MDRGN – Epidemiology & Diagnosis
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Broadcast live from the HIS/FIS conjoint conference www.hisconference.org.uk

FEDERATION OF infection societies | HEALTHCARE INFECTION SOCIETY | FIS/HIS 2012 19-21 November 2012 BT Convention Centre, Liverpool

Multi-drug resistant Gram-negative infections
Epidemiology and diagnosis

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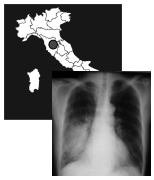
Challenges by XDR Gram-negatives

- Can cause severe, difficult-to-treat infections (impact on morbidity and mortality)
- Dearth of active antibiotics

Tuscany, November 2010 ....



62 y/o patient, hip replacement

Admitted to rehabilitation unit: pneumonia

Empiric treatment: ceftriaxone + levofloxacin

Does not improve

Transferred to district hospital

Samples for cultures

Empiric treatment: Meropenem + Linezolid

Does not improve ...

Results of sputum culture:

K. pneumoniae

XDR phenotype

Definitive therapy?

Colistin (iv + aerosol)
Rifampin
Tigecycline
Meropenem

Antibiotic	MIC mg/L(S/I/R)
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
Amikacin	>64 R
Gentamicin	2 S
Tobramycin	>16 R
Ciprofloxacin	>4 R
Levofloxacin	>8 R
Tigecycline	1.5 I
Colistin	0.5 S

Initial improvement ...

Relapse after three days

Breakthrough bacteremia and septic shock

blood culture: *K. pneumoniae*

Antibiotic	MIC mg/L(S/I/R)
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
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Levofloxacin	>8 R
Tigecycline	4 R
Colistin	8 R

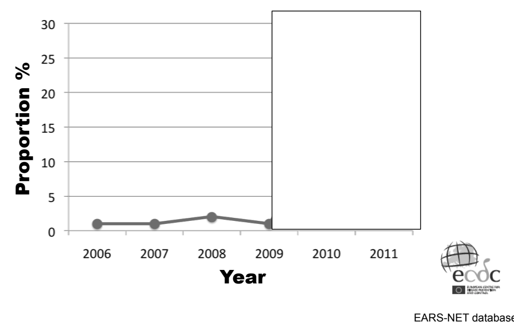
Outcomes of BSI caused by carbapenem-R *K. pneumoniae*

Author	Country	Pts	Mortality
Borer, ICHE 2009	Israel	32	crude: 72% attributable: 50%
Nguyen, DMID 2010	USA	48	30-day: 42%
Mouloudi, ICHE 2010	Greece	19	In-hospital: MBL, 56%; KPC, 79%
Ben-David, CMI 2011	Israel	42	In-hospital: 69% Infect.-related: 48%
Zarkotou, CMI 2011	Greece	53	Overall: 53%
Qureshi, AAC 2012	USA	41	28-day crude: 39%
Tumbarello, CID 2012	Italy	125	Overall: 42%

Challenges by XDR Gram-negatives

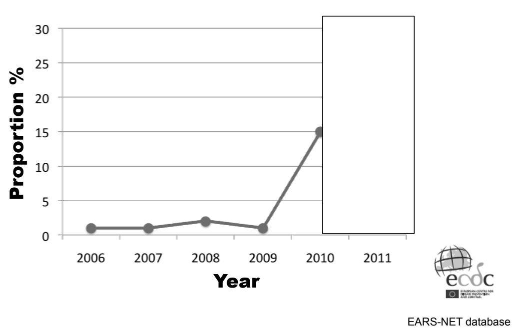
- Can cause severe, difficult-to-treat infections (impact on morbidity and mortality)
- Dearth of active antibiotics
- Can spread rapidly and pandemically in health-care settings
- Are difficult to control

Carbapenem-resistant *Klebsiella pneumoniae*, Italy



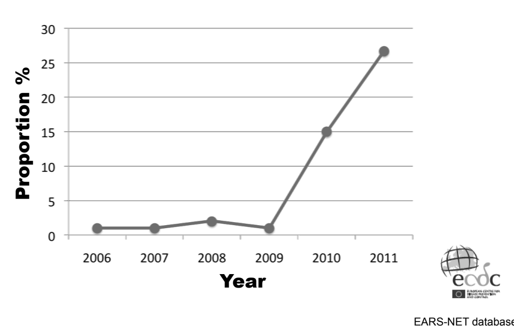
EARS-NET database

Carbapenem-resistant *Klebsiella pneumoniae*, Italy



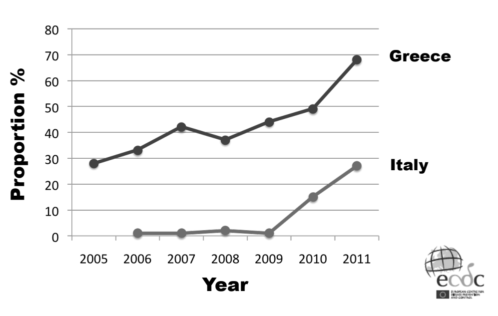
EARS-NET database

Carbapenem-resistant *Klebsiella pneumoniae*, Italy



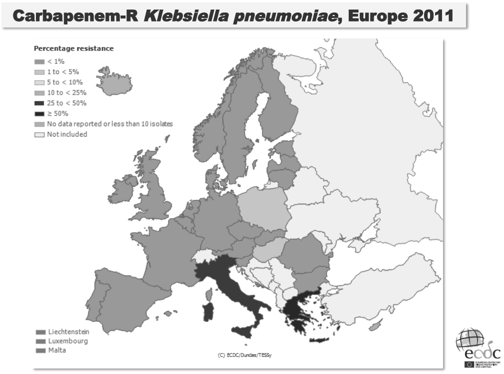
EARS-NET database

Carbapenem-resistant *Klebsiella pneumoniae*



EARS-NET database

Carbapenem-R *Klebsiella pneumoniae*, Europe 2011



EARS-NET

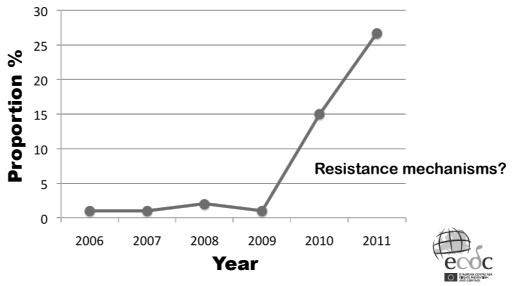
… but carbapenem-R enterics reported in most EU countries

Canton *et al* – CMI 2012
Hoenigl *et al* – AAC 2012

Carbapenem resistance mechanisms in *Enterobacteriaceae*

- **Porin loss + ESBL/ AmpC production** → Lower-level R, Not transferable
- **Carbapenemase production** → Higher-level R, Transferable
  - ◆KPC
  - ◆MBLs (NDM, VIM, IMP)
  - ◆OXA-48-like

Carbapenem-resistant *Klebsiella pneumoniae*, Italy



EARS-NET database

Carbapenem-R *K. pneumoniae*, Italy

Cross-sectional survey, 2011 (N=1964 *K. pneumoniae* isolates from 25 centers)

AMCLI-CoSA – Italian national CRE surveillance 2011

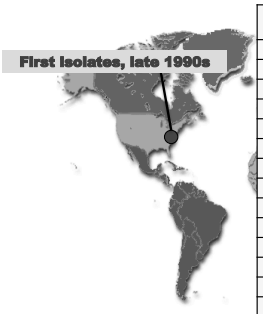
Carbapenem-R *K. pneumoniae*, Italy

Cross-sectional survey, 2011 (N=1964 *K. pneumoniae* isolates from 25 centers)

- ◆ Carbapenem-R *K. pneumoniae* detected in 23 of 25 centers (N=234 isolates)
- ◆ 95% carbapenemase producers
- ◆ 87% KPC, 7% VIM, 1% OXA-48

AMCLI-CoSA – Italian national CRE surveillance 2011

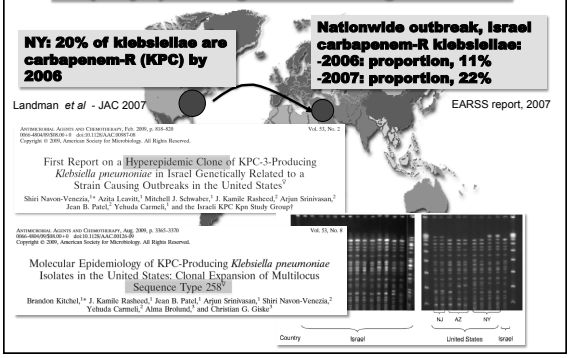
KPC = Klebsiella pneumoniae carbapenemase



Antibiotic	*K. pneumoniae* 1534 MIC (mg/L)
Imipenem	16
Meropenem	16
Ampicillin	>64
Amoxi/clav	>32/16
Pip/tazo	>128/4
Ceftazidime	32
Cefoxitin	32
Cefpodoxime	>16
Cefotaxime	64
Ceftriaxone	>64
Aztreonam	>64
Gentamicin	>16
Tobramycin	>16
TMP/SMX	>8
Chloramphenicol	32

Yigit *et al* - AAC 2001

KPC-producing *K. pneumoniae* rapidly spreading and travelling overseas

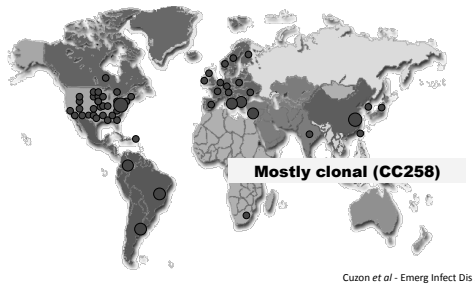


K. pneumoniae CC258: a paradigm of High-Risk Clones (HiRiCs)

MDR bacterial clones retaining virulence and notable propensity for cross-transmission and spreading ("hyperepidemic")

Woodford *et al* - FEMS Microbiol Rev 2011

KPC-producing *K. pneumoniae* pandemic diffusion



Nordmann *et al* - Emerg Infect Dis 2011

Cuzon *et al* - Emerg Infect Dis 2010
Baraniak *et al* – AAC 2011
Andrade *et al* – AAC 2011

KPC-producing *K. pneumoniae* - Italian experience

late 2008

The first reported cases of KPC-Kp (ST258)

Giani *et al* – JCM 2009
Rossolini GM – unpublished

early 2011

ST258, ST512 (CC258)

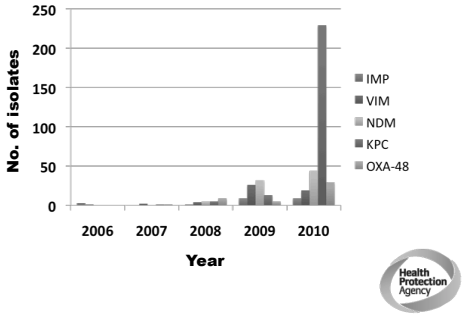
Fontana *et al* – BMC Res Notes 2010
Marchese *et al* – J Chemother 2010
Ambretti *et al* – New Microb 2010
Gaibani *et al* – Eurosurv 2011
Mezzatesta *et al* – CMI 2011
Agodi *et al* – JCM 2011
Richter *et al* – JCM 2011
Di Carlo *et al* – BMC Gastroenterol 2011
Rossolini GM – unpublished

late 2012

ST512
ST258
ST101
ST15

AMCLI – CoSA CRE network
Frasson *et al* – JCM 2012
Rossolini GM – unpublished

Enterobacteriaceae from UK Labs confirmed to have carbapenemases



Emergence of colistin-R KPC-Kp

Clin Infect Dis. 2011 Aug;53(4):373-6.

Colistin-resistant, Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneu

SURVEILLANCE AND OUTBREAK REPORTS

Bogdani

Microbiological and molecular characteristics of carbapenemase-producing *Klebsiella pneumoniae* endemic in a tertiary Greek hospital during 2004-2010

Eurosurveillance 2012

COL-R: 3.5% (2008) → 20.8% (2010)

Multifocal emergence of COL-R KPC-Kp

Also independent of COL exposure

Stable R phenotype

Variable proportions (6 - 45%)

Giani *et al* – ICAAC 2011, and unpublished data

COL-R *K. pneumoniae* producing KPC

Antibiotic	MIC mg/L(S/I/R)
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
Amikacin	>64 R
Gentamicin	2 S
Tobramycin	>16 R
Ciprofloxacin	>4 R
Levofloxacin	>8 R
Tigecycline	1.5 I
Colistin	16 R

Isolated from blood and rectal swab of a 24 y/o neutropenic patient (induction for SCT) died of sepsis

COL-R *K. pneumoniae* producing KPC

Antibiotic	MIC mg/L(S/I/R)
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
Amikacin	>64 R
Gentamicin	4 I
Tobramycin	>16 R
Ciprofloxacin	>4 R
Levofloxacin	>8 R
Tigecycline	4 R
Fosfomycin	>128 R
Colistin	32 R

Isolated from sputum and rectal swab of a 20 y/o CF patient candidate for lung transplantation

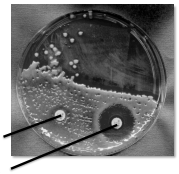
Transplantation on hold

KPC-Kp: challenges to infection control

- **Propensity to colonise**
  - **Gut**
  - **Pharynx & resp. tract**
  - **Urinary tract**

Rectal swab

High-level intestinal carriage

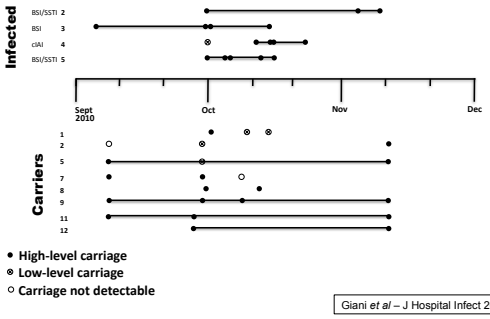


MER

MER + APB

Giani *et al* – J Hospital Infect 2012

Persistent intestinal carriage of KPC-Kp



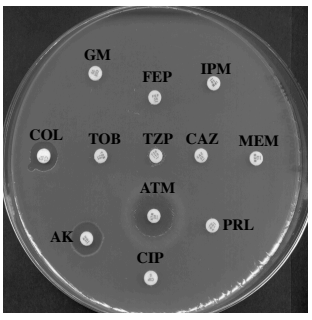
- High-level carriage
- Low-level carriage
- Carriage not detectable

Giani *et al* – J Hospital Infect 2012

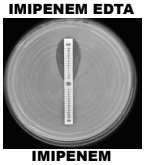
Challenging XDR Gram-negatives: a long list

- **Carbapenem-R Enterics (CRE)**
  - ***K. pneumoniae* KPC**
  - **Enterics MBL+ (NDM, VIM)**
  - ***K. pneumoniae* OXA-48**

Pseudomonas aeruginosa producing metallo-beta-lactamase (MBL)



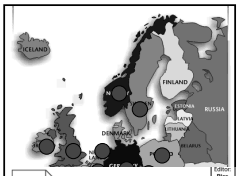
IMIPENEM EDTA



IMIPENEM

Colistin Only Susceptible phenotype

MBL+ *P. aeruginosa* : widespread in Europe



Enzymes:
- **VIM**
- **IMP**
- **GIM**
- **SPM**
- **NDM**
- **FIM**

AAC 2013

FIM-1, a New Acquired Metallo-β-Lactamase from a *Pseudomonas aeruginosa* Clinical Isolate from Italy

Simona Pollini,[a] Simona Maradei,[a] Patrizia Pecile,[b] Giuseppe Olivo,[c] Francesco Luzzaro,[d] Jean-Denis Docquier,[a] Gian Maria Rossolini[a]*

Sporadic cases or outbreaks

Miriagou *et al* – CMI 2010
Cornaglia *et al* – Lancet ID 2011
Jovcic *et al* – AAC 2011

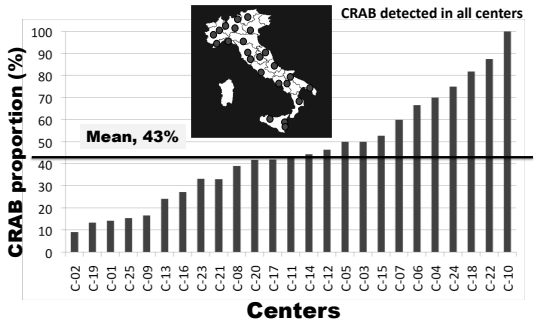
Challenging MDR Gram-negatives: a long list

- **Carbapenem-R Enterics (CRE)**
  - ***K. pneumoniae* KPC**
  - **Enterics MBL+ (NDM, VIM)**
  - ***K. pneumoniae* OXA-48**
- **MBL-producing *P. aeruginosa***
- **Carbapenem-R *Acinetobacter* (CRAB)**

Antibiotic	MIC mg/L(S/I/R)
Imipenem	>16 R
Meropenem	>16 R
Doripenem	>8 R
Amikacin	>32 R
Tobramycin	>16 R
Gentamicin	>16 R
Ciprofloxacin	>4 R
Co-trimoxazole	>4 R
Colistin	2 S
Tigecycline	2
Amp/Sulbactam	16

Carbapenem-R *Acinetobacter* (CRAB)

CRAB data: first Italian surveillance (2011)



AMCLI-CoSA – Italian national surveillance 2011

Conclusions

- **XDR Gram-negatives: now a major challenge in health-care settings**
- **CRE are the major emerging issue globally, but XDR *Acinetobacter* and *P. aeruginosa* should not be neglected**
- **Dearth of new treatment options**
- **Surveillance and aggressive infection control, combined with antibiotic stewardship, remain the only reliable options to combat XDR Gram-negatives**