Laboratory Response to a KPC Outbreak at the NIH Clinical Center

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INTRODUCTION

Klebsiella pneumoniae carbapenemase-producing *K. pneumoniae* (KPC-KP) are notorious nosocomial pathogens that are resistant to nearly all antimicrobials and can rapidly develop further resistance upon exposure to the remaining active agents.

Resistance is caused by the enzyme-encoding KPC gene that is carried on a plasmid transmissible among the Enterobacteriaceae. The KPCs comprise 10 variants (KPC_{2-11}) that are uniquely characterized by single nucleotide substitutions[1].

The epidemiological challenge of KPC-KP along with high attributable mortality (40-60%) has prompted heavy investment on infection control and preventive measures.

Between June to December 2011, the NIH Clinical Center experienced its first KPC-KP outbreak in the ICU. Prompt laboratory response was crucial for hospital epidemiological guidance and limiting the spread of disease.

ACKNOWLEDGEMENTS

We would like to acknowledge all the microbiology staff & HES at the NIH CC

OUTBREAK TIMELINE

Alive
Died

6/13: Pt #1 Transferred to NIH ICU from OSH with known KPC-KP & MDRAB colonization. ICU 24h stay

6/29: Index case had 2nd 24h stay in ICU

8/5: Pt #2

8/15: Pt #3

8/23: Pt #4

8/29: Pt #5 Co-colonized with KPC-*E. cloacae* & MDRAB

9/15: Pt #6

9/19: Pt #7 Co-colonized with MDRAB

9/22: Pt #8

9/26: Pt #9 Co-colonized with MDRAB

10/6: Pt #10

10/17: Pt #11 Co-colonized with MDRAB

10/17: Pt #12 Co-colonized with KPC-*E. aerogenes*

11/3: Pt #13

11/10: Pt #14

11/17: Pt #15

11/18: Pt #16

11/27: Pt #17

12/14: Pt #18

Jun | Jul | Aug | Sep | Oct | Nov | Dec

LABORATORY RESPONSE

6/29:
- Two rounds of throat & groin surveillance cxs initiated. Subbed onto SBA & MAC
- Any GNR was identified by MALDI-TOF MS
- Full susceptibility testing performed
- Carbapenemase activity confirmed by MHT

8/5:
- Weekly throat & groin surveillance cxs initiated in ICU and later on other wards
- SBA & MAC proved inefficient
- Evaluation of KPC Chromagar against CDC protocol
- Rectal swabs added to surveillance cultures to increase sensitivity

8/15:
- KPC Chromagar implemented for throat, groin & rectal surveillance cxs
- Identification confirmed by MALDI-TOF MS
- Full susceptibility testing performed
- Carbapenemase activity confirmed by MHT

9/15: KPC PCR developed for colonies

9/30: Outbreak strain Whole Genome Sequencing (*Snitkin et al*, pers com)

10/30:
- Evaluation & validation of a KPC Taqman PCR to detect *bla*KPC directly from rectal swabs
- Implemented into routine diagnostic use 1/17/12

9/1 to 1/20/12 Environmental cultures detected KPC-KP from 5 environmental sites (patient room, ventilator & 3 sink drains) and KPC-*E. cloacae* from 2 drain cxs

Table 1. Isolation Source of KPC-KP

Pt #	Date	Thrt/ Grn	Rectal	Blood	Other sterile Fluids	BAL	Spt	Trach asp	Urine	Wound	Autopsy multi-organ	Co-colonization/ infection
1	6/13/11	✔							✔ (1°)			MDRAB (throat, 6/30)
2	8/5/11	✔		✔	✔ (peritoneal, pleural)			✔ (1°)		✔		
3	8/15/11	✔ (2°)	✔	✔	✔ (peritoneal)	✔				✔		
4	8/23/11			✔	✔ (peritoneal, bil)		✔	✔	✔			
5	8/29/11	✔ (2°)						✔	✔			KPC E. cloacae (trach asp, 9/29) MDRAB (throat, 10/3)
6	9/15/11		✔ (1°)	✔				✔				
7	9/19/11	✔	✔ (1°)	✔							✔ (lung, liver, spleen, gallbladder)	MDRAB (rectal, 9/15)
8	9/22/11	✔	✔ (1°)									
9	9/26/11		✔ (1°)									MDRAB (rectal, 9/26)
10	10/6/11	✔	✔ (1°)	✔					✔		✔ (lung, liver)	
11	10/17/11		✔ (1°)		✔ (peritoneal)			✔	✔			MDRAB (blood, 9/21)
12	10/17/11	✔ (2°)										KPC E. aerogenes (wound, 11/1)
13	11/3/11	✔ (2°)										
14	11/10/11	✔	✔ (1°)	✔		✔	✔					
15	11/17/11		✔ (1°)									
16	11/18/11		✔ (1°)									
17	11/27/11		✔ (1°)	✔						✔		
18	12/14/11		✔ (1°)									

	Total pts (18)	Died (11)	Alive (8)
Clinical isolates	13 (72%)	10 (91%)	4 (50%)
Surveillance cxs only	5 (28%)	1 (9%)	4 (50%)

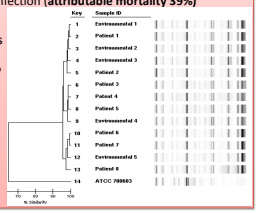
DATA SUMMARY

A total of 602 pts were screen between 6/2011 & 1/2012 (674 throat, 699 groin & 1,333 rectal)

KPC-KP was isolated from 18 pts
- 5 (28%) were colonized only
- 13 (72%) developed KPC-KP infections
  - 8 (62%) were bloodstream infections
- 5 were co-colonized/infected with MDRAB
- 1 was co-infected with KPC-*E. cloacae*
- 1 was co-infected with KPC-*E. aerogenes*

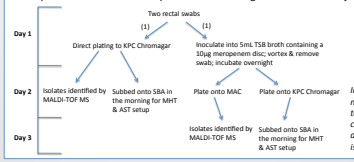
11 pts died (**overall mortality 61%**)
- 7 from KPC-KP infection (**attributable mortality 39%**)

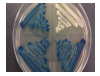
>95% similarity was established between all KPC-KP isolates by rep-PCR (Aligent)



KPC Chromagar Validation

KPC Chromagar (Paris) was tested in parallel with the CDC Laboratory Protocol for the "Detection of Carbapenem-Resistant or Carbapenemase Producing *Klebsiella or E. coli from* Rectal Swabs"





In addition, 9 MHT positive, 10 MHT negative and 6 ATCC control strains were tested to demonstrate selection for carbapenem resistant isolates and species differentiation based on color. All 25 isolates correlated with expected results.

KPC PCR Development & Validation

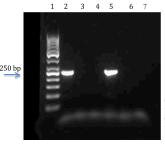
- A real-PCR assay was developed to detect a 246bp region of the bla_{KPC} gene (inclusive $bla_{KPC2-11}$) using primers and probes described by Hindiyeh *et al*[2]

KPC bla FOR	5-GAT ACC ACG TTC CGT CTG G-3
KPC bla REV	5-GCAGGTTCCGGTTTTGTCTC-3
bla_{KPC} probe	5-FAM-AGC GGC AGC AGT TTG TTG ATT G-TAMRA-3

- DNA was extracted from one rectal swab using the NucliSENS easyMag system (BioMerieux)

- The assay was validated in parallel with KPC Chromagar using 60 rectal swabs

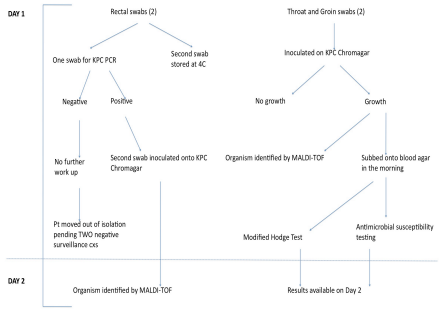
- Assay correlation efficiency was 1. No cross reactivity was observed with human DNA, stool flora or other carbapenem resistant non-KPC organisms (eg. MDRAB)



1. Ladder; 2. KPC-KP Pt #1; 3. MDRAB; 4. *E. coli*; 5. *K. pneumoniae* ATCC-1705; 6. *K. pneumoniae* ATCC-1706; and 7. No DNA control

KPC RESPONSE ALGORITHM

Following this outbreak and the changes implemented, we have developed the following algorithm for laboratories to respond to future KPC outbreaks



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1. Chen L *et al.* Multiplex real-time PCR assay for detection and classification of *Klebsiella pneumoniae* carbapenemase gene (bla_{KPC}) variants. JCM 2011; 49(2):579-85.
2. Hindiyeh M *et al.* Rapid detection of bla_{KPC} carbapenemase genes by real-time PCR. JCM 2008; 46(9):2879-83.