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Infections by multidrug-resistant Gram-negative Bacteria: What's new in our arsenal and what's in the pipeline?

By: Koulenti, D (Koulenti, Despoina)^[1,2,3]; Song, A (Song, Andrew)^[1]; Ellingboe, A (Ellingboe, Aaron)^[1]; Abdul-Aziz, MH (Abdul-Aziz, Mohd Hafiz)^[1,4]; Harris, P (Harris, Patrick)^[1,5,6]; Gavey, E (Gavey, Emile)^[1]; Lipman, J (Lipman, Jeffrey)^[1,2,7]

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Abstract

The spread of multidrug-resistant bacteria is an ever-growing concern, particularly among Gram-negative bacteria because of their intrinsic resistance and how quickly they acquire and spread new resistance mechanisms. Treating infections caused by Gram-negative bacteria is a challenge for medical practitioners and increases patient mortality and cost of care globally. This vulnerability, along with strategies to tackle antimicrobial resistance development, prompts the development of new antibiotic agents and exploration of alternative treatment options. This article summarises the new antibiotics that have recently been approved for Gram-negative bacterial infections, looks down the pipeline at promising agents currently in phase I, II, or III clinical trials, and introduces new alternative avenues that show potential in combating multidrug-resistant Gram-negative bacteria. (c) 2018 Elsevier B.V. and International Society of Chemotherapy. All rights reserved.

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KeyWords Plus: IN-VITRO ACTIVITY; BETA-LACTAMASE INHIBITOR; TERM INTRAVENOUS-INFUSION; URINARY-TRACT-INFECTIONS; CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE; COMPLICATED INTRAABDOMINAL INFECTIONS; GENERATION AMINOGLYCOSIDE PLAZOMICIN; VENTILATOR-ASSOCIATED PNEUMONIA; CARE-ASSOCIATED INFECTIONS; PSEUDOMONAS-AERUGINOSA

Author Information

Reprint Address: Koulenti, D (reprint author)

+ Univ Queensland, Fac Med, Ctr Clin Res, Burns Trauma & Crit Care Res Ctr, Brisbane, Qld, Australia.

Reprint Address: Koulenti, D (reprint author)

Bldg 71-918, Herston, Qld, Australia.

Addresses:

- + [1] Univ Queensland, UQ Ctr Clin Res, Fac Med, Brisbane, Qld, Australia
- + [2] Univ Queensland, Royal Brisbane Clin Unit, Fac Med, Brisbane, Qld, Australia
- + [3] Attikon Univ Hosp, Crit Care Dept 2, Athens, Greece
- + [4] Int Islamic Univ, Sch Pharm, Kuantan, Malaysia
- [5] Pathol Queensland, Cent Lab, Herston, Qld, Australia
- [6] Princess Alexandra Hosp, Infect Management Serv, Woolloongabba, Qld, Australia
- + [7] Royal Brisbane & Womens Hosp, Dept Intens Care Med, Brisbane, Qld, Australia

E-mail Addresses: d.koulenti@uq.edu.au

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Koulenti, Despoina; Xu, Elena; Mok, Isaac Yin Sum; et al.
[Novel Antibiotics for Multidrug-Resistant Gram-Positive Microorganisms.](#)
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- Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis** Times Cited: 90
By: Abdul-Aziz, Mohd H.; Sulaiman, Helmi; Mat-Nor, Mohd-Basri; et al.
INTENSIVE CARE MEDICINE Volume: 42 Issue: 10 Pages: 1535-1545 Published: OCT 2016
- Applying Pharmacokinetic/Pharmacodynamic Principles in Critically Ill Patients: Optimizing Efficacy and Reducing Resistance Development** Times Cited: 47
By: Abdul-Aziz, Mohd H.; Lipman, Jeffrey; Mouton, Johan W.; et al.
SEMINARS IN RESPIRATORY AND CRITICAL CARE MEDICINE Volume: 36 Issue: 1 Pages: 136-153 Published: FEB 2015
- ACHAOPEN: developing novel antibacterials to treat multi-drug resistant gram-negative bacterial infections** Times Cited: 1
Group Author(s): Achaopen Inc
ACHAOPEN DEV NOV ANT Published: 2014
accessed 11/10/2018
Publisher: Achaopen
- Pseudomonas aeruginosa II lectin stops human ciliary beating: Therapeutic implications of fucose** Times Cited: 51
By: Adam, EC; Mitchell, BS; Schumacher, DU; et al.
AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE Volume: 155 Issue: 6 Pages: 2102-2104 Published: JUN 1997
- Synthesis and Spectrum of the Neoglycoside ACHN-490** Times Cited: 129
By: Aggen, James B.; Armstrong, Eliana S.; Goldblum, Adam A.; et al.
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY Volume: 54 Issue: 11 Pages: 4636-4642 Published: NOV 2010
- Carbapenem-Resistant Klebsiella pneumoniae Strains Exhibit Diversity in Aminoglycoside-Modifying Enzymes, Which Exert Differing Effects on Plazomicin and Other Agents** Times Cited: 61
By: Almaghrabi, Reem; Clancy, Cornelius J.; Doi, Yohei; et al.
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY Volume: 58 Issue: 8 Pages: 4443-4451 Published: AUG 2014
- Efficacy of murepavadin co-administered with standard-of-care in a phase 2 study in patients with ventilator-associated pneumonia due to Pseudomonas aeruginosa infection** Times Cited: 2
By: Armaganidis, A; Torres, A; Zakynthinos, S; et al.
EFFICACY MUREPAVADIN Published: 2017
accessed 11/10/2018
URL: <https://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1629-x#Sec288>
[Show additional data]
- Substantial Impact of Altered Pharmacokinetics in Critically Ill Patients on the Antibacterial Effects of Meropenem Evaluated via the Dynamic Hollow-Fiber Infection Model** Times Cited: 9
By: Bergen, Phillip J.; Bulitta, Jurgen B.; Kirkpatrick, Carl M. J.; et al.
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY Volume: 61 Issue: 5 Article Number: e02642-16 Published: MAY 2017
- Differences in suppression of regrowth and resistance despite similar initial bacterial killing for meropenem and piperacillin/tazobactam against Pseudomonas aeruginosa and Escherichia coli** Times Cited: 1
By: Bergen, Phillip J.; Bulitta, Jurgen B.; Sime, Fekade B.; et al.
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE Volume: 91 Issue: 1 Pages: 69-76 Published: MAY 2018

10. **Effect of different renal function on antibacterial effects of piperacillin against Pseudomonas aeruginosa evaluated via the hollow-fibre infection model and mechanism-based modelling** Times Cited: 14
By: Bergen, Phillip J.; Bulitta, Jurgen B.; Kirkpatrick, Carl M. J.; et al.
JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY Volume: 71 Issue: 9 Pages: 2509-2520 Published: SEP 2016
11. **Mode of Antibacterial Action of the Monobactam LYS228 and Characterization of Spontaneous Single Step Enterobacteriaceae Mutants with Decreased Susce**
By: Bermingham, A; Blais, J; Casey, F; et al.
MODE ANTIMICROBIAL A Published: 2017
accessed 11/10/2018
URL:
https://www.researchgate.net/publication/317784520_Mode_of_Antibacterial_Action_of_the_Monobactam_LYS228_and_Characterization_of_Spontaneous_Single_Step_Enterobacteriaceae_Mutants_with_Deceased_Susceptibility
[Show additional data]
12. **Discovery of MK-7655, a beta-lactamase inhibitor for combination with Primaxin (R)** Times Cited: 69
By: Blizzard, Timothy A.; Chen, Helen; Kim, Seongkon; et al.
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS Volume: 24 Issue: 3 Pages: 780-785 Published: FEB 1 2014
13. **10 x '20 Progress-Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America** Times Cited: 445
By: Boucher, Helen W.; Talbot, George H.; Benjamin, Daniel K., Jr.; et al.
Group Author(s): Infect Dis Soc Amer
CLINICAL INFECTIOUS DISEASES Volume: 56 Issue: 12 Pages: 1685-1694 Published: JUN 15 2013
14. **Use of bacteriophage endolysin EL188 and outer membrane permeabilizers against Pseudomonas aeruginosa** Times Cited: 57
By: Briers, Y.; Walmagh, M.; Lavigne, R.
JOURNAL OF APPLIED MICROBIOLOGY Volume: 110 Issue: 3 Pages: 778-785 Published: MAR 2011
15. **Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study** Times Cited: 116
By: Carmeli, Yehuda; Armstrong, Jon; Laud, Peter J.; et al.
LANCET INFECTIOUS DISEASES Volume: 16 Issue: 6 Pages: 661-673 Published: JUN 2016
16. **Pharmacokinetics and Safety of Single and Multiple Doses of ACHN-490 Injection Administered Intravenously in Healthy Subjects** Times Cited: 41
By: Cass, Robert T.; Brooks, Carter D.; Havrilla, Nancy A.; et al.
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY Volume: 55 Issue: 12 Pages: 5874-5880 Published: DEC 2011
17. **A doubleblind, randomized, placebo-controlled study to assess the safety, tolerability, plasma pharmacokinetics and lung penetration of intravenous plazomicin in healthy subjects** Times Cited: 1
By: Cass, RT; Kostrub, CF; Gotfried, M; et al.
DOUBLE BLIND RANDOMI Published: 2013
accessed 11/10/18
URL: <http://www.achaogen.com/media-all/2013/5/1/a-double-blind-randomized-placebo-controlled-study-to-assess-the-safety-tolerability-plasma-pharmacokinetics-and-lung-penetration-of-intravenous-plazomicin-in-healthy-subjects>
[Show additional data]
18. **Optimal dosing of antibiotics in critically ill patients by using continuous/extended infusions: a systematic review and meta-analysis** Times Cited: 26
By: Chant, Clarence; Leung, Ann; Friedrich, Jan O.
CRITICAL CARE Volume: 17 Issue: 6 Article Number: R279 Published: 2013
19. **Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: A multicenter, randomized study** Times Cited: 179
By: Chastre, Jean; Wunderink, Richard; Prokocimer, Philippe; et al.
CRITICAL CARE MEDICINE Volume: 36 Issue: 4 Pages: 1089-1096 Published: APR 2008
20. **Plazomicin vs. meropenem for complicated urinary tract infection (cUTI) and acute pyelonephritis (AP): diagnosis-specific results from the phase 3 EPIC study** Times Cited: 7
By: Cloutier, DJ; Komirenko, AS; Cebrik, DS; et al.
Open Forum Infect Dis Volume: 4 Pages: S532 Published: 2017
[Show additional data]

21. **Ceftolozane-tazobactam: A new-generation cephalosporin** Times Cited: 18
 By: Cluck, David; Lewis, Paul; Stayer, Brooke; et al.
 AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY Volume: 72 Issue: 24 Pages: 2135-2146 Published: DEC 15 2015
22. **Diazabicyclooctanes (DBOs): a potent new class of non-beta-lactam beta-lactamase inhibitors** Times Cited: 113
 By: Coleman, Ken
 CURRENT OPINION IN MICROBIOLOGY Volume: 14 Issue: 5 Pages: 550-555 Published: OCT 2011
23. **Plazomicin (PLZ) Associated with Improved Survival and Safety Compared to Colistin (CST) in Serious Carbapenem-Resistant Enterobacteriaceae (CRE) Infection**
 By: Connolly, LE; Jubb, AM; O'Keefe, B; et al.
 PLAZOMICIN PLZ ASS I Published: 2017
 accessed 11/10/2018
 Publisher: The American Society of Microbiology
 URL:
<https://static1.squarespace.com/static/51199d96e4b084d1d0b105c3/t/5932ec1c20099e36dc1def02/1496509470262/ASMLConnolly.Plazomicin28PLZ29AssociatedwithImprovedResistantC2A0EnterobacteriaceaeC2A028CRE29Infections-ResultsoftheCAREStudy2.pdf>
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24. **In Vivo Activities of Ceftolozane, a New Cephalosporin, with and without Tazobactam against Pseudomonas aeruginosa and Enterobacteriaceae, Including Strains with Extended-Spectrum beta-Lactamases, in the Thighs of Neutropenic Mice** Times Cited: 69
 By: Craig, W. A.; Andes, D. R.
 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY Volume: 57 Issue: 4 Pages: 1577-1582 Published: APR 2013
25. **In Vitro Activity of Cefepime/AAI101 and Comparators against Cefepime Non-susceptible Enterobacteriaceae** Times Cited: 13
 By: Crandon, Jared L.; Nicolau, David P.
 PATHOGENS Volume: 4 Issue: 3 Pages: 620-625 Published: SEP 2015
26. **Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050?** Times Cited: 121
 By: de Kraker, Marlieke E. A.; Stewardson, Andrew J.; Harbarth, Stephan
 PLOS MEDICINE Volume: 13 Issue: 11 Article Number: e1002184 Published: NOV 2016
27. **Differing Effects of Combination Chemotherapy with Meropenem and Tobramycin on Cell Kill and Suppression of Resistance of Wild-Type Pseudomonas aeruginosa PAO1 and Its Isogenic MexAB Efflux Pump-Overexpressed Mutant** Times Cited: 39
 By: Drusano, G. L.; Liu, Weiguo; Fregeau, Christine; et al.
 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY Volume: 53 Issue: 6 Pages: 2266-2273 Published: JUN 2009
28. **A Multicenter Randomized Trial of Continuous versus Intermittent beta-Lactam Infusion in Severe Sepsis** Times Cited: 91
 By: Dulhunty, Joel M.; Roberts, Jason A.; Davis, Joshua S.; et al.
 Group Author(s): BLING II Investigators; ANZICS Clinical Trials Grp
 AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE Volume: 192 Issue: 11 Pages: 1298-1305 Published: DEC 1 2015
29. **Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial** Times Cited: 196
 By: Dulhunty, Joel M.; Roberts, Jason A.; Davis, Joshua S.; et al.
 CLINICAL INFECTIOUS DISEASES Volume: 56 Issue: 2 Pages: 236-244 Published: JAN 15 2013
30. **ETX2514 is a broad-spectrum beta-lactamase inhibitor for the treatment of drug-resistant Gram-negative bacteria including Acinetobacter baumannii** Times Cited: 48
 By: Durand-Reville, Thomas F.; Guler, Satenig; Comita-Prevoir, Janelle; et al.
 NATURE MICROBIOLOGY Volume: 2 Issue: 9 Article Number: 17104 Published: SEP 2017

Showing 30 of 201 [View All in Cited References page](#)

