1601. Evaluation of Synergy with β-Lactams Plus Aztreonam Against *Pseudomonas aeruginosa* (PSA)

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Background. Combination therapy is often employed in the treatment of PSA infections. Agents commonly used in combination with β-lactams include aminoglycosides, polymyxins, and fluoroquinolones but are limited by resistance and toxicity concerns. The use of dual β-lactam therapy is an emerging area of interest for the treatment of patients with resistant Gram-negative pathogens. This study evaluated synergy between β-lactam agents and aztreonam (ATM) against PSA isolates with varying degrees of susceptibility.

Methods. 4 PSA clinical isolates were collected from Albany Medical Center; 1 ATCC isolate was used (Table 1). Synergy with cefepime (FEP), meropenem (MER), and ceftazidime (CAZ), each in combination with ATM, was assessed using fractional inhibitory concentration index determined by checkerboard method. Synergistic combinations were tested in 24-hour time-kill, utilizing minimum and steady-state physiological concentrations (C_{min} and C_{ss}). Tested bacteria were grown to late log phase, diluted to 1×10^6 cfu/mL and incubated at 37°C for 24 hours. Samples were drawn at 0, 2, 4, 6 and 24 hours. Synergy in time-kill was defined as ≥ 2 $\log_{10}$ cfu/mL kill greater than the most active individual agent at 24 hours.

Results. In checkerboard studies, combinations with ATM resulted in 80% synergy with FEP and 60% synergy with MER or CAZ combinations. ATM/MER and ATM/CAZ time-kill experiments resulted in indifference for most organisms and concentrations tested. For both single and combination regimens, initial killing was observed but varying degrees of regrowth occurred by 24 hours. The only strain with no regrowth at 24 hours was AMC-PSA2 (bactericidal activity and no regrowth at 24 hours observed for MER C_{min} MER C_{ss}, and MER+ATM C_{ss}). Against AMC-PSA2, CAZ+ATM at C_{min} was synergistic with limited regrowth observed.

Conclusion. Against PSA, tested β-lactam combinations with ATM resulted in lack of synergy in time-kill experiments, despite checkerboard results. Due to the extent of regrowth observed with nearly all single agent and combination regimens, testing of alternative combinations, including those that evade common resistance mechanisms such as efflux pumps or β-lactamases, and studies of dynamic concentrations are warranted.

Table 1. Isolate MICs (mg/L) and Checkerboard Results

	MER MIC	CAZ MIC	FEP MIC	ATM MIC	MER/ATM MIC	CAZ/ATM MIC	FEP/ATM MIC
AMC-PSA2	0.5	2	4	4	0.03/1 (S)	0.125/1 (S)	0.5/1 (S)
AMC-PSA7	16	4	4	16	4/2 (S)	1/2 (S)	1/4 (S)
AMC-PSA9	16	2	8	8	4/8 (I)	1/8 (I)	4/8 (I)
AMC-PSA10	4	32	2	16	0.125/1 (S)	0.5/1 (S)	0.5/4 (S)
ATCC 27853	1	2	2	4	0.125/4 (I)	0.5/2 (I)	0.5/0.5 (S)

S: Synergy; I: Indifference; A: Antagonism

Figure 1. Time-kill curves for MER+ATM and CAZ+ATM against AMC-PSA2

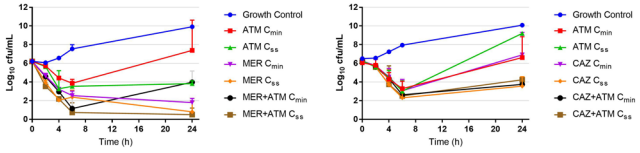
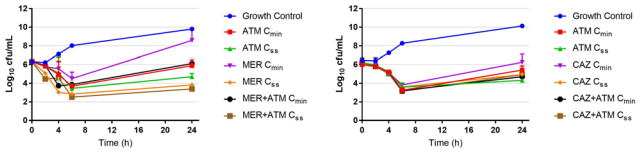


Figure 2. Time-kill curves for MER+ATM and CAZ+ATM against AMC-PSA10



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1602. Antibiotic Resistance Patterns of Clinical *Escherichia coli* Urinary Isolates by Outpatient Practice Type

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Background. Antibiotic-resistant *E. coli* (EC) infections represent a major cause of morbidity and mortality, and pose a challenge to antibiotic stewardship. At present, clinicians in outpatient facilities may not have access to local antibiogram data to guide stewardship. Additionally, antibiotic resistance may vary between types of outpatient practices.

Methods. Using the database of a major clinical reference lab, this study analyzed several years of antibiotic susceptibility results for outpatient urinary EC isolates from Washington State. We compared rates of resistance to antibiotics between different types of outpatient practices, categorized using a modification of published ambulatory practice categories. Logistic regression was used to examine the association of outpatient practice type with antibiotic resistance, controlling year, sex, and age.

Results. After adjusting for year, sex, and age, logistic regression found significantly higher odds of resistance in urology compared with the reference groups of general family practice for ampicillin (OR 1.35), ciprofloxacin (OR 2.27), trimethoprim-sulfa (OR 1.51) and gentamicin (OR 1.73). We also saw increased odds of resistance to ciprofloxacin in patients from an oncology clinic (OR 1.56) as well as patients from "All other specialties" (OR 1.37). A lower odds of resistance was found in OBGYN clinics for ampicillin (OR 0.86), trimethoprim-sulfa (0.81) while a greater odds or resistance in OBGYN clinics was found for nitrofurantoin (OR 1.36).

Conclusion. Antibiotic resistance in EC urinary isolates can vary across types of outpatient practices according to clinical practice type. This may reflect differences in patient morbidity and/or differences in antibiotic stewardship practices and deserves further investigation. Patients with recurrent cases of resistant UTIs are generally referred to a urologist, and this was reflected in our data as there a higher odds of resistance was found in urology clinics. Similarly, we found higher odds of resistance into nitrofurantoin, a commonly prescribed antibiotic for UTIs in pregnant women, in OBGYN clinics that may reflect prescribing practices. Use of clinical data to create facility and specialty-specific antibiograms in outpatient settings may enable improved and "precise" antibiotic stewardship.

Table 1. Clinical specialty and age category

	Age category (n)			
Clinical specialty	0-18 yrs	19-50 yrs	>50 yrs	*Total*
General family practice	1275	7852	8125	*17252*
Internal medicine	16	374	1570	*1960*
Pediatrics	807	70	1	*878*
Obstetrics and gynecology	83	1524	507	*2114*
Urology	2	54	301	*357*
Oncology	0	22	202	*224*
All other	62	664	704	*1430*
All clinical specialties	2245	10560	11410	*24215*

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1603. Observation of Treatment Outcomes During an Outbreak of Multidrug-Resistant *Shigella sonnei* Infections in a Retirement Community—Vermont, 2018

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Background. In 2018, CDC and the Vermont Department of Health investigated an outbreak of multidrug-resistant *Shigella sonnei* infections in a retirement community. Most *Shigella* infections are self-limited, but antibiotics are indicated for severe illness and sometimes to limit transmission. The Clinical and Laboratory Standards Institute has not yet established breakpoints for azithromycin, so laboratories cannot report resistance. Although breakpoints exist for ciprofloxacin, isolates with one fluoroquinolone resistance mechanism typically have minimum inhibitory concentrations within the susceptible range (≤ 0.25 μg/mL).

Methods. We reviewed charts for treatment outcomes of outbreak patients to evaluate clinical and microbiologic response. We defined clinical failure as ≥ 3 loose stools per day for ≥ 1 day after completion of antibiotics and microbiologic failure as a positive stool culture after completion of antibiotics. We used broth microdilution to

perform antimicrobial susceptibility testing, and whole-genome sequencing to identify resistance mechanisms.

Results. Among the 24 patients with culture-confirmed *Shigella* infection, 4 were hospitalized and 2 died. All isolates were multidrug-resistant (Table 1) and harbored mechanisms for resistance to ampicillin, ceftriaxone, trimethoprim-sulfamethoxazole, azithromycin, and ciprofloxacin. Fifteen patients received one course of ciprofloxacin, 5 received multiple courses of antibiotics, and 4 received no antibiotics. Overall, 6 patients had treatment failure (Table 2); all 4 patients who received azithromycin had subsequent clinical failure and 2 also had microbiologic failure. Two patients had failure after ciprofloxacin (1 clinical, 1 microbiologic).

Conclusion. This outbreak of highly resistant shigellosis highlights the importance of comprehensive susceptibility testing and systematic outcome studies. Evidence of treatment failure after azithromycin suggests that an appropriate clinical breakpoint is needed to inform clinical decision-making. Ciprofloxacin treatment failures were observed in patients with a susceptible strain harboring a resistance mechanism, warranting further investigation.

Table 1. Antibiotic susceptibility of *Shigella sonnei* outbreak isolates (n=24).

Antibiotic	Minimum inhibitory concentration (MIC)	Interpretation[1]
Amoxicillin-clavulanic acid	4–8 µg/ml	S
Ampicillin	> 32 µg/ml	R
Azithromycin	> 32 µg/ml	NS
Cefoxitin	2–4 µg/ml	S
Ceftriaxone	32–64 µg/ml	R
Ciprofloxacin	0.12 µg/ml	S
Meropenem	≤0.06 µg/ml	S
Nalidixic acid	≥32 µg/ml	R
Streptomycin[2]	32–>64 µg/ml	R
Tetracycline	≥32 µg/ml	R
Trimethoprim-sulfamethoxazole	> 4 µg/ml	R

[1] Interpretation of MIC is characterized according to Clinical and Laboratory Standards Institute (CLSI) breakpoints (S = susceptible; R = resistant; NS = non-susceptible) when available. Non-susceptibility is defined based on the epidemiological cutoff value (ECV) for *Shigella sonnei* of ≥32 µg/ml established by CLSI in 2015. The ECV should not be used as a clinical breakpoint to predict clinical effectiveness.
[2] CLSI breakpoints are not established for streptomycin; interpretive standards used are NARMS-established breakpoints for resistance monitoring and should not be used to predict clinical efficacy.

Table 2. Patients with treatment failures during an outbreak of multidrug-resistant shigellosis (n=6).

Age (years)	Sex	Antibiotic course (listed in sequence given)[1]	Clinical failure following completion of antibiotics?	Days to diarrhea resolution[2]	Microbiologic failure following completion of antibiotics?	Days to negative culture or PCR[3]
90	F	Azithromycin 250–500mg PO QD x4d[4]	Yes	6	Unknown[5]	-
		Ceftriaxone 1000mg IV QD x5d[4]	Yes	5	Unknown[5]	-
		Ampicillin 500mg IV QD x5d[4]	Yes	3	No	8
88	M	Ceftriaxone 1000–2000mg IV QD x3d	Yes	1	Unknown[5]	-
		Ciprofloxacin 250mg PO BID x3d	No	-1	No	12
88	F	Ciprofloxacin 500mg PO BID x3d	Yes	4	No	7
82	F	Azithromycin 500mg PO TID x3d	Yes	2	No	11
79	F	Azithromycin 500mg IV QD x2d[4]	Yes	12	Yes	-
		Ceftriaxone 1000–2000mg IV QD x4d[4]	Yes	9	Yes	43
42	M	Azithromycin 500mg PO QD x3d	Yes	3	Yes	-
		Ciprofloxacin 500mg PO BID x3d	No	-14	Yes	-
		Ciprofloxacin 500mg PO BID x3d	No	-25	No	1

[1] Median days between courses was 1 day (range 0–15).
[2] Days from end of antibiotic course to end of diarrhea (defined as ≥3 loose stools per day).
[3] Days from end of antibiotic course to first negative culture obtained. Daily cultures following antibiotic completion were not obtained for any patients; therefore these values should not be interpreted as days to microbiologic cure.
[4] Administered concurrently.
[5] Patients who did not have cultures between antibiotic courses are listed as having unknown microbiologic outcomes for these courses.

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1604. Response to a Cluster of *Haemophilus influenzae* Serotype A Cases in a Small Alaska Community, 2018

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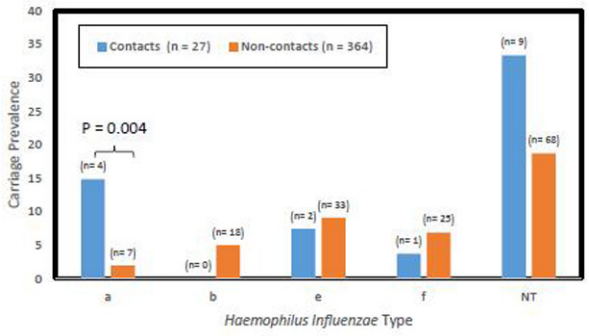
Background. Between May and July 2018, four invasive cases of *Haemophilus influenzae* type a (Hia) occurred in a remote Alaska community. A public health response was performed to prevent further illness and to understand local Hia transmission.

Methods. The team identified close contacts of the Hia patients, collected oropharyngeal (OP) swabs and provided prophylactic rifampin. Close contacts were persons who spent ≥4 hours with a Hia patient for ≥ 5 of the 7 days preceding hospitalization. Five days later, OP swabs were collected community-wide and prophylactic rifampin was offered to community members aged <10 years. Eight weeks later, OP swabs were collected from all willing community members. Samples were tested using PCR and culture to identify Hi carriage.

Results. No Hia cases occurred in this community after the response. The pretreatment carriage prevalence is shown in Figure 1. There was a significant difference in prevalence of Hia carriage between contacts (4/27, 14.8%) and non-contacts (7/364, 1.9%) ($P = 0.0043$). Contacts aged <10 years were significantly more likely to carry Hia compared with contacts aged ≥10 years (11/18 [61.1%] vs. 3/34 [8.8%], $P = 0.0001$). The case households had the highest proportion of individuals who carried Hia at any time, with 54%–60% of individuals in three case households carrying Hia at least once. Hia carriage was eliminated in two carriers who completed treatment and were tested immediately after rifampin prophylaxis. Testing 8 weeks later found that the prevalence of carriage did not significantly change in the contacts (5/42 [11.9%] to 6/25 [24%], $P = 0.18$) or the non-contacts (7/368 [1.9%] to 2/114 [1.8%], $P = 0.47$).

Conclusion. Children aged <10 years who had close contact with the Hia patients were the most likely to carry Hia. These findings suggest that people who do not have close contact do not benefit from prophylaxis as they have very low Hia carriage. While rifampin prophylaxis eliminated carriage of Hia in the short term, carriage prevalence did not change in the long term. Further research is needed to understand why contacts have such a high prevalence of carriage even after receiving appropriate prophylactic medication.

Figure 1: *Haemophilus influenzae* carriage prior to antimicrobial treatment, Alaska 2018.



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1605. Temperature Modulates the Rate of Increase of Antibiotic Resistance Across Europe

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Background. Widely recognized as a major public health threat globally, the rapid increase of antibiotic resistance in bacteria could soon render our most effective method to combat infections obsolete. Factors influencing the burden of resistance in human populations remain poorly described, though temperature is known to play an important role in mechanisms of bacterial growth and transmission.