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

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Abstract

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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. © 2019 Elsevier Ltd

SciVal Topic Prominence

Topic: Ceftazidime | Beta-Lactamases | B-lactamase inhibitor

Prominence percentile: 99.026

Author keywords

Ceftazidime/avibactam | Ceftolozane/tazobactam | Eravacycline | Meropenem/vaborbactam | Multidrug-resistant Gram-negative bacteria | Plazomicin

Indexed keywords

EMTREE drug terms: antibiotic agent | avibactam plus ceftazidime | aztreonam | carbapenem | cefepime | cefiderocol | ceftazidime | ceftolozane plus tazobactam | cilastatin plus imipenem | colistin | doripenem | eravacycline | ertapenem | gsk 3342830 | levofloxacin | lys 228 | meropenem | meropenem plus vaborbactam | metronidazole | murepavadin | nacubactam | piperacillin plus tazobactam | plazomicin | relebactam | spr 741 | spr 994 | sulopenem | tp 6076 | unclassified drug | unindexed drug | wck 5222 | antiinfective agent

EMTREE medical terms:

abdominal infection | acute pyelonephritis | antibiotic resistance | antimicrobial activity | bacteriophage | bloodstream infection | clinical effectiveness | diarrhea | dizziness | drug safety | drug tolerability | Enterobacteriaceae infection | gastrointestinal disease | Gram negative bacterium | Gram negative infection | Gram positive infection | headache | hospital acquired pneumonia | hospital infection | human | hypertension | hypesthesia | hypotension | minimum inhibitory concentration | multidrug resistance | nausea | nonhuman | pharmacodynamic parameters | pharmacokinetic parameters | priority journal | Review | somnolence | treatment indication | treatment outcome | treatment response | urinary tract infection | ventilator associated pneumonia | vomiting | clinical trial (topic) | drug approval | drug development | drug effect | Gram negative bacterium | Gram negative infection | isolation and purification | microbiology | trends

MeSH:

Anti-Bacterial Agents | Clinical Trials as Topic | Drug Approval | Drug Discovery | Drug Resistance, Multiple, Bacterial | Gram-Negative Bacteria | Gram-Negative Bacterial Infections | Humans

Chemicals and CAS Registry Numbers:

aztreonam, 78110-38-0; carbapenem, 83200-96-8; cefepime, 88040-23-7; cefiderocol, 1225208-94-5, 2009350-94-9, 2135543-94-9; ceftazidime, 72558-82-8; cilastatin plus imipenem, 92309-29-0; colistin, 1066-17-7, 1264-72-8; doripenem, 148016-81-3; eravacycline, 1207283-85-9, 1334714-66-7; ertapenem, 153773-82-1, 153832-38-3, 153832-46-3; levofloxacin, 100986-85-4, 138199-71-0; meropenem, 96036-03-2; metronidazole, 39322-38-8, 443-48-1; murepavadin, 944252-63-5; nacubactam, 1452458-86-4; plazomicin, 1154757-24-0, 1380078-95-4; relebactam, 1174018-99-5, 1174020-13-3, 1502858-91-4; sulopenem, 96865-21-3, 120788-07-0;

Anti-Bacterial Agents

Drug tradename:

avycaz, Allergan, cp 70429, Pfizer, Japan, gsk 3342830, lys 228, Novartis, mk 7655, Merck Sharp and Dohme, s 649266, Shionogi, spr 741, Spero Therapeutics, spr 994, tp 6076, vabomere, Rempex, wck 5222, Wockhardt, xerava, Tetraphase, zavicefta, Pfizer, zemdri, Achaogen, zerbaxa, Merck Sharp and Dohme

Manufacturers:

Drug manufacturer:

Achaogen;

Allergan;

Merck Sharp and Dohme;

Novartis;

Pfizer;

Pfizer, Japan;

Rempex;

Shionogi;

Spero Therapeutics;

Tetraphase;

Wockhardt

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Funding sponsor	Funding number	Acronym
European Commission See opportunities↗		

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Seventh Framework Programme		

Funding text

Use of bacteriophages to target certain bacteria was a very early idea that has recently undergone a renaissance. Bacteriophages expressing endolysins can enter target cells when combined with permeabilisers [148] . More recently, effective reduction of P. aeruginosa load in a biofilm-associated murine model of CF has been demonstrated with nebulised phage therapy [149] . Nebulisation has been shown to be an effective delivery method for bacteriophages, and has potential to be trialled in HAV/VAP cases [150] . A phase I/II clinical trial investigating bacteriophages (NCT02116010 ; 'PhagoBurn'; Pherecydes Pharma) was launched in June 2013, and was funded by the European Commission under the Seventh Framework Programme for Research and Development [151] . However, it was stopped prematurely in January 2017 due to insufficient efficacy of anti- P. aeruginosa bacteriophage PP1131 [152] . A major limitation of the study was that stability issues resulted in a lower than expected dose (1000... View all

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