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BRIEF REPORT

Cost Analysis of New Antibiotics to Treat Multidrug-Resistant Bacterial Infections: Mind the Gap

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ABSTRACT

Introduction: Guidelines for treatment of multidrug-resistant (MDR) bacteria rely on newly approved antibiotics, with limited evidence of their effectiveness for treating these infections. Data regarding cost of such an approach are lacking. We aimed to evaluate estimated cost of using newly approved antibiotic drugs compared to older antibiotics for the treatment of difficult-to-treat pathogens.

Methods: MDR bacteria of interest included those defined by the World Health Organization as critical or of high priority for research. Old and newly approved antibiotics for these bacteria, defined as approved before or after January 2010, respectively, were evaluated for treatment cost and for 14-day treatment course. Estimated annual costs were calculated based on the Centers for Disease Control and Prevention's' report on MDR bacteria prevalence in US hospitalized patients. Old and new drugs costs were compared.

Results: The cost of a 14-day treatment course for methicillin-resistant *Staphylococcus aureus* bacteremia with a newly approved drug was found to be 6 to 60 times higher than that of older drugs. Similarly, the cost of a 14-day course for carbapenem-resistant Enterobacterales or MDR *Pseudomonas aeruginosa* was doubled with new drugs; and for carbapenem-resistant *Acinetobacter baumannii*, ~ 20 times higher with newer drugs. Annual incremental costs of treating difficult-to-treat Gram-negative bacteria with new drugs ranged from 30 million to over 500 million USD.

Conclusions: Using newly approved antibiotic drugs for MDR infections carries a large incremental cost. Additional data to support survival benefit of these drugs are required to justify the price differences. Subgroups of patients who would benefit most from treatment should be defined.

Keywords: Antibiotics; Costs analysis; Guidelines; MDR

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Key Summary Points

Why carry out this study?

Guidelines for treatment of multidrug-resistant (MDR) bacteria rely on newly approved antibiotics.

We aimed to assess how much would it cost to base treatment for multidrug-resistant bacterial infections on those new antibiotics.

What was learned from the study?

Annual incremental cost of new antibiotics could reach 30–500 million USD for some bacteria.

Lack of solid evidence for superior effectiveness of new antibiotics for these bacteria complicates treatment decisions.

Cost should be part of the discussion while considering use of newly approved antibiotics until further evidence for effectiveness accumulates.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13663976.

INTRODUCTION

Multidrug-resistant (MDR) bacterial infections are a growing problem worldwide. According to a recent Centers for Disease Control and Prevention (CDC) report, over 2.8 million cases of antibiotic-resistant infections occur annually in the US, resulting in over 35,000 deaths [1]. In addition to the medical challenges posed by these infections, they also constitute a public health and economic burden. The spending for one MDR infection has been reported to be 165% higher than for non-MDR infection, with an incremental cost of 1383 USD. This has been translated to a national annual cost of 2.2 billion USD in 2014, mostly attributed to antibiotic costs [2, 3].

Recently, the Infectious Diseases Society of America (IDSA) issued guidelines for treatment of antimicrobial-resistant Gram-negative bacteria. Newly approved drugs dominate treatment recommendations in these guidelines, although their effectiveness for specific MDR infections is supported by limited evidence for survival benefit [4, 5].

We aimed to evaluate the estimated cost of using newly approved antibiotics compared to old antibiotics for the treatment of specific difficult-to-treat pathogens.

METHODS

We searched the US Food and Drugs Administration (FDA) website for antibacterial drugs with in vitro activity against specific MDR ESKAPE bacteria [vancomycin-resistant *Enterococcus faecium* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Klebsiella pneumoniae*, carbapenem-resistant *Acinetobacter,* MDR *Pseudomonas aeruginosa*, and carbapenem-resistant *Enterobacter* spp.) [6]. ESKAPE pathogens were chosen as bacteria of interest based on World Health Organization definition of these bacteria as critical or high priority for research and drug development [7]. Drugs approved between 1 January 2010 and 14 November 2020 were included, and were considered "new" [6]. For each resistant pathogen, we created a list of potentially covering antibiotics, divided into "old" and "new" according to approval before and after 1 January 2010, respectively [4, 6, 8]. Drugs not approved for use in the US were excluded (teicoplanin, intravenous fosfomycin). For each drug, the cost per day and for a 14-day treatment course were determined using the IBM Micromedex Red Book website [9]. The annual price of treating each bacteria using its individual drug options was calculated by multiplying the cost of a 14-day treatment

Table 1 Included bacteria, relevant "old" and "new" drugs, dosages, and costs

Bacteria name	Estimated number of cases in the US in hospitalized patients (2017)	Old antibiotic drugs				New antibiotic drugs			
		Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)	Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)
Vancomycin-resistant *Enterococcus faecium* (VRE)	54,500	Daptomycin	8-10 mg/kg × 1/day (~ 750 mg × 1/day)	1093	59,544,520	Omadacycline	IV: loading 200 mg; Maintenance 100 mg × 1/day O: 300 mg × 1/day	IV: 6200 PO: 6951	IV: 337,900,000 PO: 378,829,500
		Linezolid	600 mg × 2/d	2188	119,226,380				
		Tigecycline	Loading: 200 mg; Maintenance: 100 mg × 2/day	6989	380,889,600	Oritavancin	1200 mg (Single dose)	2987	162,791,500
		Telavancin	10 mg/kg × 1/day (~ 750 mg × 1/day)	8595	468,443,850				

Table 1 continued

Bacteria name	Estimated number of cases in the US in hospitalized patients (2017)	Old antibiotic drugs				New antibiotic drugs			
		Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)	Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	323,700	Vancomycin	15 mg/kg × 2/day (~ 1 gr × 2/day)	115	37,225,500	Ceftaroline	600 mg × 2/day	6778	2,194,038,600
		Daptomycin	8-10 mg/kg × 1/day (~ 750 mg × 1/day)	1093	353,804,100	Dalbavancin	1,000 mg (single dose) + 500 mg (1 week later)	5691	1,842,176,700
		Linezolid	600 mg × 2/d	2188	708,255,600	Oritavancin	1200 mg (Single dose)	2987	966,891,900
		Telavancin	10 mg/kg × 1/day (~ 750 mg × 1/day)	8595	2,782,201,500	Tedizolid	200 mg × 1/day	5170	1,673,529,000
						Lefamulin	IV: 150 mg × 2/day PO: 600 mg × 2/day	IV: 3444 PO: 4620	IV: 1,114,822,800 PO: 1,495,494,000
						Delafloxacin	IV: 300 mg × 2/day PO: 450 mg × 2/day	IV: 4452 PO: 2380	IV: 1,441,112,400 PO: 770,406,000
						Omadacycline	IV: loading 200 mg, maintenance 100 mg × 1/day PO: 300 mg × 1/day	IV: 6200 PO: 6951	IV: 2,006,940,000 PO: 2,250,038,700

Table 1 continued

Bacteria name	Estimated number of cases in the US in hospitalized patients (2017)	Old antibiotic drugs				New antibiotic drugs			
		Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)	Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)
Carbapenem-resistant Enterobacterales	13,100	Meropenem	2 g × 3/day	717	9,392,700	Ceftazidime-avibactam	2.5 g × 3/day	18,084	236,900,400
		Colistimethate	Loading: 9 MU (∼ 300 mg); Maintenance: 4.5 MU × 2/day (∼ 150 mg × 2/day)	941	12,327,100	Meropenem-Vaborbactam	4 g × 3/day	16,632	217,879,200
		Amikacin	15 mg/kg × 1/day (∼ 1 gr × 1/day)	260	3,406,000	Cilastatin / Imipenem / Relebactam	1.25 g × 4/day	17,976	235,485,600
		Gentamicin	240 mg × 1/day	44	576,400	Cefiderocol	2 g × 3/day	18,480	242,088,000
		Tigecycline	Loading: 200 mg once; Maintenance: 100 mg × 2/day	6989	91,555,900	Eravacycline	1 mg/kg × 2/day (∼ 100 mg × 2/day)	3293	43,138,300
						Plazomicin	15 mg/kg × 1/day (∼ 1000 mg × 1/day)	10,584	138,650,400
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)	8500	Colistimethate	Loading: 9 MU (∼ 300 mg); Maintenance: 4.5 MU × 2/day (∼ 150 mg × 2/day)	941	7,998,500	Cefiderocol	2 g × 3/day	18,480	157,080,000
		Minocycline	100 mg × 2/day	5448	46,308,000				
		Tigecycline	Loading: 200 mg once; Maintenance: 100 mg × 2/day	6989	59,406,500				
		Meropenem	2 g × 3/day	717	6,094,500				

Table 1 continued

Bacteria name	Estimated number of cases in the US in hospitalized patients (2017)	Old antibiotic drugs				New antibiotic drugs			
		Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)	Drug name	Dose	Cost per treatment course (USD)[a]	Estimated annual cost (USD)
Multidrug-resistant *Pseudomonas aeruginosa*	32,600	Gentamicin	240 mg × 1/day	44	30,676,600	Ceftazidime-avibactam	2.5 g × 3/day	18,084	589,538,400
		Amikacin	15 mg/kg × 1/day (~ 1 gr × 1/day)	260	8,476,000	Ceftolozane-tazobactam	HAP/VAP: 3 g × 3/day UTI: 1.5 g × 3/day	HAP/VAP: 12,628 UTI: 6314	HAP/VAP: 411,672,800 UTI: 205,836,400
		Colistimethate	Loading: 9 MU (~ 300 mg); Maintenance: 4.5 MU × 2/day (~ 150 mg × 2/day)	941	1,434,400	Cefiderocol	2 g × 3/day	18,480	602,448,000
						Cilastatin / Imipenem / Relebactam	1.25 g × 4/day	17,976	586,017,600

HAP Hospital-acquired pneumonia, *IV* intravenous, *PO* Pers. ob., *UTI* urinary tract infection, *VAP* ventilator-associated pneumonia

[a] All treatment costs were calculated for a 14-day treatment course, unless mentioned otherwise

course and the estimated number of annual infections, as detailed in the recent CDC report [1] (see details regarding cost calculation in Supplement 1). Ethical approval was not required for this study, as data were collected from public databases.

RESULTS

The list of included bacteria, their relevant "old" and "new" drugs, and daily costs are provided in Table 1.

For VRE, the most commonly used old drug cost for a 4-day treatment course ranged between 1093 USD (daptomycin) and 2188 USD (linezolid), and reached up to 6989 USD (tigecycline) and 8595 USD (telavancin). New drug options for VRE are limited, and include omadacycline (6200 USD per course), and oritavancin (2987 USD per course of one dose).

For MRSA bacteremia, a 14-day course of the new drug ceftaroline would cost over six times more than a course of daptomycin (6778 vs. 1093 USD), and ~ 60 times the cost of 14 days of vancomycin, the current first-line treatment for these infections [10]. For other sources of infection, the costs of old drugs are also significantly lower for MRSA pneumonia, with 14 days of ceftaroline or lefamulin treatment costing at least 2–3 times more than for linezolid and 40–60 times than for vancomycin, while, for skin and soft tissue infections, clindamycin, trimethoprim-sulfamethoxazole, and doxycycline would have negligible costs compared to lipoglycopeptides, delafloxacin, or omadacycline (Table 1).

For MDR Gram-negative infections, treatment with old drugs is based on various combinations of colistin, tigecycline, meropenem, and aminoglycosides. Recent IDSA guidelines recommend as preferred treatments for carbapenem-resistant Enterobacterales (CRE) and difficult-to-treat *Pseudomonas aeruginosa* mainly new drugs, including ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol [4]. A treatment course with any of these would cost double that for the colistin-tigecycline combination and ~ 20 times the cost of colistin monotherapy, commonly used for Carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections [11].

Considering 8500 annual CRAB infections in hospitalized patients [1], treating all of them with cefiderocol instead of colistin would have an annual incremental cost of ~ 150 million USD, 20 times that of colistin, based on randomized controlled trials (RCT) showing increased mortality with the former drug [12]. Similarly, the additional treatment cost of 3100 annual carbapenem-resistant Enterobacteriaceae infections with ceftaizidime-avibactam over the colistin-tigecycline combination would have an incremental cost of ~ 31 million USD, more than doubling the cost. For 32,600 MDR *P. aeruginosa* annual cases, imipenem-relebactam treatment would cost 577 million USD more than amikacin, 69 times the cost of the older drug.

DISCUSSION

Infections with ESKAPE pathogens are life-threatening, severe infections, carrying substantial mortality. Preventive strategies have accomplished a reduction/stabilization in the number of ESKAPE infections in the US [1]. Yet, highly resistant Gram-negative infections were recently estimated to require between 39 and 138.2 days of therapy for 10,000 patient encounters. In other countries, rates are even higher, with over 10% of Gram-negative bacteremias caused by difficult-to-treat resistant pathogens [13].

Due to the severity and poor outcome of these infections, development of new drugs has been prioritized by policy-makers. Four years after FDA's approval of ceftazidime-avibactam, new anti-CRE drugs were reported to be used less widely than expected. Explanations suggested for the relatively low uptake (estimated at 35%) include high cost, shortage or non-availability issues, and lack of evidence from RCTs supporting superior efficacy and safety [14]. Ongoing emergence of resistance to these new drugs could also contribute to the restricted use, as well as delays in the availability of susceptibility testing methods [13, 15]. Even with

restricted use, annual sales of ceftazidime-avibactam, meropenem-vaborbactam, and plazomicin in 2018–9 were estimated at 101 million USD, while it has been estimated that, with a 100% uptake, the cost would have been 289 million [13].

Recent IDSA guidelines for the treatment of difficult-to-treat Gram-negative infections rely mainly on new antibiotics [4]. Recommendations in these guidelines were based on observational studies and two small RCTs, showing mortality benefit of meropenem-vaborbactam for carbapenem-resistant Enterobacterales infections and imipenem-relebactam for MDR *Pseudomonas* infections [16]. Cefiderocol, as treatment for carbapenem-resistant Gram-negative bacteria, was demonstrated to result in increased all-cause mortality compared with colistin-based therapy in the only RCT published for this indication [12].

We found that the incremental cost of selecting new drugs over older ones could reach hundreds of millions of USD annually, with limited evidence for superior effectiveness. These costs were calculated for hospitalized patients, not considering the increased burden of such infections in other institutional sites of care, such as nursing homes.

Trials addressing new drugs specifically for highly resistant pathogens are scarce, and the evidence for the use of some of these drugs is sometimes very poor. We found that using the ceftaroline for MRSA bacteremia, which has never been tested in an RCT, would cost 60 times the cost of vancomycin. Nevertheless, Gram-positive infections are less of a problem compared to Gram-negative ones. Many options are available for treating skin and soft tissue infections caused by MDR Gram-positive infections, and the choice of using new drugs may be only for the purpose of oral step-down or the use of single-dose administration. For Gram-negative bacteria, clinicians may face infections that are resistant to all older drugs, since resistance to colistin and meropenem have increased, and the use of new drugs would likely be necessary. Regarding Gram-negative infections, the annual cost of cefiderocol for CRAB infections was estimated to be 20 times that of colistin. The only RCT comparing the two showed increased all-cause mortality with cefiderocol [12, 17]. Trials like the latter, specifically including patients with MDR infections, are difficult to conduct. Their performance involves identifying a sufficient number of patients with a possibly life-threatening infection, and obtaining their consent to receive an old drug perceived to be less effective.

It should be noted that our cost analysis is limited to the situation in the US. Hence, the generalization of our data may be limited, and may depend on the cost of the drugs in other countries, the epidemiology of resistant bacteria, and the availability of new drugs.

The discussion regarding antibiotic cost may change in the near future if the UK's innovative 'subscription-type' payment model gets broad acceptance. In this model, the UK's National Health Service will pay a bulk sum for an annual payment to pharmaceutical companies, purchasing the whole yearly supply of necessary antibiotics based on the health benefits to patients according to NHS consideration. This will likely negate the need to specifically consider the price of each antibiotic before treating a patient, and is also thought to be able to secure a constant pipeline of new antimicrobials, by providing companies with an upfront payment which can be used in future development ventures. Two antibiotic drugs that were first selected for purchase in this model are cefiderocol and ceftazidime-avibactam [18].

CONCLUSIONS

Older drugs have limited effectiveness and some have considerable toxicities [4]. The development of new drugs is of high priority, and their use may provide important benefits for patients, including a survival benefit. Nevertheless, additional proof of such benefits should come from clinical trials, and drug prices should be part of the discussion while considering the use of these drugs. Local protocols regarding antibiotic use should take into account regional costs and the availability of new antibiotics, in addition to the epidemiology of various MDR bacteria. Assessment of the risk of toxicity and/or reduced effectiveness should be conducted

on a case-by-case basis prior to decisions on an antibiotic regimen. Subgroups of patients who would benefit most from these new, expensive drugs, should be defined, and include populations often excluded or under-represented in RCTs, e.g., immunocompromised patients, patients with baseline renal dysfunction, and elderly patients. Future studies should include these patients and report results specifically for these subgroups.

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Authorship Contributions. Study concept was perceived by Noam Tau; study design: Noam Tau, Dafna Yahav; acquisition of data: Noam Tau, interpretation of data: Noam Tau, Dafna Yahav, Daniel Shepshelovich, drafting of the manuscript: Noam Tau, Dafna Yahav; critical revision of the manuscript: all authors.

Disclosures. Dafna Yahav, Daniel Shepshelovich and Noam Tau have nothing to disclose.

Compliance with Ethics Guidelines. Ethical approval was not required for this study, as data were collected from public databases.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current stud other than the data provided in Table 1.

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REFERENCES

1. CDC (Centers for Disease Control and Prevention). ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 2019. 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Accessed 1 Dec 2020.

2. Thorpe KE, Joski P, Johnston KJ. Antibiotic-resistant infection treatment costs have doubled since 2002, now exceeding USD2 billion annually. Health Aff Proj Hope. 2018;37(4):662–9. https://doi.org/10.1377/hlthaff.2017.1153.

3. Serra-Burriel M, Keys M, Campillo-Artero C, et al. Impact of multi-drug resistant bacteria on economic and clinical outcomes of healthcare-associated infections in adults: Systematic review and meta-analysis. PLoS ONE. 2020;15:1. https://doi.org/10.1371/journal.pone.0227139.

4. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of america antimicrobial resistant treatment guidance: gram-negative bacterial infections. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa1478.

5. Yahav D, Tau N, Shepshelovich D. Assessment of data supporting the efficacy of new antibiotics for treating infections caused by multidrug-resistant bacteria. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa457.

6. Drugs@FDA: FDA Approved Drug Products. 2019. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed 12 Jul 2019.

7. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3): 318–27. https://doi.org/10.1016/S1473-3099(17)30753-3.

8. Theuretzbacher U, Bush K, Harbarth S, et al. Critical analysis of antibacterial agents in clinical development. Nat Rev Microbiol. 2020;18(5):286–98. https://doi.org/10.1038/s41579-020-0340-0.

9. IBM. IBM Micromedex RED BOOK. 2020. https://www.ibm.com/products/micromedex-red-book. Accessed 1 Dec 2020.

10. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011;52(3):e18-55. https://doi.org/10.1093/cid/ciq146.

11. Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018;18(4):391–400. https://doi.org/10.1016/S1473-3099(18)30099-9.

12. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2020. https://doi.org/10.1016/S1473-3099(20)30796-9.

13. Strich JR, Warner S, Lai YL, et al. Needs assessment for novel Gram-negative antibiotics in US hospitals: a retrospective cohort study. Lancet Infect Dis. 2020;20(10):1172–81. https://doi.org/10.1016/S1473-3099(20)30153-5.

14. Clancy CJ, Potoski BA, Buehrle D, Nguyen MH. Estimating the treatment of carbapenem-resistant enterobacteriaceae infections in the United States using antibiotic prescription data. Open Forum Infect Dis. 2019;6(8):344. https://doi.org/10.1093/ofid/ofz344.

15. Satlin MJ. Languid uptake of ceftazidime-avibactam for carbapenem-resistant gram-negative infections and continued reliance on polymyxins. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa065.

16. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-lactamase inhibitor combinations. Clin Microbiol Rev. 2020;34:1. https://doi.org/10.1128/CMR.00115-20.

17. Powers Iii JH. Scientific evidence, regulatory decision making and incentives for therapeutics in infectious diseases: the example of cefiderocol. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa1795.

18. Robinson, J. First antimicrobial drugs purchased via new 'subscription' payment model. Pharmaceut J. 2021;306:7945.