Patogeni emergenti nelle infezioni urinarie complicate

La Gestione Multidisciplinare delle Infezioni Complicate delle Vie Urinarie nel Terzo Millennio

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Nuovo "Arcispedale S. Anna", Cona
Aula Congressi

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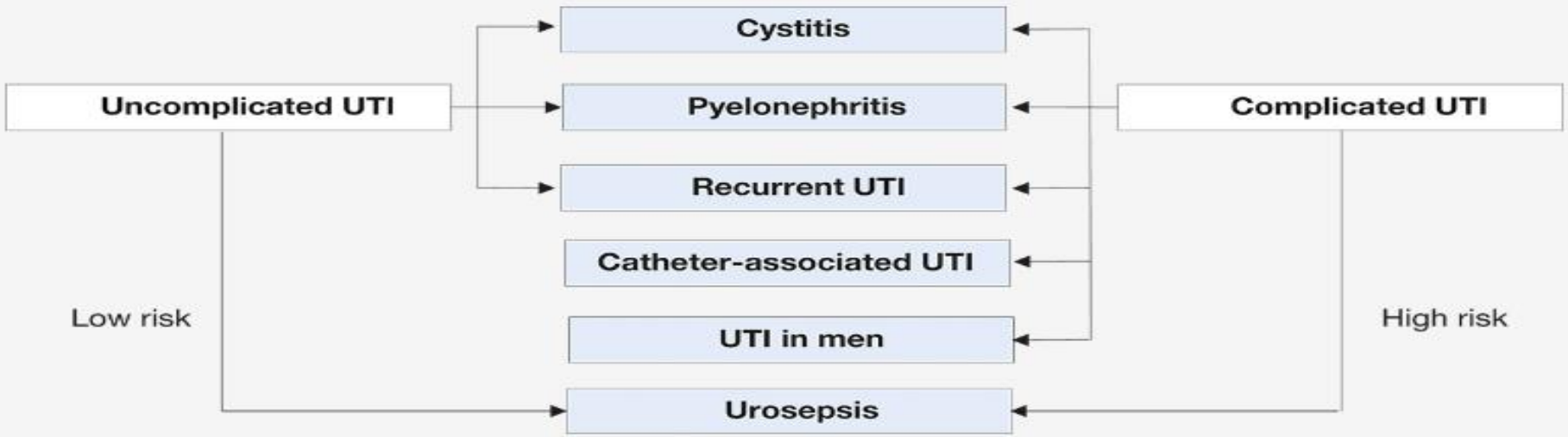
AOU Careggi, Firenze

Figure 1 – Concept of uncomplicated and complicated UTI



uroweb.org/guideline/urological-infections/#3

Presentazione clinica	Grado di severità	ORENUC	Patogeni
UR: uretriti **CY**: cistiti **PN**: pielonefriti **US**: urosepsi **MA**: ghiandole genitali maschili	**1**: basso, **CY** **2**: moderato, **PN** **3**: severo, **PN** **4**: SIRS, **US** **5**: disfunzione d'organo, **US** **6**: insufficienza d'organo, **US**	**O**: nessun fattore **R**: IVU ricorrenti **E**: extra-genitali **N**: nefropatie **U**: fattori urologici **C**: fattori legati al catetere	Specie Grado di sensibilità • Sensibilità • Ridotta sensibilità • Multi-resistente

Tabella 3. Parametri additivi di classificazione delle IVU, secondo criterio di severità, rielaborato da EAU European Section of Infection in Urology (ESIU)

Microbiology methods

It is not necessary to request microbiological examination of urine in all clinical situations. Low-risk symptomatic patients consist of adult females with recurrent dysuria/urgency symptoms without fever, and without known diseases predisposing to urinary tract infection (Page 26). Urine cultures from these cystitis patients are discouraged for routine purposes – they are necessary, however, for epidemiological purposes. Rapid methods for detecting bacteriuria can be used in acute treatment decisions (Page 26) after appreciating the possibility of false-negative findings. All other symptomatic patients belong in the high-risk group, whose specimens should be sent for bacterial culture, including identification of species and antimicrobial susceptibility testing.

Scand J Clin Lab Invest 2000; 60: 1–96

European Urinalysis Guidelines

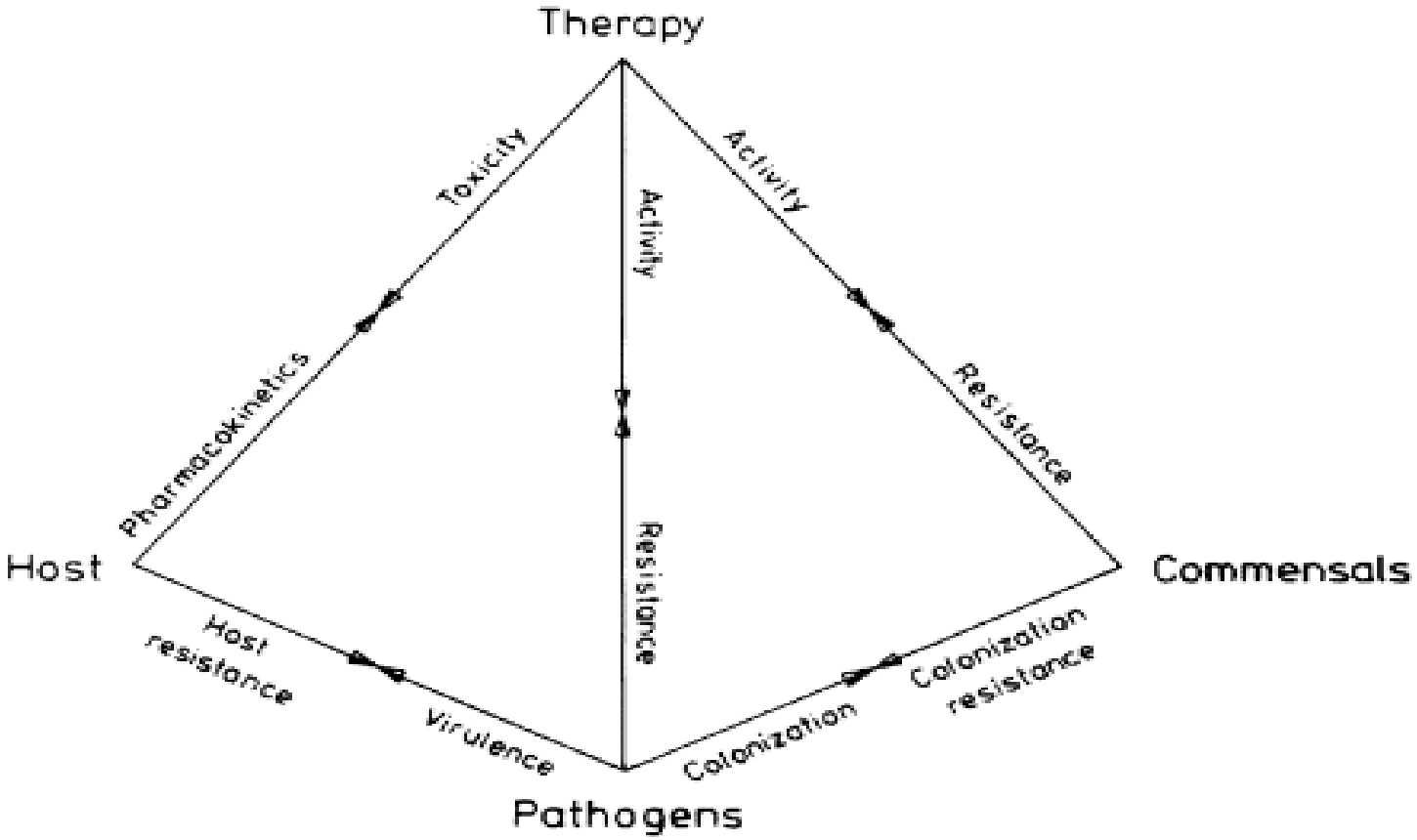


Fig. 1. The pyramid of infectious diseases.

Drug Benefits and Risks: International Textbook of Clinical Pharmacology, Christoffel Jos van Boxtel,Budiono

Community Associated –UTI : CAUTI

Healthcare Associated-UTI : HAUTI

Community onset healthcare-associated UTI

- ✓ Short hospital stay→diagnosis after discharge
- ✓ Healthcare received at home (e.g.catheter exchange)
- ✓ Daily healthcare services

Prevalenza?

Tandogdu Z, Wagenlehner FM. Curr Opin Infect Dis 2016;29:73–79.

Prevalence of healthcare associated infections (HAI):

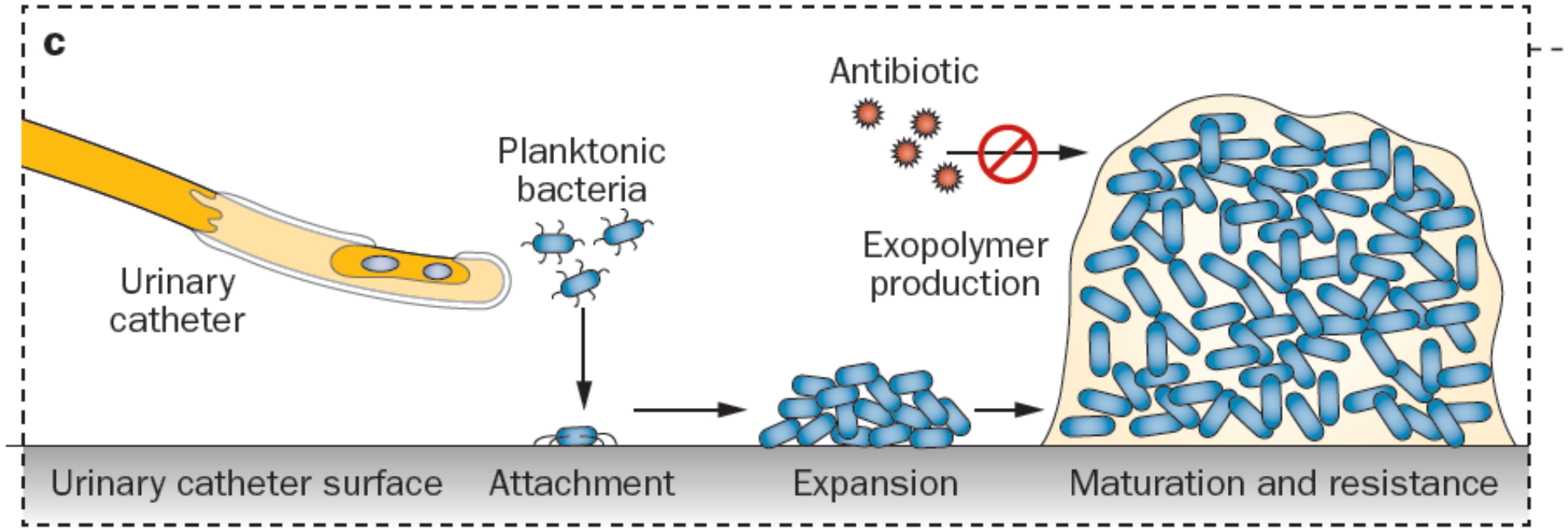
- ✓ USA: 4%
- ✓ Europa: 6%
- ✓ Paesi in via di sviluppo: 15,5%

Frequency of HAUTI among HAI:

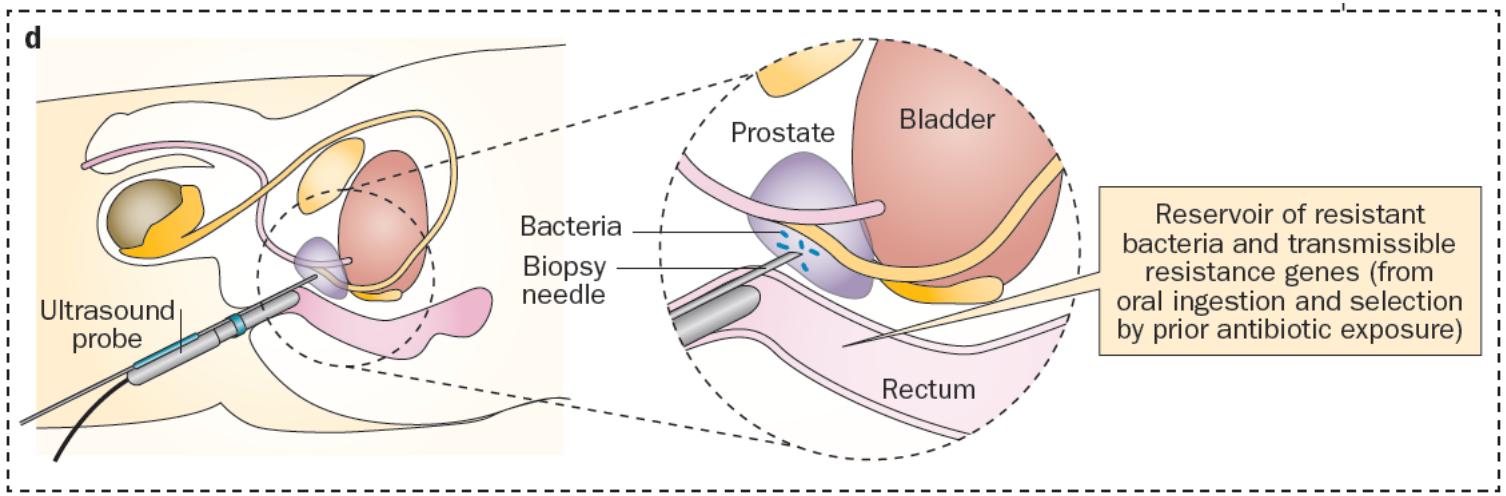
- ✓ USA: 12,9%
- ✓ Europa: 19,6%
- ✓ Paesi in via di sviluppo: 24%

Tandogdu Z, Wagenlehner FM. Curr Opin Infect Dis 2016;29:73–79.

Catheter associated UTI



TRUBP (biopsia prostatica transrettale ecoguidata)



World J Urol (2016) 34:1193–1200
DOI 10.1007/s00345-015-1722-1

ORIGINAL ARTICLE

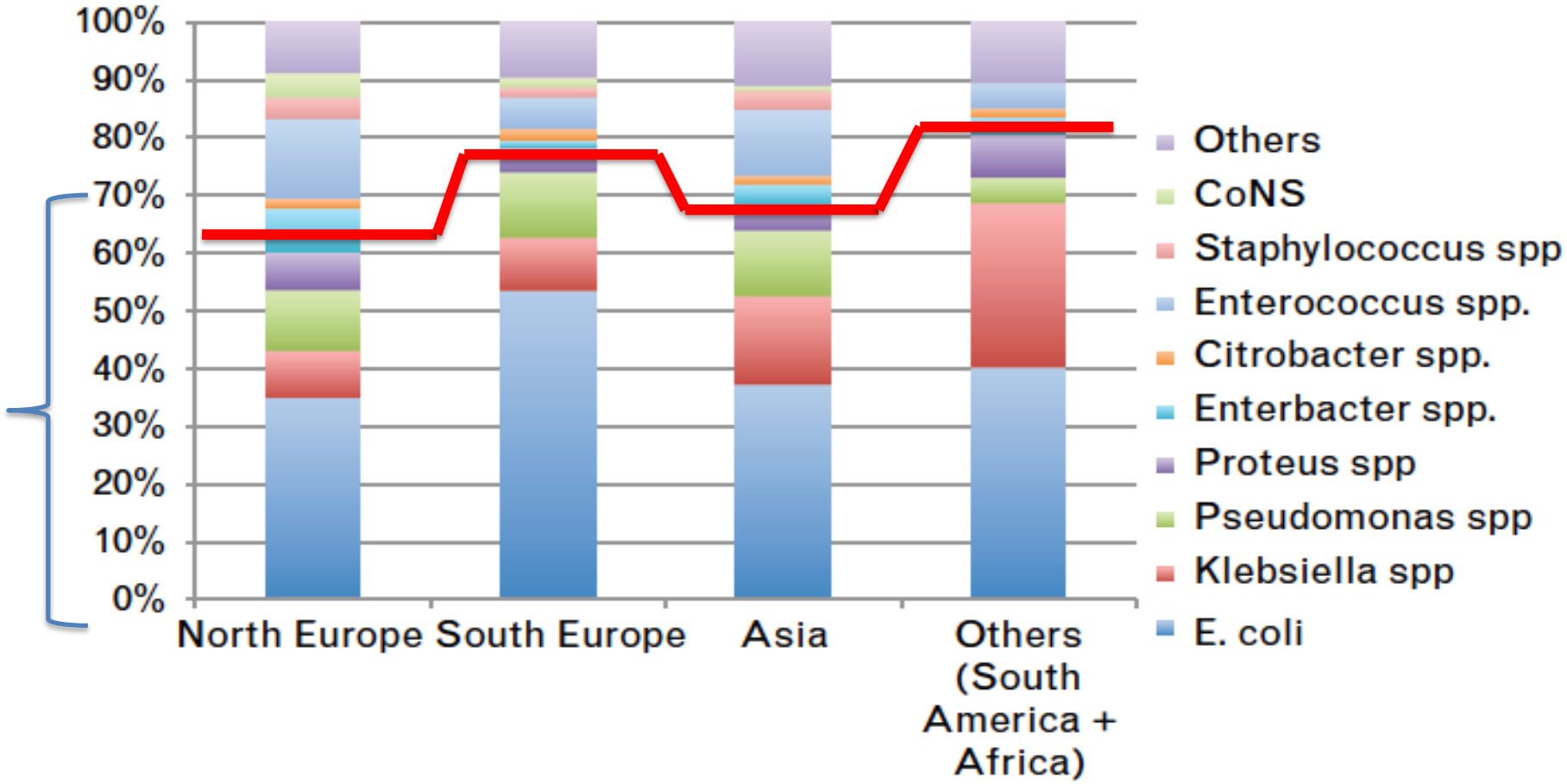
Antimicrobial resistance in urosepsis: outcomes from the multinational, multicenter global prevalence of infections in urology (GPIU) study 2003–2013

Pathogens and susceptibility profile in urosepsis

Annual pathogen spectrum was similar throughout the 11-year study time frame. Gram negatives contributed to approximately 75 %. This is different than reports of overall sepsis showing Gram positives (52 %) as the leading

Pathogens in healthcare-associated UTIs

Gram-negatives



CoNS, coagulase-negative staphylococcal; UTI, urinary tract infection.
Tandogdu Z, Wagenlehner FM. Curr Opin Infect Dis 2016;29:73–79.

Cortesia Prof. G.M. Rossolini

Table 2 Resistance profile of antibiotics and antibiotic combinations in urosepsis, its subgroups (geographical location, sepsis severity) and other HAUTIs (MAGI, cystitis, pyelonephritis)

Pathogen	Geographical location				Sepsis severity[a]			Clinical diagnosis				Overall urosepsis
	Europe %(R/total)	Asia %(R/total)	Africa %(R/total)	Americas %(R/total)	Simple %(R/total)	Severe and shock %(R/total)	p[c]	MAGI %(R/total)	Cystitis %(R/total)	Pyelonephritis %(R/total)	p [b]	
Amx/BLI	58 % (100/172)	70 % (21/30)	92 % (11/12)	75 % (3/4)	60 % (82/136)	64 % (21/33)	NS	52 % (65/124)	46 % (160/345)	60 % (149/248)	0.003	62 % (135/218)
								NS	OR 0.5 (CI 0.3–0.8) $p = 0.002$	NS		
TZP	34 % (47/137)	40 % (10/25)	50 % (4/8)	67 % (2/3)	37 % (40/109)	35 % (12/34)	NS	26 % (26/99)	33 % (84/258)	30 % (57/189)	NS	36 % (63/173)
TMP/SMX	56 % (87/156)	50 % (15/30)	86 % (12/14)	63 % (5/8)	59 % (84/143)	61 % (22/36)	NS	54 % (63/117)	52 % (182/353)	53 % (122/232)	NS	57 % (119/208)
CIP	59 % (106/181)	61 % (22/36)	47 % (8/17)	22 % (2/9)	53 % (79/148)	55 % (23/42)	NS	49 % (76/155)	47 % (196/420)	49 % (157/324)	NS	57 % (138/243)
LVX	59 % (57/97)	57 % (4/7)	50 % (6/12)	67 % (2/3)	56 % (40/71)	63 % (12/19)	NS	42 % (41/98)	45 % (122/271)	39 % (76/196)	0.009	58 % (69/119)
								OR 0.4 (CI 0.2–0.7), $p = 0.006$	OR 0.5 (CI 0.3–0.9) $p = 0.03$	OR 0.4 (CI 0.2–0.7) $p = 0.002$		
CXM	57 % (78/137)	56 % (14/25)	71 % (10/14)	67 % (4/6)	60 % (68/113)	52 % (14/27)	NS	48 % (50/104)	42 % (142/339)	45 % (109/245)	0.008	58 % (106/182)
								NS	OR 0.5 (CI 0.3–0.7) $p = 0.001$	OR 0.5 (CI 0.3–0.8), $p = 0.007$		
CTX	52 % (77/147)	42 % (15/36)	31 % (5/16)	56 % (5/9)	50 % (68/135)	43 % (13/30)	NS	36 % (41/115)	36 % (130/363)	39 % (110/208)	0.02	49 % (102/208)
								OR 0.5 (CI 0.3–0.9) $p = 0.03$	OR 0.5 (CI = 0.3–0.8), $p = 0.003$	OR 0.6 (CI 0.4–0.9) $p = 0.01$		
CAZ	42 % (52/124)	71 % (17/24)	33 % (4/12)	67 % (2/3)	49 % (47/96)	27 % (8/29)	0.005	30 % (31/102)	35 % (114/326)	33 % (83/251)	0.008	46 % (75/163)
					(OR = 4.07,CI 1.45–11.44,	–		OR 0.4 (CI 0.2–0.8), $p = 0.01$	OR 0.5 (CI 0.3–0.8), $p = 0.005$	OR 0.4 (CI 0.3–0.7), $p = 0.002$		
IPM	8 % (11/141)	13 % (4/32)	0 (0/7)	IPM	8 ‹	8 % (15/186)	NS	12 %(14/114)	7 % (19/289)	12 % (29/252)	NS	8 % (15/186)
GEN	36 % (68/187)	46 % (21/46)	75 % (12/16)	44 % (4/9)	37 % (57/154)	42 % (23/55)	NS	42 % (63/150)	36 % (150/418)	40 % (130/326)	NS	40 % (105/258)

MDR pathogens

MDR rates for *Enterobacteriaceae* (*n*:259–63.4 %) was 45 %, and for *P. aeruginosa* (*n*:42–10.3 %) it was 21 %. Remaining rare pathogen subgroups (*n*:107–26.2 %) were not classified for MDR due to insufficient numbers to carry

World J Urol (2016) 34:1193–1200

TABLE 6. Definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria

Bacterium	MDR	XDR	PDR
Staphylococcus aureus	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 1[a]	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 1.	Non-susceptibility to all agents in all antimicrobial categories for each bacterium in Tables 1–5
Enterococcus spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 2	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 2.	
Enterobacteriaceae	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 3	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 3.	
Pseudomonas aeruginosa	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 4	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 4.	
Acinetobacter spp.	The isolate is non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed in Table 5	The isolate is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories in Table 5.	

[a]All MRSA isolates are defined as MDR because resistance to oxacillin or cefoxitin predicts non-susceptibility to all categories of β-lactam antimicrobials listed in this document, with the exception of the anti-MRSA cephalosporins (i.e. all categories of penicillins, cephalosporins, β-lactamase inhibitors and carbapenems currently approved up until 25 January 2011).
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

Clin Microbiol Infect. 2012 Mar;18(3):268-81

The emerging threat of multidrug-resistant Gram-negative bacteria in urology

Hosam M. Zowawi, Patrick N. A. Harris, Matthew J. Roberts, Paul A. Tambyah, Mark A. Schembri, M. Diletta Pezzani, Deborah A. Williamson and David L. Paterson

NATURE REVIEWS | UROLOGY VOLUME 12 | OCTOBER 2015 |

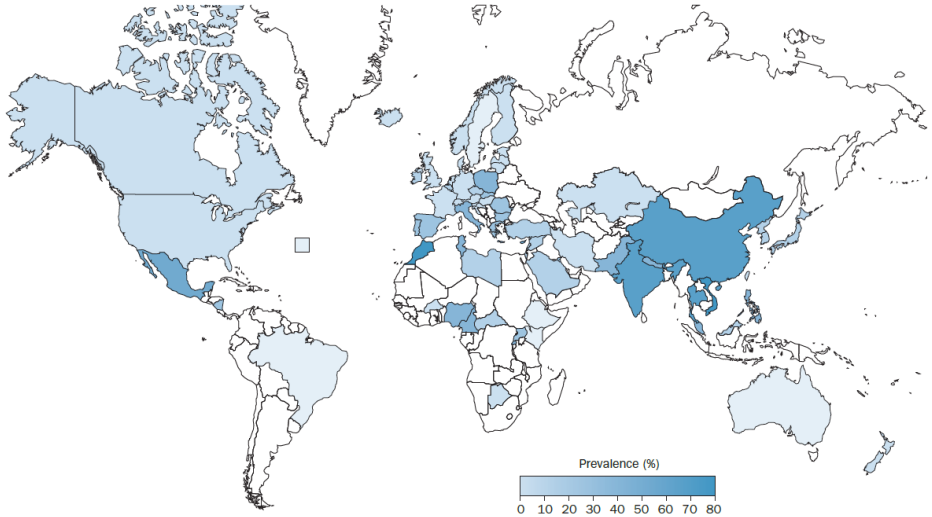


Figure 2 | Global epidemiology of resistance in Gram-negative uropathogens—fluoroquinolones. Prevalence of resistance to fluoroquinolones in Gram-negative urinary pathogens by country. Data obtained from studies published 2009–2014. The accuracy of these prevalence estimates is affected by the number and heterogeneity of studies undertaken in each country, and reflects resistance data from clinical isolates, which only represent a subset of the total resistance burden in colonized patients.

Figure 3 | Global epidemiology of resistance in Gram-negative uropathogens—third-generation cephalosporins. Prevalence of resistance to third-generation cephalosporins in Enterobacteriaceae isolated from patients with urinary infections by country. Data obtained from studies published 2009–2014. The accuracy of these prevalence estimates is affected by the number and heterogeneity of studies undertaken in each country, and reflects resistance data from clinical isolates, which only represent a subset of the total resistance burden in colonized patients.

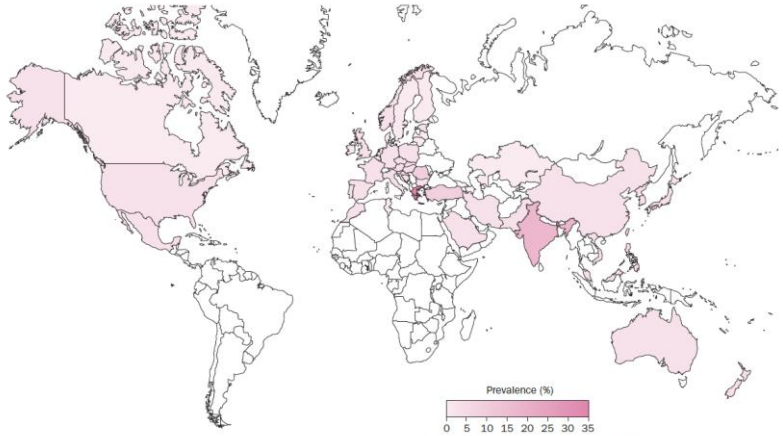


Figure 4 | Global epidemiology of resistance in Gram-negative uropathogens—carbapenems. Prevalence of carbapenem-resistant Enterobacteriaceae in urinary isolates by country. Data obtained from studies published 2009–2014. The accuracy of these prevalence estimates is affected by the number and heterogeneity of studies undertaken in each country, and reflects resistance data from clinical isolates, which only represent a subset of the total resistance burden in colonized patients.

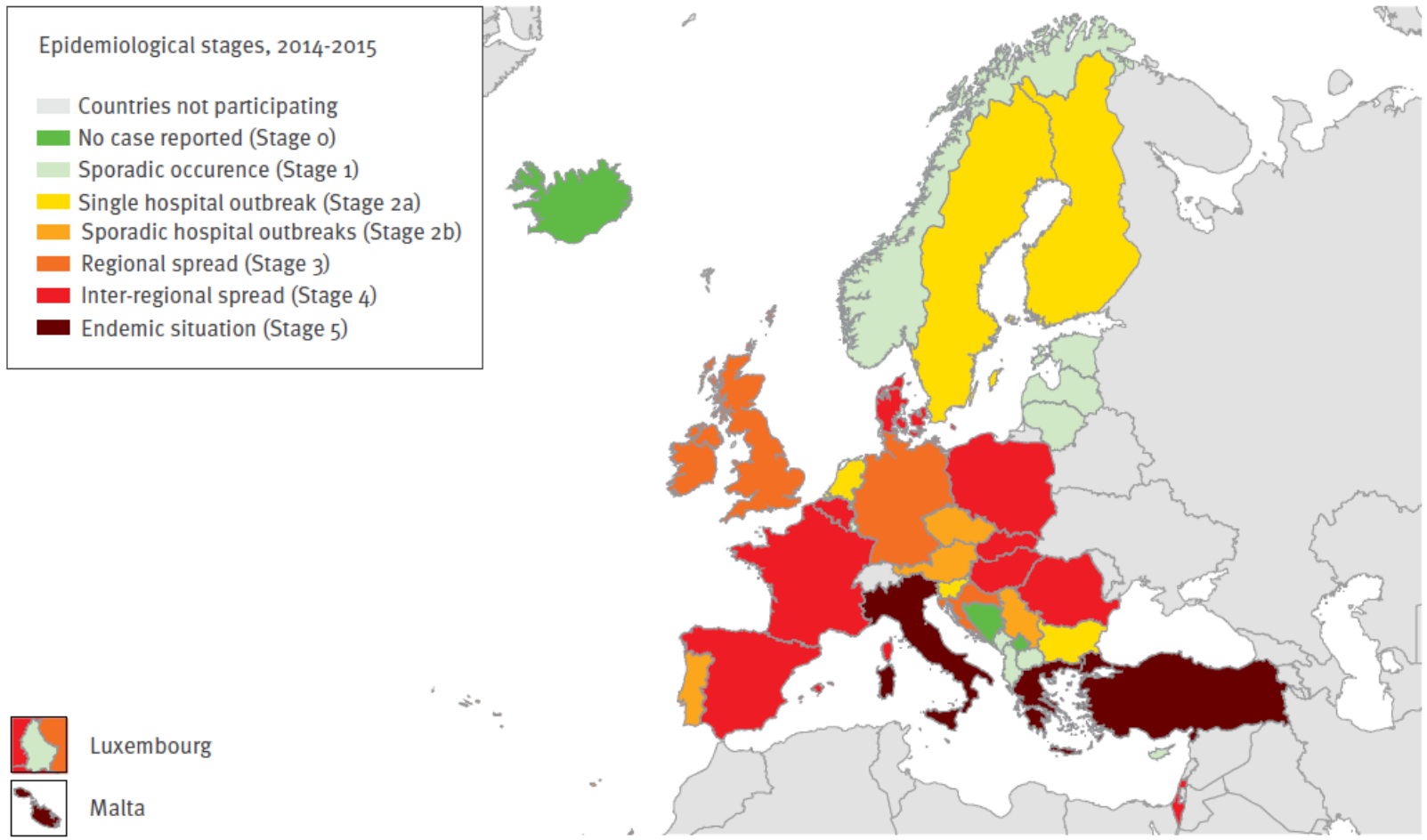
Table 2. Resistance of antibiotics in the Global Prevalence of Infections in Urology study (2003–2010) to select antibiotics for *E.coli*

	North Europe	South Europe	Asia	Other areas (S. America and Africa)	Overall
Ciprofloxacin	35%	53%	57%	44%	45%
Cefuroxime	20%	58%	53%	35%	33%
Aminopenicillin+β-lactamase inhibitor	42%	59%	60%	53%	50%
Gentamicin	18%	35%	48%	33%	30%

Tandogdu Z[1], Wagenlehner FM.; Curr Opin Infect Dis. 2016 Feb;29(1):73-9

FIGURE 1

Occurrence of carbapenemase-producing *Enterobacteriaceae* based on self-assessment by national experts, 38 European countries, May 2015



Albiger B et al.,Euro Surveill. 2015;20(45)

Beta lattamasi

Table 2. Major groups of β-lactamases in Gram-negative bacteria that threaten the role of β-lactam antibiotics

Functional group[a]	Molecular class[b]	Common name	β-Lactams to which resistance is conferred	
			Primary[c]	Secondary[d]
1	C	Cephalosporinase	Penicillins, cephalosporins	Carbapenems, monobactams
2b	A	Penicillinase	Penicillins, early cephalosporins	β-lactamase inhibitor combinations
2be	A	Extended-spectrum β-lactamase	Penicillins, cephalosporins, monobactams, β-lactamase inhibitor combinations	None
2d	D	Cloxacillinase	Penicillins, including oxacillin and cloxacillin	None
2df	D	Carbapenemase	Carbapenems and other β-lactams	None
2f	A	Carbapenemase	All current β-lactams	None
3	B	Metallo-β-lactamase	All β-lactams except monobactams	None

[a]Classification based on Bush, Jacoby, and Medeiros [11] and Bush and Jacoby [7]. [b]Classified according to primary amino acid sequence [8-10]. [c]β-lactams that are resistant solely as a function of β-lactamase production. [d]β-lactams that are resistant as a function of β-lactamase production, usually at high levels, in combination with efflux or porin modifications.

Bush *Critical Care* 2010, **14**:224

Le Carbapenemasi di classe A

KPC (Klebsiella pneumoniae carbapenemase)

Identificate soprattutto in K.pneumoniae,

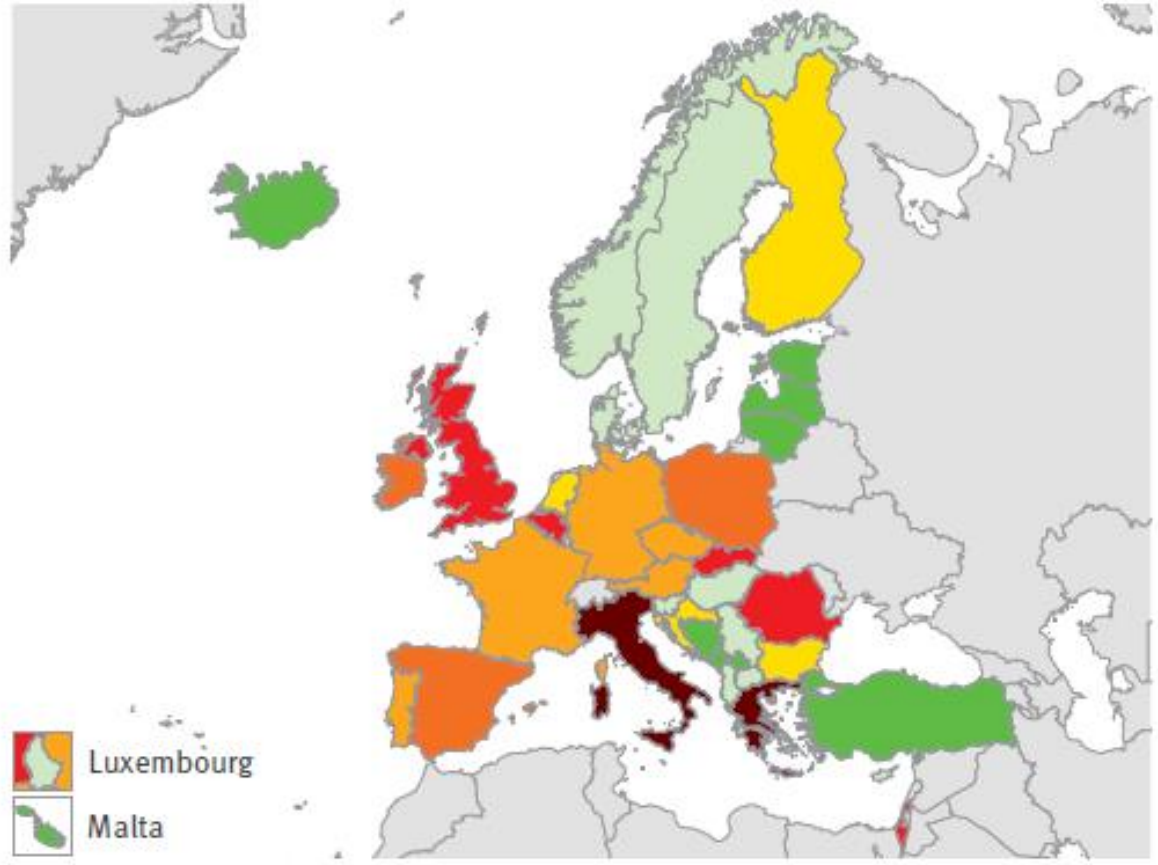
Conferiscono resistenza ai carbapenemi e alla maggior parte delle beta lattamine, comprese le cefalosporine a spettro esteso ed aztreonam.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1]
ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[1] CHRISTINE D. STEWARD,[1]
SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

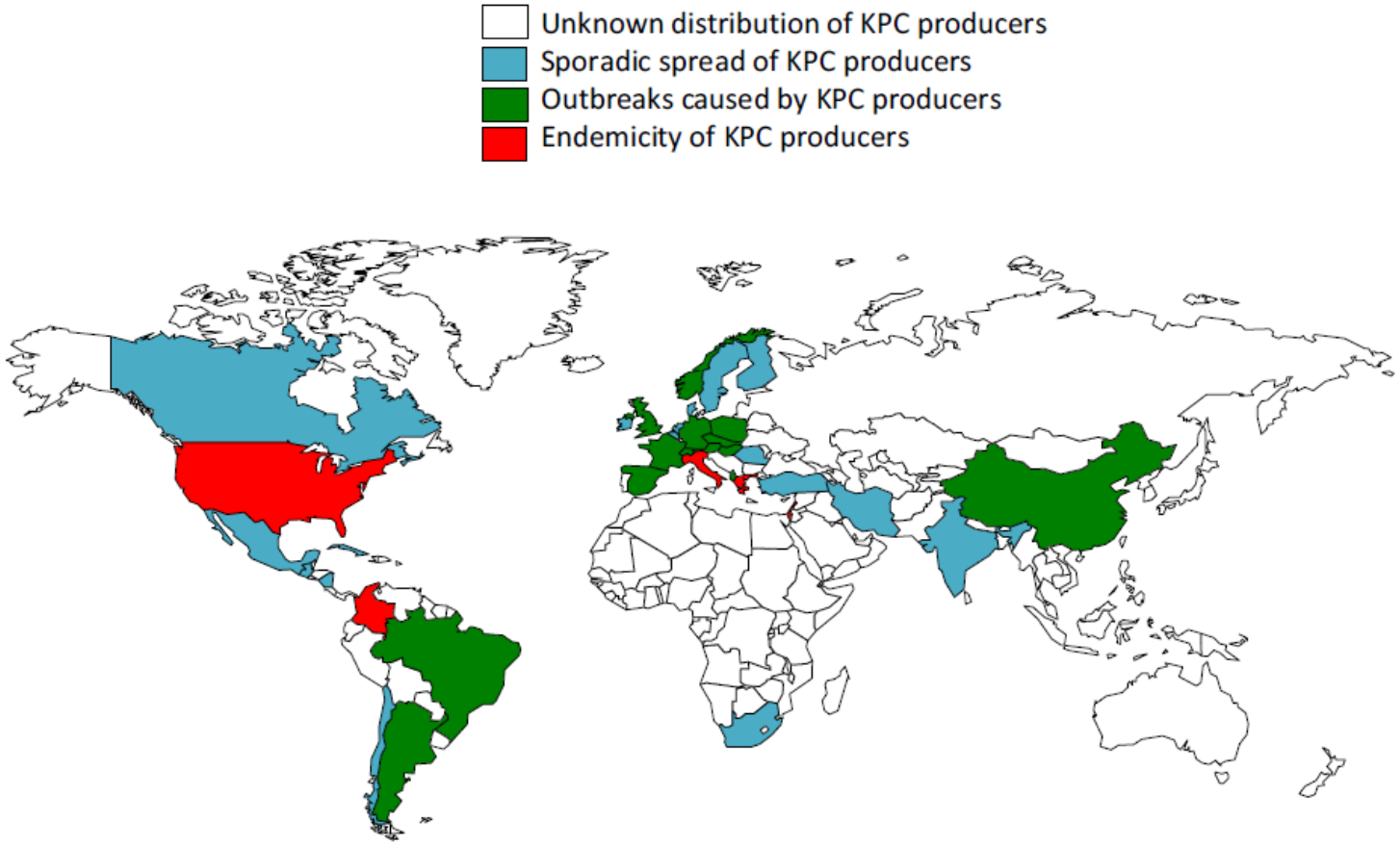
A. *Klebsiella pneumoniae* carbapenemase (KPC)



Countries not participating
No case reported (Stage 0)
Sporadic occurence (Stage 1)
Single hospital outbreak (Stage 2a)
Sporadic hospital outbreaks (Stage 2b)
Regional spread (Stage 3)
Inter-regional spread (Stage 4)
Endemic situation (Stage 5)

Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015.
Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL; European Survey of **Carbapenemase**-Producing Enterobacteriaceae (EuSCAPE) working group..
Euro Surveill. 2015;20(45).

Distribuzione geografica dei produttori di KPC



In Europa: KPC sono endemiche in Italia, Grecia. Endemiche in Israele.

Clin Microbiol Infect. 2014 Sep;20(9):821-30. Nordmann P[1], Poirel L.

Le Metallo-β-lattamasi (classe B)

Le MBL sono intrinseche in molte specie ambientali opportuniste.

Dagli anni 90, sono stati descritte MBL acquisite, in *Pseudomonas aeruginosa* e nelle *Enterobacteriaceae*

IMP: le prime MBL acquisite identificate; sono state descritte in *Enterobacteriaceae, Pseudomonas, Acinetobacter*. Ne sono state descritte decine di varianti. Sono diffuse in tutto il mondo (ma soprattutto in Asia- Taiwan, Giappone, Cina orientale)

VIM (Verona integron-encoded MBLs), VIM-1 la prima descritta (Italia, 1997) . La famiglia include ormai decine di varianti, diffuse in tutto il mondo ma soprattutto in Europa meridionale e bacino del Mediterraneo. VIM-2 è la più diffusa nel mondo (endemica in Europa meridionale, Sud-Est asiatico).

Outbreaks in Africa (Tunisia, ma anche Costa d'Avorio, Sudafrica), Germania, Olanda, Francia: isolati di *P.aeruginosa*, raramente Enterobatteri.

VIM-1 è endemica in Grecia nelle *Enterobacteriaceae* (*K. Pneumoniae, E. coli, C. freundii, Serratia spp, Morganella morganii, K.oxytoca*)

Le Metallo-β-lattamasi (classe B)

Antimicrob Agents Chemother. 2009 Dec;53(12):5046-54. doi: 10.1128/AAC.00774-09. Epub 2009 Sep 21.

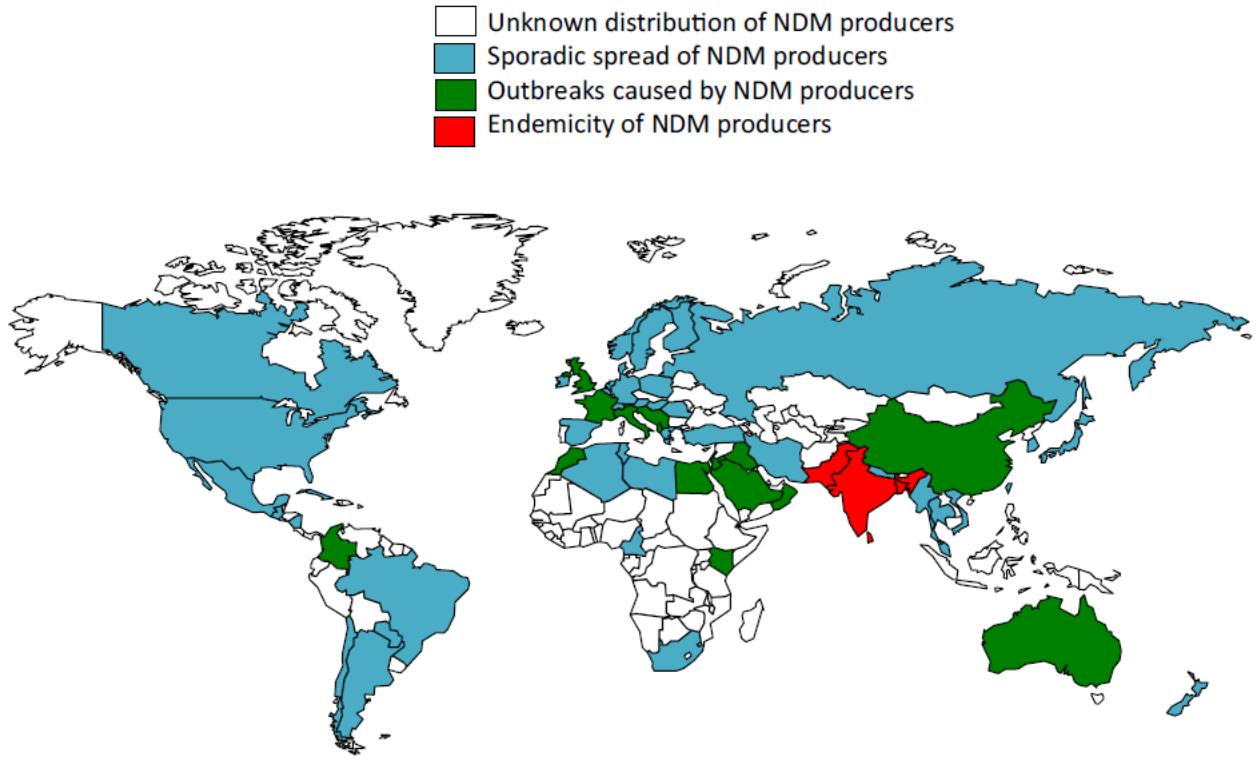
Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India.

Yong D[1], Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, Walsh TR.

NDM New Delhi Metallo β-lattamasi. Idrolizza molti beta lattamici (penicilline, cefalosporine, carbapenemi), non i monobattami. Sono sistematicamente associate ad altri determinanti di resistenza (Amp-C plasmidiche, ESBL, altre carbapenemasi, enzimi che conferiscono resistenza a aminoglicosidi, chinoloni, rifampicina, etc).

Distribuzione geografica dei produttori di NDM

Il principale reservoir è il subcontinente indiano, da lì si sono diffuse in Gran Bretagna; ormai sono diffuse in quasi tutto il mondo. Altre fonti importanti (Reservoir secondari): Penisola arabica, Nord Africa, paesi balcanici.



Clinical Microbiology and Infection ©2014 European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **20**, 821–830

Le Carbapenemasi di classe D (OXAs)

In genere, le carbapenemasi di classe D non idrolizzano le cefalosporine a spettro esteso; tutte hanno una debole attività di idrolisi dei carbapenemi, così che non conferiscono alta resistenza ai carbapenemi, se non accompagnate da altri meccanismi di resistenza.
La maggioranza delle OXA è stata identificata in Acinetobacter,

OXA 48 nelle Enterobacteriaceae.

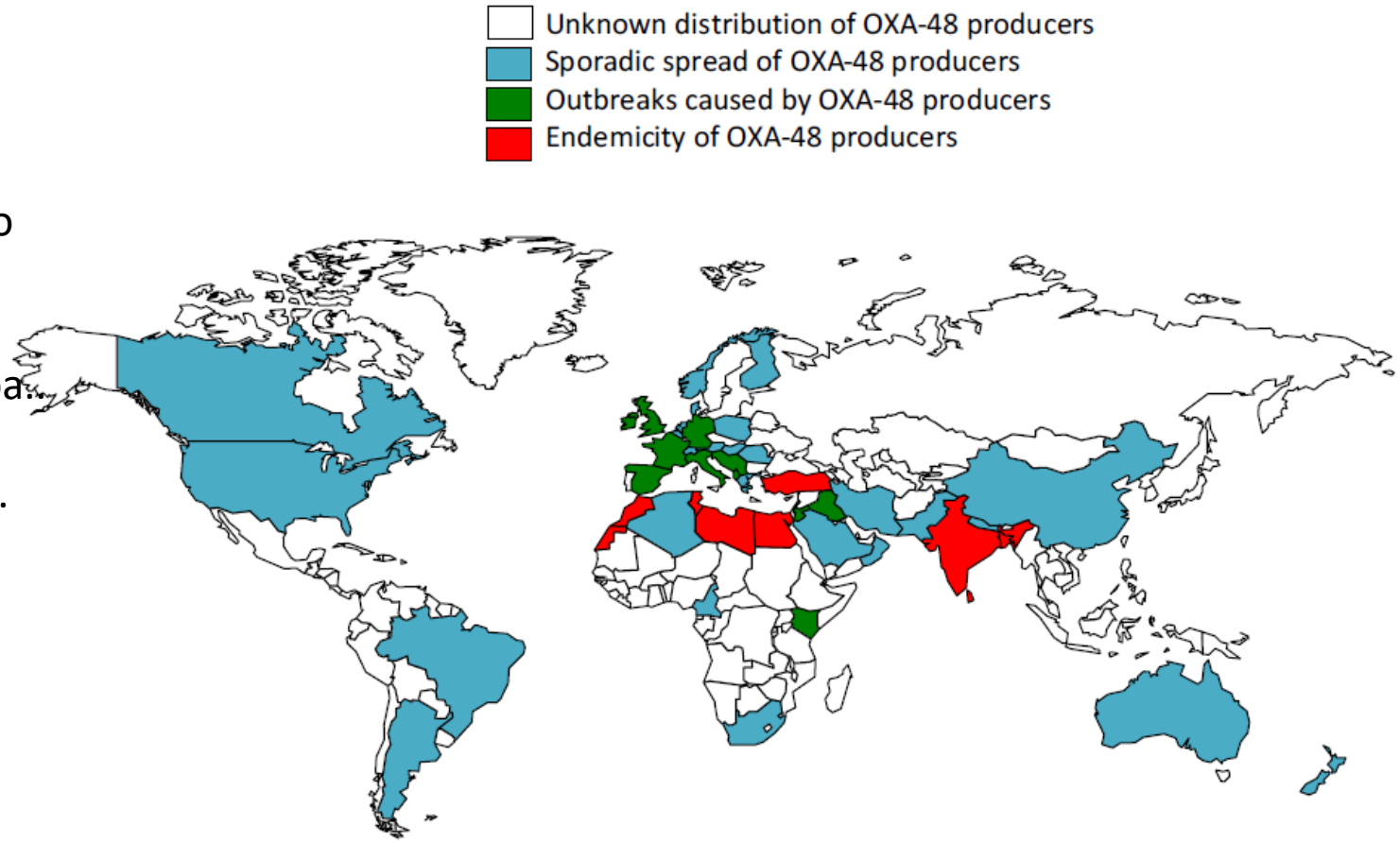
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 15–22 Vol. 48, No. 1
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.1.15–22.2004

Emergence of Oxacillinase-Mediated Resistance to Imipenem in *Klebsiella pneumoniae*

Laurent Poirel,[1] Claire Héritier,[1] Venus Tolün,[2] and Patrice Nordmann[1]*

Distribuzione geografica dei produttori di OXA-48-like

Idenrìtificata e spesso descritta in Turchia (reservoir), ora si è diffusa in tutta Europa. Probabile nuovo reservoir Nord Africa.



OXA-181
OXA-204
OXA-163

Esempi di patogeni Gram-negativi ultraresistenti

Antibiotico	MIC mg/L (S/I/R)
Pip/Tazo	>128 R
Ceftazidime	64 R
Cefepime	64 R
Aztreonam	>64 R
Imipenem	32 R
Meropenem	16 R
Amikacina	>64 R
Gentamicina	>32 R
Ciprofloxacina	>32 R
Colistina	1 S

XDR *Pseudomonas aeruginosa*

Antibiotico	MIC mg/L (S/I/R)
Imipenem	>32 R
Meropenem	64 R
Amikacina	32 R
Gentamicina	>16 R
Ciprofloxacina	>32 R
TMP/SMZ	>320 R
Colistina	1 S

Carbapenem-R *Acinetobacter*

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>256 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Fosfomicina	>128 R
Amikacina	>64 R
Gentamicina	1 S
Ciprofloxacina	>4 R
Tigeciclina	1 S
Colistina	>8 R

Carbapenem-R
Klebsiella pneumoniae

Cortesia Prof. G.M. Rossolini

Colistina e mcr-1

The recently recognised global distribution of a self-transferable plasmid-borne colistin resistance determinant (*mcr-1* gene) poses a substantial public health risk to the EU/EEA. This specific mode of molecular dissemination of drug resistance is an example of a so-called plasmid-mediated gene epidemic.

This plasmid-mediated gene epidemic is of exceptional public health concern because it further limits treatment options in patients with infections caused by multidrug-resistant (MDR) gram-negative bacteria and can spread colistin resistance more easily between bacteria and humans than colistin resistance resulting from chromosomal mutation. MDR gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae strains that acquire the *mcr-1* gene, remain susceptible to only a few antimicrobial agents, which means that infections caused by these strains are very difficult to treat and result in excess mortality. As the limited development of new antimicrobials is unlikely to provide a solution anytime soon, it is crucial to take measures to control the spread of *mcr-1* and thus protect the activity of colistin.

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

2016

Table 2 | Treatment options for MDR Gram-negative uropathogens

Indication	First-choice antibiotic therapy	Second-choice antibiotic therapy
Uncomplicated lower UTI with MDR organisms	Fosfomycin, nitrofurantoin, pivmecillinam	Quinolone, temocillin (if available), nitroxoline (if available)
Complicated UTI with MDR infection (specialist advice required)	Carbapenems (for example, against ESBL or AmpC-producers) Piperacillin–tazobactam might be an alternative against ESBL-producers that are susceptible (but their role is controversial)	Combination therapy (including XDR isolates) Colistin* plus carbapenem‡ Colistin* plus aminoglycoside (for example, amikacin) Carbapenem‡ plus aminoglycoside Dual carbapenems

*Polymyxin B is an alternative to colistin but is less widely available. ‡Consider extended or continuous infusions of carbapenems to optimize pharmacokinetic and pharmacodynamic parameters.
Abbreviations: MDR, multidrug resistant; UTI, urinary tract infection; XDR, extensively drug resistant.

Table 3 | Future treatment options for MDR Gram-negative uropathogens

Drug	Phase I*	Phase II*	Phase III*	FDA approved
β-lactam combined with β-lactamase inhibitors				
Ceftazidime–avibactam[138]	✓	✓	✓	✓
Ceftolozane–tazobactam[139]	✓	✓	✓	✓
Ceftaroline fosamil–avibactam	✓	✓	–	–
Carbapenems				
Panipenem–betamipron[143‡]	✓	✓	✓	–
Biapenem[144§]	✓	✓	–	–
Quinolones				
Finafloxacin[141]	✓	✓	–	–
Aminoglycosides				
Plazomicin[140]	✓	✓	–	–
Tetracyclines				
Eravacycline[142]	✓	✓	–	–
β-lactamase inhibitors combined with carbapenem				
Relebactam (MK-7655)–imipenem cilastatin	✓	✓	✓	–
RPX7009–meropenem	✓	✓	–	–
Other agents in development				
S-649266 (novel cephalosporin)	✓	✓	–	–
GSK2251052 (Boron-containing agent targeting Leucyl tRNA synthetase)	✓	✓	–	–

*Clinical trial phases according to *ClinicalTrials.gov*. ‡Only approved in China, Korea and Japan. §Only approved in Japan.

Conclusioni

- ✓ Sorveglianza epidemiologica sia livello globale che locale
- ✓ Infection control
- ✓ Antimicrobial stewardship
- ✓ Nuovi farmaci

Grazie per l’attenzione!