protein surfactant protein-D (SP-D). sRAGE is expressed by type I alveolar epithelial cells in the lungs and correlated with alveolar epithelial damage. In ARDS, Ang-2 is produced mainly by type II pneumocytes and secreted by endothelial cells and is an important marker mediating endothelial damage. SP-D is involved in the regulation of pulmonary surfactant homeostasis, binds pathogens, and promotes phagocytosis.

### DISCUSSION

Infection by microorganisms causes inflammation with generation of extravascular fluid, which in the case of the lungs, can enter the alveoli, causing serious consequences. Microorganisms infect the lung and activate immune cells, including neutrophils that colonize the tissue and release inflammatory cytokines. These reactions cause neutrophilia with the release of proteases and ROS that damage the alveolar epithelium and capillary endothelium, leading to hypoxia. Edema occurs in the alveoli with increased vascular permeability and leakage of protein-rich fluid. The inflammatory state alters gas exchange and causes the onset of ARDS in the pulmonary alveoli and consequent reduction in oxygen flow with reduced pulmonary compliance and pulmonary hypertension.

ARDS can cause rapid and difficult breathing, severe shortness of breath, and cyanosis. Symptoms that may appear after a few hours or a few days from the infection may also include mental confusion, pulmonary fibrosis, and fatigue. Inflammatory cells may cause a "cytokine storm", in which they promote the recruitment of other cytokines and activate endothelial to release inflammatory compounds (1). Oxidative stress mediated by neutrophils and macrophages leads to the release of ROS and reactive nitrogen species (RNS). This causes damage to DNA, lipids, and proteins of alveolar

Received: 21 October, 2022

Accepted: 15 November, 2022

1972-6945 (2022)

Copyright © by Biolife-Publisher

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

cells with loss of VE-cadherin in the endothelium and vascular leakage. In addition, hyaline membranes consisting of fibrin-rich deposits and necrotic epithelial cells are formed. In ARDS, there is damage to type II pneumocytes with reduced production of surfactant, a lipoprotein complex secreted by pneumocytes, and an increase in surface tension with alveolar collapse and decreased lung compliance (2).

Biomarkers have been found in ARDS that have helped to better understand the disease. sRAGE is a key biomarker in ARDS, particularly linked to alveolar epithelial injury. sRAGE is a soluble decoy receptor for RAGE expressed primarily on alveolar type I epithelial cells in the lungs (3). In inflammatory processes, sRAGE binds the proteins AGE, HMGB1, and S100 (4). In ARDS, where alveolar type I epithelial cells are damaged, plasma levels of sRAGE are highly and early expressed, and are an important marker for this disease (5).

Another important biomarker for ARDS is Ang-2, which mediates endothelial damage. Ang-2 is a glycoprotein that is secreted by endothelial cells and is involved in vascular permeability, edema, and inflammation. It regulates angiogenesis and stability of the vascular endothelium (6). In diseases such as ARDS or sepsis, Ang-2 plays an important role in vascular damage and inflammatory processes (7).

A third biomarker in ARDS is the pulmonary immune protein SP-D, which is involved in the regulation of pulmonary surfactant homeostasis (8). It is produced mainly by type II pneumocytes, epithelial cells of the respiratory tract, which recognize and bind pathogens, promote macrophage phagocytosis, and modulate the inflammatory response.

## CONCLUSIONS

ARDS is a condition characterized by reduced lung ventilation, edema, and alveolar collapse. Lung inflammation must be treated immediately to avoid serious consequences. The ARDS biomarkers sRAGE, Ang-2, and SP-D, which are elevated in individuals with ARDS, are important for improving diagnosis and therapy in this complicated disease.

### *Conflict of interest*

The author declares that they have no conflict of interest.

## REFERENCES

1. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nature Reviews Immunology*. 2020;20(7):389-391. doi:<https://doi.org/10.1038/s41577-020-0343-0>
2. Katsura H, Sontake V, Tata A, et al. Human Lung Stem Cell-Based Alveolospheres Provide Insights into SARS-CoV-2-Mediated Interferon Responses and Pneumocyte Dysfunction. *Cell Stem Cell*. 2020;27(6):890-904. doi:<https://doi.org/10.1016/j.stem.2020.10.005>
3. Izushi y, Teshigawara k, Liu K, et al. Soluble form of the receptor for advanced glycation end-products attenuates inflammatory pathogenesis in a rat model of lipopolysaccharide-induced lung injury. *Journal of Pharmacological Sciences*. 2016;130(4):226-234. doi:<https://doi.org/10.1016/j.jphs.2016.02.005>
4. Scavello F, Zeni F, Tedesco CC, et al. Modulation of soluble receptor for advanced glycation end-products (RAGE) isoforms and their ligands in healthy aging. *Aging*. 2019;11(6):1648-1663. doi:<https://doi.org/10.18632/aging.101860>
5. Manichaikul a, Sun L, Borczuk AC, et al. Plasma Soluble Receptor for Advanced Glycation End Products in Idiopathic Pulmonary Fibrosis. *Annals of the American Thoracic Society*. 2017;14(5):628-635. doi:<https://doi.org/10.1513/annalsats.201606-485oc>
6. Akwii RG, Sajib MS, Zahra FT, Mikelis CM. Role of Angiopoietin-2 in Vascular Physiology and Pathophysiology. *Cells*. 2019;8(5):471. doi:<https://doi.org/10.3390/cells8050471>
7. Zinter MS, Spicer A, Orwoll BO, et al. Plasma angiopoietin-2 outperforms other markers of endothelial injury in prognosticating pediatric ARDS mortality. *American Journal of Physiology-Lung Cellular and Molecular Physiology*. 2016;310(3):L224-L231. doi:<https://doi.org/10.1152/ajplung.00336.2015>
8. Sorensen GL. Surfactant Protein D in Respiratory and Non-Respiratory Diseases. *Frontiers in Medicine*. 2018;5. doi:<https://doi.org/10.3389/fmed.2018.00018>



## OBESITY, INFLAMMATION, AND INFECTION

Raffaello Pellegrino\*

Physiatry and Pain Therapy, Lecce-Castromediano/Cavallino, Lecce, Italy.

\*Correspondence to:

Dr. Raffaello Pellegrino,  
Physiatrist and Pain Therapist,  
Lecce-Castromediano/Cavallino,  
Via S. Pelico 34,  
73100 Lecce, Italy.  
e-mail: [drpellegrino@yahoo.it](mailto:drpellegrino@yahoo.it)

**KEYWORDS:** *Obesity, inflammation, infection, immunity, inflammatory mediator*

### INTRODUCTION

Obesity is a disease characterized by a high volume of body fat in which there is chronic low-grade inflammation. Inflammation is mediated by elevated levels of cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), and C-reactive protein (CRP). Fat accumulation occurs especially in some specific regions, including the abdomen and visceral regions, where it creates hypoxia and death of adipocytes. Both innate and adaptive immunity are involved in obesity, which induces the activation of anti-inflammatory M1 macrophages that are transformed into inflammatory M2 types. Microbial infections are a risk factor where the inflammatory environment induced by obesity can weaken the body's immune response, with serious consequences for human health. Chronic inflammation not only predisposes individuals to infections but also contributes to the development of metabolic disorders and cardiovascular disease.

### DISCUSSION

Statin therapy lowers cholesterol and reduces the incidence of death from cardiovascular disease and atherosclerosis, although some people treated with these drugs still suffer from cardiovascular diseases (1). People affected by obesity and infection present a stronger degree of inflammation, compared to the low degree inflammatory state that is present in obesity alone. Elevated lipid levels, mostly in the form of cholesterol and cholesteryl ester, are associated with obesity, atherosclerosis, and cardiovascular diseases. Obesity causes narrowing of the artery, predisposition to thrombosis, calcification, weakening of the muscles, and aneurysm dilatation.

In obesity, there is a low grade of inflammation, and in the case of infection, the production of cytokines can influence the inflammatory state induced by obesity (2). However, lipids can be lowered by diet and/or medication in most patients.

Monocytes and macrophages are innate immune inflammatory cells that respond to the excessive uptake of lipoproteins in obese patients by generating chemokines and cytokines. The adaptive immune response involves antigen-specific T cells, as well as the activation of B cells, which all produce inflammatory cytokines and chemokines. In this case, IL-12 serves as an important bridge between innate and adaptive immunity (3).

When the endothelium becomes inflamed, it expresses adhesion molecules that bind cognate ligands on leukocytes. Selectins, integrins, and chemokines mediate and favor the action of white inflammatory blood cells such as adherent leukocytes, diapedesis, migration and chemotactic stimulus. The Th1 cytokines involved in the effector T-cell response aggravate inflammation, whereas Th2 cytokines, such as IL-10 and IL-4, are anti-inflammatory and relieve

inflammation. Leukocytes, as well as endothelial cells, secrete cytokines and growth factors that promote the migration and proliferation of smooth muscle cells (4).

Cytokines of the IL-1 family, such as IL-18, have an important function in host defense, immune regulation, and inflammation. IL-18 is an immunoregulatory cytokine which requires cleavage with caspase-1 to become active, and it was originally discovered as a factor that enhances IFN-gamma production from Th1 cells in the presence of anti-CD3 or anti-TcR Ab (5). IL-18 is essential to host defenses against severe infections and is a potent pro-inflammatory cytokine able to induce IFN-gamma, GM-CSF, TNF, and IL-1 in immunocompetent cells, and to activate killing by lymphocytes. Human pre-adipocytes of all differentiation stages spontaneously secrete IL-18, supporting the concept that adipocytes participate in innate immunity and that IL-18 mediates a fraction of the complications of obesity such as cardiovascular disease. It is known that IL-18 release from adipocytes of patients with obesity exceeds approximately 3-fold that from adipocytes of non-obese subjects (6). An augmentation of IL-18 is correlated with a significantly increased risk of developing cardiovascular diseases and type 2 diabetes. These concepts suggest that IL-18 measurement may add prognostic information to lipid and inflammatory markers in patients with or without obesity.

Inflammation is the defense response against infectious microorganisms and the low degree of inflammation that is already present in obesity can be exacerbated by infectious organisms. These reactions aggravate the pathological state that has been established in obesity.

## CONCLUSIONS

Obesity is characterized by chronic, low-grade inflammation. The adipose tissue, in particular the visceral fat, secretes various pro-inflammatory cytokines such as TNF, IL-6, and CRP that promote systemic inflammation. Adipocytes and immune cells in the adipose tissue, such as macrophages, perform crucial roles in maintaining this inflammatory state. Chronic inflammation in obesity contributes to insulin resistance and cytokines interfere with insulin signaling pathways, exacerbating metabolic syndrome and type 2 diabetes.

Understanding the mechanisms that regulate inflammation in infected subjects with obesity can certainly help improve health strategies. Reducing obesity and treating the infectious state improves the inflammatory state, leading to improvements in health.

### *Conflict of interest*

The author declares that they have no conflict of interest.

## REFERENCES

1. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *New England Journal of Medicine*. 2017;376(18):1713-1722. doi:<https://doi.org/10.1056/nejmoa1615664>
2. Khanna D, Khanna S, Khanna P, Kahar P, Patel BM. Obesity: A Chronic Low-Grade Inflammation and Its Markers. *Cureus*. 2022;14(2). doi:<https://doi.org/10.7759/cureus.22711>
3. Brombacher F, Dorfmueller A, Magram J, et al. IL-12 is dispensable for innate and adaptive immunity against low doses of *Listeria monocytogenes*. *International Immunology*. 1999;11(3):325-332. doi:<https://doi.org/10.1093/intimm/11.3.325>
4. Chrysanthopoulou A, Mitroulis I, Apostolidou E, et al. Neutrophil extracellular traps promote differentiation and function of fibroblasts. *The Journal of Pathology*. 2014;233(3):294-307. doi:<https://doi.org/10.1002/path.4359>
5. Nakanishi K. Unique Action of Interleukin-18 on T Cells and Other Immune Cells. *Frontiers in Immunology*. 2018;9. doi:<https://doi.org/10.3389/fimmu.2018.00763>
6. Fain JN, Tichansky DS, Madan AK. Most of the interleukin 1 receptor antagonist, cathepsin S, macrophage migration inhibitory factor, nerve growth factor, and interleukin 18 release by explants of human adipose tissue is by the non-fat cells, not by the adipocytes. *Metabolism*. 2006;55(8):1113-1121. doi:<https://doi.org/10.1016/j.metabol.2006.04.008>



## ENTEROBACTERIACEAE AND ANTIBIOTIC RESISTANCE

Alessandro Perrella<sup>1\*</sup>, Giovanni Martinotti<sup>2</sup>, Adriano Lauri<sup>3</sup> and Pietro Romualdi<sup>4</sup>

<sup>1</sup> Unit of Infectious Disease and Immunology, Hospital Domenico Cotugno, Naples, Italy;

<sup>2</sup> Department of Neurosciences, Imaging and Clinical Sciences, University "G. D'Annunzio" of Chieti-Pescara, Chieti, Italy;

<sup>3</sup> Department of Gastroenterology, Pescara Civil Hospital, Pescara, Italy;

<sup>4</sup> Department of Otolaryngology, "G.Mazzini" Civil Hospital, Teramo, Italy.

\*Correspondence to:

Alessandro Perrella,

Unit of Infectious Disease and Immunology,

Hospital Domenico Cotugno,

Naples, Italy.

e-mail: [alex.perrella@hotmail.com](mailto:alex.perrella@hotmail.com)

### ABSTRACT

*Enterobacteriaceae* such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* species are non-spore-forming, Gram-negative bacilli found in the intestine, urinary tract, bloodstream, and lung of humans. These bacteria can cause meningitis and be potentially lethal. In anaerobic conditions, *Enterobacteriaceae* produce cytochrome and obtain energy by oxidizing pyruvic acid. Resistant *Enterobacteriaceae* are an unsolved problem, due to their ability to evade standard antibiotic treatments. Their resistance is mediated by the production of beta-lactamases, efflux pumps, loss of porins, modification of target sites, and metabolic bypass. Bacteria can alter the sites of action of antibiotics, rendering them ineffective, and bacterial resistance at the genetic level can involve plasmids that can carry multiple antibiotic resistance genes. New antibiotics are now being used against *Enterobacteriaceae*, but with still unsatisfactory results. Carbapenem-resistant *Enterobacteriaceae* are a clinical and public health problem due to their high transmission capacity.

**KEYWORDS:** *Enterobacteriaceae*, antibiotic resistance, meningitis, infection, *Enterobacter* species, *Escherichia coli*, *Klebsiella pneumoniae*

### INTRODUCTION

The *Enterobacteriaceae* are a large family of Gram-negative, non-spore-forming bacilli, which usually inhabit the intestines of humans and other mammals (1). This family includes many pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* species that are common causes of urinary tract infections (UTIs), bloodstream infections, and pneumonia (2,3).

The *Enterobacteriaceae* family presents antigenic and biochemical characteristics typical of the entire group (4). Their classification is important on a clinical level, but difficult, as their characteristics can appear to varying degrees (5). They are bacteria equipped with filamentous protein appendages called "pili" and can be mobile or immobile. *Enterobacteriaceae* are facultative aerobic-anaerobic bacteria that can be grown in normal culture media (6). If they are grown aerobically, they are producers of cytochrome and obtain energy through the Krebs cycle by oxidizing pyruvic acid, an effect that is inhibited by small concentrations of potassium cyanide (7).

Treatment for infections resistant to *Enterobacteriaceae* can cause meningitis and are life-threatening (3). Therefore, the clinical symptoms of the infection, the risk factors, and the therapy are increasingly of interest to the scientific community even if the cases of infection are limited (8). Rigorous infection control practices, including hand hygiene,

Received: 28 July, 2022

Accepted: 15 November, 2022

1972-6945 (2022)

Copyright © by Biolife-Publisher

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

use of personal protective equipment, and isolation of infected patients, are essential to prevent the spread of resistant *Enterobacteriaceae* (9). In addition, the prudent use of antibiotics, guided by susceptibility testing and clinical guidelines, is critical to reduce the selection pressure that drives the emergence of resistance (10).

## DISCUSSION

Resistant *Enterobacteriaceae* infections are a significant concern in both clinical and public health contexts due to their ability to evade standard antibiotic treatments (11). Understanding the biology and molecular aspects of these infections is crucial for developing effective strategies to combat them.

The resistance in *Enterobacteriaceae* is mediated through several mechanisms including beta-lactamase production, efflux pumps, porin loss, modification of target sites, and metabolic bypass (12). For example, certain enzymes, such as extended-spectrum beta-lactamases and carbapenemases, can hydrolyze beta-lactamase production. In addition, bacterial efflux pumps can expel a wide range of antibiotics from the cell, reducing the intracellular concentration of the drug to sub-lethal levels. These pumps can be specific to one antibiotic class or can handle multiple classes. Changes or loss of porin channels in the bacterial outer membrane can also decrease antibiotic uptake (13). This is particularly relevant for carbapenem resistance where the combination of porin loss and beta-lactamase production can lead to high-level resistance (14).

Bacteria can alter the target sites of antibiotics through mutations or enzymatic modifications, rendering the antibiotic ineffective (15). For instance, modifications in penicillin-binding proteins can lead to resistance to beta-lactam antibiotics. Some bacteria can also bypass the metabolic pathways inhibited by antibiotics (16). For example, resistance to trimethoprim-sulfamethoxazole can occur through the acquisition of a resistant dihydrofolate reductase enzyme.

Bacterial resistance at the genetic level may involve plasmids, which are extrachromosomal DNA elements that can carry multiple antibiotic resistance genes (17). They can be transferred between bacteria through conjugation, leading to resistance. Transposons and integrons are mobile genetic elements that can capture and spread resistance genes. Furthermore, spontaneous mutations in chromosomal genes can confer resistance. Genetic resistance can be rapidly detected using polymerase chain reaction (PCR) and quantitative PCR (qPCR) (18). Whole genome sequencing can also provide complete data on the genetic composition of resistant strains. Molecular typing techniques, such as multilocus sequential typing and pulsed-field gel electrophoresis, can also help monitor the spread of resistant strains (19).

Today, new antibiotics are available that can better contain the infectious state of *Enterobacteriaceae*, but they are still unsatisfactory. In addition, meningitis caused by the *Enterobacteriaceae* family can cause obstructive hydrocephalus and brain abscesses, which are difficult to treat and can cause death. These infections can occur after neurosurgery and have poor prognosis, leading to disability and possible mortality. Therefore, to reduce the infection rate it is necessary to use strong disinfectant treatment and rigorous aseptic operations. Therapy is difficult because most antibiotics cannot cross the blood-brain barrier (BBB) and reach the central nervous system (CNS). With resistance, the cytostatic effect of antibiotics does not prevent the bacterium from causing serious and often lethal infections.

The diagnosis of species within the *Enterobacteriaceae* family is of considerable practical importance since the isolation and identification of these germs from pathological materials and the environment are indispensable premises both for the correct therapy of pathological processes and for the prophylaxis of infectious diseases. However, the diagnostic procedures that bring results of almost absolute certainty are based on very numerous biochemical tests, and sometimes, on the use of specific immune sera, and these methods can be too complex. To meet these needs, some laboratories have developed equipment that allows the simultaneous detection of different bacterial biochemical activities in a relatively short time, which allows to reach diagnoses of species that are found to be in unsatisfactory agreement with those obtained with the use of the most extensive classical methods. On the other hand, it should be kept in mind that differences have been highlighted in the detection of individual biochemical characters depending on the method used, and there are variable percentages of false results with the use of some of the said equipment (20).

The spread of *Enterobacteriaceae* strains that are resistant to carbapenems represents an important clinical problem, as they present multiple resistance to different classes of antibiotics. *Enterobacteriaceae* are also a public health problem, due to their high capacity for diffusion and transmission in the population which occurs through genetic elements (21).

The most common *Enterobacter* carbapenemase are classes A and B, which spread via plasmids (22). Less frequently, carbapenem resistance is due to excessive production of extended-spectrum  $\beta$ -Lactamase or AmpC enzymes or by the presence of class D carbapenems (23).

## CONCLUSIONS

Ongoing research is needed to develop new antibiotics and alternative therapies, such as bacteriophage therapy and antimicrobial peptides, to treat infections caused by resistant *Enterobacteriaceae*. Combating resistant *Enterobacteriaceae* infections requires a multifaceted approach involving molecular biology to understand the mechanisms of resistance, advanced diagnostics for rapid detection, and coordinated public health efforts to control the spread of these pathogens.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

## REFERENCES

1. Nordmann P, Dortet L, Poirel L. Carbapenem resistance in Enterobacteriaceae: here is the storm! *Trends in Molecular Medicine*. 2012;18(5):263-272. doi:https://doi.org/10.1016/j.molmed.2012.03.003
2. Zhang Y, Wang Q, Yin Y, et al. Epidemiology of Carbapenem-Resistant Enterobacteriaceae Infections: Report from the China CRE Network. *Antimicrobial Agents and Chemotherapy*. 2018;62(2). doi:https://doi.org/10.1128/AAC.01882-17
3. Martin RM, Bachman MA. Colonization, Infection, and the Accessory Genome of *Klebsiella pneumoniae*. *Frontiers in Cellular and Infection Microbiology*. 2018;8(1). doi:https://doi.org/10.3389/fcimb.2018.00004
4. Janda JM, Abbott SL. The Changing Face of the Family Enterobacteriaceae (Order: “Enterobacterales”): New Members, Taxonomic Issues, Geographic Expansion, and New Diseases and Disease Syndromes. *Clinical Microbiology Reviews*. 2021;34(2). doi:https://doi.org/10.1128/CMR.00174-20
5. Tenailon O, Skurnik D, Picard B, Denamur E. The Population Genetics of Commensal *Escherichia Coli*. *Nature Reviews Microbiology*. 2010;8(3):207-217. doi:https://doi.org/10.1038/nrmicro2298
6. Brook I. Recovery of Aerobic and Anaerobic Bacteria in Sinus Fungal Ball. *Otolaryngology*. 2011;145(5):851-852. doi:https://doi.org/10.1177/0194599811417066
7. Elzinga LW, Mela-Riker LM, Widener LL, Bennett WM. Renal cortical mitochondrial integrity in experimental cyclosporine nephrotoxicity. *Transplantation*. 1989;48(1):102-106. doi:https://doi.org/10.1097/00007890-198907000-00024
8. Gal-Mor O. Persistent Infection and Long-Term Carriage of Typhoidal and Nontyphoidal Salmonellae. *Clinical Microbiology Reviews*. 2018;32(1). doi:https://doi.org/10.1128/cmr.00088-18
9. Monaghan JM, Hutchison ML. Ineffective hand washing and the contamination of carrots after using a field latrine. *Letters in Applied Microbiology*. 2016;62(4):299-303. doi:https://doi.org/10.1111/lam.12549
10. 36th International Symposium on Intensive Care and Emergency Medicine : Brussels, Belgium. 15-18 March 2016. *Critical care: the official journal of the Critical Care Forum*. 2016;20(Suppl 2):94. doi:https://doi.org/10.1186/s13054-016-1208-6
11. Durante-Mangoni E, Andini R, Zampino R. Management of carbapenem-resistant Enterobacteriaceae infections. *Clinical Microbiology and Infection*. 2019;25(8):943-950. doi:https://doi.org/10.1016/j.cmi.2019.04.013
12. Jacoby GA. AmpC -Lactamases. *Clinical Microbiology Reviews*. 2009;22(1):161-182. doi:https://doi.org/10.1128/cmr.00036-08
13. Masi M, Winterhalter M, Pagès JM. Outer Membrane Porins. *Subcellular Biochemistry*. 2019;92:79-123. doi:https://doi.org/10.1007/978-3-030-18768-2\_4
14. Yang Q, Wang H, Sun H, Chen H, Xu Y, Chen M. Phenotypic and Genotypic Characterization of *Enterobacteriaceae* with Decreased Susceptibility to Carbapenems: Results from Large Hospital-Based Surveillance Studies in China. *Antimicrobial Agents and Chemotherapy*. 2010;54(1):573-577. doi:https://doi.org/10.1128/aac.01099-09
15. Bachman J. Site-directed mutagenesis. *Methods in enzymology*. 2013;529:241-248. doi:https://doi.org/10.1016/B978-0-12-418687-3.00019-7
16. Wen X, Cao J, Mi J, et al. Metabonomics reveals an alleviation of fitness cost in resistant *E. coli* competing against susceptible *E. coli* at sub-MIC doxycycline. *Journal of Hazardous Materials*. 2021;405:124215-124215. doi:https://doi.org/10.1016/j.jhazmat.2020.124215

17. Rozwandowicz M, Brouwer MSM, Fischer J, et al. Plasmids carrying antimicrobial resistance genes in Enterobacteriaceae. *Journal of Antimicrobial Chemotherapy*. 2018;73(5):1121-1137. doi:<https://doi.org/10.1093/jac/dkx488>
18. Potter RF, D'Souza AW, Dantas G. The rapid spread of carbapenem-resistant Enterobacteriaceae. *Drug Resistance Updates*. 2016;29:30-46. doi:<https://doi.org/10.1016/j.drug.2016.09.002>
19. Xie S, Fu S, Li M, et al. Microbiological Characteristics of Carbapenem-Resistant Enterobacteriaceae Clinical Isolates Collected from County Hospitals. *Infection and Drug Resistance*. 2020;Volume 13:1163-1169. doi:<https://doi.org/10.2147/idr.s248147>
20. Mitra S, Pramanik K, Sarkar A, Ghosh PK, Soren T, Maiti TK. Bioaccumulation of cadmium by *Enterobacter* sp. and enhancement of rice seedling growth under cadmium stress. *Ecotoxicology and Environmental Safety*. 2018;156:183-196. doi:<https://doi.org/10.1016/j.ecoenv.2018.03.001>
21. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. *The Journal of Infectious Diseases*. 2017;215(suppl\_1):S28-S36. doi:<https://doi.org/10.1093/infdis/jiw282>
22. Tooke CL, Hinchliffe P, Bragginton EC, et al.  $\beta$ -Lactamases and  $\beta$ -Lactamase Inhibitors in the 21st Century. *Journal of Molecular Biology*. 2019;431(18):3472-3500. doi:<https://doi.org/10.1016/j.jmb.2019.04.002>
23. González-Fandos E, Martínez-Laorden A, Abad-Fau A, et al. Effect of Intramuscularly Administered Oxytetracycline or Enrofloxacin on Vancomycin-Resistant Enterococci, Extended Spectrum Beta-Lactamase- and Carbapenemase-Producing Enterobacteriaceae in Pigs. *Animals*. 2022;12(5):622. doi:<https://doi.org/10.3390/ani12050622>