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Review

Dual beta-lactam therapy for serious Gram-negative infections: is it time to revisit?

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ABSTRACT

We are rapidly approaching a crisis in antibiotic resistance, particularly among Gram-negative pathogens. This, coupled with the slow development of novel antimicrobial agents, underscores the exigency of redeploying existing antimicrobial agents in innovative ways. One therapeutic approach that was heavily studied in the 1980s but abandoned over time is dual beta-lactam therapy. This article reviews the evidence for combination beta-lactam therapy. Overall, *in vitro*, animal and clinical data are positive and suggest that beta-lactam combinations produce a synergistic effect against Gram-negative pathogens that rivals that of beta-lactam–aminoglycoside or beta-lactam–fluoroquinolone combination therapy. Although the precise mechanism of improved activity is not completely understood, it is likely attributable to an enhanced affinity to the diverse penicillin-binding proteins found among Gram negatives. The collective data indicate that dual beta-lactam therapy should be revisited for serious Gram-negative infections, especially in light of the near availability of potent beta-lactamase inhibitors, which neutralize the effect of problematic beta-lactamases.

1. Introduction

Despite our best efforts, antibiotic resistance continues to be a pressing public health concern. Evidence shows that the only way to stay ahead of the resistance curve is to follow the best infection control practices, use antibiotics prudently, and bring new agents to market (WHO, 2001, 2012). From a drug development perspective, there has been an impressive response to combat infections due to resistant Gram-positive pathogens. Since 2000, 7 antibiotics were approved with activity against infections due to methicillin-resistant *Staphylococcus aureus* (Boucher et al., 2009; Liu et al., 2011). This is in stark contrast to the Gram-negative antibiotic landscape. Over the past 15 years, only 3 antibiotics (doripenem, ertapenem, and tigecycline) with expanded Gram-negative activity have been approved by the US Food and Drug Administration, and none are considered chemically novel compounds (Boucher et al., 2009). The dismal progress in expanding our antibiotic armamentarium is further exacerbated by the rising rate of resistance among key Gram-negative pathogens (Anonymous, 2004; Master et al., 2011; Nordmann et al., 2011; Spellberg et al., 2011). Not only are we observing increases in resistance to frequently encountered Gram-negative pathogens like *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, but we are also witnessing a rise in the number of multidrug-resistant (MDR) strains. In certain areas of the world, pan-drug–resistant Gram-negative infections are becoming commonplace and forcing healthcare providers to use older, previously used antibiotics such as colistin (Bradford et al., 2004; Falagas and Bliziotis, 2007; Falagas and Kasiakou, 2005; Nicasio et al., 2008; Nordmann et al., 2011; Urban et al., 2008).

Growing resistance rates, combined with a diminishing arsenal of safe and effective antimicrobial agents, have created an impetus to utilize existing antimicrobial agents in innovative ways for invasive Gram-negative infections. One therapeutic approach that is often employed in practice is combination therapy involving the use of agents from different antibiotic classes. Such therapy is advocated by the Infectious Diseases Society of America guidelines for treatment of many serious Gram-negative infections (Baddour et al., 2005; Freifeld et al., 2011; Mandell et al., 2007; Mermel et al., 2009; Osmon et al., 2013; Tunkel et al., 2004). The 2 most frequently recommended combinations are a beta-lactam with an aminoglycoside or a fluoroquinolone. While often employed in clinical practice, evidence supporting the enhanced efficacy of dual-agent therapy is limited, and there are concerns due to the potential risk for toxicity and unintended ecologic sequelae (Paul et al., 2003, 2004; Safdar et al., 2004; Tamma et al., 2012; Traugott et al., 2011).

The discouraging outcomes with these aforementioned combinations have served as a catalyst for investigations into alternative combination therapies for Gram-negative infections. One combination approach that was heavily studied in the 1980s but later abandoned is dual beta-lactam therapy. Overall, *in vitro*, animal, and human data were largely positive, but perceived need for this combination therapy was low due to the high success and susceptibility rates with single beta-lactam agents (DeJace and Klastersky, 1986; Gutmann et al., 1986). However, the rising resistance rates, lack of new agents, and limited success of current combination approaches have created an impetus to re-investigate the existing literature on currently available beta-lactam

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Table 1
Penicillin-binding protein affinities of beta-lactam antibiotics.

Antibiotic	PBP	IC_{50} (μg/mL)	
		P. aeruginosa	*E. coli*
Penicillins			
Amoxicillin (Curtis et al., 1979a, 1979b; Noguchi et al., 1979)	1a	5.2	0.7–8
	1b	7	2.2–4.2
	2	1.2	0.9–3
	3	4.6	4.1–10
Ampicillin (Curtis et al., 1979a, 1979b; Noguchi et al., 1979)	1a	0.7	1.4–13
	1b	5.6	3.9–5.6
	2	1	0.7–12
	3	0.7	0.9–10
Azlocillin (Zimmermann, 1980)	1a	0.1	NA
	1b	0.4–0.47	NA
	2	NA	NA
	3	0.02	NA
Carbenicillin (Curtis et al., 1979a, 1979b; Noguchi et al., 1979; Zimmermann, 1980; Labia et al., 1985)	1a	0.06–1.3	2–2.1
	1b	0.26–1.4	5–6
	2	2.6	4–4.5
	3	0.03–0.9	2.1–2.5
Mecillinam (Curtis et al., 1979a, 1979b; Noguchi et al., 1979)	1a	>25 to >250	>25 to >250
	1b	>25 to >250	>25 to >250
	2	<0.1–0.25	<0.1–0.25
	3	>25 to >250	>25 to >250
Methicillin (Curtis et al., 1979a, 1979b; Noguchi et al., 1979)	1a	NA	9 to >25
	1b	NA	>25–250
	2	NA	>25–30
	3	NA	5.5–11
Mezlocillin (Curtis et al., 1979a, 1979b)	1a	NA	1.5
	1b	NA	8
	2	NA	0.9
	3	NA	0.025
Moxalactam (Komatsu and Nishikawa 1980; Labia et al., 1985)	1a	<0.016	0.3–35.1
	1b	0.9	2–33.6
	2	NA	28
	3	<0.016	0.08–72.7
Piperacillin (Noguchi et al., 1979)	1a	0.9	18
	1b	3.0	0.6
	2	0.2	0.2
	3	<0.1	0.1
Temocillin (Labia et al., 1984)	1a	NA	32
	1b	NA	97
	2	NA	> 250
	3	NA	110
Ticarcillin (Noguchi et al., 1979; Labia et al., 1984)	1a	1.0	2
	1b	1.3	28
	2	6.2	20
	3	0.7	4
Cephalosporins			
Cefamandole (Curtis et al., 1979a, 1979b)	1a	NA	<0.25
	1b	NA	16
	2	NA	37
	3	NA	1
Cefazolin (Curtis et al., 1979a, 1979b; Nozaki et al., 1979)	1a	NA	0.19 to <0.25
	1b	NA	4.7–5.3
	2	NA	3.6–4.6
	3	NA	5.1–5.8
Cefepime (Pucci et al., 1991; Kohler et al., 1999; Davies et al., 2007; Davies et al., 2008)	1a	0.1	1.5–3.8
	1b	0.035–2	1.5–3.7
	2	8 to >25	0.25–0.6
	3	<0.0025–0.1	0.03–0.1
Cefoperazone (Curtis et al., 1979a, 1979b; Matsubara et al., 1980)	1a	Good	0.5
	1b	Good	1.5
	2	Poor	0.9
	3	Good	0.05
Cefotaxime (Curtis et al., 1979a, 1979b; Maejima et al., 1991)	1a	0.041	0.05–0.11
	1b	0.92	0.39–0.7
	2	>100	3.93–5
	3	0.049	<0.05–0.14
Cefotiam (Nozaki et al., 1979)	1a	NA	0.075
	1b	NA	0.7
	2	NA	2.2–42
	3	NA	0.11
Cefoxitin (Matsuhashi and Tamaki 1978; Curtis et al., 1979a, 1979b; Noguchi et al., 1979; Zimmermann, 1980; Labia, Baron et al. 1984)	1a	0.13–5	0.1–0.3
	1b	0.09–3	0.5–3.9
	2	>25 to >250	>25 to >250
	3	0.09–1.4	1.1–5.8