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**AVALIAÇÃO DA ATIVIDADE BACTERICIDA DA
PIOCINA S8 CONTRA CEPAS DE *Pseudomonas*
aeruginosa MULTIRRESISTENTES**

Tese apresentada ao Programa de Pós-Graduação em Microbiologia do Instituto de Ciências Biomédicas da Universidade de São Paulo, para obtenção do Título de Doutor em Ciências.

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RESUMO

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Pseudomonas aeruginosa é um patógeno oportunista que ocasiona diferentes infecções em humanos. O surgimento de linhagens multirresistentes (MRs), contra os antibióticos comercialmente disponíveis, tem causado elevados níveis de morbidade e mortalidade. O objetivo deste estudo foi identificar uma molécula de piocina que apresente potente atividade bactericida contra cepas de *P. aeruginosa* MRs. Uma piocina de baixo peso molecular, produzida por uma cepa de *P. aeruginosa* (ET02) isolada da microbiota intestinal humana, apresentou potente atividade bactericida contra treze linhagens de *P. aeruginosa* produtoras de β -lactamases clinicamente importantes (SPM-1, GIM-1, VIM-1, IMP-1, KPC-2 e GES-5). Essa piocina foi purificada e identificada como S8 através de espectrometria de massas e sequenciamento de DNA. Os genes codificadores da piocina S8 estão presentes no interior de um novo transposon (Tn6350), localizado no cromossomo bacteriano da cepa ET02. Estes resultados demonstraram que S8 possui potente atividade bactericida contra linhagens de *P. aeruginosa* MRs, podendo vir a ser utilizada como um composto antimicrobiano no tratamento de infecções associadas.

Palavras chave: *Pseudomonas aeruginosa*. Piocina S8. Multirresistente. Bacteriocina.

ABSTRACT

Turano HG. Evaluation of the bactericidal activity of the pyocin S8 against multiresistant *Pseudomonas aeruginosa* strains. [Ph. D. thesis (Microbiology)]. São Paulo: Instituto de Ciências Biomédicas, Universidade de São Paulo; 2017.

Pseudomonas aeruginosa is an opportunist pathogen that causes human infections. The emergence of multidrug resistant strains (MRs) against antibiotics commercially available has been causing elevated mortality and morbidity levels. The purpose of this study was to identify a molecule of pyocin with a potent bactericidal activity against *P. aeruginosa* MRs strains. A low molecular weight pyocin, produced by ET02 strain, isolated from human microbiota, has presented wide bactericidal activity against thirteen lineages of *P. aeruginosa*, producers of β -lactamases (SPM-1, GIM-1, VIM-1, IMP-1, KPC-2 e GES-5). This pyocin was purified and identified as S8 through mass spectrometry and DNA sequencing. The pyocin S8 encoding genes are present in the interior of a transposon located in the bacterial chromosome of the ET02 strain. These results demonstrate that S8 have potent bactericidal activity against *P. aeruginosa* MRs lineages, and may well be used as an antimicrobial compound on treatment of hospital infections.

Keywords: *Pseudomonas aeruginosa*. Pyocin S8. Multiresistant. Bacteriocin.

INTRODUÇÃO

Pseudomonas aeruginosa é uma bactéria Gram-negativa que possui um caráter oportunista, podendo colonizar uma ampla variedade de hospedeiros (Aujoulat et al., 2012). Em humanos, esse patógeno é comumente encontrado em feridas causadas por queimaduras (Church et al., 2006), infecções do trato urinário (Sievert et al., 2013) e doenças pulmonares obstrutivas, sendo esta última, muito comum em pacientes com fibrose cística (Driscoll et al., 2007).

Atualmente, há uma crescente prevalência de cepas de *P. aeruginosa* resistentes a praticamente todas as classes de antibióticos disponíveis (Oliver et al., 2015). Esse fenótipo de multirresistência, associado à capacidade de *P. aeruginosa* de formar biofilmes durante as infecções crônicas, tem colocado este patógeno em uma categoria de organismos praticamente intratáveis (McCaughey et al., 2016b). Dessa forma, urge a necessidade de desenvolvimento de novas estratégias terapêuticas que possam ser utilizadas no tratamento de infecções causadas por *P. aeruginosa* multirresistentes.

Uma estratégia alternativa frente aos antibióticos atualmente disponíveis é a utilização das piocinas produzidas pelas próprias células de *P. aeruginosa* (Smith et al., 2012; McCaughey et al., 2016b). Piocinas são antibióticos proteicos produzidos por *P. aeruginosa* que possuem atividade bactericida contra outras linhagens da mesma espécie, atuando, assim, na competição intraespecífica (Michel-Briand, Baysse, 2002). As atividades bactericidas descritas até o momento incluem DNase, tRNase, rRNase, formação de poros na membrana plasmática e inibição da síntese de peptidoglicano (Ghequire, De Mot, 2014). Durante sua ação sobre as células alvos, as moléculas de piocinas reconhecem receptores específicos presentes na superfície celular, desencadeando a morte seletiva de competidores. Tal especificidade reduz o seu espectro de ação, porém facilita seu direcionamento para linhagens específicas, como bactérias multirresistentes ou altamente virulentas (McCaughey et al., 2016).

Após a primeira descrição das piocinas no início da década de 1950, numerosos estudos foram desenvolvidos, culminando em avanços no entendimento do mecanismo de ação dessas moléculas. A potência e a especificidade das piocinas levantou a possibilidade de que essas moléculas poderiam ser utilizadas como antibióticos clinicamente úteis no tratamento de infecções causadas por *P. aeruginosa*. De fato, a atividade bactericida das moléculas de piocinas tem sido eficientemente testada em modelos de animais infectados com

P. aeruginosa (Merrikin, Terry, 1972; Williams, 1976; Scholl, Martin, 2008; Williams et al., 2008; Scholl et al., 2009; Ritchie et al., 2011; Smith et al., 2012; McCaughey et al., 2016a,b). No entanto, não há estudos que reportem a utilização dessas moléculas contra linhagens de *P. aeruginosa* multirresistentes.

A disponibilização de sequências genômicas de linhagens de *P. aeruginosa* tem possibilitado a identificação de um grande número de novas piocinas (Ghequire, De Mot, 2014), revelando a complexa evolução dessas moléculas. Visando aprofundar o conhecimento sobre a possível utilização das piocinas como antibióticos proteicos, este trabalho teve como principal objetivo a identificação de uma nova molécula de piocina com potente atividade bactericida contra linhagens de *P. aeruginosa* multirresistentes.

7 CONCLUSÕES

1. As cepas CIB, CI3 e ET02 produzem piocinas com ampla atividade bactericida contra as cepas MRs. Dentre essas, a cepa ET02 produziu os maiores halos de inibição do crescimento das linhagens multirresistentes.
2. A cepa ET02 produz três tipos de piocinas: S2, S8 e R5.
3. No teste da monocamada a piocina S8 matou treze de dezoito cepas MRs. Dentre essas, pode-se afirmar que dez cepas (48-1997A, 247-B, PaGIM, Pa PHB64, Pa BH6, 1088, 24, 44, 19 e 151) foram mortas unicamente pela S8. A CBM foi determinada para um total de seis cepas (179, PaIMP, PaGIM, 19, 1088 e Pa PHB64).
4. No teste da monocamada, a piocina R5 matou quatro de dezoito cepas MRs (C916, 392, 395 e 141). A CBM foi determinada para três cepas (392, C916 e 141).
5. Os genes codificadores da piocina S8 estão inseridos no interior de um novo transposon da família Tn3. O transposon é composto por oito ORFs: uma transposase, uma resolvase, uma ATPase, três proteínas hipotéticas e os dois genes da piocina S8.
6. Há uma baixa frequência da piocina S8 nas linhagens MRs (somente a linhagem C916 produz essa piocina), explicando sua ampla atividade bactericida.
7. Há uma elevada frequência das piocinas S1 e S2 nas linhagens MRs (treze cepas produzem S1 e/ou S2). Dessa forma, essas linhagens são resistentes frente a ação dessas piocinas.
8. A piocina S8 possui 90% de identidade de aminoácidos com a piocina AP41. Os domínios I, II e III da subunidade citotóxica são praticamente idênticos entre ambas as piocinas.
9. A piocina S8 possui o motivo HNH endonuclease presente nas piocinas S1, S2, AP41 e S9 e também nas colicinas ColE2, ColE7, ColE8 e ColE9.
10. As piocinas S8 e AP41 possuem diferenças significativas no domínio IV da subunidade citotóxica. As principais diferenças estão localizadas na região de interação entre a subunidade citotóxica e a proteína imunitária.
11. A ligação da proteína imunitária causa um rearranjo dos resíduos de histidinas do centro ativo da enzima impossibilitando a ligação do íon metálico divalente.

REFERÊNCIAS*

- Adams PD, Afonine PV, Bunkóczi G, Chen VB, Davis IW, Echols N, Headd JJ, Hung LW, Kapral GJ, Grosse-Kunstleve RW, McCoy AJ, Moriarty NW, Oeffner R, Read RJ, Richardson DC, Richardson JS, Terwilliger TC, Zwart PH. PHENIX: a comprehensive Python-based system for macromolecular structure solution. *Acta Crystallogr D Biol Crystallogr*. 2010;66(Pt 2):213-21.
- Ambler RP. The structure of beta-lactamases. *Philos Trans R Soc Lond B Biol Sci*. 1980;289(1036):321-31.
- Amoureux L, Riedweg K, Chapuis A, Bador J, Siebor E, Péchinot A, Chrétien ML, de Curraize C, Neuwirth C. Nosocomial Infections with IMP-19-Producing *Pseudomonas aeruginosa* Linked to Contaminated Sinks, France. *Emerg Infect Dis*. 2017;23(2):304-7.
- Andersson DI, Hughes D. Microbiological effects of sublethal levels of antibiotics. *Nat Rev Microbiol*. 2014;12(7):465-78.
- ANVISA, Agência nacional de vigilância sanitária boletim de segurança do paciente e qualidade em serviços de saúde nº14: Avaliação dos indicadores nacionais das infecções relacionadas à assistência à saúde (IRAS) e resistência microbiana do ano de 2015. Brasília, 2016. Disponível em: <http://www20.anvisa.gov.br/segurancadopaciente/index.php/publicacoes/category/boletins-estatisticos>.
- Arthur TD, Cava VL, Chikindas ML. On bacteriocin delivery systems and potential applications. *Future Microbiol*. 2014;9(2):235-48.
- Aujoulat F, Roger F, Bourdier A, Lotthé A, Lamy B, Marchandin H, Jumas-Bilak E. From environment to man: genome evolution and adaptation of human opportunistic bacterial pathogens. *Genes (Basel)*. 2012;3(2):191-232.
- Baba T, Schneewind O. Instruments of microbial warfare: bacteriocin synthesis, toxicity and immunity. *Trends Microbiol*. 1998;6(2):66-71.
- Bakkal S, Robinson SM, Ordonez CL, Waltz DA, Riley MA. Role of bacteriocins in mediating interactions of bacterial isolates taken from cystic fibrosis patients. *Microbiology*. 2010;156(Pt 7):2058-67.
- Bakkal S. The Use of Pyocins in Treating *Pseudomonas aeruginosa* Infections. In: Dorit RL, Roy SM, Riley MA, editors. *The Bacteriocins: Current Knowledge and Future Prospects*. Amherst, M.A.: Caister Academic; 2016. p. 81-102.
- Balsalobre LC, Dropa M, Matté MH. An overview of antimicrobial resistance and its public health significance. *Braz J Microbiol*. 2014;45(1):1-5.
- Barreteau H, Bouhss A, Fourgeaud M, Mainardi JL, Touzé T, Gérard F, Blanot D, Arthur M, Mengin-Lecreulx D. Human- and plant-pathogenic *Pseudomonas* species produce

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bacteriocins exhibiting colicin M-like hydrolase activity towards peptidoglycan precursors. J Bacteriol. 2009;191(11):3657-64.

Barreteau H, Tiouajni M, Graille M, Josseaume N, Bouhss A, Patin D, Blanot D, Fourgeaud M, Mainardi JL, Arthur M, van Tilbeurgh H, Mengin-Lecreulx D, Touzé T. Functional and structural characterization of PaeM, a colicin M-like bacteriocin produced by *Pseudomonas aeruginosa*. J Biol Chem. 2012;287(44):37395-405.

Bassetti M, Merelli M, Temperoni C, Astilean A. New antibiotics for bad bugs: where are we? Ann Clin Microbiol Antimicrob. 2013;12:22.

Bassetti M, Righi E. Development of novel antibacterial drugs to combat multiple resistant organisms. Langenbecks Arch Surg. 2015;400(2):153-65.

Baysse C, Meyer JM, Plesiat P, Geoffroy V, Michel-Briand Y, Cornelis P. Uptake of pyocin S3 occurs through the outer membrane ferripyoverdine type II receptor of *Pseudomonas aeruginosa*. J Bacteriol. 1999;181(12):3849-51.

Blondel-Hill E, Henry DA, Speert DP. *Pseudomonas*. In: Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, editors. Manual of Clinical Microbiology. 9th ed. Washington, D.C.: ASM Press; 2007. p. 734-48.

Bodey GP, Bolivar R, Fainstein V, Jadeja L. Infections caused by *Pseudomonas aeruginosa*. Rev Infect Dis. 1983;5(2):279-313.

Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: no *ESKAPE*! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(1):1-12.

Bouza E, Muñoz P. Monotherapy versus combination therapy for bacterial infections. Med Clin North Am. 2000;84(6):1357-89.

Brazas MD, Hancock RE. Ciprofloxacin induction of a susceptibility determinant in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother. 2005;49(8):3222-7.

Brockner C, Thompson DC, Vasiliou V. The role of hyperosmotic stress in inflammation and disease. Biomol Concepts. 2012;3(4):345-64.

Brogan DM, Mossialos E. A critical analysis of the review on antimicrobial resistance report and the infectious disease financing facility. Global Health. 2016;12:8.

Brown CL, Smith K, McCaughey L, Walker D. Colicin-like bacteriocins as novel therapeutic agents for the treatment of chronic biofilm-mediated infection. Biochem Soc Trans. 2012;40(6):1549-52.

Bush K. Proliferation and significance of clinically relevant β -lactamases. Ann N Y Acad Sci. 2013;1277:84-90.

Campana EH, Xavier DE, Petrolini FV, Cordeiro-Moura JR, Araujo MR, Gales AC. Carbapenem-resistant and cephalosporin-susceptible: a worrisome phenotype among *Pseudomonas aeruginosa* clinical isolates in Brazil. *Braz J Infect Dis*. 2017;21(1):57-62.

Carroll KC, Bartlett JG. Biology of *Clostridium difficile*: implications for epidemiology and diagnosis. *Annu Rev Microbiol*. 2011;65:501-21.

Casacuberta E, González J. The impact of transposable elements in environmental adaptation. *Mol Ecol*. 2013;22(6):1503-17.

Cascales E, Buchanan SK, Duché D, Kleanthous C, Lloubès R, Postle K, Riley M, Slatin S, Cavard D. Colicin biology. *Microbiol Mol Biol Rev*. 2007;71(1):158-229.

Castanheira M, Toleman M, Jones R, Schmidt F, Walsh T. Molecular Characterization of a β -Lactamase Gene, *bla*_{GIM}, Encoding a New Subclass of Metallo-beta-Lactamase Antimicrob Agents Chemother. 2004;48(12):4654–61.

Cavard D, Lazdunski C. Involvement of BtuB and OmpF proteins in binding and uptake of colicin A. *FEMS Microbiol Lett*. 1981;12(4):311–6.

CDC, Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States 2013. Atlanta: CDC; 2013. Disponível em: <https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=69>

Chang W, Small DA, Toghrol F, Bentley WE. Microarray analysis of *Pseudomonas aeruginosa* reveals induction of pyocin genes in response to hydrogen peroxide. *BMC Genomics*. 2005;6:115.

Chapman PA, Ellin M, Ashton R, Shafique W. Comparison of culture, PCR and immunoassays for detecting *Escherichia coli* O157 following enrichment culture and immunomagnetic separation performed on naturally contaminated raw meat products. *Int. J. Food Microbiol*. 2001;68:11-20.

Chatzinikolaou I, Abi-Said D, Bodey GP, Rolston KV, Tarrand JJ, Samonis G. Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: Retrospective analysis of 245 episodes. *Arch Intern Med*. 2000;160(4):501-9.

Chauleau M, Mora L, Serba J, de Zamaroczy M. FtsH-dependent processing of RNase colicins D and E3 means that only the cytotoxic domains are imported into the cytoplasm. *J Biol Chem*. 2011;286(33):29397-407.

Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. *Clin Microbiol Rev*. 2006;19(2):403-34.

Cleveland J, Montville TJ, Nes IF, Chikindas ML. Bacteriocins: safe, natural antimicrobials for food preservation. *Int J Food Microbiol*. 2001;71(1):1-20.

Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests or bacteria that grow aerobically. Approved standard – Tenth edition. CLSI document M07-A10. Wayne, PA: 2015.

Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Disk Susceptibility Tests. Approved standard - Twelfth edition. CLSI document M02-A12. Wayne, PA: 2015.

Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. Approved standard - Twenty-Sixth informational Supplement. CLSI document M100-S26. CLSI, Wayne, PA: 2016.

Coates AR, Halls G, Hu Y. Novel classes of antibiotics or more of the same? Br J Pharmacol. 2011;163(1):184-94.

Coil D, Jospin G, Darling AE. A5-miseq: an updated pipeline to assemble microbial genomes from Illumina MiSeq data. Bioinformatics. 2015;31(4):587-9.

Cornelis P, Dingemans J. *Pseudomonas aeruginosa* adapts its iron uptake strategies in function of the type of infections. Front Cell Infect Microbiol. 2013;3:75.

Cornelis P. Iron uptake and metabolism in pseudomonads. Appl Microbiol Biotechnol. 2010;86(6):1637-45.

Cotter PD, Hill C, Ross RP. Bacteriocins: developing innate immunity for food. Nat Rev Microbiol. 2005;3(10):777-88.

Cotter PD, Ross RP, Hill C. Bacteriocins - a viable alternative to antibiotics? Nat Rev Microbiol. 2013;11(2):95-105.

Cox CD, Parker J. Use of 2-aminoacetophenone production in identification of *Pseudomonas aeruginosa*. J Clin Microbiol. 1979;9(4):479-84.

Crouch Brewer S, Wunderink RG, Jones CB, Leeper KV Jr. Ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. Chest. 1996;109(4):1019-29.

Crousilles A, Maunders E, Bartlett S, Fan C, Ukor EF, Abdelhamid Y, Baker Y, Floto A, Spring DR, Welch M. Which microbial factors really are important in *Pseudomonas aeruginosa* infections? Future Microbiol. 2015;10(11):1825-36.

Davies J, Davies D. Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev. 2010;74(3):417-33.

Denayer S, Matthijs S, Cornelis P. Pyocin S2 (Sa) kills *Pseudomonas aeruginosa* strains via the FpvA type I ferripyoverdine receptor. J Bacteriol. 2007;189(21):7663-8.

Dennis JJ, Lafontaine ER, Sokol PA. Identification and characterization of the *tolQRA* genes of *Pseudomonas aeruginosa*. J Bacteriol. 1996;178(24):7059-68.

Diaz MH, Hauser AR. *Pseudomonas aeruginosa* cytotoxin ExoU is injected into phagocytic cells during acute pneumonia. Infect Immun. 2010;78(4):1447-56.

- Diaz MH, Shaver CM, King JD, Musunuri S, Kazzaz JA, Hauser AR. *Pseudomonas aeruginosa* induces localized immunosuppression during pneumonia. *Infect Immun*. 2008;76(10):4414-21.
- Diene SM, Rolain JM. Investigation of antibiotic resistance in the genomic era of multidrug-resistant Gram-negative bacilli, especially Enterobacteriaceae, *Pseudomonas* and *Acinetobacter*. *Expert Rev Anti Infect Ther*. 2013;11(3):277-96.
- Dingemans J, Ghequire MG, Craggs M, De Mot R, Cornelis P. Identification and functional analysis of a bacteriocin, pyocin S6, with ribonuclease activity from a *Pseudomonas aeruginosa* cystic fibrosis clinical isolate. *Microbiologyopen*. 2016;5(3):413-23.
- Doudeva LG, Huang H, Hsia KC, Shi Z, Li CL, Shen Y, Cheng YS, Yuan HS. Crystal structural analysis and metal-dependent stability and activity studies of the ColE7 endonuclease domain in complex with DNA/Zn²⁺ or inhibitor/Ni²⁺. *Protein Sci*. 2006;15(2):269-80.
- Drenkard E, Ausubel FM. *Pseudomonas* biofilm formation and antibiotic resistance are linked to phenotypic variation. *Nature*. 2002;416(6882):740-3.
- Driscoll JA, Brody SL, Kollef MH. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. *Drugs*. 2007;67(3):351-68.
- Duan K, Lafontaine ER, Majumdar S, Sokol PA. RegA, iron, and growth phase regulate expression of the *Pseudomonas aeruginosa* tol-oprL gene cluster. *J Bacteriol*. 2000;182(8):2077-87.
- Duché D, Frenkian A, Prima V, Lloubès R. Release of immunity protein requires functional endonuclease colicin import machinery. *J Bacteriol*. 2006;188(24):8593-600.
- Duport C, Baysse C, Michel-Briand Y. Molecular characterization of pyocin S3, a novel S-type pyocin from *Pseudomonas aeruginosa*. *J Biol Chem*. 1995;270(15):8920-7.
- Eggleston K, Zhang R, Zeckhauser RJ. The global challenge of antimicrobial resistance: insights from economic analysis. *Int J Environ Res Public Health*. 2010;7(8):3141-9.
- Elfarash A, Dingemans J, Ye L, Hassan AA, Craggs M, Reimann C, Thomas MS, Cornelis P. Pore-forming pyocin S5 utilizes the FptA ferripyochelin receptor to kill *Pseudomonas aeruginosa*. *Microbiology*. 2014;160(Pt 2):261-9.
- Elfarash A, Wei Q, Cornelis P. The soluble pyocins S2 and S4 from *Pseudomonas aeruginosa* bind to the same FpvAI receptor. *Microbiologyopen*. 2012;1(3):268-75.
- Emsley P, Cowtan K. Coot: model-building tools for molecular graphics. *Acta Crystallogr D Biol Crystallogr*. 2004;60(Pt 12 Pt 1):2126-32.
- Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. Hospitals (2011-2012). *Antimicrob Agents Chemother*. 2013;57(12):6305-10.

Fodor AA, Klem ER, Gilpin DF, Elborn JS, Boucher RC, Tunney MM, Wolfgang MC. The adult cystic fibrosis airway microbiota is stable over time and infection type, and highly resilient to antibiotic treatment of exacerbations. *PLoS One*. 2012;7(9):e45001.

Fontes LC, Neves PR, Oliveira S, Silva KC, Hachich EM, Sato MI, Lincopan N. Isolation of *Pseudomonas aeruginosa* coproducing metallo- β -lactamase SPM-1 and 16S rRNA methylase RmtD1 in an urban river. *Antimicrob Agents Chemother*. 2011;55(6):3063-4.

Fyfe JA, Harris G, Govan JR. Revised pyocin typing method for *Pseudomonas aeruginosa*. *J Clin Microbiol*. 1984;20(1):47-50.

Gales AC, Castanheira M, Jones RN, Sader HS. Antimicrobial resistance among Gram-negative bacilli isolated from Latin America: results from SENTRY Antimicrobial Surveillance Program (Latin America, 2008-2010). *Diagn Microbiol Infect Dis*. 2012;73(4):354-60.

Gales AC, Torres PL, Vilarinho DS, Melo RS, Silva CF, Cereda RF. Carbapenem-resistant *Pseudomonas aeruginosa* outbreak in a intensive care unit of a teaching hospital. *Braz J Infect Dis*. 2004;8(4):267-71.

Gang RK, Bang RL, Sanyal SC, Mokaddas E, Lari AR. *Pseudomonas aeruginosa* septicaemia in burns. *Burns*. 1999;25(7):611-6.

Gardner A, West SA, Buckling A. Bacteriocins, spite and virulence. *Proc Biol Sci*. 2004;271(1547):1529-35.

Garsa AK, Kumariya R, Sood SK, Kumar A, Kapila S. Bacteriocin production and different strategies for their recovery and purification. *Probiotics Antimicrob Proteins*. 2014;6(1):47-58.

Ge P, Scholl D, Leiman PG, Yu X, Miller JF, Zhou ZH. Atomic structures of a bactericidal contractile nanotube in its pre- and postcontraction states. *Nat Struct Mol Biol*. 2015;22(5):377-82.

Ghequire MG, De Mot R. Ribosomally encoded antibacterial proteins and peptides from *Pseudomonas*. *FEMS Microbiol Rev*. 2014;38(4):523-68.

Ghequire MG, De Mot R. The Tailocin Tale: Peeling off Phage Tails. *Trends Microbiol*. 2015;23(10):587-90.

Ghequire MG, Dillen Y, Lambrichts I, Proost P, Wattiez R, De Mot R. Different Ancestries of R Tailocins in Rhizospheric *Pseudomonas* Isolates. *Genome Biol Evol*. 2015;7(10):2810-28.

Ghequire MG, Dingemans J, Pirnay JP, De Vos D, Cornelis P, De Mot R. O serotype-independent susceptibility of *Pseudomonas aeruginosa* to lectin-like pyocins. *Microbiologyopen*. 2014;3(6):875-84.

Ghoul M, West SA, Johansen HK, Molin S, Harrison OB, Maiden MC, Jelsbak L, Bruce JB, Griffin AS. Bacteriocin-mediated competition in cystic fibrosis lung infections. *Proc Biol Sci.* 2015;282(1814).

Gillies RR, Govan JR. Typing of *Pseudomonas pyocyanea* by pyocine production. *J Pathol Bacteriol.* 1966;91(2):339-45.

Gierløff B. *Pseudomonas aeruginosa*. IV. IV. Pyocine typing of strains isolated from the blue fox (*Alopex lagopus*), mink (*Mustela vison*), and dog (*Canis familiaris*) and from their environment. *Nord Vet Med.* 1980;32(3-4):147-60.

Goldberg JB. Why is *Pseudomonas aeruginosa* a pathogen? *F1000 Biol Rep.* 2010;2(29):1-4.

Gorkiewicz G. Nosocomial and antibiotic-associated diarrhoea caused by organisms other than *Clostridium difficile*. *Int J Antimicrob Agents.* 2009;33 Suppl 1:S37-41.

Govan JR, Deretic V. Microbial pathogenesis in cystic fibrosis: mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia*. *Microbiol. Rev.* 1996; 60:539-74.

Govan JR, Gillies RR. Further studies in the pyocine typing of *Pseudomonas pyocyanea*. *J Med Microbiol.* 1969;2(1):17-25.

Govan JR. Studies on the pyocins of *Pseudomonas aeruginosa*: morphology and mode of action of contractile pyocins. *J Gen Microbiol.* 1974;80(1):1-15.

Govan JR. Studies on the pyocins of *Pseudomonas aeruginosa*: production of contractile and flexuous pyocins in *Pseudomonas aeruginosa*. *J Gen Microbiol.* 1974;80(1):17-30.

Graille M, Mora L, Buckingham RH, van Tilbeurgh H, de Zamaroczy M. Structural inhibition of the colicin D tRNase by the tRNA-mimicking immunity protein. *EMBO J.* 2004;23(7):1474-82.

Gupta S, Bram EE, Weiss R. Genetically programmable pathogen sense and destroy. *ACS Synth Biol.* 2013;2(12):715-23.

Haas H, Sacks T, Saltz N. Protective effect of pyocin against lethal *Pseudomonas aeruginosa* infections in mice. *J Infect Dis.* 1974;129(4):470-2.

Hammond JB, Kruger NJ. The bradford method for protein quantitation. *Methods Mol Biol.* 1988;3:25-32.

Hancock RE, Speert DP. Antibiotic resistance in *Pseudomonas aeruginosa*: mechanisms and impact on treatment. *Drug Resist Updat.* 2000;3(4):247-55.

Hauser A, Ozer EA. *Pseudomonas aeruginosa*. *Nature Reviews Microbiology* 2011;9(3).

Hauser AR. *Pseudomonas aeruginosa* virulence and antimicrobial resistance: two sides of the same coin? *Crit Care Med.* 2014;42(1):201-2.

Hector A, Griese M, Hartl D. Oxidative stress in cystic fibrosis lung disease: an early event, but worth targeting? *Eur Respir J*. 2014;44(1):17-9.

Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, Camporez JP, Shulman GI, Gordon JI, Hoffman HM, Flavell RA. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature*. 2012;482(7384):179-85.

Heo YJ, Chung IY, Choi KB, Cho YH. R-type pyocin is required for competitive growth advantage between *Pseudomonas aeruginosa* strains. *J Microbiol Biotechnol*. 2007;17(1):180-5.

Higerd TB, Baechler CA, Berk RS. Morphological studies on relaxed and contracted forms of purified pyocin particles. *J Bacteriol*. 1969;98(3):1378-89.

Højby N, Krogh Johansen H, Moser C, Song Z, Ciofu O, Kharazmi A. *Pseudomonas aeruginosa* and the in vitro and in vivo biofilm mode of growth. *Microbes Infect*. 2001;3(1):23-35.

Holloway BW, Rossiter H, Burgess D, Dodge J. Aeruginocin tolerant mutants of *Pseudomonas aeruginosa*. *Genet Res*. 1973;22(3):239-53.

Housden NG, Loftus SR, Moore GR, James R, Kleanthous C. Cell entry mechanism of enzymatic bacterial colicins: porin recruitment and the thermodynamics of receptor binding. *Proc Natl Acad Sci U S A*. 2005;102(39):13849-54.

Housden NG, Wojdyla JA, Korczynska J, Grishkovskaya I, Kirkpatrick N, Brzozowski AM, Kleanthous C. Directed epitope delivery across the *Escherichia coli* outer membrane through the porin OmpF. *Proc Natl Acad Sci USA*. 2010;107(50):21412-7.

Howell HA, Logan LK, Hauser AR. Type III secretion of ExoU is critical during early *Pseudomonas aeruginosa* pneumonia. *MBio*. 2013;4(2):e00032-13.

Hsia KC, Chak KF, Liang PH, Cheng YS, Ku WY, Yuan HS. DNA binding and degradation by the HNH protein ColE7. *Structure*. 2004;12(2):205-14.

IDSA. Infectious Diseases Society of America. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. *Clin Infect Dis*. 2010;50(8):1081-3.

Ikeda K, Egami F. Receptor substance for pyocin R. I. Partial purification and chemical properties. *J Biochem*. 1969;65(4):603-9.

Inglis RF, Gardner A, Cornelis P, Buckling A. Spite and virulence in the bacterium *Pseudomonas aeruginosa*. *Proc Natl Acad Sci U S A*. 2009;106(14):5703-7.

Inglis RF, Hall AR, Buckling A. The role of 'soaking' in spiteful toxin production in *Pseudomonas aeruginosa*. *Biol Lett*. 2013;9(1):20120569.

- Inglis RF, Scanlan P, Buckling A. Iron availability shapes the evolution of bacteriocin resistance in *Pseudomonas aeruginosa*. ISME J. 2016;10(8):2060-6.
- Ishii SI, Nishi Y, Egami F. The fine structure of a pyocin. J Mol Biol. 1965;13(2):428-31.
- Ito S, Kageyama M, Egami F. Isolation and characterization of pyocins from several strains of *Pseudomonas aeruginosa*. J Gen Appl Microbiol. 1970;(16):205-14.
- Jakes KS, Cramer WA. Border crossings: colicins and transporters. Annu Rev Genet. 2012;46:209-31.
- Jimenez PN, Koch G, Thompson JA, Xavier KB, Cool RH, Quax WJ. The multiple signaling systems regulating virulence in *Pseudomonas aeruginosa*. Microbiol Mol Biol Rev. 2012;76(1):46-65.
- Jones LF, Pinto BV, Thomas ET, Farmer JJ 3rd. Simplified method for producing pyocins from *Pseudomonas aeruginosa*. Appl Microbiol. 1973;26(1):120-1.
- Jones LF, Zakanycz JP, Thomas ET, Farmer JJ 3rd. Pyocin typing of *Pseudomonas aeruginosa*: a simplified method. Appl Microbiol. 1974;27(2):400-6.
- Jones AM, Dodd ME, Morris J, Doherty C, Govan JR, Webb AK. Clinical outcome for cystic fibrosis patients infected with transmissible *Pseudomonas aeruginosa*: an 8-year prospective study. Chest. 2010;137(6):1405-9.
- Joshi A, Grinter R, Josts I, Chen S, Wojdyla JA, Lowe ED, Kaminska R, Sharp C, McCaughey L, Roszak AW, Cogdell RJ, Byron O, Walker D, Kleanthous C. Structures of the Ultra-High-Affinity Protein-Protein Complexes of Pyocins S2 and AP41 and Their Cognate Immunity Proteins from *Pseudomonas aeruginosa*. J Mol Biol. 2015;427(17):2852-66.
- Jurado Chacón D, Cueto Espinar A, Rodriguez-Contreras Pelayo D, Rodriguez López MJ, Galvez Vergas R. Prevalence of pyocin types of *P. aeruginosa* in a university hospital during 1981-1986. Eur J Epidemiol. 1987;3(4):431-5. Erratum in: Eur J Epidemiol 1988;4(1):134.
- Kabsch W. XDS. Acta Crystallogr D Biol Crystallogr. 2010;66(Pt 2):125-32.
- Kageyama M. Studies of a pyocin. I. Physical and chemical properties. J. Biochem. 1964;55:49-53.
- Kageyama M, Egami F. On the purification and some properties of a pyocin, a bacteriocin produced by *Pseudomonas aeruginosa*. Life Sci. 1962;1:471-6.
- Kageyama M, Ikeda K, Egami F. Studies of a pyocin. III. Biological properties of the pyocin. J Biochem. 1964;55:59-64.
- Kageyama M, Kobayashi M, Sano Y, Masaki H. Construction and characterization of pyocin-colicin chimeric proteins. J Bacteriol. 1996;178(1):103-10.
- Kageyama M. Genetic mapping of pyocin R1 factor in *Pseudomonas aeruginosa*, J. Gen. Appl. Microbiol. 1974;20:269-75.

Kageyama M, Shinomiya T, Aihara Y, Kobayashi M. Characterization of a bacteriophage related to R-type pyocins. *J. Virol.* 1979; 32:951–7.

Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. *Mayo Clin Proc.* 2011;86(3):250-9.

Karaïskos I, Giamarellou H. Multidrug-resistant and extensively drug-resistant Gram-negative pathogens: current and emerging therapeutic approaches. *Expert Opin Pharmacother.* 2014;15(10):1351-70.

Karam G, Chastre J, Wilcox MH, Vincent JL. Antibiotic strategies in the era of multidrug resistance. *Crit Care.* 2016;20(1):136.

Kaye KS, Gales AC, Dubourg G. Old antibiotics for multidrug-resistant pathogens: from in vitro activity to clinical outcomes. *Int J Antimicrob Agents.* 2017. pii: S0924-8579(17)30014-6.

Kaziroy Y, Tanaka M. Studies on the mode of action of pyocin. I. Inhibition of macromolecular synthesis in sensitive cells. *J Biochem.* 1965;57(5):689-95.

Khan SN, Khan AU. Breaking the Spell: Combating Multidrug Resistant 'Superbugs'. *Front Microbiol.* 2016;7:174.

Kiska DL, Gilligan PH. *Pseudomonas*. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Tenover FC, Tenover FC, editors. *Manual of Clinical Microbiology*. 8th ed. Washington, D.C.: ASM Press; 2003. vol. 1, p.719-28.

Klaenhammer TR. Bacteriocins of lactic acid bacteria. *Biochimie.* 1988;70(3):337-49.

Kleanthous C, Kühlmann UC, Pommer AJ, Ferguson N, Radford SE, Moore GR, James R, Hemmings AM. Structural and mechanistic basis of immunity toward endonuclease colicins. *Nat Struct Biol.* 1999;6(3):243-52.

Kleanthous C, Walker D. Immunity proteins: enzyme inhibitors that avoid the active site. *Trends Biochem Sci.* 2001;26(10):624-31.

Kleanthous C. Swimming against the tide: progress and challenges in our understanding of colicin translocation. *Nat Rev Microbiol.* 2010;8(12):843-8.

Klein A, Wojdyla JA, Joshi A, Josts I, McCaughey LC, Housden NG, Kaminska R, Byron O, Walker D, Kleanthous C. Structural and biophysical analysis of nuclease protein antibiotics. *Biochem J.* 2016;473(18):2799-812.

Ko TP, Liao CC, Ku WY, Chak KF, Yuan HS. The crystal structure of the DNase domain of colicin E7 in complex with its inhibitor Im7 protein. *Structure.* 1999;7(1):91-102.

Köhler T, Donner V, van Delden C. Lipopolysaccharide as shield and receptor for R-pyocin-mediated killing in *Pseudomonas aeruginosa*. *J Bacteriol.* 2010;192(7):1921-8.

Komiyama K, Habbick BF, Martin T, Tumber SK. Characterization by pyocine typing and serotyping of oral and sputum strains of *Pseudomonas aeruginosa* isolated from cystic fibrosis patients. *Can J Microbiol.* 1987;33(3):221-5.

Kühlmann UC, Moore GR, James R, Kleanthous C, Hemmings AM. Structural parsimony in endonuclease active sites: should the number of homing endonuclease families be redefined? *FEBS Lett.* 1999;463(1-2):1-2.

Kühlmann UC, Pommer AJ, Moore GR, James R, Kleanthous C. Specificity in protein-protein interactions: the structural basis for dual recognition in endonuclease colicin-immunity protein complexes. *J Mol Biol.* 2000;301(5):1163-78.

Kumazaki T, Ishii S. Comparative study on fibers isolated from four R-type pyocins, phage-tail-like bacteriocins of *Pseudomonas aeruginosa*. *J Biochem.* 1982;92:1559–66.

Kumazaki T, Ogura Y, Ishii S. Isolation and characterization of pyocin R1 fibers. *J Biochem.* 1982;91:825–35.

Kuroda K, Kageyama M. Biochemical properties of a new flexuous bacteriocin, pyocin F1, produced by *Pseudomonas aeruginosa*. *J Biochem.* 1979;85(1):7-19.

Kuroda K, Kageyama M. Comparative study of F-type pyocins of *Pseudomonas aeruginosa*. *J Biochem.* 1981;89(6):1721-36.

Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature.* 1970;227(5259):680-5.

Lafontaine ER, Sokol PA. Effects of iron and temperature on expression of the *Pseudomonas aeruginosa tolQRA* genes: role of the ferric uptake regulator. *J Bacteriol.* 1998;180(11):2836-41.

Lam MY, McGroarty EJ, Kropinski AM, MacDonald LA, Pedersen SS, Høiby N, Lam JS. Occurrence of a common lipopolysaccharide antigen in standard and clinical strains of *Pseudomonas aeruginosa*. *J Clin Microbiol.* 1989;27(5):962-7.

Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, Agodi A, Frank U, Mertens K, Schumacher M, Wolkewitz M. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis.* 2011;11(1):30-8.

Larkin MA, Blackshields G, Brown NP, Chenna R, McGettigan PA, McWilliam H, Valentin F, Wallace IM, Wilm A, Lopez R, Thompson JD, Gibson TJ, Higgins DG. Clustal W and Clustal X version 2.0. *Bioinformatics.* 2007;23(21):2947-8.

Lauretti L, Riccio ML, Mazzariol A, Cornaglia G, Amicosante G, Fontana R, Rossolini GM. Cloning and Characterization of *bla_{VIM}*, a New Integron-Borne Metallo- β -Lactamase Gene from a *Pseudomonas aeruginosa* Clinical Isolate. 1999;43:1584-90.

Lee G, Chakraborty U, Gebhart D, Govoni GR, Zhou ZH, Scholl D. F-Type Bacteriocins of *Listeria monocytogenes*: a New Class of Phage Tail-Like Structures Reveals Broad Parallel

Coevolution between Tailed Bacteriophages and High-Molecular-Weight Bacteriocins. *J Bacteriol.* 2016;198(20):2784-93.

Lee K, Yum J H, Yong D, Lee HM, Kim HD, Docquier JD, Rossolini GM, Chong Y. Novel acquired metallo-beta-lactamase gene, *bla_{SIM-1}*, in a class 1 integron from *Acinetobacter baumannii* clinical isolates from Korea. *Antimicrob Agents Chemother.* 2005;49(11):4485-91.

Levin AS, Oliveira MS. The challenge of multidrug resistance: the treatment of gram-negative rod infections. *Shock.* 2008;30 Suppl 1:30-3.

Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med.* 2004;10(12 Suppl):S122-9.

Lincopan N, Trabulsi LR. *Pseudomonas aeruginosa*. In: Trabulsi LR, Alterthum F. *Microbiologia*. 5th ed. São Paulo: Atheneu; 2008. p. 369-81.

Lincopan N. Caracterização fenotípica de cepas endêmicas de *Pseudomonas aeruginosa* isoladas de pacientes de um hospital de referência de queimados do Estado de São Paulo. [Dissertação (Mestrado em Análises Clínicas)]. São Paulo: Faculdade de Ciências Farmacêuticas, Universidade de São Paulo; 1999.

Ling H, Saeidi N, Rasouliha BH, Chang MW. A predicted S-type pyocin shows a bactericidal activity against clinical *Pseudomonas aeruginosa* isolates through membrane damage. *FEBS Lett.* 2010;584(15):3354-8.

Livermore DM. Has the era of untreatable infections arrived? *J Antimicrob Chemother.* 2009;64 Suppl 1:i29-36.

Livermore DM. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? *Clin Infect Dis.* 2002;34(5):634-40.

Llamas MA, Mooij MJ, Sparrius M, Vandenbroucke-Grauls CM, Ratledge C, Bitter W. Characterization of five novel *Pseudomonas aeruginosa* cell-surface signalling systems. *Mol Microbiol.* 2008;67(2):458-72.

Lopes SP, Azevedo NF, Pereira MO. Microbiome in cystic fibrosis: Shaping polymicrobial interactions for advances in antibiotic therapy. *Crit Rev Microbiol.* 2015;41(3):353-65.

López-Causapé C, Rojo-Molinero E, Macià MD, Oliver A. The problems of antibiotic resistance in cystic fibrosis and solutions. *Expert Rev Respir Med.* 2015;9(1):73-88.

Lucena A, Dalla Costa LM, Nogueira KS, Matos AP, Gales AC, Paganini MC, Castro ME, Raboni SM. Nosocomial infections with metallo-beta-lactamase-producing *Pseudomonas aeruginosa*: molecular epidemiology, risk factors, clinical features and outcomes. *J Hosp Infect.* 2014;87(4):234-40.

Ma B, Zhang K, Hendrie C, Liang C, Li M, Doherty-Kirby A, Lajoie G. PEAKS: powerful software for peptide de novo sequencing by tandem mass spectrometry. *Rapid Commun Mass Spectrom.* 2003;17(20):2337-42.

Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.

Mah TF, Pitts B, Pellock B, Walker GC, Stewart PS, O'Toole GA. A genetic basis for *Pseudomonas aeruginosa* biofilm antibiotic resistance. Nature. 2003;426(6964):306-10.

Manichanh C, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. Nat Rev Gastroenterol Hepatol. 2012;9(10):599-608.

Maté MJ, Kleanthous C. Structure-based analysis of the metal-dependent mechanism of H-N-H endonucleases. J Biol Chem. 2004;279(33):34763-9.

Matsui H, Sano Y, Ishihara H, Shinomiya T. Regulation of pyocin genes in *Pseudomonas aeruginosa* by positive (prtN) and negative (prtR) regulatory genes. J Bacteriol. 1993;175(5):1257-63.

McCarthy K. *Pseudomonas aeruginosa*: evolution of antimicrobial resistance and implications for therapy. Semin Respir Crit Care Med. 2015;36(1):44-55.

McCaughey LC, Grinter R, Josts I, Roszak AW, Waløen KI, Cogdell RJ, Milner J, Evans T, Kelly S, Tucker NP, Byron O, Smith B, Walker D. Lectin-like bacteriocins from *Pseudomonas* spp. utilise D-rhamnose containing lipopolysaccharide as a cellular receptor. PLoS Pathog. 2014;10(2):e1003898.

McCaughey LC, Josts I, Grinter R, White P, Byron O, Tucker NP, Matthews JM, Kleanthous C, Whitchurch CB, Walker D. Discovery, characterization and in vivo activity of pyocin SD2, a protein antibiotic from *Pseudomonas aeruginosa*. Biochem J. 2016a;473(15):2345-58.

McCaughey LC, Ritchie ND, Douce GR, Evans TJ, Walker D. Efficacy of species-specific protein antibiotics in a murine model of acute *Pseudomonas aeruginosa* lung infection. Sci Rep. 2016b;6:30201.

Meadow P, Wells PL. Receptor Sites for R-type Pyocins and Bacteriophage E79 in the Core Part of the Lipopolysaccharide of *Pseudomonas aeruginosa* PAC1. J Gen Microbiol. 1978;(108):339-43.

Medina-Presentado JC, Margolis A, Teixeira L, Lorier L, Gales AC, Pérez-Sartori G, Oliveira MS, Seija V, Paciel D, Vignoli R, Guerra S, Alborno H, Arteta Z, Lopez-Arredondo A, García S. Online continuing interprofessional education on hospital-acquired infections for Latin America. Braz J Infect Dis. 2016; S1413-8670(16)30561-X.

Merrikin DJ, Terry CS. Use of pyocin 78-C2 in the treatment of *Pseudomonas aeruginosa* infection in mice. Appl Microbiol. 1972;23(1):164-5.

Michel-Briand Y, Baysse C. The pyocins of *Pseudomonas aeruginosa*. Biochimie. 2002;84(5-6):499-510.

Molina G, Pimentel MR, Pastore GM. *Pseudomonas*: a promising biocatalyst for the bioconversion of terpenes. *Appl Microbiol Biotechnol*. 2013;97(5):1851-64.

Moore ERB, Tindall BJ, Dos Santos VAPM, Pieper DH, Ramos JL, Palleroni NJ. Nonmedical: *Pseudomonas*. In: Dworkin M, Falkow S, Rosenberg E, Schleifer K-H, Stackebrandt E, editors. *The Prokaryotes*. New York, N.Y.: Springer; 2006. Vol. 6, p. 646-703.

Morita Y, Tomida J, Kawamura Y. Responses of *Pseudomonas aeruginosa* to antimicrobials. *Front Microbiol*. 2014;4:422.

Morse SA, Vaughan P, Johnson D, Iglewski BH. Inhibition of *Neisseria gonorrhoeae* by a bacteriocin from *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 1976;10(2):354-62.

Mota-Meira M, LaPointe G, Lacroix C, Lavoie MC. MICs of mutacin B-Ny266, nisin A, vancomycin, and oxacillin against bacterial pathogens. *Antimicrob Agents Chemother*. 2000;44(1):24-9.

Moura JP, Gir E. Conhecimento dos profissionais de enfermagem referente à resistência bacteriana a múltiplas drogas. *Acta Paul Enferm*. 2007;20(3):351-6.

Muller C, Plésiat P, Jeannot K. A two-component regulatory system interconnects resistance to polymyxins, aminoglycosides, fluoroquinolones, and β -lactams in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2011;55(3):1211-21.

Mushin R, Ziv G. An epidemiological study of *Pseudomonas aeruginosa* in cattle and other animals by pyocine typing. *J Hyg (Lond)*. 1973;71(1):113-22.

Nakayama K, Takashima K, Ishihara H, Shinomiya T, Kageyama M, Kanaya S, Ohnishi M, Murata T, Mori H, Hayashi T. The R-type pyocin of *Pseudomonas aeruginosa* is related to P2 phage, and the F-type is related to lambda phage. *Mol Microbiol*. 2000;38(2):213-31.

Nateche F, Martin A, Baraka S, Palomino JC, Khaled S, Portaels F. Application of the resazurin microtitre assay for detection of multidrug resistance in *Mycobacterium tuberculosis* in Algiers. *J Med Microbiol*. 2006;55(Pt 7):857-60.

Neves PR. Alterações da Permeabilidade e Expressão de Bombas de Efluxo em Isolados Clínicos de *Pseudomonas aeruginosa* Resistente ao Imipenem. [Tese (Doutorado em Análises Clínicas)]. São Paulo: Faculdade de Ciências Farmacêuticas, Universidade de São Paulo; 2010.

Nigam A, Gupta D, Sharma A. Treatment of infectious disease: beyond antibiotics. *Microbiol Res*. 2014;169(9-10):643-51.

Noinaj N, Guillier M, Barnard TJ, Buchanan SK. TonB-dependent transporters: regulation, structure, and function. *Annu Rev Microbiol*. 2010;64:43-60.

O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. *Rev Antimicrob Resist*. 2016. Disponível em: <http://amr-review.org/Publications>.

- Ogawa T, Inoue S, Yajima S, Hidaka M, Masaki H. Sequence-specific recognition of colicin E5, a tRNA-targeting ribonuclease. *Nucleic Acids Res.* 2006;34(21):6065-73.
- Ohkawa I, Kageyama M, Egami F. Purification and properties of pyocin S2. *J Biochem.* 1973;73(2):281-9.
- Ohkawa I, Shiga S, Kageyama M. Effect of iron concentration in the growth medium on the sensitivity of *Pseudomonas aeruginosa* to pyocin S2. *J Biochem.* 1980;87(1):323-31.
- Ohsumi M, Shinomiya T, Kageyama M. Comparative study on R-type pyocins of *Pseudomonas aeruginosa*. *J Biochem.* 1980;87(4):1119-25.
- Oliver A, Mulet X, López-Causapé C, Juan C. The increasing threat of *Pseudomonas aeruginosa* high-risk clones. *Drug Resist Updat.* 2015;21-22:41-59.
- ONU, Organização das Nações Unidas. Resolution adopted by the General Assembly on 5 October 2016 Political declaration of the high-level meeting of the General Assembly on antimicrobial resistance United Nations. New York; 2016. Disponível em: http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/71/3
- Orlova EV. A molecular syringe that kills cells. *Nat Struct Mol Biol.* 2015;22(5):357-9.
- Özen AI, Ussery DW. Defining the *Pseudomonas* genus: where do we draw the line with *Azotobacter*? *Microb Ecol.* 2012;63(2):239-48.
- Palleroni NJ, Kunisawa R, Contopoulou R, Doudoroff M. Nucleic acid homologies in the genus *Pseudomonas*. *Int J Syst Evol Microbiol.* 1973;23(4):333-9.
- Palleroni NJ. Prokaryote taxonomy of the 20th century and the impact of studies on the genus *Pseudomonas*: a personal view. *Microbiology.* 2003;149(Pt1):1-7.
- Papadakos G, Wojdyla JA, Kleanthous C. Nuclease colicins and their immunity proteins. *Q Rev Biophys.* 2012;45(1):57-103.
- Parret A, De Mot R. Novel bacteriocins with predicted tRNase and pore-forming activities in *Pseudomonas aeruginosa* PAO1. *Mol Microbiol.* 2000;35(2):472-3.
- Parret AH, De Mot R. Bacteria killing their own kind: novel bacteriocins of *Pseudomonas* and other gamma-proteobacteria. *Trends Microbiol.* 2002;10(3):107-12.
- Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med.* 1990;113(3):227-42.
- Paterson DL, Lipman J. Returning to the pre-antibiotic era in the critically ill: the XDR problem. *Crit Care Med.* 2007;35(7):1789-91.
- Peix A, Ramírez-Bahena MH, Velázquez E. Historical evolution and current status of the taxonomy of genus *Pseudomonas*. *Infect Genet Evol.* 2009;9(6):1132-47.

- Pellegrino FL, Teixeira LM, Carvalho MGS, Nouér SA, Oliveira MP, Sampaio JLM, Freitas D'A, Ferreira ALP, Amorim ELT, Riley LW, Moreira BM. Occurrence of a multidrug-resistant *Pseudomonas aeruginosa* clone in different hospitals in Rio de Janeiro, Brazil. J Clin Microbiol. 2002;40(7):2420-4.
- Penterman J, Singh PK, Walker GC. Biological cost of pyocin production during the SOS response in *Pseudomonas aeruginosa*. J Bacteriol. 2014;196(18):3351-9.
- Peterson LR. Bad bugs, no drugs: no ESCAPE revisited. Clin Infect Dis. 2009;49(6):992-3.
- Piddock LJ. The crisis of no new antibiotics--what is the way forward? Lancet Infect Dis. 2012;12(3):249-53.
- Piddock LJ. Reflecting on the final report of the O'Neill Review on Antimicrobial Resistance. Lancet Infect Dis. 2016;16(7):767-8.
- Pinheiro MR, Lacerda HR, Melo RG, Maciel MA. *Pseudomonas aeruginosa* infections: factors relating to mortality with emphasis on resistance pattern and antimicrobial treatment. Braz J Infect Dis. 2008;12(6):509-15.
- Piper C, Cotter PD, Ross RP, Hill C. Discovery of medically significant lantibiotics. Curr Drug Discov Technol. 2009;6(1):1-18.
- Pires DP, Vilas Boas D, Sillankorva S, Azeredo J. Phage Therapy: a Step Forward in the Treatment of *Pseudomonas aeruginosa* Infections. J Virol. 2015;89(15):7449-56.
- Pommer AJ, Cal S, Keeble AH, Walker D, Evans SJ, Kühlmann UC, Cooper A, Connolly BA, Hemmings AM, Moore GR, James R, Kleanthous C. Mechanism and cleavage specificity of the H-N-H endonuclease colicin E9. J Mol Biol. 2001;314(4):735-49.
- Pommer AJ, Wallis R, Moore GR, James R, Kleanthous C. Enzymological characterization of the nuclease domain from the bacterial toxin colicin E9 from *Escherichia coli*. Biochem J. 1998;334(Pt 2):387-92.
- Poole K. *Pseudomonas aeruginosa*: resistance to the max. Front Microbiol. 2011;2(65):1-13.
- Portelli R, Dodd IB, Xue Q, Egan JB. The late-expressed region of the temperate coliphage 186 genome. Virology. 1998;248(1):117-30.
- Potron A, Poirel L, Nordmann P. Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: Mechanisms and epidemiology. Int J Antimicrob Agents. 2015;45(6):568-85.
- Pulcrano G, Iula DV, Raia V, Rossano F, Catania MR. Different mutations in *mucA* gene of *Pseudomonas aeruginosa* mucoid strains in cystic fibrosis patients and their effect on *algU* gene expression. New Microbiol. 2012;35(3):295-305.
- Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen

T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*. 2012;490(7418):55-60.

Rajan S, Saiman L. Pulmonary infections in patients with cystic fibrosis. *Semin Respir Infect*. 2002;17(1):47-56.

Ramírez-Estrada S, Borgatta B, Rello J. *Pseudomonas aeruginosa* ventilator-associated pneumonia management. *Infect Drug Resist*. 2016;9:7-18.

Rasouliha BH, Ling H, Ho CL, Chang MW. A predicted immunity protein confers resistance to pyocin S5 in a sensitive strain of *Pseudomonas aeruginosa*. *Chembiochem*. 2013;14(18):2444-6.

Riley MA, Gordon DM. The ecological role of bacteriocins in bacterial competition. *Trends Microbiol*. 1999;7(3):129-33.

Riley MA, Wertz JE. Bacteriocin diversity: ecological and evolutionary perspectives. *Biochimie*. 2002a;84(5-6):357-64.

Riley MA, Wertz JE. Bacteriocins: evolution, ecology, and application. *Annu Rev Microbiol*. 2002b;56:117-37.

Riley MA. Molecular mechanisms of bacteriocin evolution. *Annu Rev Genet*. 1998;32:255-78.

Ritchie JM, Greenwich JL, Davis BM, Bronson RT, Gebhart D, Williams SR, Martin D, Scholl D, Waldor MK. An *Escherichia coli* O157-specific engineered pyocin prevents and ameliorates infection by *E. coli* O157:H7 in an animal model of diarrheal disease. *Antimicrob Agents Chemother*. 2011;55(12):5469-74.

Rizek C, Ferraz JR, van der Heijden IM, Giudice M, Mostachio AK, Paez J, Carrilho C, Levin AS, Costa SF. In vitro activity of potential old and new drugs against multidrug-resistant gram-negatives. *J Infect Chemother*. 2015;21(2):114-7.

Rizek C, Fu L, Dos Santos LC, Leite G, Ramos J, Rossi F, Guimaraes T, Levin AS, Costa SF. Characterization of carbapenem-resistant *Pseudomonas aeruginosa* clinical isolates, carrying multiple genes coding for this antibiotic resistance. *Ann Clin Microbiol Antimicrob*. 2014;13:43.

Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. *Curr Opin Pharmacol*. 2014;18C:56-60.

Ruhnke M, Arnold R, Gastmeier P. Infection control issues in patients with haematological malignancies in the era of multidrug-resistant bacteria. *Lancet Oncol*. 2014;15(13):e606-19.

Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals:

results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. *Int J Antimicrob Agents*. 2014;43(4):328-34.

Sader HS, Gales AC, Pfaller MA, Mendes RE, Zoccoli C, Barth A, Jones RN. Pathogen frequency and resistance patterns in Brazilian hospitals: summary of results from three years of the SENTRY Antimicrobial Surveillance Program. *Braz J Infect Dis*. 2001;5(4):200-14.

Sader HS, Rhomberg PR, Farrell DJ, Jones RN. Arbekacin activity against contemporary clinical bacteria isolated from patients hospitalized with pneumonia. *Antimicrob Agents Chemother*. 2015;(6)3263-70.

Saeidi N, Wong CK, Lo TM, Nguyen HX, Ling H, Leong SS, Poh CL, Chang MW. Engineering microbes to sense and eradicate *Pseudomonas aeruginosa*, a human pathogen. *Mol Syst Biol*. 2011;7:521.

Sano Y, Kageyama M. Genetic determinant of pyocin AP41 as an insert in the *Pseudomonas aeruginosa* chromosome. *J. Bacteriol*. 1984;158:562–70.

Sano Y, Kageyama M. A novel transposon-like structure carries the genes for pyocin AP41, a *Pseudomonas aeruginosa* bacteriocin with a DNase domain homology to E2 group colicins. *Mol Gen Genet*. 1993;237(1-2):161-70.

Sano Y, Kageyama M. Purification and properties of an S-type pyocin, Pyocin AP41. *J Bacteriol*. 1981;146(2):733-9.

Sano Y, Kageyama M. The sequence and function of the *recA* gene and its protein in *Pseudomonas aeruginosa* PAO. *Mol Gen Genet*. 1987;208(3):412-9.

Sano Y, Kobayashi M, Kageyama M. Functional domains of S-type pyocins deduced from chimeric molecules. *J Bacteriol*. 1993a;175(19):6179-85.

Sano Y, Matsui H, Kobayashi M, Kageyama M. Molecular structures and functions of pyocins S1 and S2 in *Pseudomonas aeruginosa*. *J Bacteriol*. 1993b;175(10):2907-16.

Sano Y. The inherent DNase of pyocin AP41 causes breakdown of chromosomal DNA. *J Bacteriol*. 1993;175(3):912-5.

Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. *Biomed Res Int*. 2016;2016:2475067.

Scher JU, Abramson SB. The microbiome and rheumatoid arthritis. *Nat Rev Rheumatol*. 2011;7(10):569-78.

Schmieder R, Edwards R. Insights into antibiotic resistance through metagenomic approaches. *Future Microbiol*. 2012;7(1):73-89.

Scholl D, Cooley M, Williams SR, Gebhart D, Martin D, Bates A, Mandrell R. An engineered R-type pyocin is a highly specific and sensitive bactericidal agent for the food-borne pathogen *Escherichia coli* O157:H7. *Antimicrob Agents Chemother*. 2009;53(7):3074-80.

- Scholl D, Martin DW Jr. Antibacterial efficacy of R-type pyocins towards *Pseudomonas aeruginosa* in a murine peritonitis model. *Antimicrob Agents Chemother*. 2008;52(5):1647-52.
- Schurek KN, Sampaio JL, Kiffer CR, Sinto S, Mendes CM, Hancock RE. Involvement of pmrAB and phoPQ in polymyxin B adaptation and inducible resistance in non-cystic fibrosis clinical isolates of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2009;53(10):4345-51.
- Seo Y, Galloway DR. Purification of the pyocin S2 complex from *Pseudomonas aeruginosa* PAO1: analysis of DNase activity. *Biochem Biophys Res Commun*. 1990;172(2):455-61.
- Settanni L, Corsetti A. Application of bacteriocins in vegetable food biopreservation. *Int J Food Microbiol*. 2008;121(2):123-38.
- Shinomiya T, Osumi M, Kageyama M. Defective pyocin particles produced by some mutant strains of *Pseudomonas aeruginosa*. *J Bacteriol*. 1975;124(3):1508-21.
- Shinomiya T, Shiga S, Kageyama M. Genetic determinant of pyocin R2 in *Pseudomonas aeruginosa* PAO. I. Localization of the pyocin R2 gene cluster between the trpCD and trpE genes. *Mol Gen Genet*. 1983a;189(3):375-81.
- Shinomiya T, Shiga S, Kikuchi A, Kageyama M. Genetic determinant of pyocin R2 in *Pseudomonas aeruginosa* PAO. II. Physical characterization of pyocin R2 genes using R-prime plasmids constructed from R68.45. *Mol Gen Genet*. 1983b;189(3):382-9.
- Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S; National Healthcare Safety Network (NHSN) Team and Participating NHSN Facilities. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. *Infect Control Hosp Epidemiol*. 2013;34(1):1-14.
- Silva Filho LV, Ferreira Fde A, Reis FJ, Britto MC, Levy CE, Clark O, Ribeiro JD. *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: scientific evidence regarding clinical impact, diagnosis, and treatment. *J Bras Pneumol*. 2013;39(4):495-512.
- Smith AW, Hirst PH, Hughes K, Gensberg K, Govan JR. The pyocin Sa receptor of *Pseudomonas aeruginosa* is associated with ferripyoverdin uptake. *J Bacteriol*. 1992;174(14):4847-9.
- Smith K, Martin L, Rinaldi A, Rajendran R, Ramage G, Walker D. Activity of pyocin S2 against *Pseudomonas aeruginosa* biofilms. *Antimicrob Agents Chemother*. 2012;56(3):1599-601.
- Soelaiman S, Jakes K, Wu N, Li C, Shoham M. Crystal structure of colicin E3: implications for cell entry and ribosome inactivation. *Mol Cell*. 2001;8(5):1053-62.
- Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. *Euro Surveill*. 2008;13(47). pii: 19045.

Stoddard BL. Homing endonuclease structure and function. *Q Rev Biophys.* 2005;38(1):49-95.

Stover CK, Pham XQ, Erwin AL, Mizoguchi SD, Warrenner P, Hickey MJ, Brinkman FS, Hufnagle WO, Kowalik DJ, Lagrou M, Garber RL, Goltry L, Tolentino E, Westbrook-Wadman S, Yuan Y, Brody LL, Coulter SN, Folger KR, Kas A, Larbig K, Lim R, Smith K, Spencer D, Wong GK, Wu Z, Paulsen IT, Reizer J, Saier MH, Hancock RE, Lory S, Olson MV. Complete genome sequence of *Pseudomonas aeruginosa* PAO1, an opportunistic pathogen. *Nature.* 2000;406(6799):959-64.

Strateva T, Yordanov D. *Pseudomonas aeruginosa* - a phenomenon of bacterial resistance. *J Med Microbiol.* 2009;58(Pt 9):1133-48.

Sun Z, Shi J, Liu C, Jin Y, Li K, Chen R, Jin S, Wu W. PrtR homeostasis contributes to *Pseudomonas aeruginosa* pathogenesis and resistance against ciprofloxacin. *Infect Immun.* 2014;82(4):1638-47.

Szuplewska M, Ludwiczak M, Lyzwa K, Czarnecki J, Bartosik D. Mobility and generation of mosaic non-autonomous transposons by Tn3-derived inverted-repeat miniature elements (TIMES). *PLoS One.* 2014;9(8):e105010.

Takeda Y, Kageyama M. Subunit arrangement in the extended sheath of pyocin R. *J Biochem.* 1975;77(3):679-84.

Takeya K, Minamishima Y, Amako K, Ohnishi Y. A small rod-shaped pyocin. *Virology.* 1967;31(1):166-8.

Talbot GH. β -Lactam antimicrobials: what have you done for me lately? *Ann N Y Acad Sci.* 2013;1277:76-83.

Tan Y, Riley MA. Nucleotide polymorphism in colicin E2 gene clusters: evidence for nonneutral evolution. *Mol Biol Evol.* 1997;14(6):666-73.

Theuretzbacher U. Accelerating resistance, inadequate antibacterial drug pipelines and international responses. *Int J Antimicrob Agents.* 2012;39(4):295-9.

Tillotson GS. Where does novel antibiotics ReD stand among other pharmaceutical products: an industrial perspective? *Expert Rev Anti Infect Ther.* 2008;6(5):551-2.

Timmis KN. *Pseudomonas putida*: a cosmopolitan opportunist par excellence. *Environ Microbiol.* 2002;4(12):779-81.

Timurkaynak F, Can F, Azap OK, Demirbilek M, Arslan H, Karaman SO. In vitro activities of non-traditional antimicrobials alone or in combination against multidrug-resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolated from intensive care units. *Int J Antimicrob Agents.* 2006;27(3):224-8.

Tindall BJ, Kämpfer P, Euzéby JP, Oren A. Valid publication of names of prokaryotes according to the rules of nomenclature: past history and current practice. *Int J Syst Evol Microbiol.* 2006;56(Pt 11):2715-20.

Toleman MA, Simm AM, Murphy TA, Gales AC, Biedenbach DJ, Jones RN, Walsh TR. Molecular characterization of SPM-1, a novel metallo-beta-lactamase isolated in Latin America: report from the SENTRY antimicrobial surveillance programme. *J Antimicrob Chemother.* 2002;50(5):673-9.

Trecarichi EM, Pagano L, Candoni A, Pastore D, Cattaneo C, Fanci R, Nosari A, Caira M, Spadea A, Busca A, Vianelli N, Tumbarello M; HeMABIS Registry—SEIFEM Group, Italy. Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. *Clin Microbiol Infect.* 2015;21(4):337-43.

Turano H, Gomes F, Medeiros M, Oliveira S, Fontes LC, Sato MI, Lincopan N. Presence of high-risk clones of OXA-23-producing *Acinetobacter baumannii* (ST79) and SPM-1-producing *Pseudomonas aeruginosa* (ST277) in environmental water samples in Brazil. *Diagn Microbiol Infect Dis.* 2016;86(1):80-2.

Turano H, Gomes F, Barros-Carvalho GA, Lopes R, Cerdeira L, Netto LES, Gales AC, Lincopan N. Tn6350, a Novel Transposon Carrying Pyocin S8 Genes Encoding a Bacteriocin with Activity against Carbapenemase-Producing *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother.* 2017;61(5). pii: e00100-17.

Uratani Y, Hoshino T. Pyocin R1 inhibits active transport in *Pseudomonas aeruginosa* and depolarizes membrane potential. *J Bacteriol.* 1984;157(2):632-6.

Uratani Y. Dansyl chloride labeling of *Pseudomonas aeruginosa* treated with pyocin R1: change in permeability of the cell envelope. *J Bacteriol.* 1982;149(2):523-8.

Vagin AA, Steiner RA, Lebedev AA, Potterton L, McNicholas S, Long F, Murshudov GN. REFMAC5 dictionary: organization of prior chemical knowledge and guidelines for its use. *Acta Crystallogr D Biol Crystallogr.* 2004;60(Pt 12 Pt1):2184-95.

van der Wal FJ, Luirink J, Oudega B. Bacteriocin release proteins: mode of action, structure, and biotechnological application. *FEMS Microbiol Rev.* 1995;17(4):381-99.

Vankemmelbeke M, Housden NG, James R, Kleanthous C, Penfold CN. Immunity protein release from a cell-bound nuclease colicin complex requires global conformational rearrangement. *Microbiology open.* 2013;2(5):853-61.

Vankemmelbeke M, Zhang Y, Moore GR, Kleanthous C, Penfold CN, James R. Energy-dependent immunity protein release during tol-dependent nuclease colicin translocation. *J Biol Chem.* 2009;284(28):18932-41.

Visca P, Imperi F, Lamont IL. Pyoverdine siderophores: from biogenesis to biosignificance. *Trends Microbiol.* 2007;15(1):22-30.

Waite RD, Curtis MA. *Pseudomonas aeruginosa* PAO1 pyocin production affects population dynamics within mixed-culture biofilms. *J Bacteriol.* 2009;191(4):1349-54.

Walker DC, Georgiou T, Pommer AJ, Walker D, Moore GR, Kleanthous C, James R. Mutagenic scan of the H-N-H motif of colicin E9: implications for the mechanistic

enzymology of colicins, homing enzymes and apoptotic endonucleases. *Nucleic Acids Res.* 2002;30(14):3225-34.

Walker D, Lancaster L, James R, Kleanthous C. Identification of the catalytic motif of the microbial ribosome inactivating cytotoxin colicin E3. *Protein Sci.* 2004;13(6):1603-11.

Walker D, Mosbahi K, Vankemmelbeke M, James R, Kleanthous C. The role of electrostatics in colicin nuclease domain translocation into bacterial cells. *J Biol Chem.* 2007;282(43):31389-97.

Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo- β -lactamases: the Quiet before the Storm? *Clin Microbiol Rev.* 2005;2:306-25.

Watanabe M, Iyobe S, Inoue M, Mitsuhashi S. Transferable imipenem resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother.* 1991;35:147-51.

Weisner AM, Chart H, Bush A, Davies JC, Pitt TL. Detection of antibodies to *Pseudomonas aeruginosa* in serum and oral fluid from patients with cystic fibrosis. *J Med Microbiol.* 2007;56(Pt 5):670-4.

Wei Q, Minh PN, Dötsch A, Hildebrand F, Panmanee W, Elfarash A, Schulz S, Plaisance S, Charlier D, Hassett D, Häussler S, Cornelis P. Global regulation of gene expression by OxyR in an important human opportunistic pathogen. *Nucleic Acids Res.* 2012;40(10):4320-33.

WHO, World Health Organization. WHA 68.7 Global action plan on antimicrobial resistance. Geneva; 2015. Disponível em: http://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_R1_REC1-en.pdf

WHO, World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. Geneva; 2017. Disponível em: <http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/>

Williams RJ. Treatment of *Pseudomonas aeruginosa* infections with pyocines. *J. Med. Microbiol.* 1976; 9:153–61.

Williams SR, Gebhart D, Martin DW, Scholl D. Retargeting R-type pyocins to generate novel bactericidal protein complexes. *Appl Environ Microbiol.* 2008;74(12):3868-76.

Winn MD, Ballard CC, Cowtan KD, Dodson EJ, Emsley P, Evans PR, Keegan RM, Krissinel EB, Leslie AG, McCoy A, McNicholas SJ, Murshudov GN, Pannu NS, Potterton EA, Powell HR, Read RJ, Vagin A, Wilson KS. Overview of the CCP4 suite and current developments. *Acta Crystallogr D Biol Crystallogr.* 2011;67(Pt4):235-42.

Winstanley C, O'Brien S, Brockhurst MA. *Pseudomonas aeruginosa* Evolutionary Adaptation and Diversification in Cystic Fibrosis Chronic Lung Infections. *Trends Microbiol.* 2016;24(5):327-37.

Wolska KI, Grześ K, Kurek A. Synergy between novel antimicrobials and conventional antibiotics or bacteriocins. *Pol J Microbiol.* 2012;61(2):95-104.

Wood SR, Firoved AM, Ornatowski W, Mai T, Deretic V, Timmins GS. Nitrosative stress inhibits production of the virulence factor alginate in mucoid *Pseudomonas aeruginosa*. Free Radic Res. 2007;41(2):208-15.

Wu W, Jin S. PtrB of *Pseudomonas aeruginosa* suppresses the type III secretion system under the stress of DNA damage. J Bacteriol. 2005;187(17):6058-68.

Yahr TL, Parsek MR. *Pseudomonas aeruginosa*. In: Dworkin M, Falkow S, Rosenberg E, Schleifer K-H, Stackebrandt E, editors. The Prokaryotes. New York, N.Y.: Springer; 2006. Vol. 6, p.704–13.

Yamashita E, Zhahnina MV, Zakharov SD, Sharma O, Cramer WA. Crystal structures of the OmpF porin: function in a colicin translocon. EMBO J. 2008;27(15):2171-80.

Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, Walsh TR. Characterization of a New Metallo- β -Lactamase Gene, *bla*_{NDM-1}, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India. Antimicrob. Agents Chemother. 2009;53(12):5046–54.

Zakharov SD, Eroukova VY, Rokitskaya TI, Zhahnina MV, Sharma O, Loll PJ, Zgurskaya HI, Antonenko YN, Cramer WA. Colicin occlusion of OmpF and TolC channels: outer membrane translocons for colicin import. Biophys J. 2004;87(6):3901-11.

Zavascki AP, Carvalhaes CG, Picão RC, Gales AC. Multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: resistance mechanisms and implications for therapy. Expert Rev Anti Infect Ther. 2010;8(1):71-93.

Zhanel GG, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, Noreddin AM, Karlowsky JA. Comparative review of the carbapenems. Drugs. 2007;67(7):1027-52.