Determining the clinical and economic impact of an formal intervention program against carbapenem-resistant *Klebsiella pneumoniae* infections

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eP036

Background

- The UPMC Antimicrobial Management Program (AMP) and XDR Pathogen Lab have collaborated to develop treatment algorithms for multi-drug resistant Gram negative bacterial infections
  - Based on strain genetics, resistance mechanisms, minimum inhibitory concentrations (MICs) and results of time-kill assays.
- In June 2013, UPMC AMP introduced a formal intervention program in which we help guide the management of carbapenem-resistant *K. pneumoniae* (CR-KP) bacteremia.

Goals

- To determine the clinical and economic impact of the intervention program against CR-KP bacteremia.

Methods

- The AMP team responds in real-time to electronic medical record (TheraDoc) alerts for (+) CR-KP bloodstream cultures in the clinical microbiology laboratory
- AMP physicians and pharmacists interact with team managing bacteremic patients to guide antimicrobial choices, dosages, duration of therapy, and monitoring for toxicity, based on our treatment algorithms and clinical expertise.
- We performed an interim analysis of clinical economic parameters for the treatment of CR-KP bacteremia in the pre-intervention (6/07-6/13) and post-intervention periods (6/13-12/13).

Results

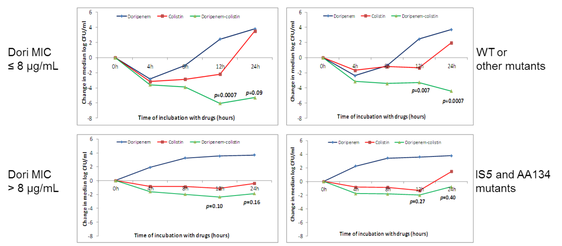
Table 1. Timeline for the development of the AMP intervention program against CR-KP bacteremia

Time frame	Achievement
January to early May 2013	-Identify best therapeutic regimen against KPC-*Klebsiella pneumoniae* in the lab (incorporating minimum inhibitory concentration (MIC) and genetic resistance data for UPMC strains) -Develop a treatment algorithm
May to early June 2013	-Work with Antimicrobial Management Program (AMP) physicians and pharmacists to refine proposed treatment algorithm - Present proposal to ID Grand Rounds to get feedback and buy-in from ID physicians
June to present	- Update the *UPMC Guide to Antimicrobial Chemotherapy* to include the finalized algorithm - Initiate intervention phase

Figure 1. XDR Pathogen Lab: Identifying optimal antimicrobial combinations against UPMC CR-KP strains

***ompK36* porin genotypes and carbapenem-colistin responses**

- 23 ST258 strains
  - 8 WT/other; 8 AA134 mutants; 7 IS*5* mutants
    - 79% (18/25) colistin-resistant (MIC >2 μg/mL)
  - Time-kills: Doripenem (8 μg/mL) and colistin (2 μg/mL)



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Aminoglycoside responses

- In our earlier experiments, doripenem-gentamicin was not as effective as doripenem-colistin against gentamicin-resistant strains
  - About 60% of UPMC CR-*Kp* strains are gentamicin-susceptible
- Time-kills against 10 gentamicin-susceptible and 5 -resistant strains

Responses of representative gentamicin-susceptible strains to gentamicin-containing regimens

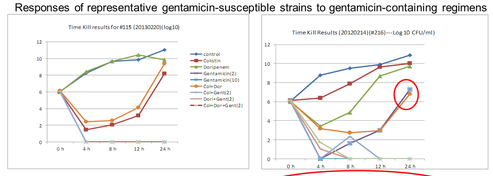

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Figure 2. Clinical data for treatment regimens among patients with CR-KP bacteremia

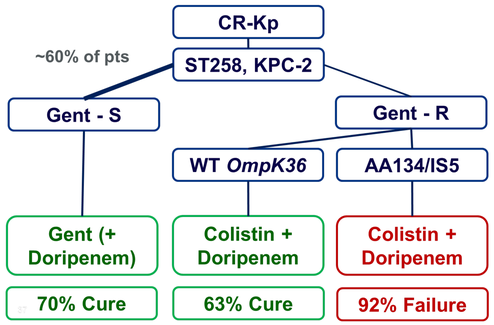
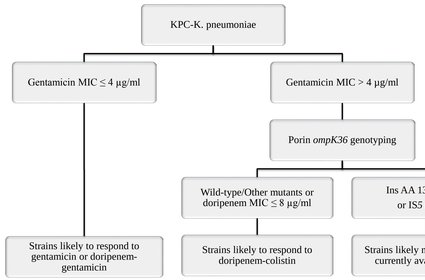


Figure 3. Developing a treatment algorithm



TREATMENT RECOMMENDATIONS FOR INFECTIONS DUE TO KLEBSIELLA PNEUMONIAE CARBAPENEMASE (KPC) PRODUCERS

Ertapenem-resistant *Klebsiella pneumoniae* (KPC) Susceptible to gentamicin	Gentamicin 7mg/kg PLUS (Doripenem 1g IV q8h OR Meropenem 1g IV q8h)
Ertapenem-resistant *Klebsiella pneumoniae* (KPC) Resistant to gentamicin, Susceptible to colistin	Doripenem 1g IV q8h PLUS Colistin IV (see colistin dosing, page 57) PLUS inhaled Ccolistin (if pneumonia) 75mg twice daily

Figure 4. Overview of the AMP intervention program

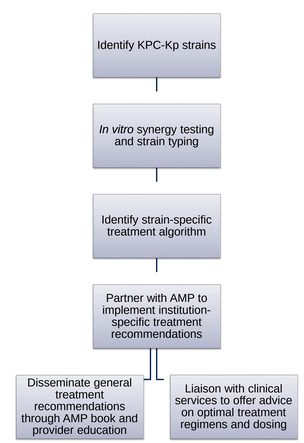


Table 2. Impact of AMP intervention on mortality and length of stay

Factors	Pre-intervention	Post-intervention
Dates	June 2007 through May 2013	June to December 31, 2013
# patients	83	9
# patients died within 3 days of blood culture*	8	2
30-day mortality rate	**45% (34/75)**	**0% (0/7)†**
Hospitalization stay after (+) blood culture	**34 days**	**14.5 days††**

***Patients who died within 3 days were excluded from analysis**
† p=0.04 †† p=0.065

Table 3. Impact of AMP intervention on readmission and total hospital charges

Dates	Pre-intervention	Post-intervention
Avg Total Charges	$ 2,013,371	$ 1,132,327
Median Total Charges	$ 1,185,198	$ 381,977
Estimated Avg Total Cost	$671,124	$377,442
Estimated Median Total Cost	$395,066	$127,326

Table 4. Breakdown of hospital charges

	Pre-intervention		Post-intervention	
	Avg	Median	Avg	Median
Antibiotic	$267,211	$104,653	$172,837	$21,045
ICU admission	$268,523	$196,617	$57,761	$41,890
Lab/Pathology services	$502,210	$284,801	$366,075	$109,641
non-ICU admission	$97,020	$33,250	$74,615	$45,135
Operating room	$47,605	$34,182	$49,465	$42,376
Other diagnostics	$3,146	$3,434	$1,986	$1,894
Other services	$216,509	$92,840	$43,581	$11,543
Outpatient	$57,706	$17,855	$35,816	$3,941
Pharmacy	$418,063	$227,450	$251,924	$56,436
Radiology	$121,586	$86,192	$65,389	$48,076
Rehab/SNF	$1,629	$37,700	$4,275	
Transplant	$12,163	$66,224	$8,603	
Total	$2,013,371	$1,185,198	$1,132,327	$381,977

- No patients in the post-intervention period developed renal failure.

Conclusions

- The clinical and economic impact of CR-KP bacteremia is substantial, reflecting propensity for transplant and other severely-ill patients
- Differences in strain genetics (e.g., *ompK36* genotypes and patterns of aminoglycoside modifying enzymes), are associated with differences in antimicrobial responses, even among ST258 strains considered to be clonal
- Preliminary data suggest that a formal intervention program directed by AMP may improve patient outcomes, shorten hospital stays, and reduce costs
  - Major cost savings are in pharmacy, antibiotics, lab services, and ICU admissions/stays
- We are continuing to collect data, and will be implementing an intervention strategy against highly-resistant *Pseudomonas* infections.