



MDRGN – Epidemiology & Diagnosis
Gian Maria Rossolini, University of Florence, Italy
 Broadcast live from the HIS/FIS conjoint conference www.hisconference.org.uk

**Multi-drug resistant Gram-negative infections
Epidemiology and diagnosis**



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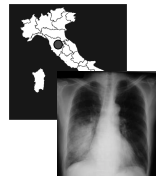


www.webbertraining.com November 19, 2012

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
Empiric treatment: Meropenem + Linezolid

↓
Samples for cultures

Does not improve ...

Results of sputum culture:

K. pneumoniae

XDR phenotype

Definitive therapy?

Colistin (iv + aerosol)
Rifampin
Tigecycline
Meropenem

Initial improvement ...

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

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
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
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Colistin	8 R

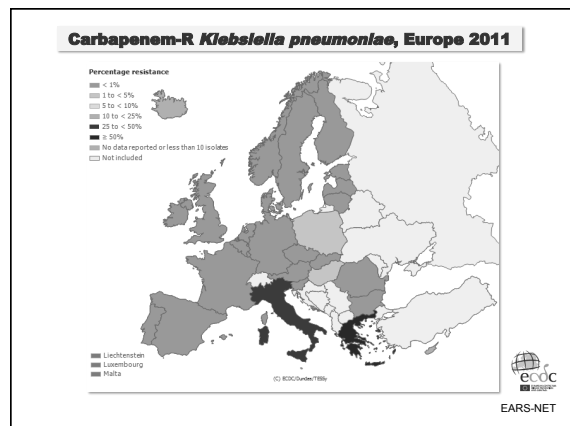
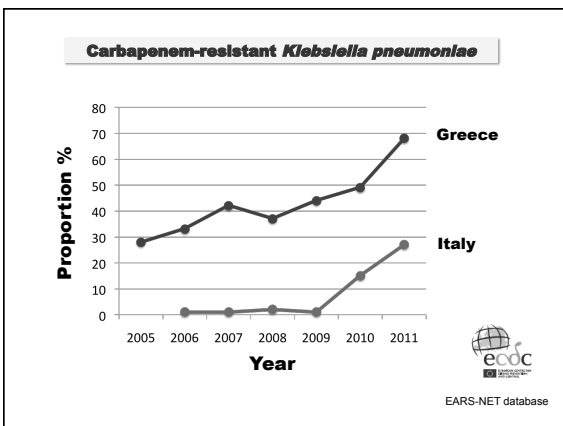
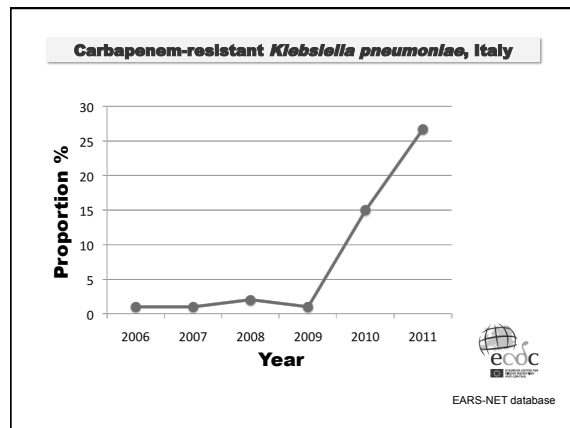
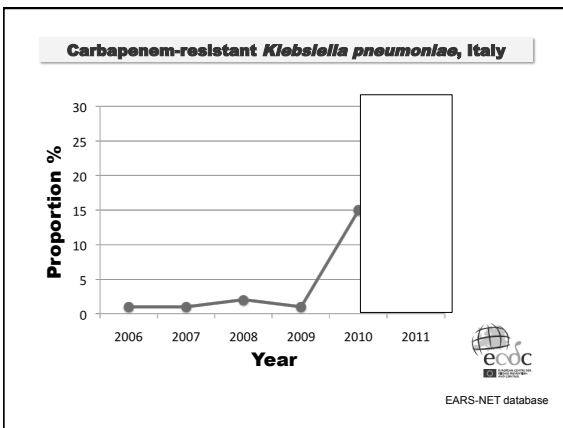
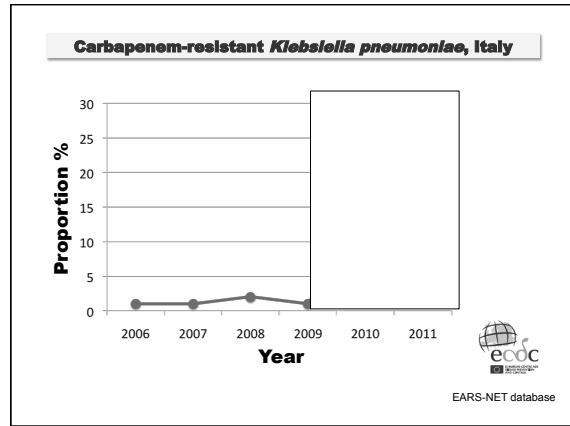
Outcomes of BSI caused by carbapenem-R *K. pneumoniae*

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%

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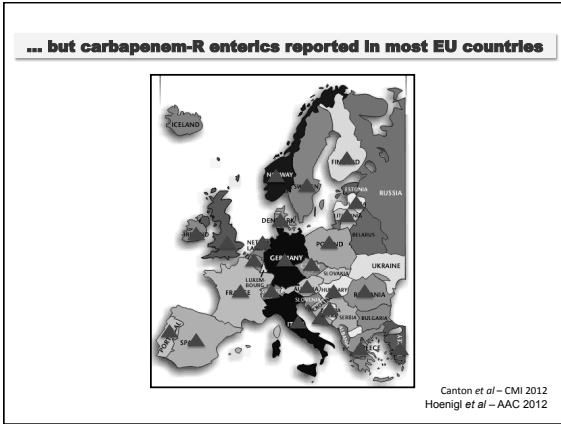
Challenges by XDR Gram-negatives

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



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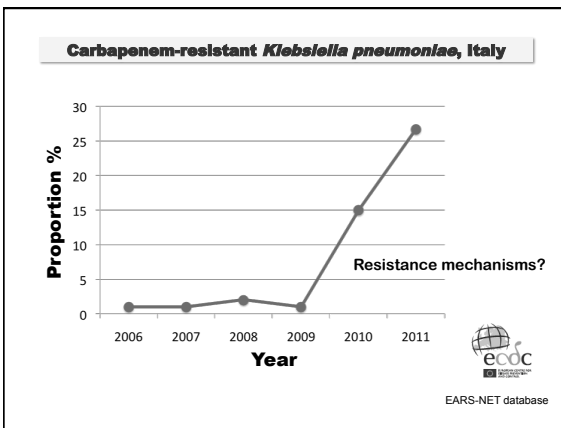
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Carbapenem resistance mechanisms in *Enterobacteriaceae*

- 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-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	<i>K. pneumoniae</i> 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

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

NY: 20% of klebsiellae are carbapenem-R (KPC) by 2006

Nationwide outbreak, Israel carbapenem-R klebsiellae: -2006: proportion, 11% -2007: proportion, 22%

Landman *et al* - JAC 2007 EARSS report, 2007

Antonie van Leeuwenhoek, Amsterdam, 2006, p. 553-559
 ISSN 0924-6460/06/070553-07
 Copyright © 2006, American Society for Microbiology. All Rights Reserved.

First Report on a Hyperepidemic Clone of KPC-3-Producing *Klebsiella pneumoniae* in Israel (Genetically Related to a Strain Causing Outbreaks in the United States)
 Shiri Navon-Venezia,^{1,2} Aitza I. Levin,¹ Mitchell J. Schwaber,¹ J. Kamile Raebecq,¹ Arjun Srinivasan,² Jean B. Patel,² Yehuda Carmeli,¹ and the Israeli KPC-Kpn Study Group¹

Antonie van Leeuwenhoek, Amsterdam, 2006, p. 563-570
 ISSN 0924-6460/06/070563-08
 Copyright © 2006, American Society for Microbiology. All Rights Reserved.

Molecular Epidemiology of KPC-Producing *Klebsiella pneumoniae* Isolates in the United States: Clonal Expansion of Multilocus Sequence Type 258^a
 Brandon Kitchel,^{1*} J. Kamile Raebecq,¹ Juan B. Patel,¹ Arjun Srinivasan,¹ Shiri Navon-Venezia,² Yehuda Carmeli,¹ Alma Brodeur,¹ and Christian G. Giske¹

Antonie van Leeuwenhoek, Amsterdam, 2007, p. 1063-1070
 ISSN 0924-6460/07/071063-08
 Copyright © 2007, American Society for Microbiology. All Rights Reserved.

Country: Israel, United States, Israel

***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

Mostly clonal (CC258)

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 **early 2011** **late 2012**

The first reported cases of KPC-Kp (ST258) **ST258, ST512 (CC258)** **ST512, ST258, ST101, ST15**

Fontana *et al* - BMC Res Notes 2010 Fontana *et al* - JCM 2011
 Marchese *et al* - J Chemother 2010 Richter *et al* - JCM 2011
 Ambretti *et al* - New Microb 2010 Di Carlo *et al* - BMC Gastroenterol 2011
 Galbani *et al* - Eurosurv 2011 Rossolini GM - unpublished
 Mezzatesta *et al* - CMI 2011 Rossolini GM - unpublished
 Agodi *et al* - JCM 2011 AMCLI - CoSA CRE network
 Frasson *et al* - JCM 2012

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

Enterobacteriaceae from UK Labs confirmed to have carbapenemases

Health Protection Agency

Emergence of colistin-R KPC-Kp

Clin Infect Dis. 2011 Aug;53(4):373-4.
 Colistin-resistant, Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneumoniae SURVEILLANCE AND OUTBREAK REPORTS
 Bioscience 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)

66%

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

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COL-R *K. pneumoniae* producing KPC

Antibiotic	MIC mg/L(S//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//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

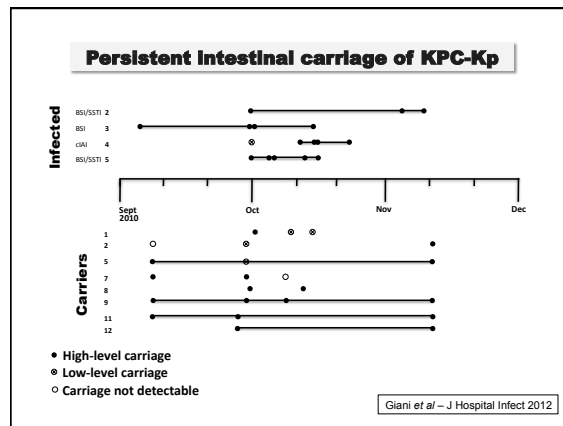
- ◆ Propensity to colonise
 - Gut
 - Pharynx & resp. tract
 - Urinary tract

Rectal swab



High-level intestinal carriage

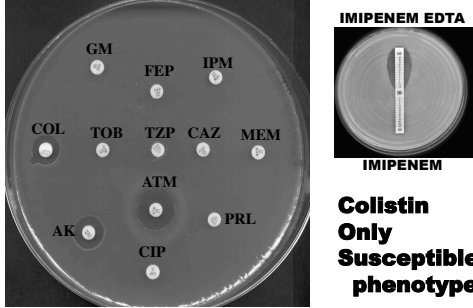
Giani et al – J Hospital Infect 2012



Challenging XDR Gram-negatives: a long list

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

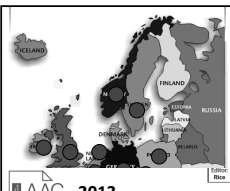
***Pseudomonas aeruginosa* producing metallo-beta-lactamase (MBL)**



Colistin Only Susceptible phenotype

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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

Sporadic cases or outbreaks

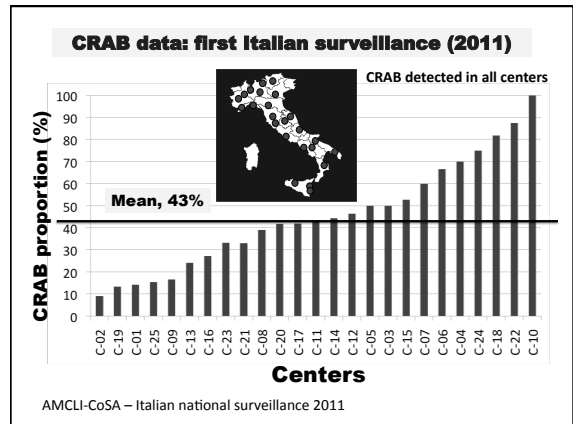
Simona Pallini,* Simona Marsili,* Patrizia Peella,* Giuseppe Olivero,* Francesco Luzzaro,* Jean-Denis Docquier,* Gian Maria Rossolini**
 Miraggiou et al – CMI 2010
 Cornaglia et al – Lancet ID 2011
 Jovicic et al – AAC 2011

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)



- 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**



FEDERATION OF infection societies
 HEALTHCARE INFECTION SOCIETY

FIS/HIS 2012 19-21 November 2012 BT Convention Centre, Liverpool

Federation of Infection Societies (FIS)
 For more information on the individual Federation of Infection Societies visit their websites by clicking on the logos below:

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 British Infection Association (BIA) www.britisheinfection.org
 British Paediatric Infection Group (BPAIG) www.bpaig.org
 British Society for Antimicrobial Chemotherapy (BSAC) www.bsac.org.uk
 Infection Prevention Society (IPS) www.ips.ac.uk
 United Kingdom College of Infection Control and Prevention (UKCIPC) www.ukcipa.org
 British Society for Microbiology (BSM) www.bsmb.org
 Clinical Virology Society (CVS) www.clinical-virology.org
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