REVIEW

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Healthcare-associated infections, infection control and the potential of new antibiotics in development in the USA

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ABSTRACT Healthcare-associated infections (HAIs) caused by drug-resistant Gram-negative pathogens are a significant burden on the US healthcare system. This problem has been further compounded by the recent decline in the development of new antibiotics targeting Gram-negative organisms. US healthcare agencies have been working to limit the occurrence of HAIs by several means, including surveillance systems, prevention practices, antimicrobial stewardship policies and financial incentives. Furthermore, efforts have been made to resume the development of antibiotics in the USA, with the US FDA and US government both implementing acts to boost the number of antibiotics in the clinical pipeline. This review discusses the policies instigated by the US government, including healthcare agencies and the FDA, and describes new antibiotics in development against HAIs.

Introduction to healthcare-associated infections

Historically, infections tended to be contracted in the distinct settings of the hospital or community, and were thus defined as hospital- or community-acquired, respectively. More recently, healthcare-associated infections (HAIs) have become an emerging infection type for patients who have had infection detected within 48 h of hospital admission, and who have also had previous contact with the healthcare service within 1 year [1]. Using data from the National Nosocomial Infections Surveillance (NNIS) system collected between 1990 and 2002, it was estimated that there were 1.7 million HAIs among hospitalized adults and children across the USA in 2002 alone [2]. HAIs caused by Gram-negative pathogens, which are the focus of this review, are a cause of significant healthcare burden in the USA.

• Healthcare-associated infections caused by Gram-negative pathogens

Of the HAIs reported to the National Healthcare Safety Network (NHSN) in 2009–2010, around 40% were known to be associated with Gram-negative organisms, including *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. [3]. These Gram-negative organisms, alongside the Gram-positive species *Enterococcus faecium* and *Staphylococcus aureus*, have been labeled the ESKAPE pathogens and they cause the majority of HAIs in the USA [4]. Magill *et al.* found that of the top ten ranked pathogens causing HAIs in their study, four were Gram-negative: *Klebsiella* spp. (*K. pneumoniae*/K. *oxytoca*), *Escherichia coli*, *P. aeruginosa* and *Enterobacter* spp. [5].

These Gram-negative pathogens are also associated with drug resistance in the nosocomial setting [6]. In the study by Sievert *et al.* [3], 20–40% of healthcare facilities reported at least one

KEYWORDS

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- Gram-negative pathogen
- healthcare-associated infection

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Gram-negative isolate, among *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* spp., with a resistant phenotype. The lowest frequency of multidrug resistance (MDR) was reported among *E. coli* and *Enterobacter* spp. (<5%), and the highest frequency among *A. baumannii* (44–78%). The problem of emerging drug resistance among Gram-negative pathogens has been publicized, particularly with the recent decline in antimicrobial research and development [6].

• Current treatment guidelines for healthcare-associated infections

HAI data collected between 2007 and 2010 showed the following rank order for the same infection types: central line-associated bloodstream infection (40%), catheter-associated urinary tract infection (26%), surgical site infection (23%) and ventilator-associated pneumonia (11%) [3].

The Infectious Diseases Society of America (IDSA) has published guidelines for the management of intravascular catheter-related infections and complicated intra-abdominal infection (cIAI) [7,8]. The IDSA in conjunction with American Thoracic Society (ATS) has also produced guidelines for the management of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) [9]. No guidelines have been published by the IDSA for complicated urinary tract infection (cUTI). This may be due to the wide variety of patient populations, genitourinary abnormalities and causative pathogens that can be associated with cUTIs [10–12]. The IDSA, however, have published guidelines for the treatment of catheter-associated urinary tract infection, and uncomplicated cystitis and pyelonephritis [8]. Additionally, no guidelines have been published by the IDSA for surgical site infections despite surgical site infections being shown to compose up to 23% of all HAI [13].

This article will review the current preventative and control measures for HAIs being implemented by US healthcare agencies and institutions, including systems for the surveillance of HAIs, antimicrobial stewardship policies to enhance the appropriate use of antibiotics and quality measures to incentivize healthcare facilities to reduce the rate of HAIs. This burden of HAIs has been exacerbated by a recent decline in the development of new antibiotics against Gram-negative pathogens, and this review will

also discuss the resumption of antimicrobial research, summarizing the potential, new antimicrobial agents in the pipeline to overcome HAIs caused by Gram-negative organisms.

Controlling healthcare-associated infections

Many measures, such as surveillance systems, prevention practices, antimicrobial stewardship policies and quality measures, have been implemented to raise the awareness of the healthcare profession to the burden of HAIs and to introduce practices to minimize this burden. This section will describe these measures in further details.

• Surveillance systems

The NHSN is a program sponsored by the Centers for Disease Control and Prevention (CDC), set up to report and monitor the occurrence of HAIs. The NHSN was formed from the integration of the NNIS system with the National Surveillance System for Health Care Workers and the Dialysis Surveillance Network in 2005 [14]. The CDC also established the Emerging Infections Program in 1995, which is a network of ten US state health departments [15] that runs the Active Bacterial Core surveillance for invasive diseases caused by pathogens such as *Haemophilus influenzae*, as well as the Healthcare Associated Infections-Community Interface projects for tracking infections and antimicrobial resistance.

The latest national progress report from the CDC, based on data reported to the NHSN, shows that central line-associated bloodstream infections decreased by 44% (2008–2012), surgical site infections decreased by 20% (2008–2012) and catheter-associated urinary tract infections increased by 3% (2009–2012) [16].

• Prevention programs & practices

The US Department of Health and Human Services (HHS) comprises 11 operating divisions [17], including the Agency for Healthcare Research and Quality (AHRQ) and the CDC, both of whom have conducted research and written policies aiming to eradicate HAIs from the US healthcare system. The AHRQ supports the Comprehensive Unit-based Safety Program (CUSP), a patient safety model designed to reduce HAIs in a nosocomial environment [18]. In 2003, the AHRQ launched the Keystone ICU project, which used CUSP to lower the rates of

catheter-related bloodstream infections in over 100 Michigan intensive care units by two-thirds in 3 months [19]. In 2008, the Keystone ICU project teams reported a 50% improvement in the safety climate of ICUs, attained a median catheter-related blood stream infection rate of zero and reported 99% compliance with evidence-based ventilator care practices [20]. In 2012, the AHRQ released the CUSP Toolkit, which assists healthcare facilities in understanding how to improve the quality of patient care and to identify potential safety problems. The toolkit is aimed at anyone in the healthcare profession and contains teaching aids, such as slide kits, presentation materials, videos and checklists. Overall, CUSP has reduced catheter-related bloodstream infections by 40%, preventing 2000 infections and saving more than 500 lives [21].

Prevention programs centered on hand washing, decolonization with topical chlorhexidine gluconate, urinary catheter protocols, surgical prophylaxis and screening protocols with eradication have had some success [22]. Hand hygiene has been reported to reduce MRSA infections by 35% in ICUs [23] and decolonization of all patients by bathing with chlorhexidine gluconate have been shown to prevent HAIs including catheter-related bloodstream infections among ICU patients [24–26].

There has also been some evidence that short-wave ultraviolet radiation might reduce the burden of bacteria [27], which is now being studied in a larger clinical trial [28].

The CDC website lists practical recommendations on how to protect patients from specific HAIs during treatment [29]. In addition, the Association of State and Territorial Health Officials (ASTHO) and CDC published a policy toolkit on the elimination of HAIs [30]. The document provided guidance on the implementation of state policies, such as the provision of financial incentives for HAI prevention, stricter requirements on the certification and training of healthcare providers, enforced adherence to evidence-based practices of infection control, public reporting of data, and ensuring that state HAI legislation is followed.

The HHS has coordinated the efforts of multiple healthcare agencies including several of its own operating divisions and outside organizations, and has set targets to reduce the majority of HAIs by 25–50% by the year 2020 [31]. The first phase of the action plan focuses on HAIs in acute care hospitals [32]. The document proposes

to reduce hospital-acquired HAIs by addressing the following areas: research, information systems and technology, incentives and oversight, and outreach and messaging strategies.

The research aspect of the action plan recommends an increased understanding of the basic science of HAIs, including the key causative pathogens, how they are acquired and the role of biofilm organisms in HAIs. A second recommendation is the strengthening of research focused on the epidemiology of HAIs. One way of achieving this would be to identify the limitations in current surveillance strategies, including labor intensiveness, poor agreement between healthcare professionals when assessing patient cases (inter-rater reliability) and an inability to track all adverse events. These limitations could be addressed by optimizing the use of existing electronic data to measure processes and outcomes. Any gaps in existing epidemiologic knowledge should be identified and explored, for example, identifying emerging MDR organisms and defining the role of vaccines in preventing HAIs.

Additionally, existing infection control prevention measures can be refined and assessed, and additional strategies developed and evaluated through the design and conduct of multicenter trials. Furthermore, a greater number of multicenter projects, like the Keystone project, are needed to elucidate practices that can successfully reduce the rates of HAIs. For practices with strong scientific evidence to support them, research should be conducted on implementing these across institutions.

• Antimicrobial stewardship

In 2007, the IDSA and the Society for Healthcare Epidemiology of America published guidelines for developing hospital-based programs to enhance antimicrobial stewardship [33]. The guidelines state that the goals of antimicrobial stewardship are to improve clinical outcomes while limiting any negative effects of antibiotic use, such as drug toxicity and pathogen resistance, and to lower healthcare expenditure without compromising the quality of patient care. The document recommendations are outlined in **Table 1**.

Studies have shown that the successful implementation of an antimicrobial stewardship program can decrease the rates of HAIs [34–36]. Nowak *et al.* [34] reported a decrease of 9.75% in antimicrobial expenditures in the first year

Subject/area	Actions	Strength of recommendation
Antimicrobial stewardship team	Formation of a multidisciplinary antimicrobial stewardship team comprising: infectious diseases physician, clinical pharmacist with infectious diseases training, hospital administrative support to measure and track antimicrobial use	Good evidence from ≥ one well-designed clinical trial, or based on clinical evidence descriptive studies or reports of expert authorities
	Optimal additions: clinical microbiologist and information system specialist to monitor antibiotic resistance, infection control professional and a hospital epidemiologist to advise on improving antimicrobial use	Good evidence based on clinical evidence descriptive studies, or reports of expert authorities
Program implementation	Development of treatment guidelines based on local microbiology and resistance patterns to improve antibiotic utilization	Good evidence from ≥ one randomized, controlled trial
	Prospective audit of antibiotic use through direct interaction and feedback to prescriber, conducted by infectious diseases physician or clinical pharmacist	Good evidence from ≥ one randomized, controlled trial
	Regulation of antimicrobials included on the hospital formulary and restriction of new agents with limited additional benefit, while monitoring antimicrobial use	Good evidence from ≥ one well-designed clinical trial
	Education of medical students and hospital staff on prescribing of antimicrobials, with incorporation of prospective audit and intervention	Good evidence based on clinical evidence, descriptive studies, or reports of expert authorities
Antimicrobial therapy	Streamlining of empiric antimicrobial therapy based on microbiological culture results	Good evidence from ≥ one well-designed clinical trial
	Adjustment of antibiotic drug dose based on causative pathogen, site of infection, patient characteristics, pharmacokinetic/pharmacodynamics characteristics of drug	Good evidence from ≥ one well-designed clinical trial
	Conversion of parenteral antibiotics to oral antibiotics with high bioavailability, when appropriate for the patient	Good evidence based on clinical evidence, descriptive studies, or reports of expert authorities
Patient care	Assisting antimicrobial management of patients through electronic medical records containing data on patient-specific microbiological cultures and susceptibilities, hepatic and renal function, drug–drug interactions	Good evidence based on clinical evidence, descriptive studies, or reports of expert authorities
	Providing patient-specific culture and susceptibility data through clinical microbiology laboratory to enhance antibiotic management of patient and to aid infection control in surveying resistant organisms for epidemiological studies	Good evidence based on clinical evidence, descriptive studies, or reports of expert authorities
Other considerations	Antimicrobial order forms to reduce antibiotic usage in longitudinal studies through automatic discontinuation of therapy and requirement of physician justification	Moderate evidence from ≥ one well-designed clinical trial
	Antimicrobial cycling (the removal of one antibiotic agent or one class and substitution with an alternative) to prevent or decrease development of drug resistance	Limited evidence from ≥ one well-designed clinical trial
	Combination therapy in certain clinical contexts, such as empiric therapy for critically ill patients with infection caused or suspected to be caused by multidrug resistance pathogens	Limited evidence from ≥ one well-designed clinical trial

Data taken from [33].

following implementation of antimicrobial stewardship program, with an estimated overall cumulative cost savings of US\$1.7 million.

Following successful implementation of microbial stewardship program, Prasad *et al.* [35] reported a reduction in incidence rates of MDR

K. pneumoniae from 17.7% in 2011 to 10.5% in 2013, *A. baumannii* from 43.3 to 39.5% and MRSA from 56.8 to 41.6%. Pasquale *et al.* [36] reported that the interventions made by the antimicrobial stewardship program were associated with significant reductions in the mean length of stay and 30-day all-cause readmission rates for patients with ABSSSI.

Table 2 contains a summary of approaches used for the prevention of HAI [37].

• Quality measures

Financial penalties have been introduced to further incentivize healthcare institutions to implement the above practice guidelines to minimize HAIs. In 2008, the Centers for Medicare and Medicaid Services (CMS) stopped reimbursing hospitals for the treatment of certain preventable HAIs acquired during hospitalization [38]. This was done in accordance with the Deficit Reduction Act, which was passed by the US Congress in 2005 to decrease federal spending on Medicare and Medicaid services. The act introduced the new Medicare-severity dose-related group (MS-DRG) system, which revised the previous DRG system whereby inpatient prospective payment system (IPPS) hospitals could increase reimbursement for a HAI or hospital-acquired condition. Under the new system, an IPPS hospital cannot increase reimbursement for a hospital-acquired condition that was not present on admission, or for a hospital-acquired condition that is the only comorbidity or complication reported.

In March 2010, the Affordable Care Act was signed into US law, which contained two sections related to improving the quality of hospital care: sections 1886 and 3025 [39]. Section 1886 describes the concept of value-based purchasing,

whereby value-based incentive payments are made in a fiscal year to hospitals that meet the required performance standards. Section 3025 describes the reduction of payments to hospitals with high readmission rates.

The Hospital-Acquired Conditions Reduction Program penalizes the lowest quartile hospitals across two domains involving central venous catheter-related infections rates, central line-associated bloodstream infections and catheter-associated urinary tract infections [40]. These pay-for-performance initiatives apply to Medicare patients but it should be noted that private insurers are adopting this model. This and the other main incentive programs introduced by the CMS, as a result of the Deficit Reduction Act and the Affordable Care Act, are summarized in **Table 3**.

As well as the implementation of preventative and control measures for HAIs by healthcare agencies and institutions, it is also important that the pharmaceutical industry continue to develop new antibiotics to treat HAIs caused by drug-resistant Gram-negative organisms, after the recent decline in antimicrobial research programs. In the next section, the status of the clinical antibiotic pipeline will be discussed, with a description of the new agents currently in development against Gram-negative pathogens.

Antimicrobial agents for healthcare-associated infections

Between 1983 and 2012, there was a gradual decrease in the number of US FDA-approved antibiotics, from 16 in 1983–1987 [45] to four from 2009 to the present date (September, 2014) [46]. These four agents, plus ceftobiprole medocaril (currently approved in Europe) are described in **Table 4**.

Table 2. Summary of approaches used for the prevention of healthcare-associated infections.

Type of approach	Actions
Pathogen specific	Active surveillance testing using surveillance systems such as National Healthcare Safety Network (NHSN) and emerging infections program Contact precautions Decolonization
Pathogen nonspecific	Antimicrobial stewardship programs such as the Comprehensive Unit-based Safety Program Hand washing Universal decolonization using short-wave ultraviolet radiation or chlorhexidine gluconate Universal use of gloves or gloves and gowns Environmental disinfection

Adapted from [37].

Table 3. Centres for Medicare and Medicaid Services quality programs for hospitals providing care to patients.

Program	Description	Reward/penalty
Hospital Inpatient Quality Reporting Program [†]	Hospitals rewarded for reporting designated quality measures	2% reduction to annual update for hospitals that do not successfully report
Hospital Value-Based Purchasing Program [‡] (IPPS)	Hospitals awarded incentive payments for the quality of care provided, based on the value-based incentive payment adjustment factor and the portion of Medicare payments subject to the adjustment factor	1.25% of base operating DRG in FY 2014, 1.5% in FY 2015
Hospital Readmissions Reduction Program [§] (IPPS)	Hospitals penalized for excess readmissions, based on the readmissions adjustment factor	2% reduction in FY 2014, 3% in FY 2015
Hospital-Acquired Conditions Reduction Program [¶]	Hospitals in the lowest-performing quartile of hospital-acquired conditions in domains 1 and 2 are not paid at a higher MS-DRG rate for patients with conditions acquired during hospitalization	1% payment reduction

[†]Data taken from [41].[‡]Data taken from [42].[§]Data taken from [43].[¶]Data taken from [40,44].

CMS: Centres for Medicare and Medicaid Services; DRG: Diagnosis-related group; FY: Fiscal year; IPPS: Inpatient prospective payment system; MS-DRG: Medicare-severity dose-related group.

Three of these agents (televancin, dalbavancin and tedizolid) are only active against Gram-positive species. The fourth, ceftaroline fosamil, is active against both Gram-positive and Gram-negative species (excluding *A. baumannii*, *P. aeruginosa* and Gram-negative strains producing derepressed AmpC or extended-spectrum β -lactamases [ESBLs]). Unlike earlier cephalosporins, ceftaroline fosamil and ceftobiprole medocartil are active against MRSA, by virtue of their affinity for penicillin-binding protein (PBP) 2a [50].

• Decline of antimicrobial drug development

The reasons for the overall decrease in new approved antibiotics are both practical and economical. There have been no new antimicrobial classes targeting Gram-negative bacteria in the past 40 years [51] and this may be due, in part, to the more complex structure of Gram-negative compared with Gram-positive bacteria [52]. Furthermore, only a handful of the 20 or so large pharmaceutical companies conducting antimicrobial drug development are still in the field, which may have meant the loss of some expertise [53].

The high costs associated with the development of antibiotics, estimated at US\$1 billion per drug [54], compared with a relatively low rate of return, mean that there are also economic factors deterring companies from drug development. A monograph from the Office of Health Economics (London, UK) found that the net

present value of an antibiotic to a drug company is minus US\$50 million at discovery [55]. The discovery and development of antimicrobials has also become less attractive to pharmaceutical companies given that these drugs are administered for relatively short courses and they can lose efficacy with overuse as pathogens gain resistance [51]. In addition, antibiotic development is also competing for resources with other therapeutic areas that have higher rates of return for pharmaceutical companies.

• Resumption of antimicrobial research

To address the problem of drug resistance and reverse the decline in antimicrobial research and development, two important programs have been initiated in the USA. The Generating Antibiotic Incentives Now (GAIN) Act was signed into US law in 2012 as part of the FDA Safety and Innovation Act [56]. The Act states that a drug that is designated a qualified infectious disease product (QIDP) can receive automatic priority review, gain an extra 5–7 years of market exclusivity without competition from generics, and obtain expedited approval from the FDA for being a ‘breakthrough therapy.’ A list of ‘qualifying pathogens,’ which are said to have ‘the potential to pose a serious threat to public health,’ is also given, for example, ‘multidrug resistant Gram-negative bacteria, including *Acinetobacter*, *Klebsiella*, *Pseudomonas* and *E. coli* species’ [57].

The 10 × 20 Initiative was launched by the IDSA to ‘develop 10 new, safe and effective antibiotics by 2020’ [58]. These new agents are to

be systemically administered, and can originate from new or existing antimicrobial classes, but should be targeted to treat MDR infections. Boucher *et al.* [59] published an update to the IDSA document in 2013, indicating that progress had been made by listing new antibiotics that were in development for the treatment of Gram-negative infections.

• New antibiotics against Gram-negative pathogens

Table 5 shows the new antibiotics with activity against Gram-negative organisms that are currently in preclinical (pre-Phase II) development. Two of these agents, POL7080 and CTIX1278, belong to novel antibiotic classes, and are synthetic compounds that mimic the action of the immune system cells protegrin (porcine

leukocyte peptide) and defensin (human neutrophil peptide), respectively.

Among the antimicrobial agents against Gram-negative organisms that are currently in the later stages of clinical development, there are single-agent antibiotics and those that are a combination of two agents. As a result of the GAIN act, many of these drugs have been designated as a QIDP by the FDA, entitling them to priority review and fast-track status.

Single-agent antibiotics

Eravacycline (TP-434) (Tetraphase Pharmaceuticals, MA, USA) is a fluorocycline tetracycline antibiotic with *in vitro* activity against *A. baumannii*, *H. influenzae* and Enterobacteriaceae (including ESBL-producing isolates) [68]. In a Phase II study for the treatment of community-acquired

Table 4. New antibiotics approved since 2009.

Agent name	Company	Antibiotic class	Indication	Pathogens	Date of approval
Ceftaroline fosamil [†]	Forest Laboratories (NY, USA)	Cephalosporin	ABSSSI	<i>Staphylococcus aureus</i> (including MSSA and MRSA), <i>Staphylococcus pyogenes</i> , <i>Staphylococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Klebsiella oxytoca</i>	November 2010
			CABP	<i>Streptococcus pneumoniae</i> , <i>S. aureus</i> (MSSA only), <i>Haemophilus influenzae</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i> , <i>E. coli</i>	
Ceftobiprole medocartil [†]	Basilea Pharmaceutica (Basel, Switzerland)	Cephalosporin	CABP, HABP (excluding VABP)	<i>S. aureus</i> (including MRSA and VRSA), <i>S. pneumoniae</i> (including PRSP, CRSP), Enterobacteriaceae and <i>Pseudomonas</i> spp.	October 2013
Dalbavancin	Durata Therapeutics (IL, USA)	Lipoglycopeptide	ABSSSI	<i>S. aureus</i> (including MSSA and MRSA), <i>S. pyogenes</i> , <i>S. agalactiae</i> and <i>Streptococcus anginosus</i> group (including <i>Streptococcus anginosus</i> , <i>Streptococcus intermedius</i> , <i>Streptococcus constellatus</i>)	May 2014
Oritavancin	The Medicines Company	Lipoglycopeptide	ABSSSI	<i>S. aureus</i> (including MSSA and MRSA), <i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. dysgalactiae</i> , <i>S. anginosus</i> group and <i>E. faecalis</i> (vancomycin susceptible isolates only)	August 2014
Tedizolid phosphate	Cubist Pharmaceuticals (MA, USA)	Oxazolidinone	ABSSSI	<i>S. aureus</i> (including MSSA and MRSA), <i>S. pyogenes</i> , <i>S. agalactiae</i> and <i>S. anginosus</i> group (including <i>S. inosus</i> , <i>S. intermedius</i> , and <i>S. constellatus</i>), and <i>E. faecalis</i>	
Telavancin	Theravance (CA, USA)	Lipoglycopeptide	ABSSSI	<i>S. aureus</i> (including MSSA and MRSA), <i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. anginosus</i> group (includes <i>S. anginosus</i> , <i>S. intermedius</i> , and <i>S. constellatus</i>), <i>E. faecalis</i> (vancomycin-susceptible strains only)	
			HABP, VABP	<i>S. aureus</i> (including MSSA and MRSA)	

[†]Data taken from [47].

[†]Ceftobiprole medocartil (Basilea Pharmaceutica) is not approved in the USA, but has been approved in Europe for the treatment of CABP and HABP (excluding VABP) [48] and was also approved in 2008 in Canada, Switzerland and Ukraine for the treatment of cSSSI [49].

ABSSSI: Acute bacterial skin and skin structure infections; CABP: Community-acquired bacterial pneumonia; CRSP: Ceftriaxone-resistant *S. pneumoniae*; cSSSI: Complicated skin and skin structure infections; HABP: Hospital-acquired bacterial pneumonia; MSSA: Methicillin-susceptible *S. aureus*; PRSP: Penicillin-resistant *S. pneumoniae*; VABP: Ventilator-associated bacterial pneumonia; VRSA: Vancomycin-resistant *S. aureus*.

Table 5. Preclinical antibiotics currently in development against Gram-negative organisms.

Agent name	Company	Antibiotic class	Gram-negative pathogens	Development status
POL7080 [†]	Polyphor Ltd (Allschwil, Switzerland)	Protegrin mimetic	<i>Pseudomonas aeruginosa</i>	Phase I trial completed, currently recruiting for Phase II trial participants
RPX2014/RPX7009 [‡]	The Medicines Company (NJ, USA)	Carbapenem/new β -lactamase inhibitor combination	<i>Klebsiella pneumoniae</i>	Phase I completed
BAL30072 [§]	Basilea Pharmaceutica (Basel, Switzerland)	Monosulfactam	<i>Acinetobacter baumannii</i> , <i>Enterobacter spp.</i> , <i>Klebsiella oxytoca</i> and <i>P. aeruginosa</i>	In Phase I
DS-8587 [¶]	Daiichi-Sankyo (Tokyo, Japan)	Quinolone	<i>A. baumannii</i>	In Phase I
CTIX1278 [#]	Cellceutix (MA, USA)	Defensin mimetic	<i>K. pneumoniae</i>	<i>In vivo</i> animal model

[†]Data taken from [60,61].

[‡]Data taken from [62].

[§]Data taken from [63–65].

[¶]Data taken from [66].

[#]Data taken from [62,67].

cIAI in hospitalized adults, the overall rate of clinical cure at the test-of-cure visit was 90% (18/20) among patients with infections due to ESBL-producing Gram-negative pathogens [69].

In July 2013, the FDA designated eravacycline as a QIDP with fast-track status [70]. Patients are currently being recruited for Phase III studies comparing eravacycline with ertapenem for the treatment of cIAIs [71], and comparing eravacycline with levofloxacin for the treatment of cUTIs [72].

Plazomicin (ACHN-490) (Achaogen, CA, USA) is an aminoglycoside derivative of sisomicin, with *in vitro* activity against *E. coli*, *K. pneumoniae* and *A. baumannii* [73,74] and similar activity against ESBL-producing strains of *Enterobacter spp.*, *E. coli* and *K. pneumoniae* [75]. Plazomicin was more active *in vitro* than gentamicin, tobramycin and amikacin against *A. baumannii* [74]. No evidence of ototoxicity or nephrotoxicity was observed in healthy subjects administered with escalating single and multiple doses of plazomicin [76].

A Phase II trial has assessed the safety and efficacy of plazomicin, compared with that of levofloxacin, in patients with cUTIs and acute pyelonephritis caused primarily by non-MDR Enterobacteriaceae [77]. Plazomicin was well-tolerated by patients and demonstrated comparable efficacy to levofloxacin, in terms of microbiological eradication of the causative pathogen and clinical outcome, specifically, resolution of baseline signs and symptoms [78]. A Phase III study is currently recruiting participants with HABP due to carbapenem-resistant Enterobacteriaceae

to evaluate the efficacy and safety of plazomicin plus meropenem or tigecycline [79].

Nemonoxacin (TG-873870) (TaiGen Biotechnology Co., Ltd, Taiwan) is a novel nonfluorinated quinolone currently in clinical development for the treatment of CABP and diabetic foot infections. Nemonoxacin has broad-spectrum of activity against both Gram-positive (*S. aureus*, *S. capitis*, *S. pneumoniae* and *E. faecalis*) and Gram-negative (*E. coli*) pathogens. It has been shown to have similar activity to ciprofloxacin, moxifloxacin and levofloxacin against Enterobacteriaceae [80]. A Phase III study is currently recruiting participants with CABP to evaluate the efficacy and safety of intravenous nemonoxacin with levofloxacin.

JNJ-Q2 (Furiex Pharmaceuticals, NC, USA) is another novel, broad-spectrum fluoroquinolone antibiotic that is in clinical development. It has been shown to be highly active against Gram-positive pathogens (including MRSA and MDR *S. pneumoniae*), Gram-negative and atypical pathogens [81]. In a Phase II clinical trial, JNJ-Q2 demonstrated efficacy and tolerability in for the treatment of ABSSSI. In 2013, JNJ-Q2 was designated a QIDP by the FDA [82].

Combination antibiotics

As well as the single-agent antibiotics, there are two β -lactam/ β -lactamase inhibitor combinations and one non- β -lactam/ β -lactamase inhibitor combination in advanced development against Gram-negative bacteria.

Ceftolozane (CXA-101, FR264205) (Cubist Pharmaceuticals, MA, USA) is a novel

oxymino-aminothiazolyl cephalosporin with potent *in vitro* activity against *P. aeruginosa* [83]. The combination of ceftolozane/tazobactam (CXA-201) showed the same *in vitro* potency against *P. aeruginosa*, and was also active against *E. coli* and *K. pneumoniae* [84]. Although the *in vitro* activity of ceftolozane/tazobactam was low against ESBL-producing *K. pneumoniae*, this agent retained activity against ESBL-producing *E. coli* [85]. Phase II trial data for ceftolozane/tazobactam plus metronidazole, versus meropenem, demonstrated clinical cure rates of 89% (47/53) and 96% (23/24), respectively, among patients with cIAI at the test-of-cure visit [86]. Ceftolozane/tazobactam demonstrated microbiological success against *E. coli* (90% [34/38]), *K. pneumoniae* (100% [8/8]) and *P. aeruginosa* (100% [4/4]).

In June 2012, ceftolozane/tazobactam was designated a QIDP by the FDA [87]. In June 2014, it was announced that the FDA had accepted a new drug application, with priority review, for ceftolozane/tazobactam for the treatment of cUTI and cIAI, based on the Phase III trial data [88].

Relebactam (Merck & Co., Inc., NJ, USA), formerly known as MK-7655, is a novel diazabicyclooctane β -lactamase inhibitor. In combination with imipenem, MK-7655 exhibited *in vitro* activity against AmpC-producing *P. aeruginosa* and KPC-producing *K. pneumoniae* [89]. In September 2014, the FDA designated relebactam as a QIDP [90]. Phase II clinical studies are currently evaluating relebactam, in combination with imipenem/cilastatin, for the treatment of cUTI and cIAI.

Avibactam (previously known as NXL104) is another diazabicyclooctane β -lactamase inhibitor, with a spectrum of antimicrobial activity comprising class A ESBLs, class A carbapenemases, class C and some class D enzymes [91]. Ceftazidime-avibactam (AstraZeneca, London, UK/Forest Laboratories, NY, USA) is a combination of an established β -lactam antibiotic with a novel non- β -lactam β -lactamase inhibitor. *In vitro* studies confirm that avibactam enhances the activity of ceftazidime against most β -lactamase-producing Enterobacteriaceae [92] including KPC-producing *K. pneumoniae* [93], and reverses AmpC-mediated resistance in *P. aeruginosa* [94].

Ceftaroline-avibactam (AstraZeneca, London, UK/Forest Laboratories), a combination of a new broad-spectrum cephalosporin

ceftaroline with avibactam is also in development [95]. Phase II clinical trials comparing ceftaroline-avibactam with doripenem in adult patients with cUTI was completed in 2014; however, the results of this study are not yet available. *In vitro* studies confirm that ceftaroline-avibactam has potent activity against Enterobacteriaceae including those that produce KPC, various ESBL types and AmpC [95].

Phase II trials have been conducted comparing ceftazidime-avibactam plus metronidazole, versus meropenem, for the treatment of cIAI [96], and comparing ceftazidime-avibactam for cUTI against imipenem-cilastatin [97]. Among cIAI patients administered with either ceftazidime-avibactam or meropenem, a favorable microbiological response (defined as eradication of the baseline pathogen) was observed at the test-of-cure visit in 90–100% of patients with *E. coli*, *K. pneumoniae* and *P. aeruginosa* (including ceftazidime-non-susceptible isolates) [96]. Rates of favorable microbiological response were 76–86% for the ceftazidime-avibactam treatment group and 70–80% for the imipenem-cilastatin group among patients with cUTI due to ceftazidime-susceptible and resistant *E. coli* [97].

In 2013, ceftazidime/avibactam was designated a QIDP [98]. A Phase III study comparing the safety, efficacy and tolerability of ceftazidime/avibactam with metronidazole, compared with meropenem, has recently been completed among patients with cIAI [99]. Participants are now being recruited for Phase III clinical trials comparing ceftazidime/avibactam against doripenem among patients with cUTI [100], and against meropenem for patients with HABP, including VABP [101].

Omadacycline (Paratek Pharmaceuticals Inc, CA, USA) is a new tetracycline derivative antibiotic belonging to the aminomethycycline class currently in clinical development for the treatment of infectious diseases including ABSSSI, CABP and UTI [80]. *In vitro* studies reported a broad-spectrum of activity of omadacycline including against Gram-positive, Gram-negative, anaerobic and atypical pathogens. Phase II study comparing omadacycline with linezolid for the treatment of SSSI initially reported to show comparable efficacy across all the study populations, however this study has been terminated [80,102].

Conclusion

Several promising new agents are in clinical development, for example, single agent

antibiotics such as ceftobiprole and eravacycline, and combination antibiotics such as ceftolozane/tazobactam and ceftazidime/avibactam. Historically, β -lactam/ β -lactamase inhibitor combinations, such as amoxicillin/clavulanic acid and piperacillin/tazobactam, have proven more resilient than single agents to β -lactamase-mediated resistance. It will be interesting to see how the combinations of new cephalosporin/old β -lactamase inhibitor (e.g., ceftolozane/tazobactam) versus old cephalosporin/new non- β -lactam β -lactamase inhibitor (e.g., ceftazidime/avibactam) compete in the HAI arena. Should these new agents be approved, the burden of HAIs could be significantly reduced and patient welfare considerably improved, but the development of new agents must still progress in the meantime.

Recent data from the NHSN gave an estimate of 721,800 HAIs among inpatients of all ages in US acute care hospitals in 2011, equating to 1 in 25 patients [5]. This study used different patient populations, different definitions of HAIs and different data collection and analysis methods to the earlier study by Klevens *et al.* [2] which may explain, in part, the difference in the total number of estimated HAIs.

The above statistics show that HAIs are significant healthcare issues that are still unresolved due, in part, to the causative Gram-negative pathogens that have acquired antimicrobial drug resistance. Policies and recommendations

have been proposed by healthcare agencies such as the AHRQ, CDC, HHS and IDSA to aid healthcare facilities to address the burden of HAIs. These policies alone are not enough, however, and there has been a resurgence in the efforts of the US government and the FDA to encourage drug developers to progress new antibiotics for combating resistant Gram-negative pathogens.

Through good infection control, blocking and tackling, and novel programs like CUSP, healthcare is making a dent in prevention. Many simple measures like hand washing remain imperative. As US healthcare moves to pay-for-performance, time will tell if this impacts real infection rates and the resultant goal of saving lives.

Future perspective

The future will entail better diagnostic testing to detect the DNA or RNA of resistant organisms at the point of care before culture results, allowing for more targeted therapy, thus reducing resistance [103,104]. Pharmacogenetics will usher in the day when we know a patient's genetic makeup will make them more likely to respond to certain antibiotics [105,106]. Host factors that affect bacterial resistance, like gut flora [107], will be explored, and interactions with our immune system. Cold plasma [108], ionization [109] and ultraviolet light [27] will kill organisms in the air, surfaces, and even topically on

EXECUTIVE SUMMARY

Healthcare-associated infections

- Healthcare-associated infections (HAIs) occur in hospitalized patients within 48 h of admission, who have also been in contact with the healthcare service in the previous year.
- HAIs caused by Gram-negative organisms are associated with antibiotic resistance.

Controlling healthcare-associated infections

- US healthcare agencies have introduced measures, such as surveillance systems, prevention programs, antimicrobial stewardship policies and quality measures to address the burden of all HAIs.
- There are data showing reductions in the rates of HAIs in US healthcare institutions, as a result of these implementing control and preventative measures.

Antimicrobial agents for healthcare-associated infections

- There has been a gradual decline in the development of new antibiotics approved by the US FDA.
- This decrease has been addressed by the introduction of new US government and FDA policies to aid pharmaceutical companies in the resumption of their antimicrobial research programs, particularly against Gram-negative pathogens.
- Several new antibiotics are currently in development, with both single-agent and combination inhibitors in the clinical pipeline.

patients. Infectious burdens will be detected in those same environments at a time when hands are cleared to be clean via sensors. Finally, many novel uses of organisms' genetic sequences will lead to new antimicrobials.

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