

Choosing more effective antimicrobial combinations for empiric antimicrobial therapy of serious gram-negative rod infections using a dual cross-table antibiogram

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Background: Early antimicrobial therapy with antibiotics effective in vitro is a powerful predictor of a favorable outcome with gram-negative rod bacteremia or pneumonia. Most clinicians rely on institutional antibiograms based on testing patient isolates with individual antimicrobials when choosing initial empiric regimens for suspected gram-negative sepsis and use 2 antibiotics at the outset to maximize the likelihood that the infecting species will be susceptible to at least 1 of those used. Current hospital antibiograms do not take into account cross-resistance among different antimicrobials, which would seem of importance in selecting initial combination regimens for serious gram-negative bacillary infections.

Methods: We examined the in vitro efficacy of various potential dual antimicrobial combinations by cross-table susceptibility analysis for bloodstream and lower respiratory tract isolates of Enterobacteriaceae and *Pseudomonas aeruginosa* from patients hospitalized in our university hospital during 2004-2006 using SafetySurveillor software (Premier Inc, Charlotte, NC). Effective regimens were defined as dual combinations in which the isolate was susceptible in vitro to at least 1 of the 2 antibiotics.

Results: Individual antimicrobial susceptibilities for the 604 hospital-wide and 145 intensive care unit gram-negative bloodstream or lower respiratory tract isolates ranged from 81% to 91%. The most effective dual combinations were imipenem based (95% for the hospital as a whole, 92%-95% susceptible in the intensive care unit), and some combinations were significantly superior ($P < .05$). Combination β -lactam antimicrobials were also effective.

Conclusion: Traditional hospital susceptibility reporting of individual antibiotic susceptibilities is currently used to guide empiric antimicrobial therapy. Cross-resistance analyses allow selection of initial dual regimens that are more likely to be effective in vitro and, most importantly, clinically. Double β -lactam regimens were among the most effective regimens; empiric use of such combinations may be underutilized and warrants reexamination. (Am J Infect Control 2008;36:S57-61.)

An increase in the prevalence of antimicrobial resistance has made the selection of effective empiric antimicrobial therapy ever more challenging because the initiation of inadequate therapy (by in vitro susceptibilities) has been associated with much worse clinical outcomes, especially with bacteremia or pneumonia.^{1,2}

In most cases, the reason why an initial empiric antimicrobial regimen is inadequate and associated with therapeutic failure is resistance of the infecting isolate or isolates to the agent or agents in the regimen chosen.^{1,2} Giving 2 drugs at the outset increases the likelihood that the potentially infecting microorganism will be susceptible to the regimen. The Society of Critical Care Medicine in its surviving sepsis guideline³ now strongly recommends the use of 2 antibiotics of different classes for the empiric treatment of suspected gram-negative infections. This concept of a dual initial gram-negative antimicrobial regimen is also endorsed by the American Thoracic Society and Infectious Disease Society of America joint guideline for the treatment of health care-associated pneumonia.⁴

Clinicians rely on traditional institutional antibiograms based on testing a large number of institutional isolates against individual antimicrobials when choosing initial empiric combination regimens for suspected gram-negative sepsis. Current hospital antibiograms do not take into account cross-resistance between various antimicrobials, which would seem important in

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selecting initial combination regimens for life-threatening gram-negative infections. This may be especially important for *Pseudomonas aeruginosa*.⁵ Clinicians are often unaware that resistance to 1 class of antibiotics may also be associated with resistance to 1 or more other classes of antibiotics.⁶⁻⁸ A recent study showed that the common practice of empirically adding a fluoroquinolone to an extended-spectrum β -lactam for treatment of suspected hospital-acquired pneumonia with *Pseudomonas aeruginosa* in an intensive care unit (ICU) was associated with an unacceptably high rate of inadequate therapy.⁹

We believe that it is essential to strive to provide clinicians with better data on which to guide their selection of antimicrobials for potentially life-threatening infections and report herein a new approach to analyzing standard susceptibility data, made possible by a new commercial software package (SafetySurveillor; Premier Inc, Charlotte, NC)—*cross-table dual susceptibility testing*, defined as calculating the susceptibilities of each isolate to at least 1 agent in each potential dual antimicrobial combination—that we believe comprises a superior method for selecting antimicrobial combinations for gram-negative infection.

METHODS

We examined conventional single-drug susceptibilities of 604 bloodstream (210 events) and lower respiratory tract (371 events) isolates of Enterobacteriaceae and *P aeruginosa* by in vitro Kirby-Bauer testing (BIOMIC V3 System; Giles Scientific, Santa Barbara, CA) from our 500-bed university hospital for the 2-year time interval from July 2004-June 2006, including 145 isolates from a 24-bed ICU with high antimicrobial utilization (Table 1). Each patient had only 1 isolate that contributed to our database. The susceptibilities of the *latest* isolate from each patient was selected using SafetySurveillor software (Premier Inc.).¹⁰

We next examined cross-table susceptibilities among these isolates using the SafetySurveillor software. Intermediate susceptibility was categorized as resistant. Effective regimens by cross-table analysis were defined as dual combinations in which the isolate was susceptible to at least 1 of the 2 drugs. Because 30% of empiric antimicrobial orders in our hospital are written for potential coverage of *P aeruginosa*,¹¹ ceftriaxone combinations were not analyzed by cross-table analysis. We further examined cross-table susceptibility data for our 24-bed ICU to determine whether there were differences between the hospital-wide versus the ICU isolates. Differences in the cross-table dual susceptibilities of various antibiotic combinations were analyzed statistically by 2-sided Fisher exact test.

Table 1. Bloodstream and lower respiratory tract isolates of gram-negative bacilli analyzed by dual cross-table susceptibility, University of Wisconsin hospital and clinics, 2004-2006

Species	No. of Isolates	
	Hospital	ICU
<i>Pseudomonas aeruginosa</i>	247	54
<i>Escherichia coli</i>	115	27
<i>Klebsiella pneumoniae</i>	75	21
<i>Enterobacter cloacae</i>	67	21
<i>Klebsiella oxytoca</i>	34	6
<i>Serratia marcescens</i>	26	7
<i>Enterobacter aerogenes</i>	17	7
<i>Citrobacter freundii</i>	10	1
<i>Proteus mirabilis</i>	7	0
<i>Citrobacter koseri</i>	6	1
Total	604	145

NOTE. Two hundred ten bloodstream events and 371 lower respiratory tract events.

RESULTS

Pseudomonas aeruginosa and *Escherichia coli* were the most common gram-negative bloodstream or lower respiratory tract isolates in our hospital (Table 1). Individual drug susceptibilities for the 604 hospital-wide bloodstream and lower respiratory tract isolates ranged from 82% to 91% (boldface data, Table 2).

The most effective hospital combinations by cross-table susceptibility analysis were all imipenem based (Table 2). By cross-table susceptibility analysis, the combination of imipenem and gentamicin (95%) or imipenem and ciprofloxacin (95%) were significantly more likely to provide a regimen likely to be effective in vitro ($P = .0049$; odds ratio [OR], 0.50; 95% confidence interval [CI]: 0.31-0.80 for an ineffective regimen). Imipenem-based combinations (95%) were superior to the very popular combination of piperacillin-tazobactam and ciprofloxacin (91%) ($P = .0089$; OR, 0.53; 95% CI: 0.38-0.84 for an ineffective regimen). Surprisingly, combinations of β -lactam antimicrobials for empiric therapy yielded excellent efficacy (93%-95%).

When we examined cross-table dual susceptibilities of isolates from our 24-bed intensive care unit, the number of isolates was lower (145) than the hospital as a whole, and susceptibilities to single drugs ranged from 81% (ciprofloxacin) to 90% (imipenem) (Table 3). The combination most likely to be effective in vitro was imipenem combined with gentamicin, which gave a 95% likelihood of in vitro susceptibility to 1 or both drugs by cross-table susceptibility analysis. An aminoglycoside-sparing regimen that utilized cefepime or imipenem in combination with ciprofloxacin had a 4% to 5% greater likelihood of in vitro efficacy by cross-table analysis than the popular institutional combination of

Table 2. Cross-table dual susceptibility analysis of 604 hospital-wide, gram-negative bloodstream and lower respiratory tract isolates, University of Wisconsin hospital and clinics, 2004-2006

	Cefepime	Piperacillin-tazobactam	Imipenem	Ciprofloxacin	Gentamicin
Cefepime	89	93	95	93	93
Piperacillin-tazobactam		87	95	91	94
Imipenem			91	95	95
Ciprofloxacin				82	91
Gentamicin					85

Table 3. Cross-table dual susceptibility analysis of 145 ICU gram-negative bloodstream and lower respiratory tract isolates, University of Wisconsin hospital and clinics, 2004-2006

	Cefepime	Piperacillin-tazobactam	Imipenem	Ciprofloxacin	Gentamicin
Cefepime	88	91	94	91	93
Piperacillin-tazobactam		83	93	87	92
Imipenem			90	92	95
Ciprofloxacin				81	91
Gentamicin					88

piperacillin-tazobactam and ciprofloxacin. However, as noted above, the combination of imipenem and gentamicin or ciprofloxacin was significantly more effective than piperacillin-tazobactam and ciprofloxacin ($P = .02$; OR, 0.34; 95% CI: 0.14-0.80 for an ineffective regimen). Combinations of β -lactam antibiotics in the ICU for initial empiric therapy were also surprisingly effective (91%-94%), comparable with combinations of β -lactams and aminoglycosides or fluoroquinolones.

DISCUSSION

Increasing reports have shown the importance of initial effective antimicrobial therapy in reducing patient mortality in bacteremia or pneumonia.^{1,2} It is known that, for patients in ICUs, mortality rises sharply if the empiric antibiotic therapy chosen does not have in vitro activity against the infecting pathogen. Recent studies have shown that not only it is essential to have an effective antimicrobial regimen, but it is also very important that empiric antibiotics be initiated in a timely fashion, whenever possible within 1 hour of presentation. Kumar et al found that the mortality in patient with sepsis and hypotension increased by 7.6% per hour that effective antimicrobial therapy was delayed.¹²

Current hospital antibiograms do not take into account cross-resistance between antimicrobials, which would seem of importance in selecting initial combination regimens for serious gram-negative infections. This may be especially important for *P aeruginosa*.¹³ Beardsley et al⁹ showed that the common assumption that a fluoroquinolone to an extended-spectrum β -lactam with *P aeruginosa* isolates from

patients with hospital-acquired pneumonia in an ICU did not improve the frequency of effective combinations. These authors examined local microbiologic data to develop institution-specific guidelines for the treatment of hospital-acquired pneumonia. Although the traditional American Thoracic Society/Infectious Disease Society of America guidelines made a distinction between early and late-onset nosocomial pneumonia at 5 days,⁴ these authors found that the infections by organisms resistant to piperacillin-tazobactam or cefepime were significantly more frequent in patients who had been hospitalized for more than 10 days, and adding ciprofloxacin did not significantly improve the in vitro efficacy of piperacillin-tazobactam or cefepime. They used a cross-table analysis of β -lactams compared with ciprofloxacin or aminoglycosides to determine that the addition of amikacin to a β -lactam improved the in vitro adequacy of empiric coverage and modified their institutional guidelines to use amikacin in patients hospitalized more than 10 days at the onset of pneumonia. No cross-table analyses were provided for other combinations.

Mizuta et al⁵ took the analysis of best combinations for empirical antimicrobial therapy 1 step further, using a combination antibiogram for *Pseudomonas aeruginosa*. They constructed a combination antibiogram in a matrix fashion and compared their combination antibiogram with the standard antibiogram. The combination antibiogram demonstrated that 1 ceftazidime-aminoglycoside combination that had slightly better activity, 97% vs 94%, respectively, but no statistical analysis was provided. Although isolates were only counted once for each patient at individual sites,

71% of the isolates were from the urinary tract. Subgroup analyses showed results that were not substantively different for urinary isolates, nonurinary isolates, or isolates from the ICU.

Cross-resistance among different classes of antibiotics may be more frequent than appreciated.⁶⁻⁸ In a 5-year summary of the SENTRY antimicrobial surveillance global program, Jones noted that there was a direct linear correlation between the fluoroquinolone susceptibility or resistance and susceptibility to other antimicrobial agents for *P aeruginosa*.¹⁴ Jones' data showed that resistance to 1 agent was likely to be associated with coresistance across 1 or more other antimicrobial classes. Similarly, a summary of *P aeruginosa* susceptibilities from ICU patients between 1993 and 2002 showed that rates of multidrug resistance to 3 or more agents increased from 4% to 14% over this period.⁷ We believe that cross-table analysis may be the best way to identify clinically relevant cross-resistance and, most importantly, select empiric regimens most likely to provide in vitro efficacy and a favorable therapeutic outcome.

Piperacillin-tazobactam and ciprofloxacin is a very popular broad-spectrum antipseudomonal combination in our and many other teaching hospitals. We found that alternative combinations, such as cefepime and gentamicin or an imipenem-based regimen, were more effective for the entire hospital and the ICU. A recent study examined the use of imipenem and gentamicin for 72 hours for all cases of suspected sepsis in a surgical ICU, followed by de-escalation, and did not find any increase in antimicrobial resistance.¹⁵ We believe that whenever very broad-spectrum regimens such as imipenem and ciprofloxacin or gentamicin are chosen, it is essential to deescalate antimicrobial therapy as soon as susceptibility data are available to try to prevent the emergence of resistance and loss of efficacy of these regimens over the long-term.¹⁶

Surprisingly, double β -lactam combinations showed excellent results as empiric regimens, comparable with a β -lactam with a fluoroquinolone or an aminoglycoside. Traditionally, double β -lactam combinations have not been viewed as acceptable options for empiric antimicrobial therapy. However, studies of double β -lactams have been published,^{17,18} showing therapeutic response rates similar to those obtained with combinations of a β -lactam and an aminoglycoside in patients with serious underlying disease and compromised host defense mechanisms. Hopefl¹⁸ reviewed the potential for synergy between double β -lactam combinations and concluded that most combinations were indifferent or additive in their effects, with very rare synergy or antagonism. He pointed out, however, that there may be a greater potential for double resistance with antimicrobials possessing a similar mechanism of action and of resistance,¹⁸ and there is in vitro and in vivo evidence

that some β -lactam combinations may be antagonistic against certain organisms such as *Enterobacter*, *Serratia*, or *P aeruginosa*, possibly mediated by induction or derepression of chromosomally mediated β -lactamases by 1 of the agents, leading to inactivation of the second.¹⁹ The true clinical relevance of this phenomenon is not clear at this time but must be kept in mind when considering the clinical use of double β -lactam combinations.

CONCLUSION

Traditional hospital antibiogram reporting of individual drug susceptibilities is currently used to guide empiric antimicrobial therapy. Standard antibiogram susceptibilities may not predict the best initial empiric drug combination because of unpredictable cross-resistance across antibacterial classes. Cross-table susceptibility analysis permits selection of dual regimens that are more likely to be effective in vitro (and clinically). Surprisingly, double β -lactam regimens were highly effective combinations, and empiric use of such combinations should be reconsidered.

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