Effect of the cyclic octasaccharide octakis(6-deoxy-6-amino)cyclomalto-octaose (am8γCD) on the sensitivity of carbapenem-resistant *Klebsiella pneumoniae* to complement-mediated killing

José R. Mediavilla, MBS, MPH; Ruchi Pandey, PhD; Scott S. Walker, PhD; Christopher M. Tan, PhD; Todd Black, PhD; Barry N. Kreiswirth, PhD

1Public Health Research Institute, Rutgers University, Newark, NJ, USA; 2The research labs of Merck & Co., Inc., Kenilworth, NJ, USA

**ABSTRACT**

Background: The global spread of carbapenem resistance and the recent identification of plasmid-encoded colistin resistance in Gram-negative Enterobacteriaceae have dramatically limited effective treatment options, thereby precipitating a call for novel approaches that circumvent antibiotic resistance. A recent study (1) demonstrated that the *Klebsiella* octasaccharide octakis(6-deoxy-6-amino)cyclomalto-octaose (am8γCD) interferes with K18 capsular polysaccharide (CPS) export by *Escherichia coli*, thereby rendering Gram-negative pathogens sensitive to complement-mediated killing by human serum. We sought to extend these studies to *Klebsiella pneumoniae*, another clinically important member of the Enterobacteriaceae family which utilizes a similar Wzy-dependent CPS synthesis pathway.

**METHODS AND MATERIALS**

A total of 50 genotypically diverse *K. pneumoniae* strains (as shown by MLST) with resistant and susceptible sequences were subjected to complement-mediated killing assays in the presence and absence of two concentrations of the cyclodextrin am8γCD (CycloLab, Budapest, Hungary).

**RESULTS**

Of the 50 *K. pneumoniae* strains, 32 (64.0%) were sensitive to serum and/or am8γCD, while 10 (20.0%) displayed intermediate sensitivity, and 8 (16.0%) were completely resistant. Use of am8γCD in the presence of complemented human serum typically had no effect. Among the 32 sensitive strains, 6 were completely sensitive to both serum and am8γCD, 4 were sensitive to am8γCD only, 2 were sensitive only to higher concentrations (1 mM) of am8γCD, and 1 was sensitive to serum alone (with no effect from am8γCD). Wza amino acid sequence correlated somewhat with assay outcome, with 20 Wza patterns associated with concordant phenotypes, vs only 7 Wza patterns associated with discordant phenotypes.

**CONCLUSIONS**

K. pneumoniae strains exhibit diverse cylcodextrin-dependent responses to human complement. The majority of strains displayed sensitive phenotypes, while resistance was randomly distributed among genotypically diverse sequence types. The observed correlations between phenotypes and Wza sequences were not consistent, suggesting that other factors may be involved. Future studies should include:

- extending the assay to other Gram-negative species
- repeating the assay using other cylcodextrin compounds
- targeting other capsular biosynthesis genes besides wza and wzy

**REFERENCES**


**CONTACT:**

José R. Mediavilla, MBS, MPH

Email: mediavlj@njms.rutgers.edu

**Website:** www.phri.org