

Optimizing Empiric Antibiotic Therapy in Patients with Severe β -lactam Allergy

Running Title: Antibiotic therapy for β -lactam allergic patients

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27 **Keywords:** gram-negative antibacterial therapy, combination antibiogram, β -lactam allergy

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29 **Abstract:**

30 Antibiotic selection is challenging in patients with severe β -lactam allergy due to declining
31 reliability of alternate antibiotics. Organisms isolated from these patients may exhibit unique
32 resistance phenotypes. The objective of this study was to determine which alternate antibiotics
33 or combinations provide adequate empiric therapy for patients with β -lactam allergy who
34 develop gram-negative infections at our institution. We further sought to determine the effect of
35 risk factors for drug resistance on empiric adequacy. A retrospective analysis was conducted of
36 adult patients hospitalized from September 2009 to May 2010 who had a severe β -lactam allergy;
37 a urine, blood, or respiratory culture positive for a gram-negative organism; and met pre-defined
38 criteria for infection. Patient characteristics, culture and susceptibility data, and pre-defined risk
39 factors for antibiotic resistance were collected. Adequacy of β -lactam and alternate antibiotics
40 was compared for all infections and selected subsets. The primary outcome was adequacy of
41 each alternate antibiotic or combination for all infections. One hundred sixteen infections (40
42 pneumonias, 67 urinary tract infections, 9 bacteremias) were identified. Single alternate agents
43 were less frequently adequate compared to β -lactams and compared to combination regimens.
44 Only in cases without risk factors for resistance did single-agent regimens demonstrate
45 acceptable adequacy rates; each factor conferred a doubling of risk for resistance. Resistance
46 risk factors should be considered when selecting empiric antibiotics for gram-negative pathogens
47 in patients unable to take β -lactams due to severe allergy.

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52 **Introduction**

53 Empiric antibiotic selection is important to optimize therapy for bacterial infections.
54 Morbidity and mortality increase for certain infections when empiric therapy is inadequate for
55 the causative pathogens.¹ Guidelines recommend consideration of local microbiologic data and
56 patient risk factors for drug resistance when choosing empiric therapy.² β -lactam antimicrobials
57 play a prominent role in the therapy of many community- and healthcare-associated infections.^{3,4}
58 Clinicians commonly encounter allergic intolerance to β -lactam antimicrobials and this may limit
59 therapeutic options, especially when the history includes a report of a severe reaction. Rates of
60 resistance among gram-negative pathogens to non- β -lactam antimicrobials are increasing,
61 rendering these alternate agents less useful.^{5,6} Studies to aid clinicians in selecting empiric
62 therapy in this population are lacking.

63 An institutional antibiogram that tabulates laboratory susceptibility of common pathogens
64 to antibacterial drugs can be a useful tool in selecting empiric therapy.^{3,7,8} The specificity of
65 antibiogram results to a given patient case can be increased by reporting on subsets of organisms
66 from various body sites or from patients in various care locations. Most antibiogram tables
67 report only single drug-organism susceptibility pairs without assessing the adequacy of
68 combinations of antibiotics.⁷ Patients with β -lactam allergy may have been exposed to other
69 classes of antimicrobials more frequently than those without allergy and may be infected with
70 pathogens exhibiting altered patterns of resistance.

71 Most β -lactam antibiotic agents are safe but allergic reactions are not uncommon. In rare
72 instances, these reactions may be severe.^{9,10} Cross-allergenicity between β -lactam agents and
73 other classes of antibiotics has been characterized.¹¹ Antimicrobials unlikely to cross-react with
74 β -lactams include: fluoroquinolones, aminoglycosides, trimethoprim sulfamethoxazole,¹¹
75 tetracyclines, and the monobactam aztreonam.^{9,10} Where severe allergy to one β -lactam agent is

76 reported (eg anaphylaxis to penicillin), many clinicians avoid the use of related β -lactam agents,
77 such as cephalosporins and carbapenems.⁹⁻¹¹

78 Recent reports document increasing rates of resistance to several non- β -lactam
79 compounds among clinically encountered gram-negative pathogens.^{5, 12-15} This may complicate
80 empiric therapy for patients with serious bacterial infections who are unable to receive β -lactam
81 drugs. Declining reliability of non- β -lactam antibiotic agents against gram-negative pathogens in
82 our health system over the past decade prompted an institution-specific study of this issue.

83 Several factors have been shown to be predictive of bacterial resistance in patients with
84 serious infections. The American Thoracic Society and the Infectious Diseases Society of
85 America mention several of these risks in their guideline documents on hospital-acquired
86 pneumonia, healthcare-associated pneumonia, and ventilator-associated pneumonia.² These
87 include recent encounters in the health system, past antimicrobial therapy, and concurrent
88 immunosuppression. Several published studies identified similar risk factors.^{6, 12-16}

89 Guidelines for the management of pharmacotherapy for patients with drug allergies have
90 been published and outline several options for patients with a history of severe reactions to β -
91 lactam drugs.¹⁷ These include a) skin testing, then b) graded challenge or desensitization, or
92 alternate (non- β -lactam) antibiotics. When treating serious infections in hospitalized patients,
93 the time constraints of empiric therapy usually limit these options to the latter. The purpose of
94 this study was to develop institution-specific recommendations for empiric therapy in patients
95 with a severe β -lactam allergy who develop gram-negative infections. The primary objective of
96 this study was to determine which alternate antibiotics or antibiotic combinations provide the
97 best empiric therapy for these infections. A secondary objective was to assess how selected risk
98 factors for drug resistance influence adequacy of antibiotics in this population.

99

100 **Materials and Methods**

101 We performed this retrospective analysis at Wake Forest Baptist Medical Center
102 (WFBMC), an 885-bed academic hospital located in Winston-Salem, North Carolina. Term
103 definitions and the criteria for the diagnosis of infection are displayed in Tables 1 and 2,
104 respectively. This study was approved by the WFBMC Institutional Review Board and informed
105 consent was waived.

106 ***Patient Population***

107 Potential patients for inclusion were identified from a computer-generated report of
108 blood, urine, and respiratory cultures. Adult patients hospitalized between 9/21/09 and 3/21/10
109 were included if they had a culture that grew a gram-negative, aerobic organism; had
110 susceptibility information available for that culture; had a history of severe β -lactam allergy;
111 were ≥ 18 years old; and were admitted to a non-pediatric service. Patients were excluded if
112 their cultures did not meet predefined criteria for infection (Table 2) or if the patient had
113 previously been included during that hospital stay. Medical records were used to collect patient
114 characteristics, including risk factors for gram-negative antibacterial resistance.

115 Only the first culture of a patient's hospital stay was included unless a second culture
116 drawn within 24 hours grew a different pathogen representing a separate infection by predefined
117 criteria.

118 ***Microbiologic Data***

119 Susceptibility data was recorded for the following antibiotics: aztreonam, ciprofloxacin,
120 amikacin, gentamicin, tobramycin, trimethoprim/sulfamethoxazole, meropenem,
121 piperacillin/tazobactam, and cefepime. Nitrofurantoin and tetracycline susceptibilities were
122 recorded for urine isolates only. Susceptibilities were determined by an automated, modified
123 broth microdilution method (Microscan) using the Clinical and Laboratory Standards Institute

124 susceptibility breakpoints.¹⁸ For the purposes of this study, susceptibility tests reported as
125 “intermediate” were considered resistant.

126 ***Outcomes Measured and Statistical Analysis***

127 The primary outcome was adequacy of each antibiotic or antibiotic combination for all
128 infections. Adequacy was defined as *in vitro* activity against gram-negative isolate(s) from each
129 culture.^{19,20} Adequacy of combination regimens required at least one antibiotic in the regimen to
130 exhibit *in vitro* activity. Secondary outcomes included adequacy based on type of infection and
131 adequacy based on selected risk factors. Differing rates of adequacy between antibiotics and
132 combinations were analyzed using the χ^2 or Fisher’s exact test, as appropriate. A goal sample
133 size of 120 patients was set to detect a difference of 15% between antibiotics or antibiotic
134 combinations for the primary outcome in order to achieve 80% power and a two-sided alpha
135 error of 0.05. To test the significance of the various risk factors for antimicrobial resistance (and
136 thus lack of adequacy), a backward-stepping multivariate regression analysis was performed for
137 three regimens (aztreonam, ciprofloxacin, and their combination). Included in this analysis were
138 the risk factors listed in Table 1, as well as patient age, infection type, and the dichotomous
139 variables of patient gender, ICU location, mechanical ventilation, presence of an indwelling
140 bladder catheter, and presence of a central venous catheter. Factors were removed from the
141 model for p-value > 0.10. We conducted a similar analysis examining the effect of the number
142 of risk factors on likelihood of resistance.

144 **Results**

145 A total of 276 cultures were screened for inclusion; 116 cultures met inclusion criteria.
146 The major reasons for exclusion were failure to meet predefined criteria for infection and
147 previous inclusion of the patient in the study. The 116 included cultures were from 109 patients;
148 five patients were included twice due to second hospitalizations and two had two cultures within

149 24 hours that represented infections at differing sites (Figure 1). Patient demographics are
150 summarized in Table 3. Forty percent of infections were hospital-acquired. One hundred thirty
151 pathogens were isolated and included *Escherichia coli*, 50 (38.5%), *Pseudomonas* species: 24
152 (18.5%), and *Klebsiella* species 20 (15.4%), *Enterobacter* species 12 (9.2%), *Proteus mirabilis* 6
153 (4.6%). Other organisms comprised 13.8% of the total.

155 **Primary Outcome**

156 Adequacy of antibiotics and antibiotic combinations for all infections is reported in
157 Figures 2 and 3. The adequacy provided by monotherapy with a traditional β -lactam exceeded
158 the adequacy provided by all alternate agents except amikacin. Combining aztreonam and
159 ciprofloxacin significantly improved adequacy of coverage to 85% versus ciprofloxacin alone,
160 while adding amikacin to ciprofloxacin or aztreonam significantly improved adequacy of
161 coverage to 91% and 88%, respectively, compared to ciprofloxacin or aztreonam monotherapy.
162 When compared to each other, these combinations did not differ significantly.

163 **Secondary Outcomes**

164 For the 40 pneumonias identified, aztreonam monotherapy was adequate in 55% of cases.
165 Ciprofloxacin monotherapy demonstrated adequacy in 63% of cases. Adding amikacin to
166 aztreonam and to ciprofloxacin resulted in improved adequacy compared to each monotherapy
167 (75% and 86%, respectively). However, only the ciprofloxacin /amikacin regimen achieved
168 statistically significant improvement. The addition of ciprofloxacin to aztreonam resulted in
169 80% adequacy, also statistically significant compared to ciprofloxacin alone. Statistically
170 significant differences were not noted between any two combination regimens. See Figure 4.

171 For the 67 urinary tract infections identified, aztreonam resulted in the highest rate of
172 adequacy (84%) among monotherapies. This was significantly higher than all other alternate
173 monotherapies. The use of amikacin in combination significantly improved adequacy of

174 ciprofloxacin to 94%. The addition of ciprofloxacin or of amikacin to aztreonam improved
175 adequacy to 85% and 94%, respectively, but these improvements were not statistically
176 significant.

177 Adequacy of the combinations examined did not differ significantly from one another.
178 See Figure 5.

179 With only nine primary bacteremias, this sub-group was not analyzed separately. We
180 included these cases in the composite primary outcome and in the analysis of the influence of
181 resistance risk factors.

182 ***Influence of Risk Factors***

183 When the effects of individual risk factors were analyzed using a backward stepping
184 logistic approach, several factors demonstrated significance depending upon the antimicrobial
185 regimen studied. These results are shown in Table 4 for three regimens: ciprofloxacin,
186 aztreonam, and their combination. Of note, for all three regimens the odds ratio for hospital-
187 acquired infection was significantly less than 1, suggesting that acquisition of infection in the
188 hospital conferred less risk of resistance to these regimens compared to community-acquired
189 infection.

190 The relationship between the number of risk factors identified and adequacy of several
191 regimens is shown graphically in Figure 6. In patients lacking these risk factors (0 risks
192 column), the adequacy provided by aztreonam or ciprofloxacin was similar to that provided by
193 their combination. Backward stepping multivariate regression analysis described the cumulative
194 relationship of the number of risk factors and decreasing adequacy. Each encountered risk factor
195 conferred approximately a two-fold risk for resistance (ciprofloxacin: OR: 1.908 (95% CI: 1.282-
196 2.84), $p=0.0015$; aztreonam: OR: 2.566 (1.597-4.123), $p<0.0001$; ciprofloxacin/aztreonam
197 combination: OR: 2.579 (1.560-4.262), $p=0.0002$.

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199 **Discussion**

200 Patients with a history of serious β -lactam allergy represent a unique patient population.
201 They are exposed to other classes of antibiotics more frequently than those without allergy,
202 which could alter patterns of antimicrobial resistance. Their allergies also reduce the antibiotic
203 options available for treatment. This study is the first to examine the issue of adequacy of
204 empiric therapy within this unique group of patients. A goal of our study was to learn how to
205 better care for infected patients with allergies to β -lactam drugs.

206 Most of the patients studied had a history of *severe* β -lactam allergy; however, patients
207 were included who had a status of *reaction unknown*. This was done because of the “real-
208 world”, clinical observation that when patients are unable to clarify their allergies, prescribers
209 frequently avoid β -lactam antimicrobials altogether.

210 Several principles can be drawn from this investigation that could assist clinicians with
211 choosing empiric therapy for patients at our institution. First, with the exception of amikacin,
212 bacteriologic adequacy with non- β -lactam “alternate” antibacterials was less than that of
213 traditional β -lactam drugs. This provides a strong motivation to ensure that a patient’s allergy
214 history is accurate and truly prevents the use of traditional β -lactam antibiotics.

215 Second, risk factors for resistance appeared to significantly influence the adequacy of
216 various antibiotic regimens in this population. For each risk factor encountered, risk of
217 resistance (and thus for lack of adequacy) approximately doubled. We observed acceptable
218 adequacy above 90% for single alternate antibiotic agents only in those patients in whom such
219 risk factors were absent. This fact highlights the importance of assessing the patient’s history
220 when designing empiric therapy.

221 Third, combination therapies may be more toxic than monotherapies, especially if they
222 include aminoglycosides. By clarifying the relative roles of the various antibiotics evaluated in
223 this population, this investigation may better equip clinicians to weigh toxicity risks against the

224 benefits of alternate antimicrobial regimens. Understanding situations in which these drugs are
225 necessary and when they can be avoided can help with empiric decision making.

226 Lastly, this study demonstrates the importance of combination therapy within this
227 population. With a few notable exceptions, single-agent, non- β -lactam empiric therapy in
228 patients with severe β -lactam allergy proved inadequate more than 25% of the time.
229 Combination regimens were found to have improved rates of adequacy compared to single
230 agents. With the exception of aztreonam monotherapy for urinary tract infections, combination
231 therapy is required to provide adequate empiric therapy if risk factors are present. We have
232 incorporated these clinical principles into care algorithms and guidelines at our institution.

233 A somewhat unexpected finding in this study was the observation that infections acquired
234 in the hospital were associated with less risk for resistance than those acquired elsewhere. Our
235 study was not designed to identify reasons for this result; however, this may be related to the fact
236 that use of ciprofloxacin and aztreonam is tightly controlled in our hospital and inpatient
237 exposure house wide to these antimicrobials has declined over the past five years. There are few
238 restrictions on the usage of these agents outside of our facility. Therefore, differences in rates of
239 resistance could be related to differences in antibiotic exposure.

240 This investigation is not without limitations. Although the study was very close to
241 achieving its target sample size, many differences between alternate therapies found to be non-
242 significant may have been statistically significant if more patients were included. Due to the
243 retrospective nature of the study, patient history data were limited to documentation in our
244 electronic medical records. Data on some aspects of care such as prior antibiotic use and
245 previous colonization or infection with resistant organisms may not have been available if not
246 documented in the medical record. It should be noted that this was a study of the pathogens
247 infecting patients admitted to our institution and specific results may not be applicable to other
248 settings.

249 In conclusion, this investigation demonstrates that compilation of patient and
250 susceptibility data into a disease-specific combination antibiogram can be used to refine empiric
251 antibiotic choices in a subpopulation of patients with severe β -lactam allergy. This approach
252 demonstrated that, in our medical center, combination therapy improves empiric adequacy
253 against infecting gram-negative pathogens in this group of patients. The source of infection and
254 risk factors for drug resistance should be considered when selecting empiric antibiotic therapy in
255 this setting. This approach could be used to develop institution-specific treatment
256 recommendations in other health care systems.

257

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318
319 **Table 1. Definitions of terms.**

Severe β-lactam allergy	Anaphylaxis, breathing difficulty, treatment requiring health care facility admission, hives, or reaction unknown
Traditional β-lactam	Penicillins, cephalosporins, cefamycins, carbapenems

Alternate agents	Aztreonam, aminoglycosides, fluoroquinolones, trimethoprim/sulfamethoxazole, nitrofurantoin, tetracyclines
Immunosuppressive disease	Currently have HIV/AIDS, hematologic malignancy, recent bone marrow transplant, neutropenia from any cause (absolute neutrophil count <1000 cells/mm ³)
Immunosuppressive therapy	>10 days systemic corticosteroid steroid use (>20 mg oral prednisone per day or equivalent), recent immunosuppressive chemotherapy ("recent" defined by expected pharmacologic effects of individual agents)
Nosocomial acquisition	Infection acquired after hospitalization of 48 hours and no history to suggest that the infection was present at time of admission
Community acquisition	Infection acquired prior to hospital length of stay of 48 hours.
Significant Culture Growth	Protected Specimen Brush (PSB) $>10^3$ cfu/mL Broncho-alveolar lavage (BAL) $>10^4$ cfu/mL Tracheal aspirate $>10^5$ cfu/mL Expectorated Sputum $\geq 2+$ Urine $>10^5$ cfu/mL
Risk factors for gram-negative antibacterial resistance	Receipt of antibiotics in the previous 90 days History of >2 days of hospitalization during the 90 days prior to the current hospitalization Immunosuppressive disease or therapy Residence in a skilled nursing facility or extended care facility prior to admission Receipt of home infusion therapy prior to admission

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	Receipt of renal replacement therapy prior to or at time of culture.
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322 Table 2. Criteria for infection

Pneumonia	Significant culture growth; new infiltrate on chest radiography without other obvious causes; and two of the following: • fever (temperature $>38^{\circ}\text{C}$) or hypothermia (temperature $<36^{\circ}\text{C}$) • leukocytosis $>10 \times 10^9$ cells/L • leukopenia $<5 \times 10^9$ cells/L • purulent secretions or production of purulent sputum • gas exchange degradation/increasing oxygen requirements
Catheter-associated urinary tract infection	Significant culture growth with no more than two species of microorganisms; indwelling urinary catheter in place at time of culture; and one of the following: • fever (temperature $>38^{\circ}\text{C}$) • suprapubic tenderness • costovertebral angle pain/tenderness
Non-Catheterized urinary tract infection	Significant culture growth with no more than two species of microorganisms and one of the following: • fever (temperature $>38^{\circ}\text{C}$) • urgency • frequency • dysuria • suprapubic tenderness • costovertebral angle pain/tenderness
Blood Stream Infection	Presence of any gram-negative bacillus on blood culture (obligate anaerobes not included)

323 **Figure 1**

324 Figure Legend: **Patients included and infection classification.**

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326 **Table 3. Patient characteristics and presence of risk factors (n=109).**

Age (years, mean +/- SD)	62 +/- 18
Males	35%
Hospital-acquired Infections	40%
ICU location at time of culture	36%
At least 1 Risk Factor Present	78%
Antibiotic in prior 90 days	59%
History of >2 day hospitalization	38%
Skilled nursing facility resident	18%
Immunosuppressive therapy	13%
Immunosuppressive disease	8%
Recipient of home infusion therapy	7%
End stage renal disease	5%

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333 **Figure 2.**

334 * $p < 0.05$ versus aztreonam alone; $^{\dagger}p < 0.05$ versus ciprofloxacin alone.

335 Figure Legend: **Percent adequacy of antibiotics for all infections (n=116)**

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337

338 **Figure 3.**

339 Black bars represent adequacy achieved by first antibiotic. White bars represent additional

340 adequacy gained by adding the second agent listed. * $p < 0.05$ versus aztreonam alone; $^{\dagger}p < 0.05$

341 versus ciprofloxacin alone.

342 Figure Legend: **Adequacy of Antibiotic Combinations for All Infections (n=116)**

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345 **Figure 4.**

346 Black bars represent adequacy achieved by first antibiotic. White bars represent additional

347 adequacy gained by adding the second agent listed. . * $p < 0.05$ versus aztreonam alone; $^{\dagger}p < 0.05$

348 versus ciprofloxacin alone.

349 Figure Legend: **Adequacy of Antibiotics for Pneumonia (n=40)**

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359 **Figure 5.**

360 Black bars represent adequacy achieved by first antibiotic. White bars represent additional

361 adequacy gained by adding the second agent listed. [†]p<0.05 versus ciprofloxacin alone.

362 Figure Legend: **Adequacy of Antibiotics for Urinary Tract Infections (n=67)**

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365 **Table 4**

366 Association between patient characteristics and antibiotic resistance

Patient characteristic	Ciprofloxacin resistance OR (95% CI)	Aztreonam resistance OR (95% CI)	Resistance to Ciprofloxacin + Aztreonam OR (95% CI)
Infection site			
Blood (reference)	1.0	1.0	
Respiratory	19.3 (1.6 – 229)†	57.0 (4.7 – 691)†	***
Urinary	27.2 (2.3 – 323)†	4.3 (0.4 – 44.0)	
Hospital-acquired infection	0.19 (0.05 – 0.69)†	0.2 (0.05 – 0.85)†	0.19 (0.04 – 0.91) †
Presence of urinary catheter	2.7 (0.97 – 7.6)	***	***
Presence of central line	4.3 (1.1 – 16.0)†	3.3 (0.98 – 10.9)	4.6 (1.2 – 18.5)†
Receipt of mechanical ventilation	***	***	3.7 (0.97 – 13.8)
Receipt of immunosuppressive therapy	***	3.5 (0.86 – 14.7)	3.7 (0.85 – 16.2)
Receipt of antibiotics within prior 90 days	3.1 (1.2 – 8.1)†	***	***
Admission to hospital within last 90 days	***	5.1 (1.6 – 16.5)†	4.0 (1.2 – 13.7)†
Admission from SNF or long-term care facility	5.3 (1.5 – 18.0)†	***	***

367 ***Factor dropped from model for p-value > 0.10

†p value < 0.05

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371 **Figure 6**

372 Figure Legend: **Adequacy of 4 regimens by number of risk factors for resistance (n=116)**

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