Issues in the Detection of Multi-Drug Resistant Gram Negative Organisms

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Overview

- Problem MDRO GNB in LTCF
- Prevalence in LTCF
- When to screen
- Who should be screened?
- How screening should be done?
- How to detect MDRO GNB

Antibiotic Resistance in LTCF ESKAPE Pathogens

- *Enterococcus faecium* (VRE)
- *Staphylococcus aureus* (MRSA,VRSA)
- *Klebsiella pneumoniae* (CRE-KPC)
- *Acintobacter baumannii* (CRAB-MBL)
- *Pseudomonas aeruginosa* (CRE-MBL)
- *Enterobacter spp*. (CRE-KPC)

Boucher HW et al. Clin Infect Dis 2009;48:1

Antibiotic Resistance - GNB β-lactamases

β-lactamases	Antibiotic Resistance	Enzymes
Broad spectrum	PCN, AMP early cephalosporins As above & Staph PCNs	TEM-1, TEM-2, SHV OXA
Extended spectrum (ESBL) ↑ Hospitals 1980s ↑ Community E. coli	PCN, AMP, Staph PCNs & 3rd cephalosporins+ monobactams As above + cefepime [CTX-M]	TEM CTX-M
Inducible (AmpC)	cephamycins (cefoxitin) β-lactamase inhibitors	

Paterson D. Am J Infect Control 2006;34:S20; Bonomo RA. CID 2011;52:485.

Antibiotic Resistance GNB Carbapenemases

Carbapenemases	Antibiotic Resistance	Enzymes
K. pneumoniae (KPC) Detected 1996 Outbreaks 2001 Endemic 4 continents Found *K. pneumoniae* first Now *E. coli, Enterobacter, Salmonella, Citrobacter*	all β-lactams all carbapenems some aminoglycosides	KPC 1 KPC 2 KPC 3 KPC 4
Metallo-β-lactamases (MBL) Detected 1991 Outbreaks 2000 worldwide *Pseudomonas aeruginosa* *Acinetobacter baumannii*	As above	IMP VIM SPM-1 GIM-1 NDM-1 OXA

Community MDR-GNB ESBLs

	Community onset	Hospital onset
Organism	*Escherichia coli*	*Klebsiella* spp (and others)
Type of ESBL	CTX-M (especially CTX-M15)	SHV (especially SHV2, SHV5) and TEM (especially TEM26, TEM51)
Infection	Most often UTIs, but also bacteraemia and gastroenteritis	Respiratory tract, intra-abdominal, and bloodstream infections
Susceptibilities	Resistance to all the penicillins and cephalosporins. High-level resistance to other classes of antibiotics, especially fluoroquinolones and co-trimoxazole	Resistance to all the penicillins and cephalosporins. High-level resistance to other classes of antibiotics, especially fluoroquinolones and co-trimoxazole
Molecular epidemiology	Most isolates often not clonally related, although clusters have been described in Canada, the UK, Italy, and Spain	Most often clonally related
Risk factors	Repeat UTIs and underlying renal pathology; previous antibiotics including cephalosporins and fluoroquinolones; previous hospitalisation; nursing-home residents; older men and women; diabetes mellitus; underlying liver pathology	Longer length of hospital stay; severity of illness (more severe, the higher the risk); longer time in the intensive-care unit; intubations and mechanical ventilation; urinary or arterial catheterisation; previous exposure to antibiotics (especially cephalosporins)

UTI=urinary-tract infection.

Table 2: **Characteristics of infections caused by ESBL-producing bacteria**

Pitout JDD et al. Lancet ID 2008;8:159

MDR-GNB in Community
ESBLs – CTX-M

- CTX-M-15 worldwide
  - New Delhi 1999; US 2003
- Originated *Kluyvera* spp.
- True community pathogens
- Associated UTI/BSI
- Most common older adults
- Quinolone resistance common
  - *E. coli, Klebsiella, Proteus*

Oteo J et al. J Clin Microbiol 2006;44:2359; Rodriguez-Bano J et al J Clin Microbiol 2004;42:1089.

ESBL in LTCF Prevalence

Author (Date)	Isolates N (%)	E. coli	Where
Muller (02)	200 (16-62)	yes	15 LTCF (Ontario, Canada)
Rooney (09)	58/294 (49%)	yes CTX-M-15	16 LTCF (N. Ireland)
March (09)	56/111 (64%)	yes CTX-M	LTCF (Italy)
Van der Mee-Marquet (10)	9/49 (22%)	CTX-M-15	LTCF (France)
Arvand (13)	25/240	CTX-M-15 CTX-M-14	11 LTCF (Germany)
Cochard (14)	114/1155 (9.9%)	Klebsiella sp (14)	38 LTCF (France)
Zhao (15)	183/487 (46.9%)	CTX-M (99%) CTX-M-14 (42%)	7 LTCF (Shanghai)
Willemsen (15)	33/160 (20.6%)	CTX-M-15 (21)	LTCF (Netherlands)

MDR-GNB in LTCF
ESBL

- *E. coli* infection monoclonal outbreaks
  - CTX-M-15, CTX-M-14
  - Ontario (2000-2002) 15 nursing homes
  - France (2001-2002)
  - UK (2004-2006) 16 nursing homes
  - France (2009)
- Associated with
  - UTI
  - Quinolone, ceftazidime use
- Colonization common
  - urine (22%), rectum (49%)
  - HCW (15%)
- Environmental contamination ~ 0.8% samples

Muller M et al. Can Commun Dis Rep 2002;28:113, Rooney PJ et al. JAC 2009;64:635. Van der Mee-Marquet et al. ICHE 2010;31:968; Leflon-Guibout et al. AAC 2004;48:3736; Cochard H et al. ICHE 2014;35:384

Screening for ESBL Microbiology Definitions

Screen for ESBL

- Disk method
  - cefpodoxime 10 μg
  - ceftazidime 30 μg
  - cefotaxime 30 μg
- Broth
  - cefpodoxime
  - ceftazidime
  - cefotaxime
- Applies only
  - *Klebsiella sp*
  - *E. coli*
  - *Proteus*

Confirm ESBL (+)

- Double disk diffusion
  - ATB alone
  - ATB + β lactamase inh
  - 5 mm zone increase
- Broth
  - ATB alone
  - ATB + β lactamase inh
  - 2-fold reduction MIC
- PCR/molecular typing
  - CTX-M

Clin Lab Standard Inst Manual M-100 S-24, 2014

ESBL Testing

ESBL Screening
When, Who, What to Consider?

- Increase infection rates
  - 3rd 4th cephalosporins, monobactams
  - Quinolones
  - *E. coli* ST 131
- No specific risk factors
- Urine and rectum

Willemsen I et al. ICHE 2015;36:394; Zhao S-Y et al. Epidemiol Infect 2015;doi:10:1017/S0950268815001879

Carbapenem^{R} Enterobacteriaceae
What Are They?

- Carbapenems – antibiotics of last resort
- Enterobacteriaceae
  - gram negative bacilli
  - lactose fermenters
  - not *Pseudomonas* or *Acinetobacter*
- Multiple mechanisms of carbapenem^{R}
  - inactivation by key enzymes the main concern
  - not all CRE produce carbapenemases (CPE)
  - many labs can identify CRE but not CPE

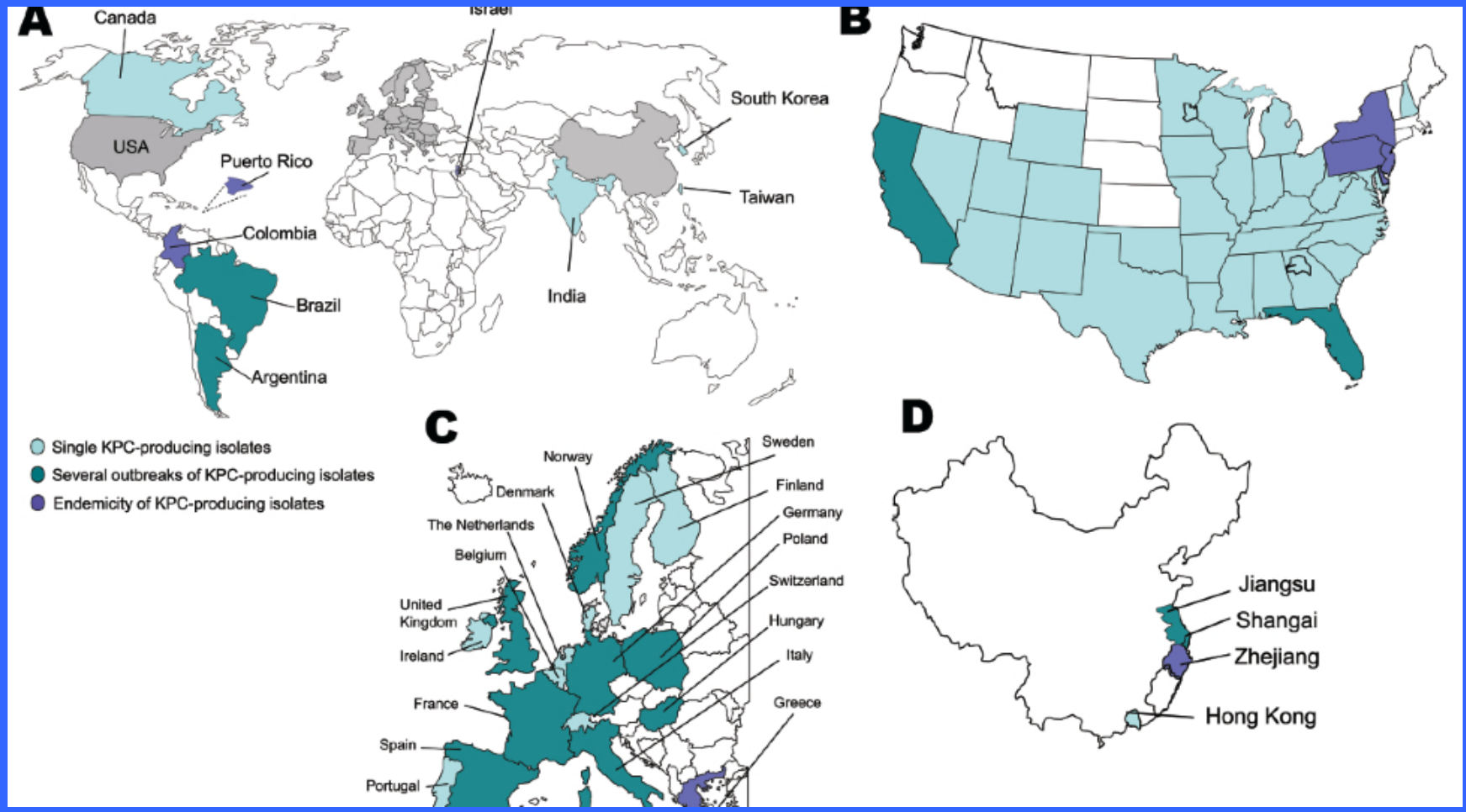
Carbapenem Resistance Identification – A Major Issue

- Carbapenemase- producing CRE (CPE)
  - — spreading rapidly world wide
  - — resistant majority antibiotic classes
  - — invasive infections 40-50% mortality

Carbapenem^{R} Enterobacteriaceae (CRE) Identification-Major Issues

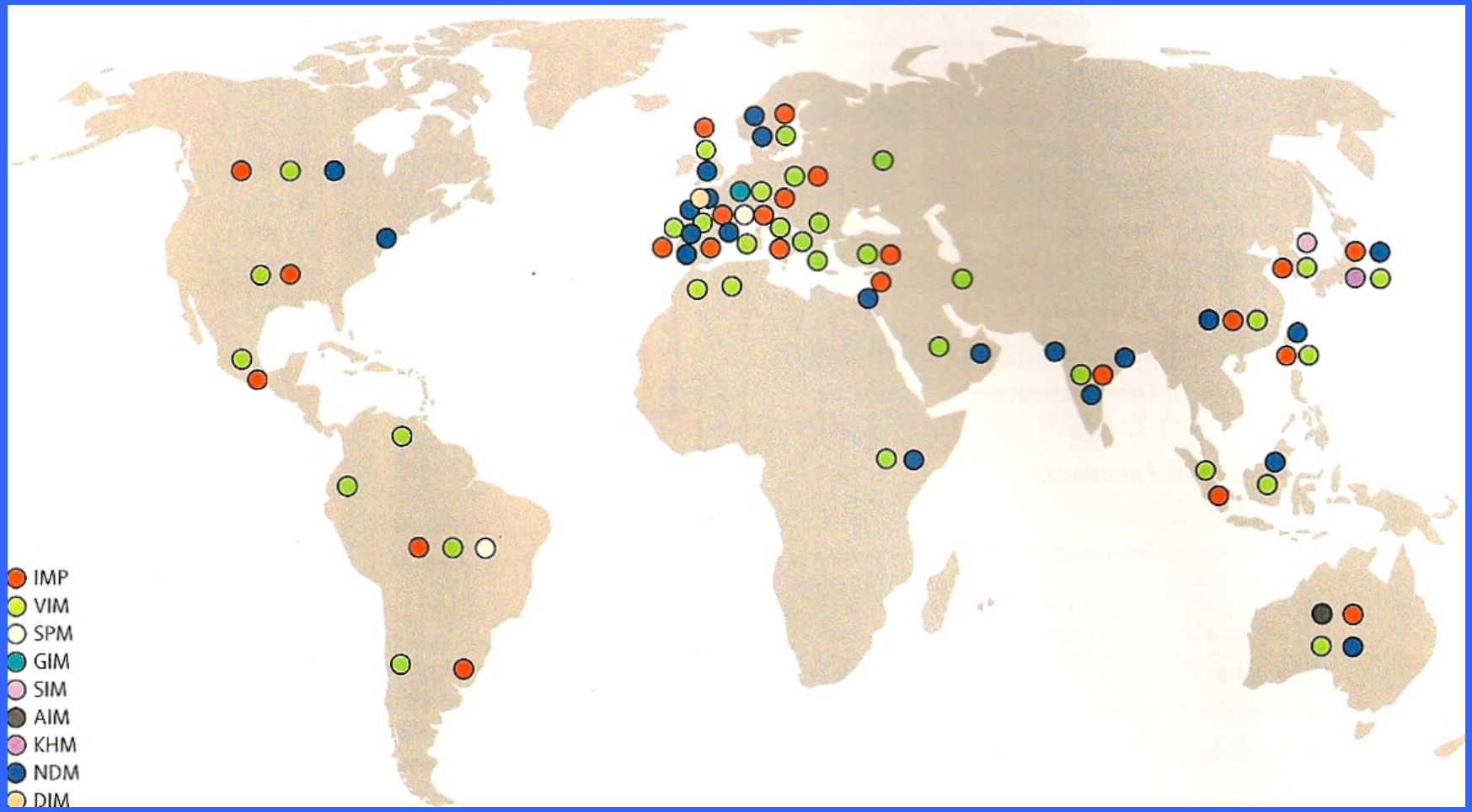
- There are many carbapenemases
  - *Klebsiella pneumoniae* carbapenemase (KPC)
  - Verona integron metallo-β-lactamase (VIM)
  - Imipenemase metallo-β-lactamase (IMP)
  - Oxacillinase-48-type carbapenemases (OXA-48)
  - New Delhi metallo-β-lactamase-1(NDM-1)
- Carbapenemases vary with geography

Carbapenem Resistance (CRE) KPCs



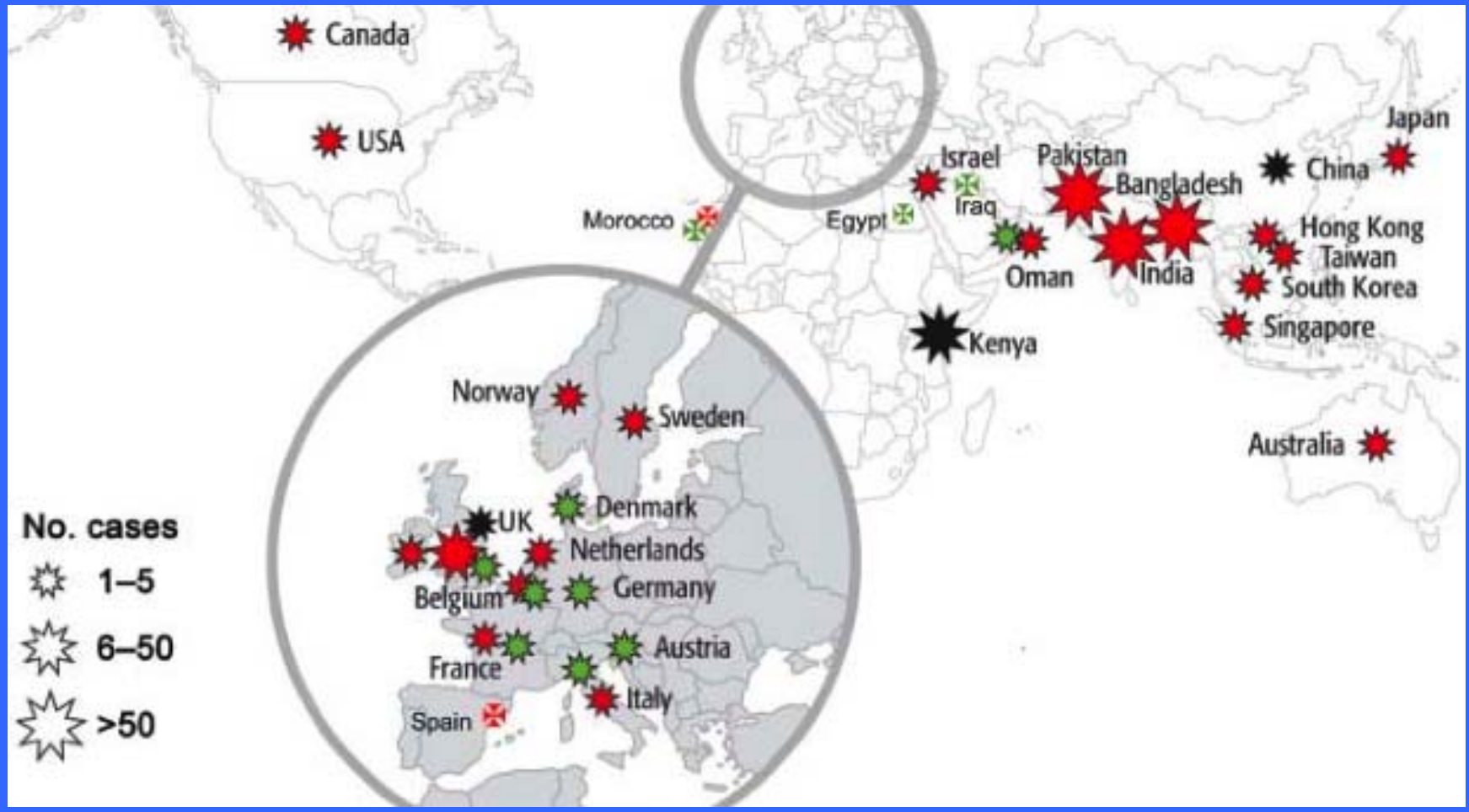
Nordmann P et al. Emerg Infect Dis 2011;17:1791

Carbapenem Resistance (CRE)
Metallo-β-lactamases (MBL)



Cornaglia G et al. Lancet ID 2011;11:381.

Metallo-β-lactamases New Delhi (NDM-1)



Nordmann P et al. Emerg Infect Dis 2011;17:1791

Metallo-β-lactamases NDM-1

- Exposure endemic areas
  - travelers
  - medical tourists
  - military
- Now non-endemic acquisition
  - France, Italy, Canada
  - community, nursing homes, rehabilitation units
  - no travel history
  - evidence transmission
  - spread multiple facilities
  - older patients

Denis C et al. CMI 2012;18:E128; Kus JV et al. CMAJ 2011;183:1257; Nordmann P et al. CID 2012;54:150; Gaibani P et al. Euro Surveill 2011;16:20037.

K. Pneumoniae Carbapenemases (KPCs) LTCFs & LTACHs

- USA, Israel (2008-2011)
- Older adults, co-morbidities, devices
- Most admitted from post-acute care facilities
- Mortality 35-69%
- Mostly related clones
  - *K. pneumoniae (38/76), ST-258*
    - mostly urinary
  - *E. coli (2)*

Endimiani A et al. JAC 2008;64:1102; Marchaim D et al. AAC 2011;55:593. Won SY et al. CID 2011;53:532,; Mills J et al. ICHE 2011;32:629; Perez F et al. JAC 2010;65:1807; Ben-David et al. ICHE 2011;32:845.

CRE in LTCF Prevalence

Author (Date)	N (%)	What	Where
Munoz-Price (2010)	8/39 (21%)	KP-CPE	LTACH (US)
Mills (2011)	7/100 (7%)	KP-CPE	LTCF (US)
Ben-David (2011)	75/357 (21%)	KP-CRE	LTCF (Israel)
Marchaim (2012)	42/93 (42.5%)	CRE	Hosp admit LTCF (US)
Lewis (2013)	20/262 (7.6%)	CPE	LTACH (US)
Saegeman (2015)	1/257 (0.4%)	CPE	LTCF (Belgium)

LTACH vs SNF
CRE present on admission to hospital
Proportion of clinical isolates from lab collections

Screening for CRE Microbiology Definitions

Screen for CRE

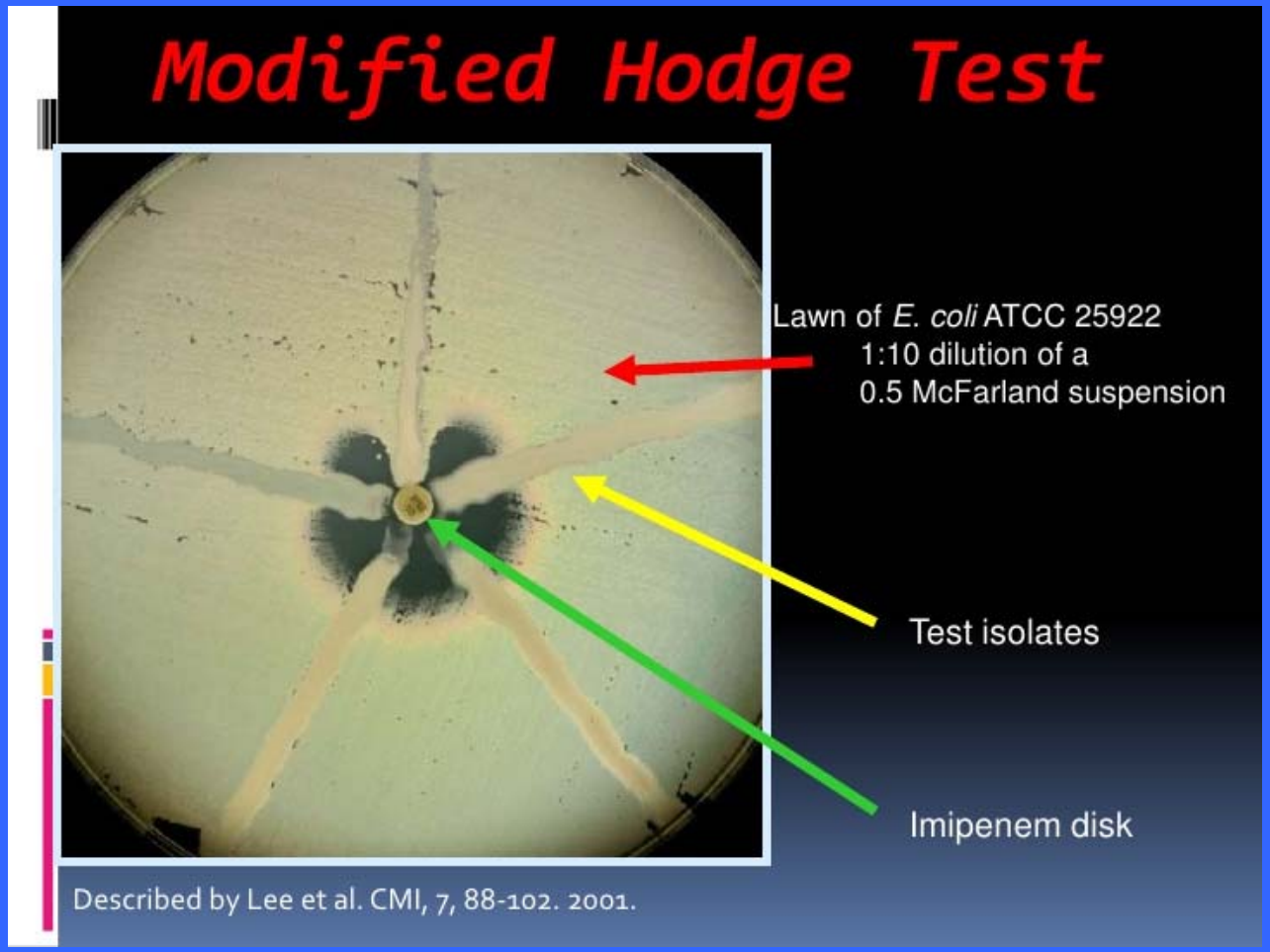
- MIC ≥ 8 μg/ml
  - doripenem,
  - imipenem,
  - meropenem
- MIC ≥ 2 μg/ml
  - ertapenem
- Intrinsic imipenem^{R}
  - *Morganella, Proteus, Providencia*
  - Must be resistant to another carbapenem

Confirm CPE (+)

- Modified Hodge Test
  - disk test, easy
  - false positives
- CARBA NP agar
- MBL inhibition assays
- PCR/molecular tests
  - KPC, VIM, NDM-1
  - IMP, OXA-48

CDC. CRE Tool Kit Update – Nov 2015; Hrbak J CMI 2014;20:839

Modified Hodge Test
CPE Detection



CRE Screening in LTCF What to Use?

- 3 Belgian SNF & Rehabilitation Center
- Access screening methods for CPE
  - optimal method & site not known
  - swab – visible fecal staining best
  - broth enrichment not helpful
  - MacConkey agar helps-adequate # gnb
  - chromogenic agars no benefit ↑ incubation leads to gpc overgrowth

Saegeman V et al. Eur J Clin Microbiol ID 2015;34:991

CRE Screening
Who to Consider?

- Patients at risk
  - Healthcare setting with high rate CPE
    - overnight stay last 6-12 months
  - Foreign countries with CPE
  - ICU patients
  - Transplant patients
  - Immunocompromised

CDC. CRE Tool Kit Update – Nov 2015; Nordmann P et al. Emerg Infect Dis 2011;17:1791

CRE Screening
When to Screen?

- Screen contacts of known CRE (+) pts
  - most important if CPE (+) pts
  - contacts with epidemiological link
    - roommates
    - common HCW
    - wards
- Active surveillance
  - high CPE rates
  - outbreaks CRE
  - control measure

CDC. CRE Tool Kit Update – Nov 2015; Nordmann P et al. Emerg Infect Dis 2011;17:1791

CRE Screening
What Sites to Screen?

- Patients
  - stool, rectum, peri-rectal most often
  - skin, wounds
- Environment
  - seems uncommon

CDC. CRE Tool Kit Update – Nov 2015; Nordmann P et al. Emerg Infect Dis 2011;17:1791

K. pneumoniae CRE Detection in 6 LTACHs

Site	Positive Cultures (N=24)	Sensitivity% (95%C)
Skin Sites		
inguinal	19	79 (58-93)
axillary	18	75 (53-90)
upper back	6	25 (10-47)
antecubital fossa	6	25 (10-47)
Non-Skin Sites		
rectal	21	88 (68-97)
urine	10	53 (29-76)
pharynx/trachea	10	42 (22-63)
Combined Sites		
rectal & inguinal	24	100 (86-100)
rectal & axillary	23	96 (79-100)
axillary & inguinal	22	92 73-99)

Thurlow CJ et al. ICHE 2013;34:56-61

MDR *A. Baumanii* in LTCF Significance

- Outbreaks MDR *Acinetobacter* reported
- LTCF-LTACH colonization (28-34%)
  - 50% (+) on hospital admission
  - ventilated residents
  - tracheostomy/sputum main site
  - environmental contamination ~10%
  - aerosolization?
  - combat injuries
- Mortality ~ 35%
  - BSI, pneumonia, UTI

A. Baumanii in LTCF Screening Issues

- Acinetobacter – 30 species
  - phenotype not helpful
  - some species not resistant or pathogens
  - A. *calcoaceticus-baumannii* complex
- Preliminary ID by fermentation (API 20E)
- Speciation difficult
  - MALDI-TOF
- MDR – resistant 3 or more classes
- Not all have carbapenemase

A. baumannii Complex in LTCF Prevalence

Author (Date)	N (%)	What	Where
Stephens (2007)	70/151 (46.4)	MDR	LTACH/Hosp Network (US)
Furuno (2008)	41/147 (28%)	Not MDR	LTCF (US)
Stengstock (2010)	153/280 (53)	MDR	17 LTCF (US)
Perez (2010)	8/39 (20.5) 5/8 (62.5)	CRAB OXA-23	LTCAH (US)
Mortensen (2014)	14/70 (20)	MDR (86%) CRAB (60%)	subacute + vents (US) LTCF
Mody (2015)	25/168 (14.9) 20/25 (80)	MDR CRAB	4 LTCF (US)

Screening for CRAB Microbiology Definitions

Screen for CRAB

- CHROMAcinetobacter
- MIC ≥ 8 μg/ml
  - doripenem,
  - imipenem,
  - meropenem

Confirm enzyme (+)

- Modified Hodge Test
- PCR/molecular tests
  - PFGE
  - OXA-23, OXA-24/40
  - OXA-58
  - IMP, VIM, SIM

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A. baumanii in LTCF
Who to Screen?

Screening for CRAB
What Sites?

Sites from 129 ICU Patients	CRE colonized N (%)
Single	
tracheal aspirate	35 (27)
rectum	24 (19)
sternal skin	7 (5)
urine	4 (3)
Detection CRE	
any 1 site	70 (54)
trachea & rectum	97 (75)
trachea, rectum & sternum	104 (80)
all 4 sites	108 (85)

Apisarnthanarak A et al. Clin Infect Dis 12/27/2012

MDRO GNB in LTCF Summary

- MDRO-GPC get more publicity!
- MDRO-GNB an increasing problem
- Transfer resistance between GNB easy
- Confers resistance to all antibiotics
- Serious infections with high mortality
- Detection MDRO-GNB is not simple
- Impact on infection control resources