

Antimicrobial Resistance in *Klebsiella pneumoniae*:  
Mechanisms and Clinical Impact and Developments

Ryan Cain

BIOM 250

Professor Heinzinger

November 27, 2015

Antimicrobial Resistance in *Klebsiella pneumoniae*:  
Mechanisms and Clinical Impact and Developments

Antimicrobial resistance is a growing problem in modern healthcare around the world. Multidrug resistant (MDR) strains of pathogenic bacteria, which are quickly becoming more common, pose a serious risk to patients. One of the most common species of bacteria that cause problems in healthcare today is *Klebsiella pneumoniae*. Today *K. pneumoniae* can be responsible for community acquired infections, but is most commonly observed as a major cause of hospital acquired infections which can be fatal. *K. pneumoniae* has been observed to develop resistance to antibiotics more easily than most bacteria through the production of new enzymes to break them down. As new resistance mechanisms develop, fewer and fewer treatments are available for infections by *K. pneumoniae*. Although some treatments still remain, few new ones are being explored, thus the best option is to control the development and spread of antimicrobial resistance.

### **Cellular Characteristics**

*K. pneumoniae* is a gammaproteobacterium and part of the family *Enterobacteriaceae*. They are facultatively anaerobic gram-negative rods that are usually encapsulated and non-motile. They are indole and ornithine decarboxylase negative, ferment lactose, and have a positive Voges-Proskauer reaction.

### **Pathogenicity Factors**

They have various pathogenicity factors that better their ability to cause disease. *K. pneumoniae* have capsules that contain complex acidic polysaccharides that protect it from phagocytosis and prevent bactericide from factors in complement activation by inhibiting the uptake or activation of complement components. *K. pneumoniae* has various adhesins that

increase its pathogenicity. Type 1 pili bind to “mannose-containing trisaccharides of the host glycoproteins” mainly on “mucus or epithelial cells of the urogenital, respiratory, and intestinal tracts.” Type 3 pili only agglutinate tannin treated erythrocytes. The CF29K adhesion, encoded by an R-plasmid, can mediate adherence to some human intestinal cells. The structure of some lipopolysaccharides’ O side chains has been shown to allow for some serum resistance by only allowing the activation of the alternative complement pathway. Their limited exposure from the capsule also causes steric hindrance in the formation of the membrane attack complex. Finally, siderophores are iron chelators that are secreted by *K. pneumoniae*. They take iron that is required for bacterial growth from proteins in the host. The two most important siderophores in *K. pneumoniae* are the phenolate-type enterobactin and the hydroxamate-type aerobactin; however, only the rarer aerobactin producers have been shown to have an observable increase in virulence. These cellular characteristics may allow for greater pathogenicity, but do not directly protect *K. pneumoniae* from the effects of antibiotics. (Podschun & Ullmann, 1998) Pili (also called fimbriae) along with lipopolysaccharides and the capsule contribute to the formation of biofilms, which increase the bacteria’s pathogenicity (Vuotto, Longo, Balice, Donelli, & Varaldo, 2014).

### **Resistance Mechanisms**

The usual antibiotic treatments for *K. pneumoniae* infections include beta-lactams such as cephalosporins and carbapenems, aminoglycosides such as gentamycin, and quinolones (Qureshi, 2015). These treatments however are ineffective against certain strains of *K. pneumoniae* that contain effective resistance mechanisms. *K. pneumoniae* have two main resistance mechanisms: production of enzymes and biofilm formation. Other resistance mechanisms have been observed, but not as thoroughly researched. Resistance has been observed

against beta-lactams, carbapenems, fluoroquinolones, aminoglycosides, trimethoprim, and sulfamethoxazoles. However, not all strains of *K. pneumoniae* express resistance. The strain JH1 shows high susceptibility to clinically used antibiotics, while strain 112281 expresses wide multidrug resistance (Kumar et al., 2011).

## **Enzymes**

*K. pneumoniae* produce various enzymes that target specific parts of drugs and deactivate them. The enzymes produced usually target beta lactam type drugs, but some target other drug classes. These enzymes include extended spectrum beta lactamases, metallo-beta-lactamases, oxacillinases, *K. pneumoniae* carbapenemases, and various others. These enzymes are encoded on plasmids which *K. pneumoniae* seems to readily uptake.

**Extended spectrum beta-lactamases (ESBLs).** ESBLs are so named due to their ability to hydrolyze a wide spectrum of beta-lactam drugs. Their action occurs through the hydrolyzation of the beta-lactam ring in beta-lactam drugs by nucleophilic attack (Papp-Wallace, Endimiani, Taracila & Bonomo, 2011). Plasmids encoding Temoniera (TEM) and Sulfhydryl variable (SVH) ESBLs are the most common to be found in isolated *K. pneumoniae*, which are active against cephaloporins. The plasmids that encode the ESBL genes also have been found to carry genes that express resistance for drugs other than beta-lactams, such as aminoglycosides (Vuotto et al., 2014). Because carbapenems are not degraded by ESBLs, they are used for treatment when ESBL producing *K. pneumoniae* are isolated from patient samples.

**Metallo-beta-lactamases (MBLs).** MBLs get their name from their mechanism of hydrolysis, in which they use divalent cations,  $Zn^{+2}$  being the most common, in the nucleophilic attack of beta-lactam rings (Tzouvelekis, Markogiannakis, Psychogiou, Tassios & Daikos, 2012). There are three phylogenetic linages of MBLs, which have been designated B1, B2, and B3.

MBL lineages B2 and B3 are encoded on plasmids, while the B1 lineage includes acquired enzymes. Tigecycline or colistin must be used for infection by MBL producing *K. pneumoniae* due to the resistance against all other antibiotics (Qureshi, 2015).

**Oxacillinases (OXAs).** Previously identified OXAs from other genera had showed limited activity against carbapenems. A different OXA enzyme, designated OXA-48, was identified from *K. pneumoniae* in 2001 (Tzouvelekis et al., 2012). OXA-48 showed much more activity than any of the previously identified OXA enzymes. This was found to be due to hydrolysis relying on a rotation of a substituent of the carbapenem molecule within the enzyme's active site.

**Klebsiella pneumoniae Carbapenemases (KPCs).** KPCs represent the most significant development in *K. pneumoniae* antimicrobial resistance in recent years. This is due to their very wide range of effect in which they “exhibit activity against a wide spectrum of beta lactams, including penicillins, older and newer cephalosporins, aztreonam and carbapenems” (Tzouvelekis et al., 2012). There has also been an emergence of distinct plasmids to encode for multiple variants of KPC enzymes, designated KPC-1 to KPC-13. In particular KPC-2 and KPC-3 have spread around the world alarmingly fast (Gasink, Edelstein, Lautenbach, Synnestvedt & Fishman, 2009). More concerning may be the observation of KPC encoding plasmids in other enterobacterial species, which confers resistance or decreased susceptibility to all beta-lactam drugs (Tzouvelekis et al., 2012).

**Other enzymes.** In 2006, a strain of *K. pneumoniae* was isolated from a soldier wounded in Iraq. The strain was found to have a novel 16S rRNA methyltransferase (16S RMTase) known as RmtH (O'Hara et al., 2013). 16S RMTase works by altering the binding site of aminoglycosides through the methylation of residue G1405, making the bacteria resistant to

aminoglycosides. Resistance to macrolides is common in *K. pneumoniae* due to its production of macrolide esterases (Broberg, Palacios & Miller, 2014).

### **Biofilm Formation**

Biofilm formation has been correlated with an increased resistance to treatment with antibiotics. *K. pneumoniae* has been found to form biofilms, especially in hospital settings, and in particular on catheters. The biofilm protects the *K. pneumoniae* from antibiotic treatments. This protection, originally thought to be a result of limited penetration of antibiotic molecules, is instead a result of slow growth of cells at the center of the biofilm (Vuotto et al., 2014)

### **Other Mechanisms**

Other resistance mechanisms include efflux pumps. A strain of *K. pneumoniae* isolated in France was found to have efflux mechanisms that increased resistance of chloramphenicol, the macrolide erythromycin, and the quinolone nalidixic acid, as well as a previously unknown efflux mechanism against beta-lactams (Pages et al., 2009).

### **Epidemiology**

*K. pneumoniae* is a part of the normal microbiota of humans where they inhabit mucosal surfaces. They can also be found in the environment in surface water, soil, sewage, and on plants. The environmental sources of *K. pneumoniae* were known in the past to commonly cause community acquired infections such as bacterial pneumonia. Community-acquired infections by *K. pneumoniae* are much less common than nosocomial infections now, but a hypervirulent variant of *K. pneumoniae* has increasingly been observed to cause a community-acquired infection that leads to liver abscesses (Shon, Bajwa & Russo, 2013). Despite these new occurrences, nosocomial infections by *K. pneumoniae* are still much more prevalent, and may be more dangerous due to the rapid development and spread of antimicrobial resistance in hospital settings. The most common

nosocomial infections reported to be caused by *K. pneumoniae* are urinary tract infections, which are commonly caused by biofilm forming strains on catheters. Other nosocomial infections caused by *K. pneumoniae* include pneumonia, intra-abdominal infections surgical wound infections, and bacteremia (Lundberg, Senn, Schüler, Meinke & Hanner, 2013). These become deadly when the strains of *K. pneumoniae* that cause them can't be treated due to antimicrobial resistance.

Antimicrobial resistance is most commonly associated with nosocomial infections. This is often due to the fact that hospitals are where the resistant strains tend to first develop. The development of resistance is most often due to the excessive use of antibiotics, sometimes unnecessarily and without monitoring or control (Harbath et al., 2015). Studies have shown that antibiotic consumption leads to selective pressure increasing beta-lactam resistance in bacteria of the genus *Enterobacteriaceae* (Sedláková et al., 2014). Fluoroquinolone resistance, however, is thought to be a result of gene circulation within the bacterial population.

Better monitoring and regulation of antibiotics as well as proper and timely infection control measures are critical to arrest the development and spread of antimicrobial resistance. Due to multidrug resistance, antibiotic therapies in *K. pneumoniae* can be limited. For KPC producing strains, colistin has become the last resort, but recently resistance to colistin has even been observed (Lim et al., 2010). Some attempts at producing vaccines have been made, including a protein-based subunit vaccine that uses *K. pneumoniae* surface antigens (Lundberg et al., 2013). However, these vaccines are still a ways off and may not give lasting immunity. This makes infection control practices and monitoring and control of antibiotics very important to control further development and spread of antimicrobial resistance in *K. pneumoniae* and other pathogenic bacteria.

## References

- Broberg, C. A., Palacios, M., & Miller, V. L. (2014). *Klebsiella*: a long way to go towards understanding this enigmatic jet-setter. *F1000Prime Reports*, 6, 64.  
<http://doi.org/10.12703/P6-64>
- Gasink, L. B., Edelstein, P. H., Lautenbach, E., Synnestvedt, M., & Fishman, N. O. (2009). Risk Factors and Clinical Impact of *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*. *Infection Control and Hospital Epidemiology : The Official Journal of the Society of Hospital Epidemiologists of America*, 30(12), 1180–1185.  
<http://doi.org/10.1086/648451>
- Harbarth, S., Balkhy, H., Goossens, H., Jarlier, V., Kluytmans, J., Laxminarayan, R., . . . Pittet, D. (2015). Antimicrobial resistance: One world, one fight! *Antimicrob Resist Infect Control Antimicrobial Resistance and Infection Control*, 4(49). doi:10.1186/s13756-015-0091-2
- Kumar, V., Sun, P., Vamathevan, J., Li, Y., Ingraham, K., Palmer, L., . . . Brown, J. R. (2011). Comparative Genomics of *Klebsiella pneumoniae* Strains with Different Antibiotic Resistance Profiles. *Antimicrobial Agents and Chemotherapy*, 55(9), 4267–4276.  
<http://doi.org/10.1128/AAC.00052-11>
- Lim, L. M., Ly, N., Anderson, D., Yang, J. C., Macander, L., Jarkowski, A., . . . Tsuji, B. T. (2010). Resurgence of Colistin: A Review of Resistance, Toxicity, Pharmacodynamics, and Dosing. *Pharmacotherapy*, 30(12), 1279–1291.  
<http://doi.org/10.1592/phco.30.12.1279>

- Lundberg, U., Senn, B. M., Schüler, W., Meinke, A., & Hanner, M. (2013). Identification and characterization of antigens as vaccine candidates against *Klebsiella pneumoniae*. *Human Vaccines & Immunotherapeutics*, 9(3), 497–505. <http://doi.org/10.4161/hv.23225>
- O'Hara, J. A., McGann, P., Snesrud, E. C., Clifford, R. J., Waterman, P. E., Lesho, E. P., & Doi, Y. (2013). Novel 16S rRNA Methyltransferase RmtH Produced by *Klebsiella pneumoniae* Associated with War-Related Trauma. *Antimicrobial Agents and Chemotherapy*, 57(5), 2413–2416. <http://doi.org/10.1128/AAC.00266-13>
- Pages, J.-M., Lavigne, J.-P., Leflon-Guibout, V., Marcon, E., Bert, F., Noussair, L., & Nicolas-Chanoine, M.-H. (2009). Efflux Pump, the Masked Side of  $\beta$ -Lactam Resistance in *Klebsiella pneumoniae* Clinical Isolates. *PLoS ONE*, 4(3), e4817. <http://doi.org/10.1371/journal.pone.0004817>
- Papp-Wallace, K. M., Endimiani, A., Taracila, M. A., & Bonomo, R. A. (2011). Carbapenems: Past, Present, and Future . *Antimicrobial Agents and Chemotherapy*, 55(11), 4943–4960. <http://doi.org/10.1128/AAC.00296-11>
- Podschun, R., & Ullmann, U. (1998). *Klebsiella* spp. as Nosocomial Pathogens: Epidemiology, Taxonomy, Typing Methods, and Pathogenicity Factors. *Clinical Microbiology Reviews*, 11(4), 589–603. Retrieved from 589-603
- Qureshi, S. (2015, October 6). *Klebsiella* Infections Treatment & Management (M. Bronze, Ed.). Retrieved November 29, 2015, from <http://emedicine.medscape.com/article/219907-treatment>
- Shon, A. S., Bajwa, R. P. S., & Russo, T. A. (2013). Hypervirulent (hypermucoviscous) *Klebsiella pneumoniae*: A new and dangerous breed. *Virulence*, 4(2), 107–118. <http://doi.org/10.4161/viru.22718>

Tzouveleakis, L. S., Markogiannakis, A., Psychogiou, M., Tassios, P. T., & Daikos, G. L. (2012).

Carbapenemases in *Klebsiella pneumoniae* and Other Enterobacteriaceae: an Evolving Crisis of Global Dimensions. *Clinical Microbiology Reviews*, 25(4), 682–707.

<http://doi.org/10.1128/CMR.05035-11>

Vuotto, C., Longo, F., Balice, M. P., Donelli, G., & Varaldo, P. E. (2014). Antibiotic Resistance

Related to Biofilm Formation in *Klebsiella pneumoniae*. *Pathogens*, 3(3), 743–758.

<http://doi.org/10.3390/pathogens3030743>