“SUPERBUGS ON MEDICAL DEVICES” – LABORATORY ASPECTS OF THE CRE OUTBREAK AT UCLA

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Overview:

- Define the “superbug”: carbapenem-resistant Enterobacteriaceae (CRE)
- Discuss how UCLA identified outbreak of CRE associated with duodenoscopes
- Review whole genome sequence analysis as a means to track CRE (and other) outbreaks

CRE: UCLA, 2009

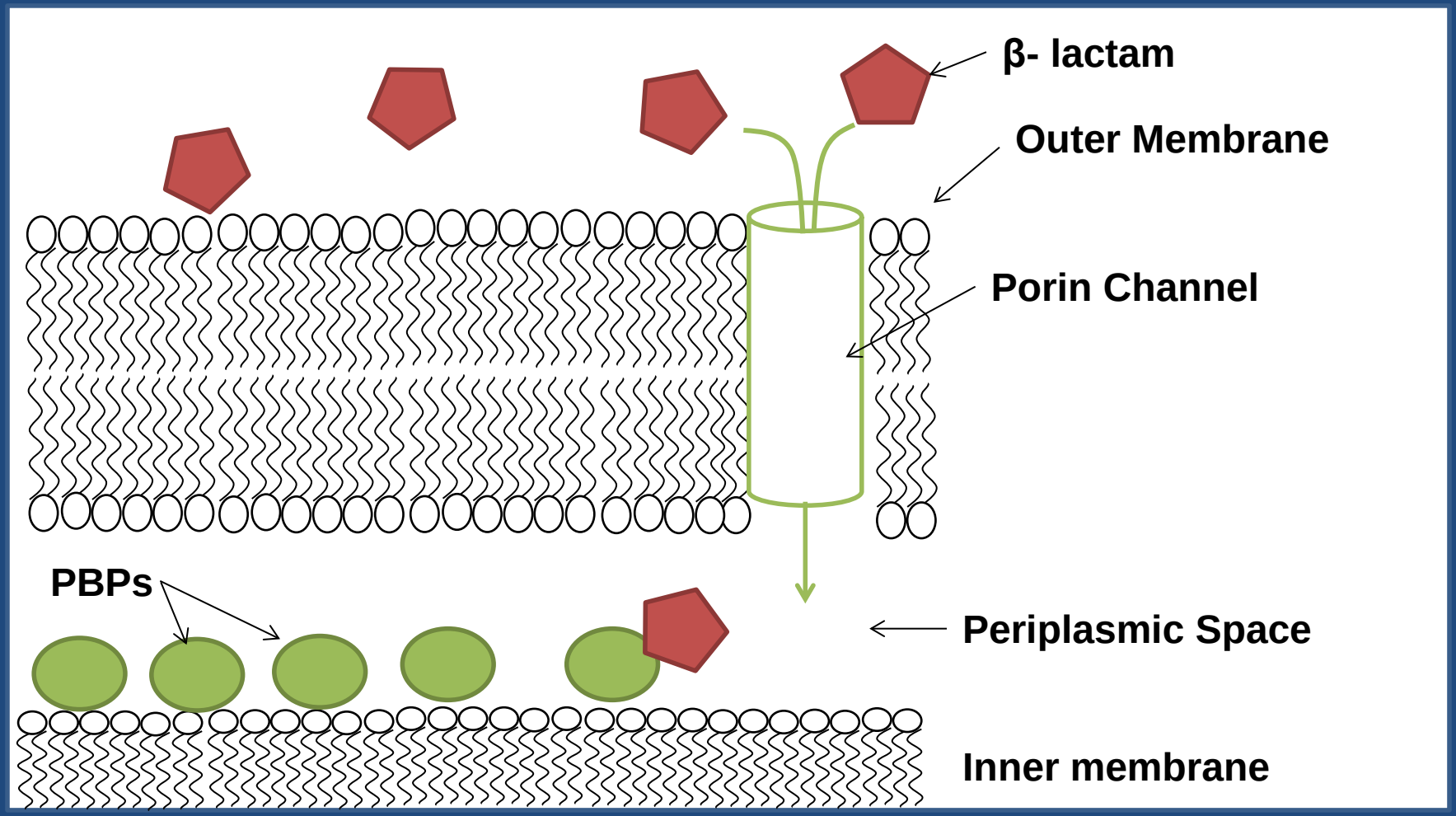
Agent	MIC (µg/ml)
Imipenem	>16 R
Meropenem	>16 R
Tigecycline	>4 R
Colistin	>4 R

CRE, 2009 UCLA

- 49-year-old male with no significant past medical history
- Admitted to Las Vegas Hospital, summer 2009
  - H1N1 influenza
  - Developed ARDS, intubated → transferred to UCLA
- *K. pneumoniae* isolated on day 1
  - Confirmed KPC-2 (our first!)
- Treated with tigecycline + colistin + amikacin
- Discharged after 185 days
- Rectal surveillance cultures positive for CR-*K. pneumoniae* → 3 years later

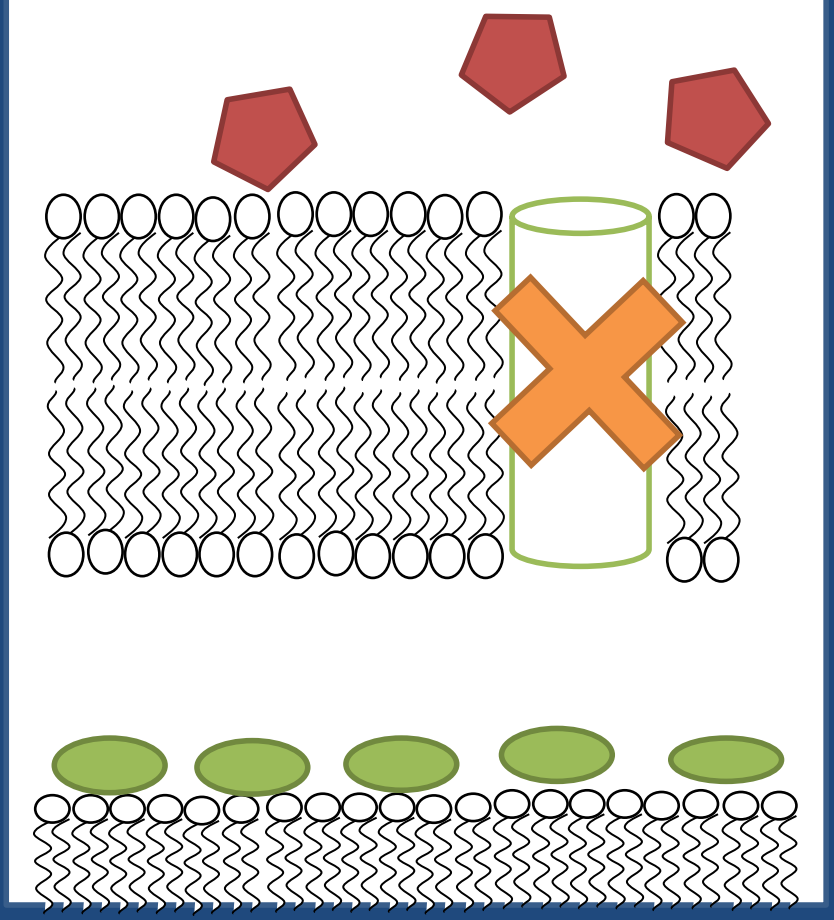
WHAT IS “CRE” ?

B-lactam activity against GNR

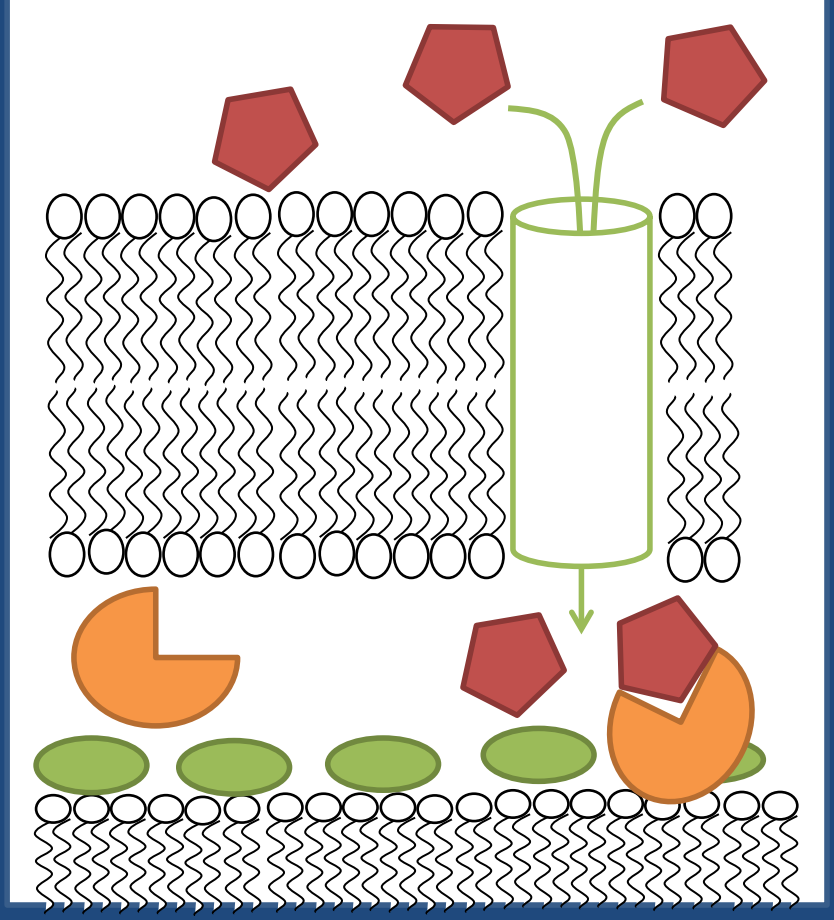


B-lactam Resistance in GNR

Porin channel obstructed / lost



B-lactamase



What IS a CRE?

CDC Surveillance Definition (revised!)

- Enterobacteriaceae that are:
  - Resistant to: ertapenem, doripenem, meropenem, or imipenem*

    OR…
  - Positive for a carbapenemase (by MHT, CarbaNP, PCR, etc)

UCLA Definition

- Enterobacteriaceae that are:
  - Nonsusceptible ("I or R") to one of the following: doripenem, meropenem, or imipenem*

Remember! Not all CRE have a "carbapenemase"

*Proteus/Providencia/Morganella exceptions for imipenem

Carbapenemases in Enterobacteriaceae

Class	Examples	Produced by:	Notes
A	KPC carbapenemases SME carbapenemases	*K. pneumoniae* and other Enterobacteriaceae *S. marcescens*	Usually on plasmids with several other resistance genes
B	Metallo-β-lactamases (MBL) (e.g. NDM, VIM, IMP, GIM, SPM carbapenemases)	*P. aeruginosa* Enterobacteriaceae *Acinetobacter* *S. maltophilia*	Inhibited by EDTA Do not hydrolyze aztreonam, unless have ESBL too
D	OXA carbapenemases	*Acinetobacter baumannii* Enterobacteriaceae	Hydrolyze carbapenems to some degree

Adapted from Queenan & Bush. 2007. Clin Microbiol Rev. 20:440.
Bush & Jacoby. 2010. AAC. 54:969; Bush, K. 2013. Ann NY Acad Sci 1277:84.

Slide from Janet Hindler

KPC

(*Klebsiella pneumoniae* Carbapenemase)

- Most common carbapenemase in USA
- First report 2001 North Carolina
- High level of enzyme produced
- Found mostly in *K. pneumoniae*
- Plasmid with KPC gene has other R genes:
  - ESBLs
  - Fluoroquinolone resistance genes
  - Aminoglycoside modifying enzymes

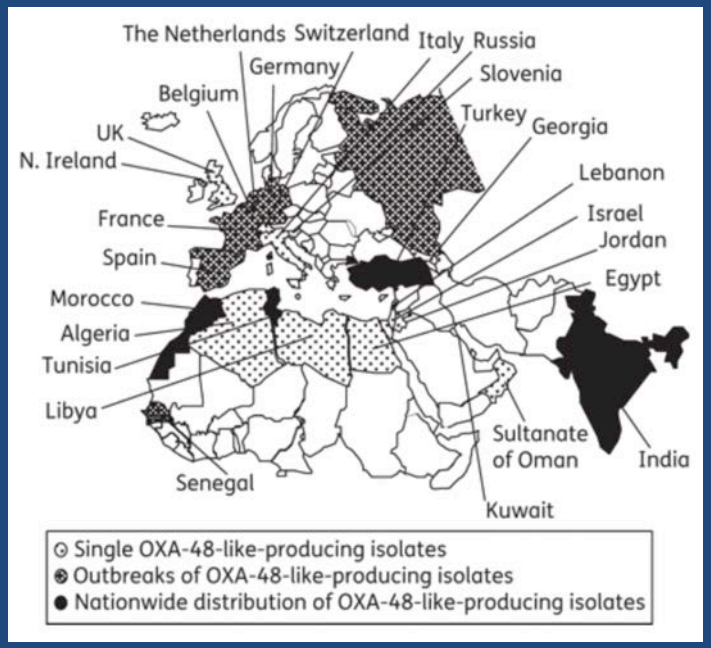
Metallo β-Lactamases (MBL)

- NDM (New Delhi MBL) most common MBL worldwide;
- India and Pakistan
- First report 2008 in Swedish patient hospitalized in India
- Zinc required for activity
- Mostly found in *K. pneumoniae* and *E. coli*
- bla_{NDM} gene highly mobile
- Outbreaks in Denver 2012, Chicago 2013
  - (MMWR Feb. 15, 2013, MMWR 2014 62:1051)

- Other MBLs reported in US: IMP, VIM

OXA Carbapenemases

- First described in *Acinetobacter baumannii* in 1985
- OXA-48-like
  - Commonly found in Europe and Africa; rare in USA
  - First report 2008 Turkey
  - Mostly *K. pneumoniae, E. coli*
- Several variants, frequently mutating



Poirel et al 2012 JAC

February 2013

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Centers for Disease Control and Prevention

CDC 24/7: Saving lives, protecting people, reducing health costs

SEARCH

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Emergency Preparedness and Response

Emergency Preparedness & Response
- Specific Hazards
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- Health Alert Network (HAN)
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- HAN00341
- HAN00340
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- Preparation & Planning
- Related Links
- Risk Communicator
- SNAPS

Emergency Preparedness & Response > Preparedness for All Hazards > Health Alert Network (HAN) > HAN Archive > 2013

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HAN

HEALTH ALERT NETWORK

This is an official

CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
February 14, 2013, 12:30 ET
CDCHAN-00341-02-14-2013

New Carbapenem-Resistant Enterobacteriaceae Warrant Additional Action by Healthcare Providers

Summary: Carbapenem-resistant Enterobacteriaceae (CRE) are untreatable or difficult-to-treat multidrug-resistant organisms that are emerging in the United States. Because of increased reports of these multidrug-resistant organisms, CDC is alerting clinicians about the need for additional prevention steps regarding CRE. Key points include:

- While still uncommon, reports of unusual forms of CRE (e.g., New Delhi Metallo-β-lactamase and Verona Integron-mediated Metallo-β-lactamase) in the United States are increasing. Of the 37 unusual forms of CRE that have been reported in the United States, the last 15 have been reported since July, 2012.

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Atlanta, GA 30333

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http://www.bt.cdc.gov/HAN/han00341.asp

- Unusual forms of CRE increasing in USA
- Majority from patients receiving overnight medical care outside USA
- MDs and Infection control (IC) should consider additional precautions when such patients are hospitalized in USA
  - Appropriate IC measures (e.g. contact precautions, rectal screening, etc.)
  - If CRE isolated, clinical labs should send isolate to reference lab to confirm CRE and characterize for R mechanism

Why are CRE Important?

- Clinically important
  - Often resistant to multiple classes of antibiotics
  - Pan-resistant CRE have been described (>10 cases at UCLA)
  - Associated with high mortality rates
    - > 50% in ICU patients
    - Combination therapy appears to improve outcomes

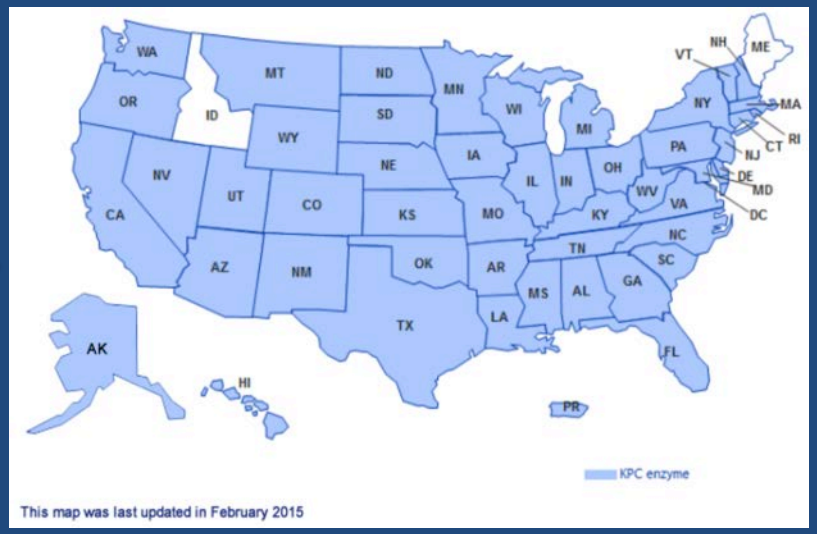
UCLA Data, n=90 CRE (2011- 2013)

Antimicrobial	% susceptible
Carbapenems	
Meropenem	2
Imipenem	0
Ertapenem	0
Cephalosporins	
Ceftriaxone	0
Ceftazidime	1
Cefepime	0
Piperacillin-Tazobactam	0
Aminoglycosides	
Gentamicin	58
Amikacin	64
Tobramycin	2
Fluoroquinolones	
Ciprofloxacin	8
Levofloxacin	8
Trimethoprim-sulfamethoxazole	22

Pollett et al JCM 52:4003, 2014

Why are CRE Important?

- Epidemiologically important
  - Highly transmissible
  - Have spread throughout healthcare settings across the United States, (endemic in some regions)
  - Potential for CRE to become widespread if not contained



States with CRE confirmed by CDC, 2010 vs. 2015

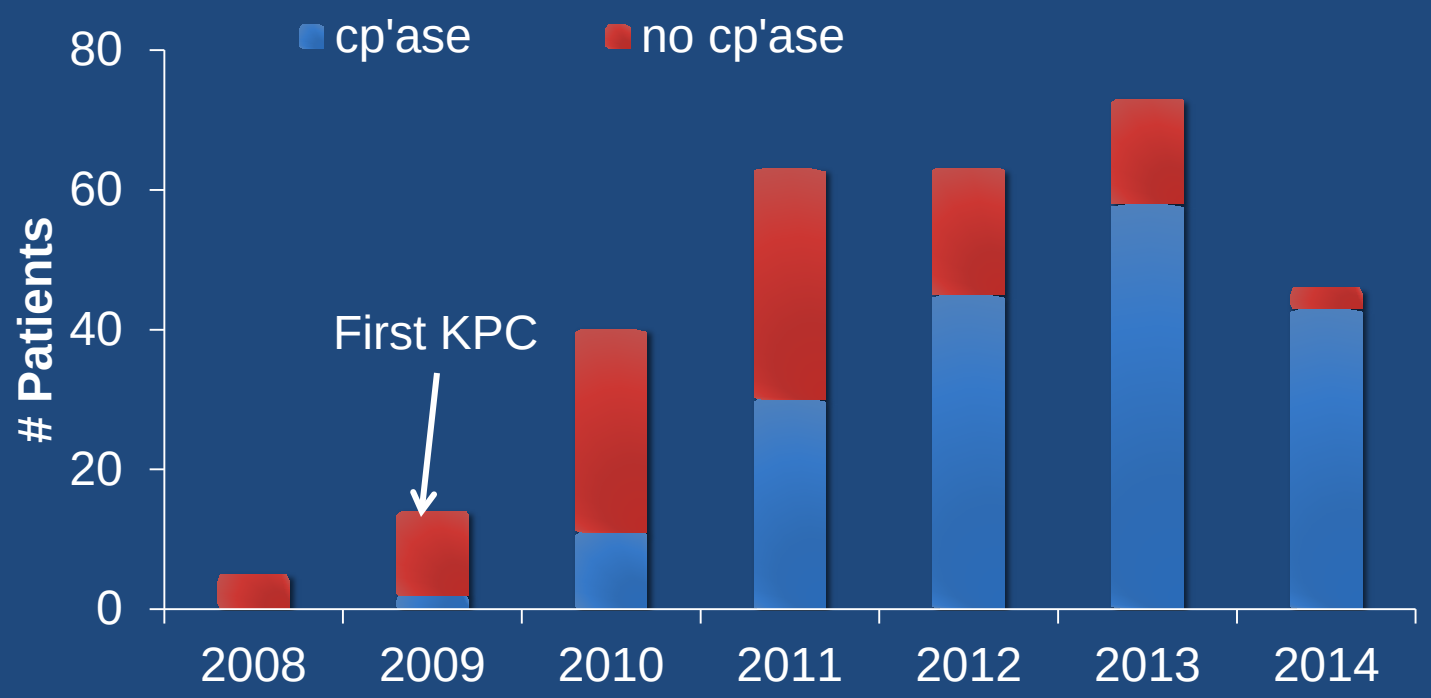
UCLA PROCEDURES

UCLA Procedure for CRE

- Use current carbapenem breakpoints
  - No routine carbapenemase testing for patient care
- When CRE isolated, called to floor so patient can be placed on appropriate contact precautions
- Laboratory saves all new CRE
- Periodic evaluation of CRE for mechanism, using LDT PCR

CRE at UCLA

CRE represent <0.5% of all *Enterobacteriaceae*



LDT PCR for:

-KPC, NDM-1, IMP, VIM, Oxa-48, SME

->85% of cp'ases are KPC

-Sporadic SME, NDM-1

-1 IMP

Pollett et al 2014 JCM 52:4003

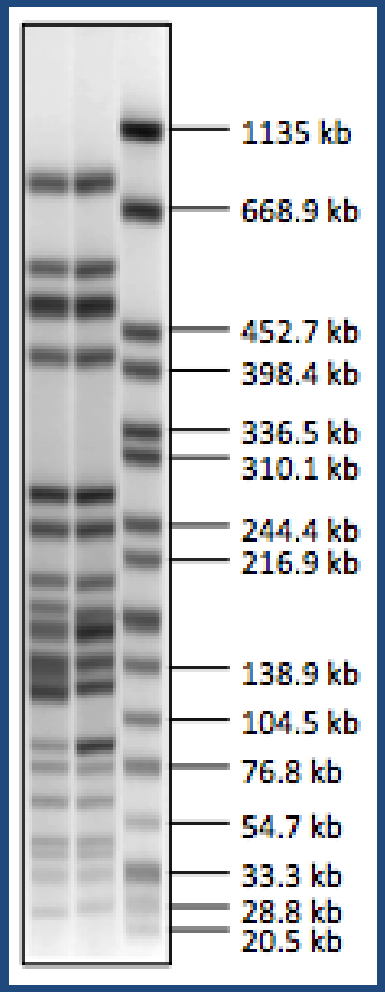
CRE cases in 2014 (RRMC)

- 34 patients:
  - 13 + cultures in first 7 days of admission
  - 24 treatment in outside hospitals, SNFs in prior 60 days
  - 11 end-stage liver disease
  - 8 cancer
  - 8 transplant patients
- Procedures:
  - 9 ERCP
  - 7 upper endoscopy
  - 3 gastrostomy tubes
  - Intubations (>20)
  - Surgical procedures (liver transplant, craniotomy, etc.)

Two cases of CRE in the surgical ICU

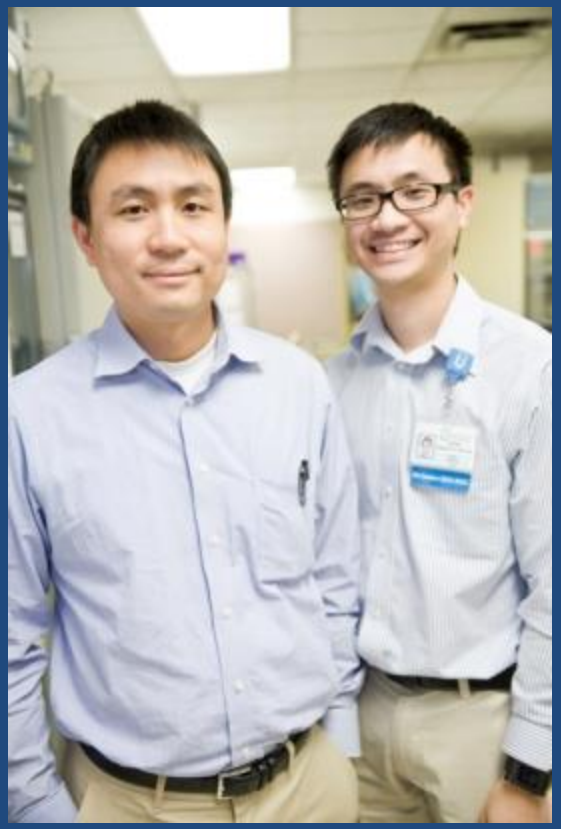
- Patient A:
  - End stage liver disease
  - Transferred to UCLA for OLT evaluation, after brief stay at OSH
  - Day 43: CRE isolated from patient's bile fluid
- Patient B:
  - Hepatitis C, alcoholic cirrhosis, sepsis
  - Admitted to UCLA from LTACH, after prolonged stay on day 42 of patient A's hospitalization
  - Housed in room adjacent to patient A for 40 days
  - Day 93: CRE isolated from blood / respiratory secretions

Laboratory testing of putative hospital-based CRE transmission



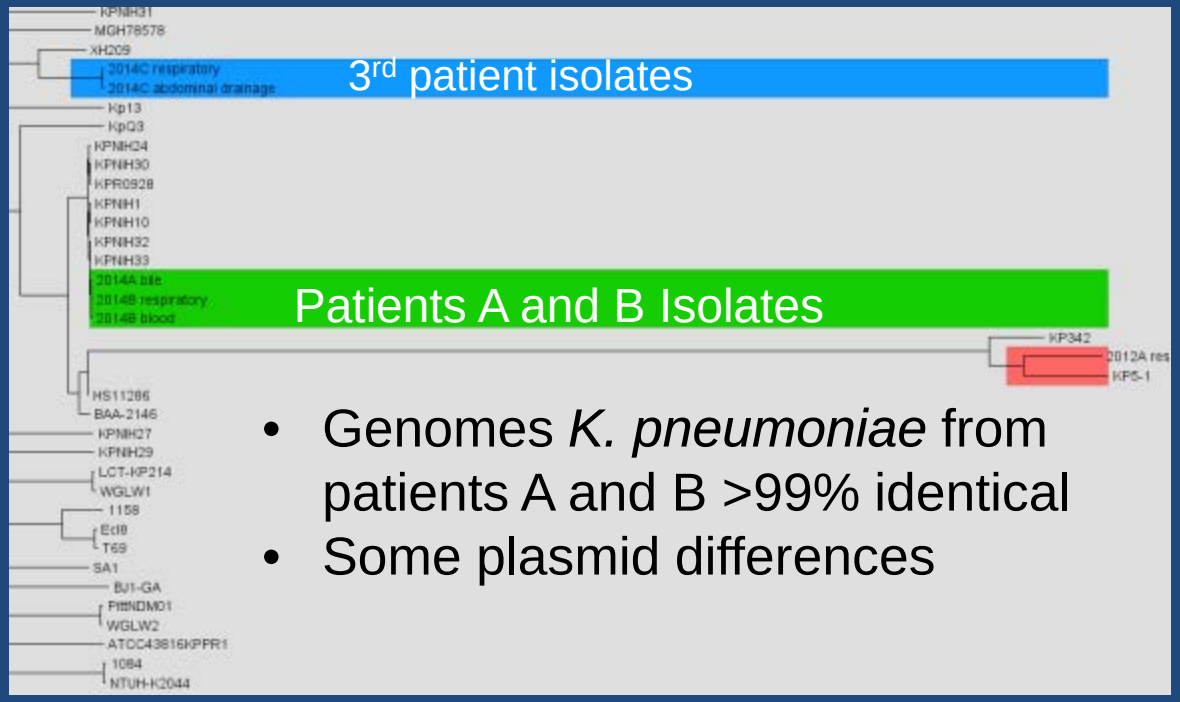
- Both isolates KPC producing *K. pneumoniae*
- PFGE strain typing performed by LACDPH
  - Inconclusive (appear to be similar, 2 band difference)
  - ? Is this the circulating CRKP in LA?

UCLA postdocs join the case



Shaun Yang
Peera Hemarajata

- Shaun and P decide to see if WGS could help resolve these 2 isolates
  - … throw in isolates from a 3rd patient for the heck of it (odd onset)



- Genomes *K. pneumoniae* from patients A and B >99% identical
- Some plasmid differences

Patient A and B – SNV analysis

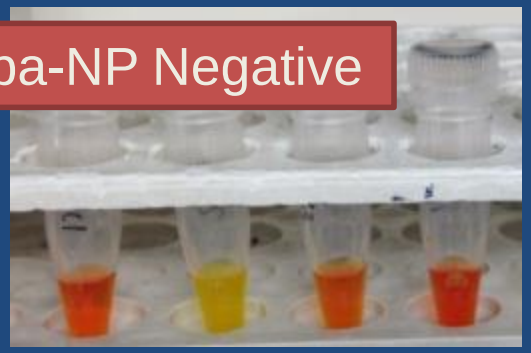
	CRKP A	CRKP B1	CRKP B2
CRKP A	-	24	26
CRKP B1	24	-	2
CRKP B2	26	2	-
KPNHI33	145	133	131

- Used "high fidelity" SNV calls from WGS data (i.e.: probably under-calls number of SNVs)
- How to interpret?
  - No current consensus definition
  - Cookson group[1]:
    - ≤3 SNV → indistinguishable
    - 4-12 → closely related
    - ≥13 → unrelated
  - In other outbreaks, between 10 and 17 SNVs observed for CRE[2-4]
  - In vitro, expect 1 SNV every 264 days

1. Salipente et al 2015 JCM 53:1072
2. Snitkin et al 2012. Sci Transl Med 3:148
3. Weterings et al 2015 Eur J Clin Micro Infect
4. Mathers et al. 2015 AAC 59:1656

… isolate from patient 3

Carba-NP Negative



Neg KPC OXA48 OXA232

- No KPC cp'ase
- Oxa-232 identified (what?!?)
  - Part of Oxa-48-like cp'ase family
  - First described in 2013
  - Only 1 report in US (Pittsburgh, late 2013)

MHT Positive

Carbapenem MICs (µg/mL):

Ertapenem >16
Meropenem >16
Imipenem 2

MIC (µg/ml)					
Old BPs			New BPs		
S	I	R	S	I	R
≤4	**8**	**≥16**	**≤1**	**2**	**≥4**

Poirel et al 2012 JAC

Patient 3

- 48 YO woman with cirrhosis of unknown etiology
- Receives liver transplant at UCLA September, 2014
  - Donor 17 YO with anoxic brain injury
- Post-operative chest x-ray shows pleural effusion
  - Tracheal suction grows CRE *(K. pneumoniae)*
- Transplant complicated by bile leak, stent placed by ERCP
- Over next several weeks, develops sepsis, and intra-abdominal infection; dies 2 months after transplant

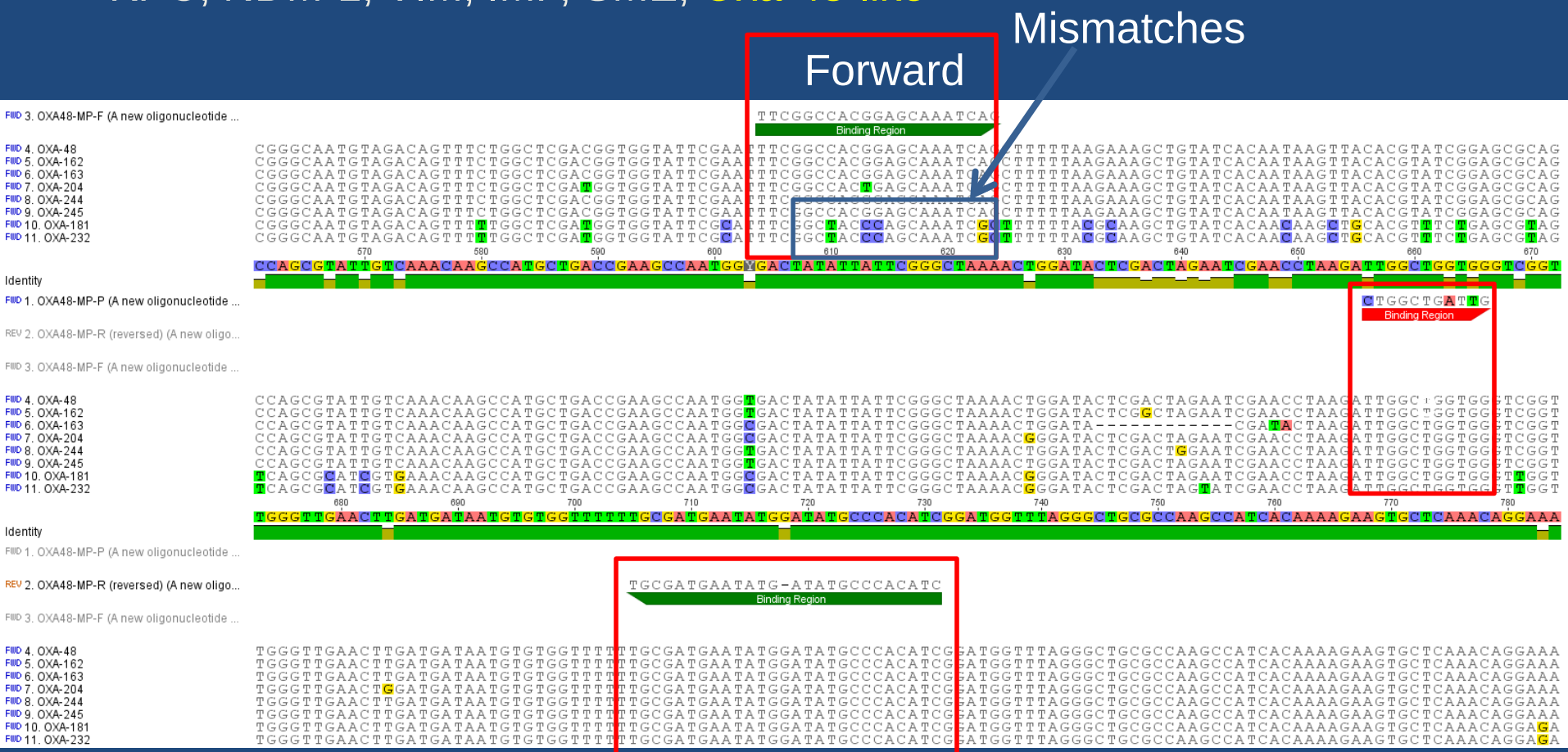
… no travel history

What's going on?

Is this the first Oxa-232 at UCLA?

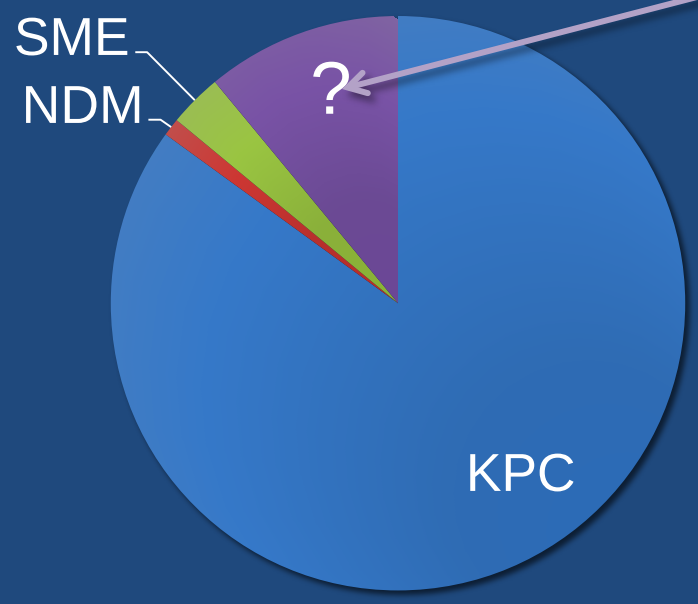
PCR for cp'ase negative for:

KPC, NDM-1, VIM, IMP, SME, Oxa-48-like



CRE at UCLA…

Distribution of CRE
UCLA, 2011-2015



Could these be Oxa-232??

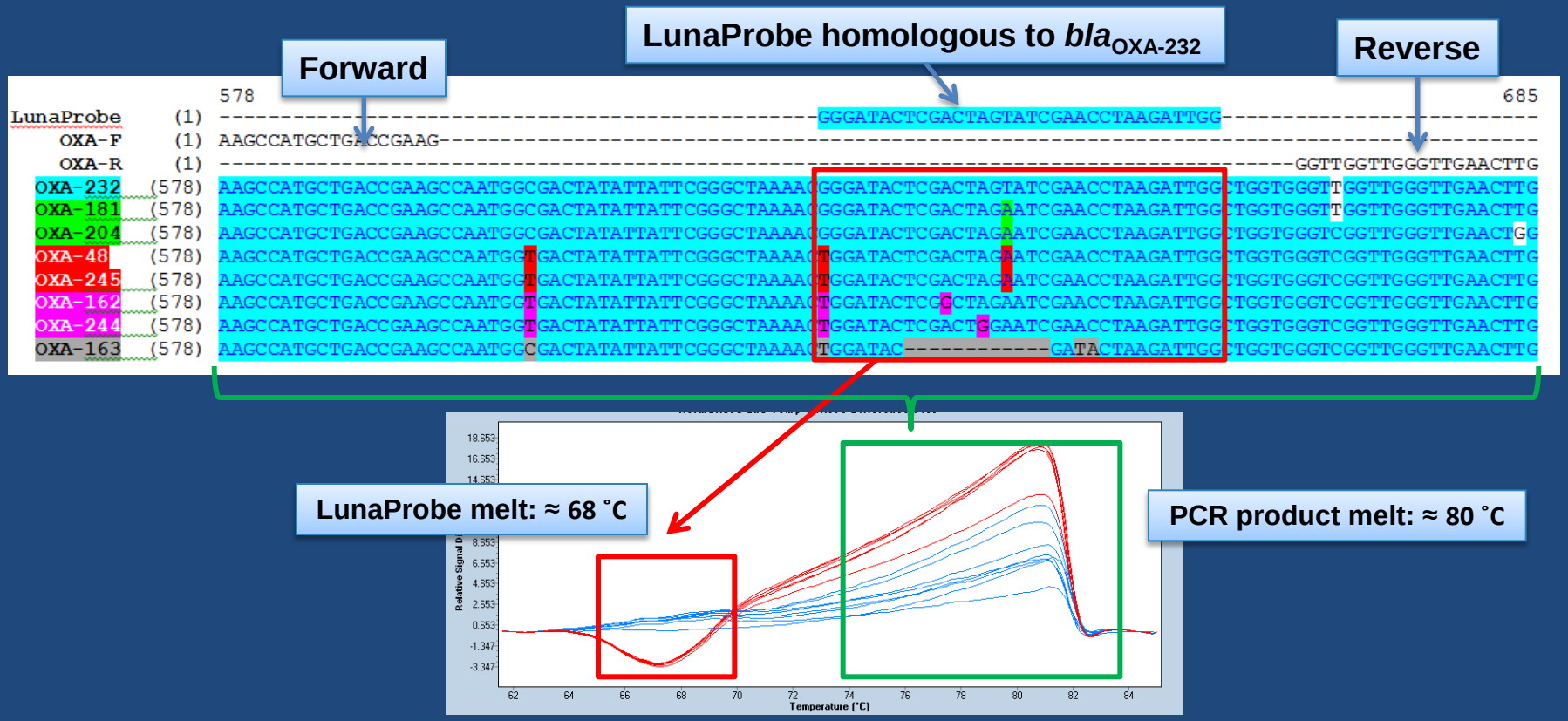
Do we have endemic Oxa-232 at UCLA?

- Check with CDC – no other reports except Pittsburgh
- Need to design a new PCR!

Pollett et al 2014 JCM 52:4003

LunaProbe HRM Assay for Oxa-48-like

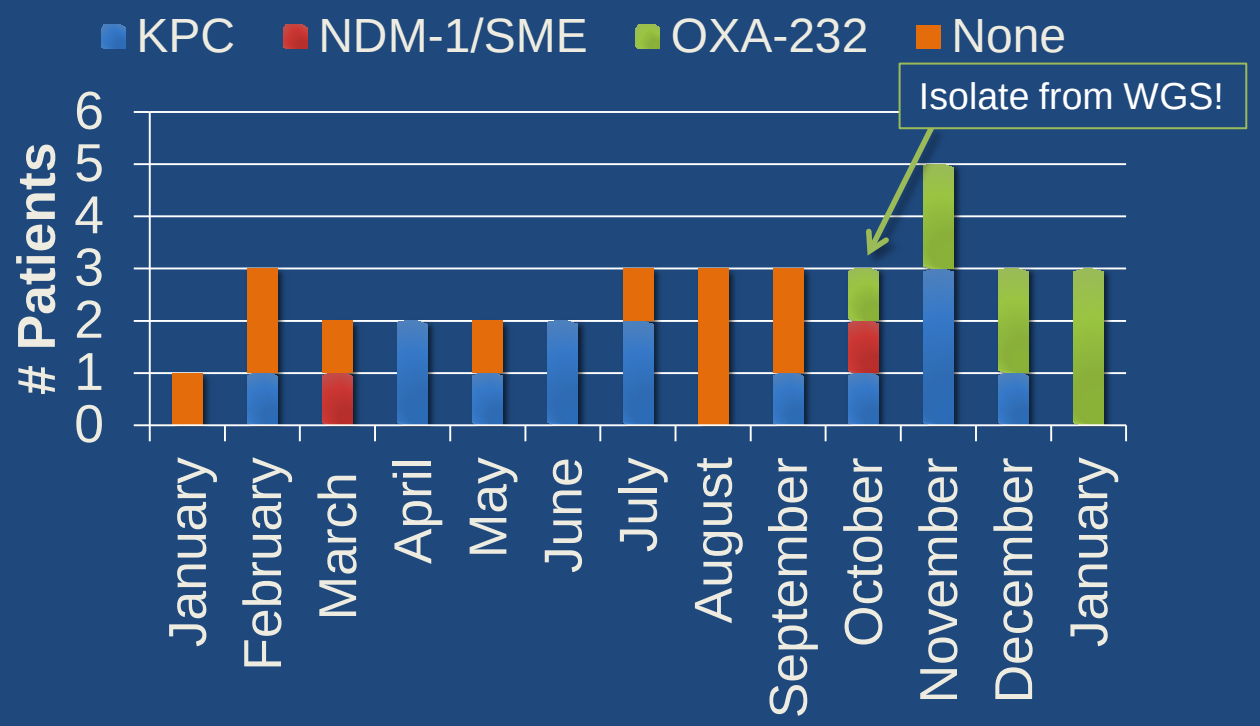
- Targeted a discriminatory region near 3' end of *bla*$_{OXA\text{-}232}$ gene
- HRM of PCR product and LunaProbe allows differentiation of types[1,2]



[1]Dwight, Zachary, Robert Palais, and Carl T. Wittwer. *Bioinformatics* 27.7 (2011): 1019-1020.
[2]Dwight, Zachary L., et al. *Human mutation* 35.3 (2014): 278-282.

Hemarajata et al Under review AAC 2015

Detection of Oxa-232s



- All CRE stocked
- Retrospectively test:
  - All 2011–2013 isolates - previously cp'ase negative
  - All 2014 isolates with low imipenem MIC

- WGS isolate is 1st case!
- …additional cases
  8 patients, 25 isolates

Epidemiology of patients with Oxa-232

- Patients from 6 units; mostly adult, some pediatrics
- Common factor: ERCP performed before isolation of Oxa-232
  Note: 35 patients with CRE, without knowledge of resistance mechanism, did not identify ERCP as risk factor

Patient	Date of ERCP	Date of 1st CRE	Specimen
1 (Source)	10/3	9/19	Respiratory
2	10/20	11/8	Blood
3	10/6	11/19	Abdominal Fluid
4	11/13	12/13	Abdominal Fluid
5	11/20	1/11	Blood
6	12/10	12/12	Blood
7	12/15	12/29	Abdominal Fluid
8	1/14	1/29	Abdominal Fluid

Endoscopy-associated Infections

- 10^5 -10^{10} CFU/ml present on endoscopes after use [2,3]
- Endoscopes are re-usable devices[1] reprocessed between patients:
  1. Thorough cleaning
  2. High-level disinfection (OPA)
- 2013 review of popular media[3]
  - 21 reports of reprocessing lapses
  - >33,000 patients exposed to improperly reprocessed scopes
- Infections associated with reprocessed scopes include:
  - HCV, HBV, HIV
  - *P. aeruginosa*
  - MDR Enterobacteriaceae (including CRE)
  - MRSA
  - *Clostridium difficile*

[1]Spaulding et al. 1974 MCM 2nd Ed; [2]Chu et al 2000 Gastrointest Endsco Clin N Am 10:233
[3]Chu et al 1998 Gastr Endosc 48:137; [3]Langlay et al 2013 AJIC 41:1188; [2] Harrell et al 2012 PloS One 7:e32545

ERCP and EUS are particularly difficult to reprocess…

Linear Endoscopic Ultrasound (EUS)

http://medical.olympusamerica.com/products/curved-linear-array-eus

Side View Duodenoscope

http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm434871.htm

OUTBREAK OFFICIALLY IDENTIFIED

January 28, 2015

Why California's Superbug Outbreak Isn't As Scary As It Seems

LA Times

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PLACE AN AD

UCLA superbug: Outbreak 'not a threat to public health,' officials say

aks outside Ronald Reagan UCLA Medical Center on Feb. 19 about infections of patients with an

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2 dead, nearly 180 possibly infected after 'superbug' outbreak at UCLA hospital

THE ASSOCIATED PRESS / Thursday, February 19, 2015, 7:37 AM

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CALIFORNIA

FDA faces more scrutiny in Congress over response to superbug outbreaks

UCLA Outbreak

- Findings:
  - 1 source patient
  - 7 secondary infections
  - 3 deaths (patient E, patient H, patient G)
  - All exposed to scope #47 or #26 (Olympus TJF-Q180V)
  - All had identical Oxa-232 strain of *Klebsiella pneumoniae*

UCLA Outbreak: response

- Immediate steps:
  - Immediately stopped ERCP
  - Reported point-source outbreak to LACDPH
- Scope cultures & ATP
  - Cultures using CDC technique were negative x 2
  - PCR of scopes for Oxa-232 was negative
  - ATP results <100 units for both scopes
- Following recommendations of CDC, LACDPH, all ERCP duodenoscopes (and EUS scopes) sent out for ethylene oxide sterilization after every use

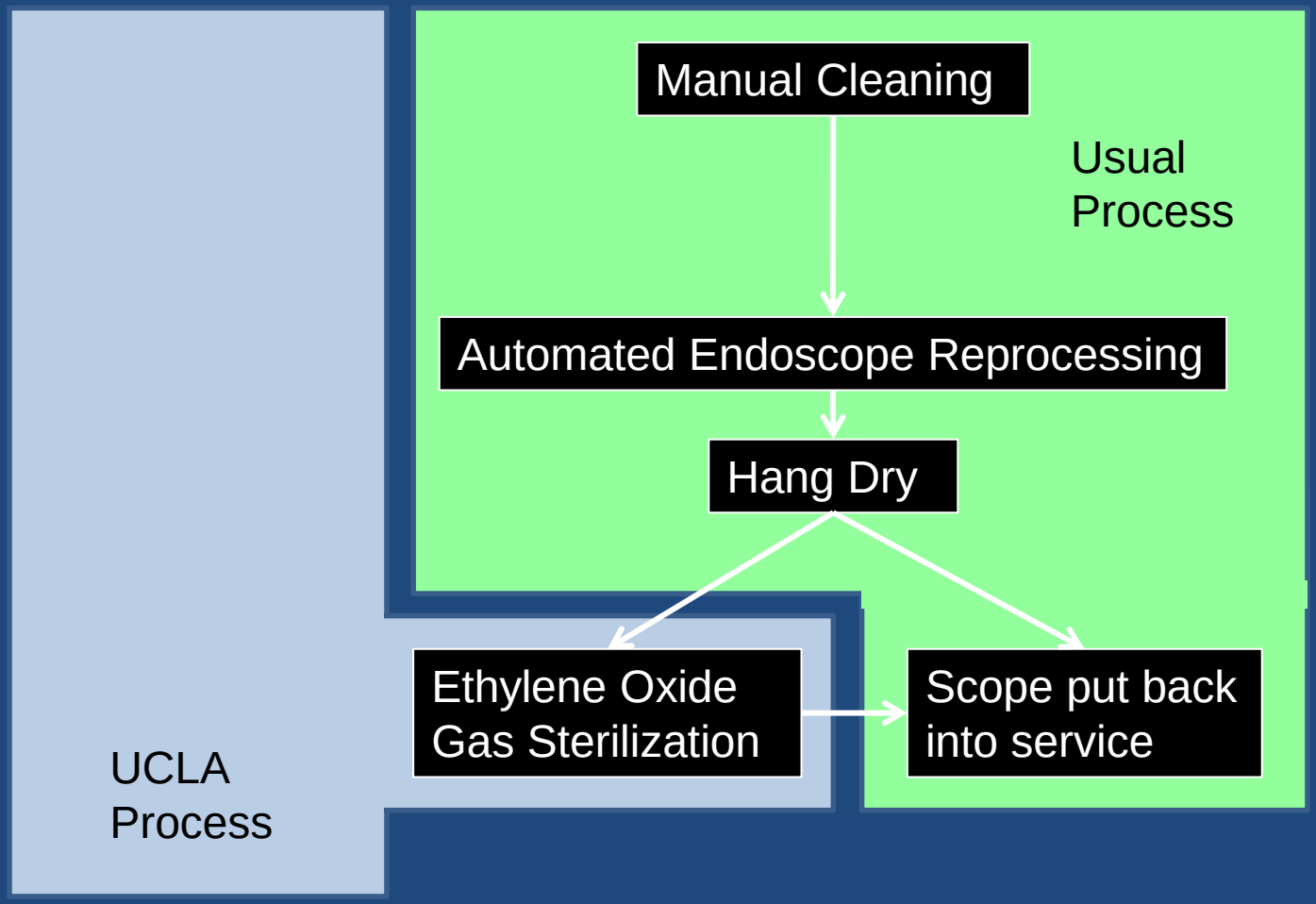
Further Investigation: High Level Disinfection review

- Scope processing was reviewed in detail
  - UCLA Infection Prevention
  - Olympus
  - Custom Ultrasonics
  - LACDPH
  - CMS/California Department of Public Health
- No significant deficiencies in scope cleaning process or other explanation for outbreak

Impact on Clinical Service

- Increased scope cleaning turn around time (48-54 hours)
  - Need to increase number of duodenoscopes (double) and linear EUS scopes
  - Short term backlog of cases
- Ethylene oxide (EtO) gas sterilization
  - Significant cost
  - Possible damage to scopes
  - Safety
    - EtO enteritis for patients if not adequately degassed
    - Technicians who use EtO
    - Not available in many hospitals
  - Limited availability

Current Practice for ERCP/EUS Reprocessing (UCLA)

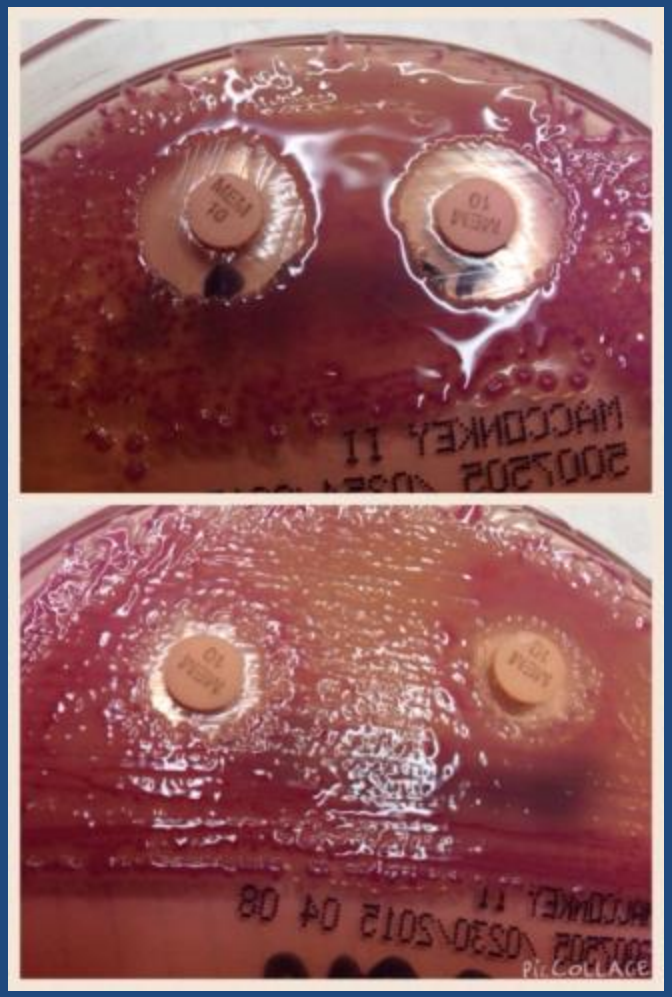


EVALUATION OF EXPOSED PATIENTS

CRE Surveillance Cultures

CRE Surveillance: UCLA method

- Adapted technique used for surveillance of carbapenem resistant *Acinetobacter baumannii*
- Inoculate rectal swab to MacConkey; add 2 meropenem disks
- Validated method with:
  - Pure cultures from known positive cases
  - Seed-and-recover study
- ≥28 mm – perform ID/AST



UCLA Health

Swab Collection Kit

Included in this packet is a swab that will be used to test for the germ, Klebsiella.

Please follow the directions below:

Step 1. Open swab packet and remove swab.

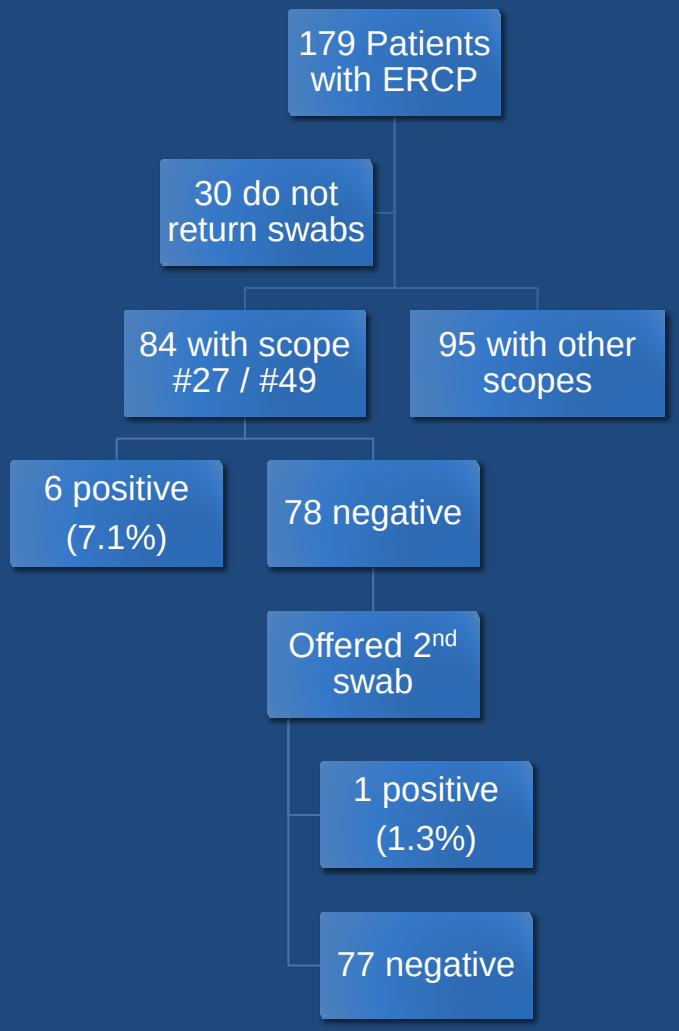
Step 2. Insert swab ½ inch (no further) into rectum as you would a rectal thermometer. Rotate gently three times.

Step 3. Transfer swab to the tube, pushing it into the gel.

Step 4. Tighten cap securely.

Step 5. Apply the provided sticker with your name and medical record number to the tube.

Step 6. Place tube into preaddressed mailer and mail back IMMEDIATELY.



2 colonized patients develop clinical infections (splenic abscesses, stents placed during ERCP)

… BUT WHERE DID THIS COME FROM?

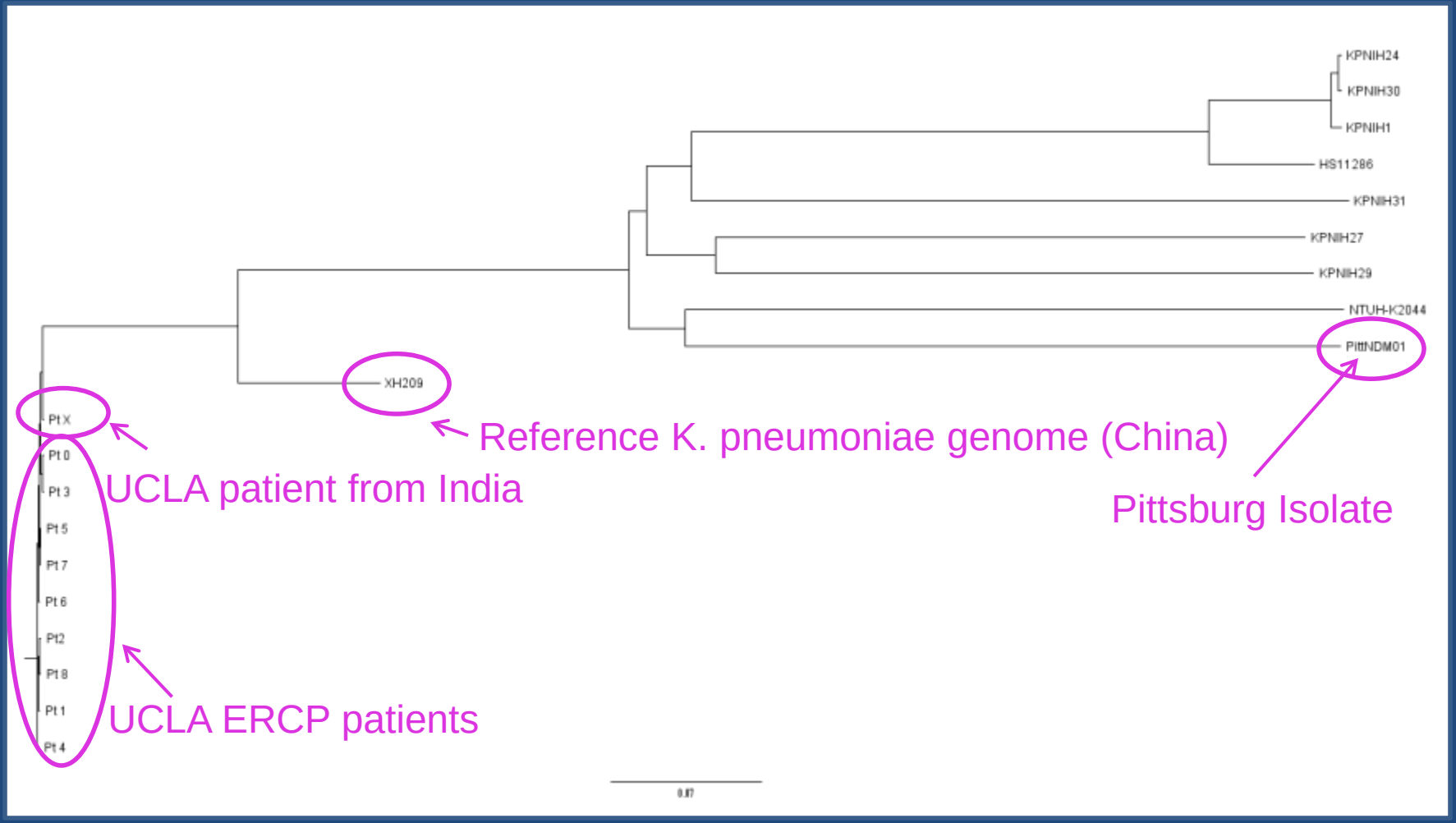
Identification of Index Patient

What about our index patient?

- Examined all CRE from 2014 for Oxa-232
- One more patient identified
  - 58 M, history of suboccipital craniectomy in India in May 2014
  - Presents to UCLA with worsening mental status
  - Several procedures at UCLA

    …but NO ERCP!

WGS data dendogram



SNV Analysis on outbreak isolates

- Maximum SNPs between isolates: 12
- Minimum: 0
- 1 patient had both clinical isolate and surveillance isolate (~2 months apart) = 1 SNV
- Can track spread across exposures

FINAL THOUGHTS

… why UCLA?

Duodenoscope outbreak: Why UCLA?

- Environment
  - High prevalence of CRE in LA County
  - UCLA is tertiary care center, many CRE patients transferred to UCLA from outside hospitals
- Luck
  - UCLA strain Oxa-232 organism is very unusual
- Opportunity
  - Ongoing research interest in CRE
  - Bank all isolates
  - Availability of molecular testing & skilled postdoctoral fellows
- Institutional desire
  - Commitment to delivering “Perfect Care” allows UCLA Clinical Epidemiology & Laboratory to be very aggressive
  - Many institutions would not have continued to look

Duodenoscope outbreak at UCLA: Lessons learned

- Epidemiological studies are challenging
  - → Testing for CRE mechanism very helpful
  - → WGS integral to this story
- Cleaning guidelines may not be entirely effective at decontaminating duodenoscopes per FDA
  - → Redesign of duodenoscopes is needed
- Scope cultures per new CDC guideline were not effective at identifying contaminated scopes

October 5, 2015

FDA News Release

FDA orders duodenoscope manufacturers to conduct postmarket surveillance studies in health care facilities

30 days to submit postmarket surveillance plans:

- How well are HCP following reprocessing instructions?
- What is the rate of contamination of clinically used duodenoscopes?
- For scopes that are contaminated, why, and how can these be decontaminated?

Thank You

- Lab
  - Peera Hemarajata
  - Shangxin Yang
  - Kevin Ward
  - Janet Hindler
- Infection Prevention
  - Zachary Rubin
  - Dana Russell
  - Alisa Trout
  - Teresa Zaroda
  - Quen Cheng
  - Daniel Uslan
- Medical Procedure Unit
  - Raman Muthusamy
  - Bennett Roth
  - Cami Kodama
  - Chris Pizzulli
  - Linsey Weigt
- LA County DPH
  - Moon Kim
  - Dawn Terashita