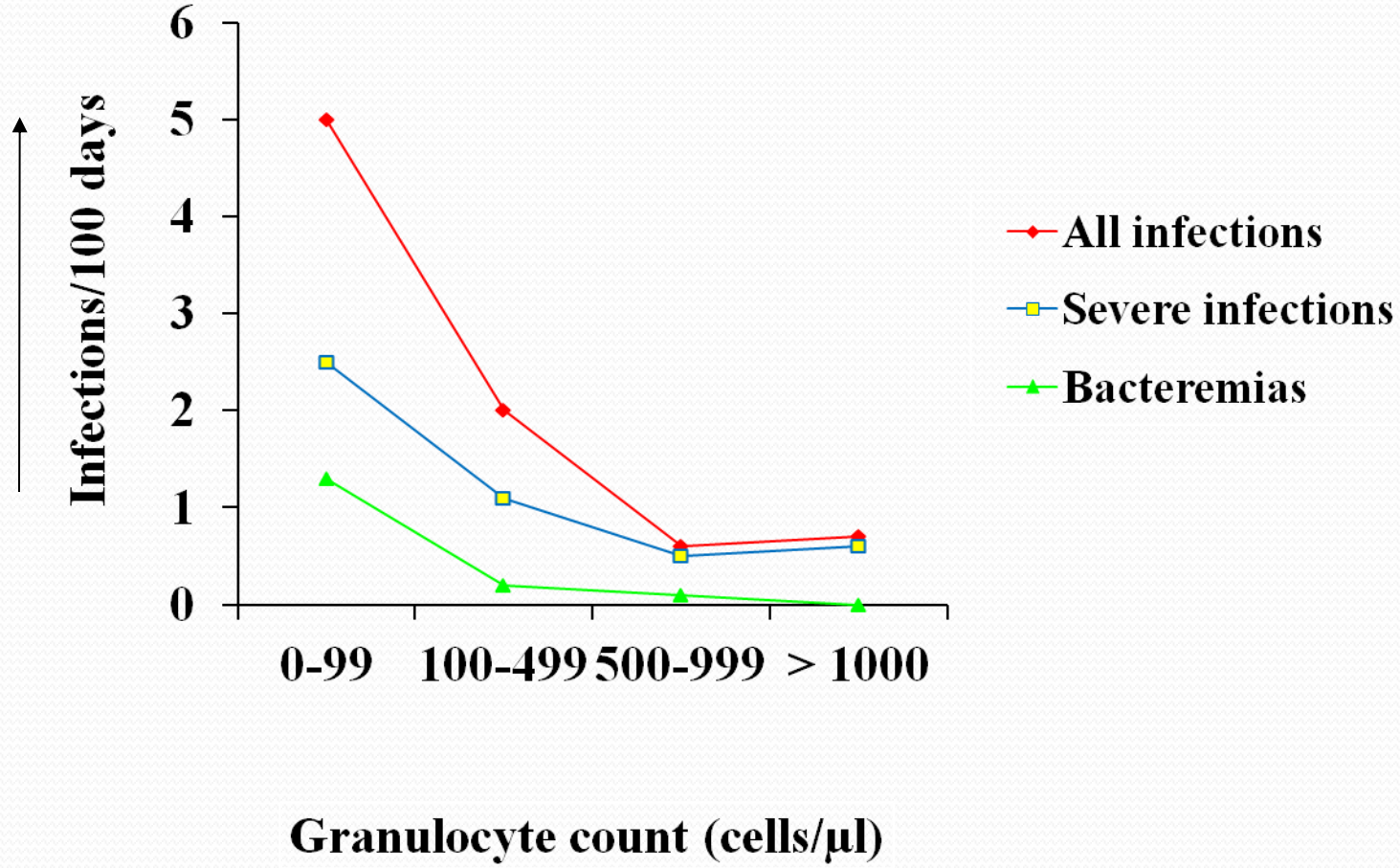
Incidence of infections in acute non-lymphocytic leukemia during induction therapy



Febrile neutropenia

some figures

- Incidence :
  - Leukemia and HSCT : 80% - 90 %
  - Solid tumor or lymphoma : 5 – 8 %
- Mortality :
  - Overall :
    - Solid tumors : 9.5 %
    - Lymphoma and leukemia : 14 %
  - Infection-related :
    - Solid tumors : 2.3 %
    - Lymphoma and leukemia : 5 %

Bucaneve et al, NEJM 2005;353:977-987
Cullen et al, NEJM 2005;353:988-998
Gafter-Gvili et al, Ann Intern Med 2005;142:979-995

Risk model for mortality in hospitalized cancer patients with FN

- A multivariate model with risk factors for mortality including
  - Age ≥65
  - Cancer type (leukemia, lung cancer)
  - Comorbidities (CHF, PE, lung, renal, liver, and cerebrovascular disease)
  - Infectious complications (hypotension, pneumonia, bacteremia and fungal infection

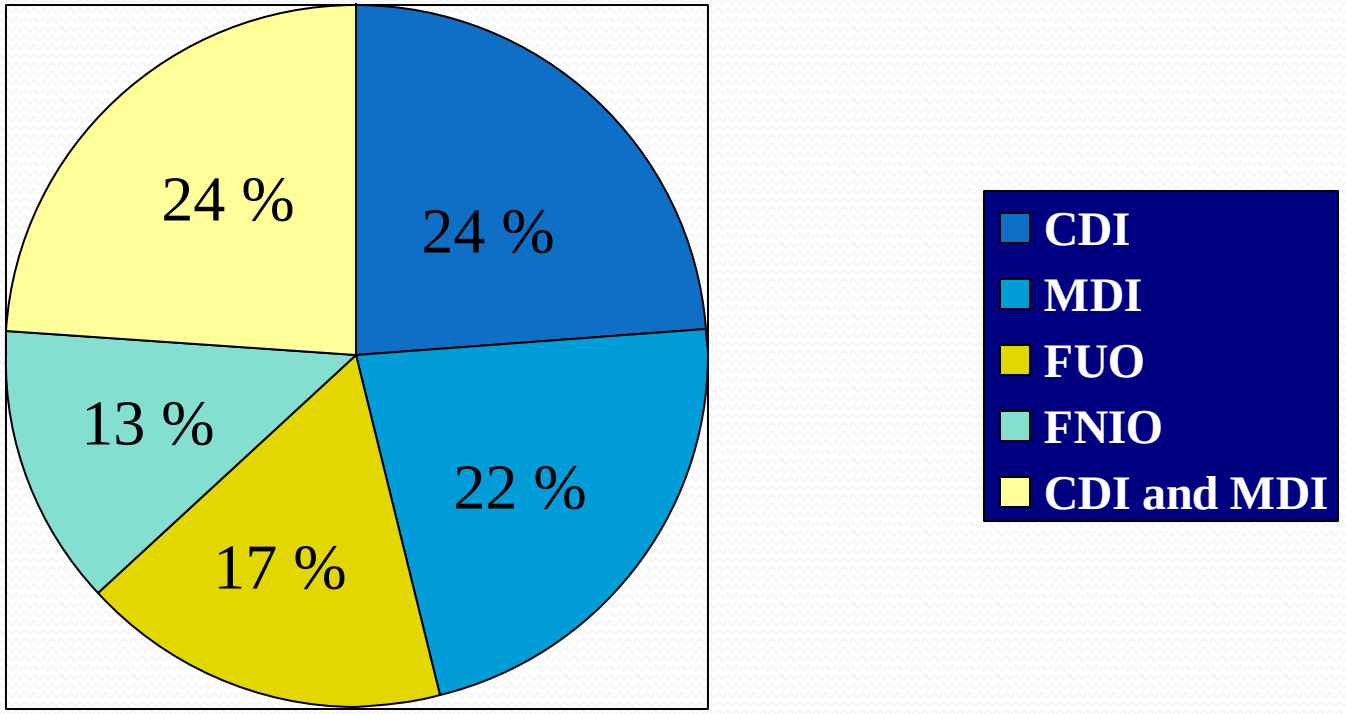
Kuderer NM et al, J Clin Oncol 2004

Prediction of mortality

- Two recent studies have reported hypotension and bacteremia as significant risk factors for prolonged hospitalization and high mortality
- Malik et al reported a mortality rate associated with FN in patients presenting with shock of 82 %
- Darmon et al reported that patient admitted to an ICU with FN experienced a 54 % 30 day mortality

Malik I et al; J Infect 2001
Darmon M et al; Intensive Care Med 2002

Causes of fever during neutropenia



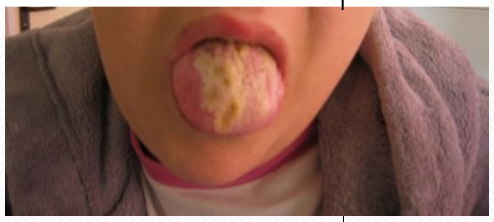
CDI : clinically documented infections
MDI : microbiologically documented infections
FUO : fever of unknown origin
FNIO : fever of non-infectious origin

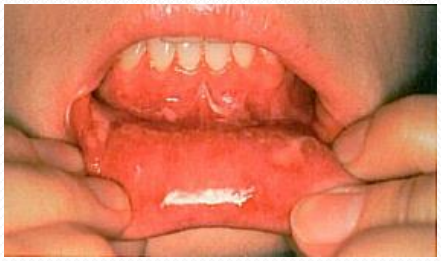
From Toussaint et al, Supp Care in Cancer 2006

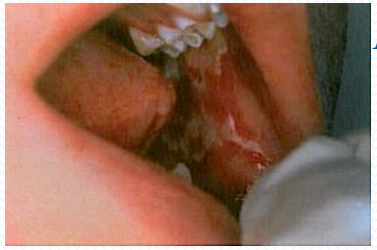
Sites of involvement and microbial pathogens

Oral mucositis

- **Oral flora : v. Streptococci,**
  Fusobacterium,
  Stomatococcus,
  Rothia dentocariosa,
  Capnocytophaga,
  Eikenella corrodens
  Bacteroides oralis (necrotizing gingivitis)
- **HSV, Candida sp (concomitant esophagitis)**





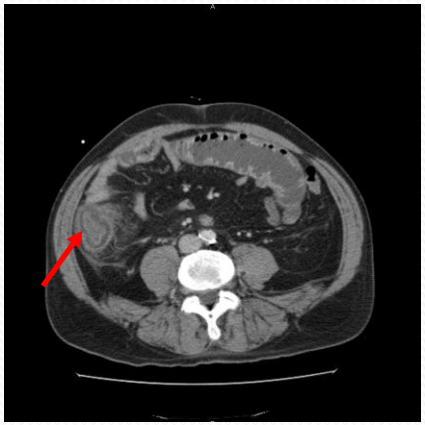


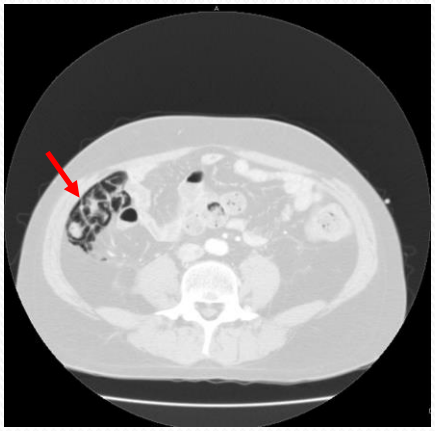
Aoun M. Médisphère 1999

Sites of involvement and microbial pathogens

Typhlitis

- **Clostridium septicum**
- **Other clostridia**
- **Enterobacteriacae**
- **Bacteroides fragilis**
- **Candida spp.**





Aoun M. Médisphère 1999

Sites of involvement and microbial pathogens

Perianal abscess

Polymicrobial :
- GNB (E.coli),
•Anaerobes (B. fragilis)
•Enterococci

Aoun M. Médisphère 1999

Sites of involvement and microbial pathogens

Short duration of neutropenia

(N<7 days)

Conventional bacteria (70 % associated bacteremia)

- S. pneumoniae
- H. influenzae
- Enterobacteriacae
- P. aeruginosa

Long duration of neutropenia

(N>7 days)

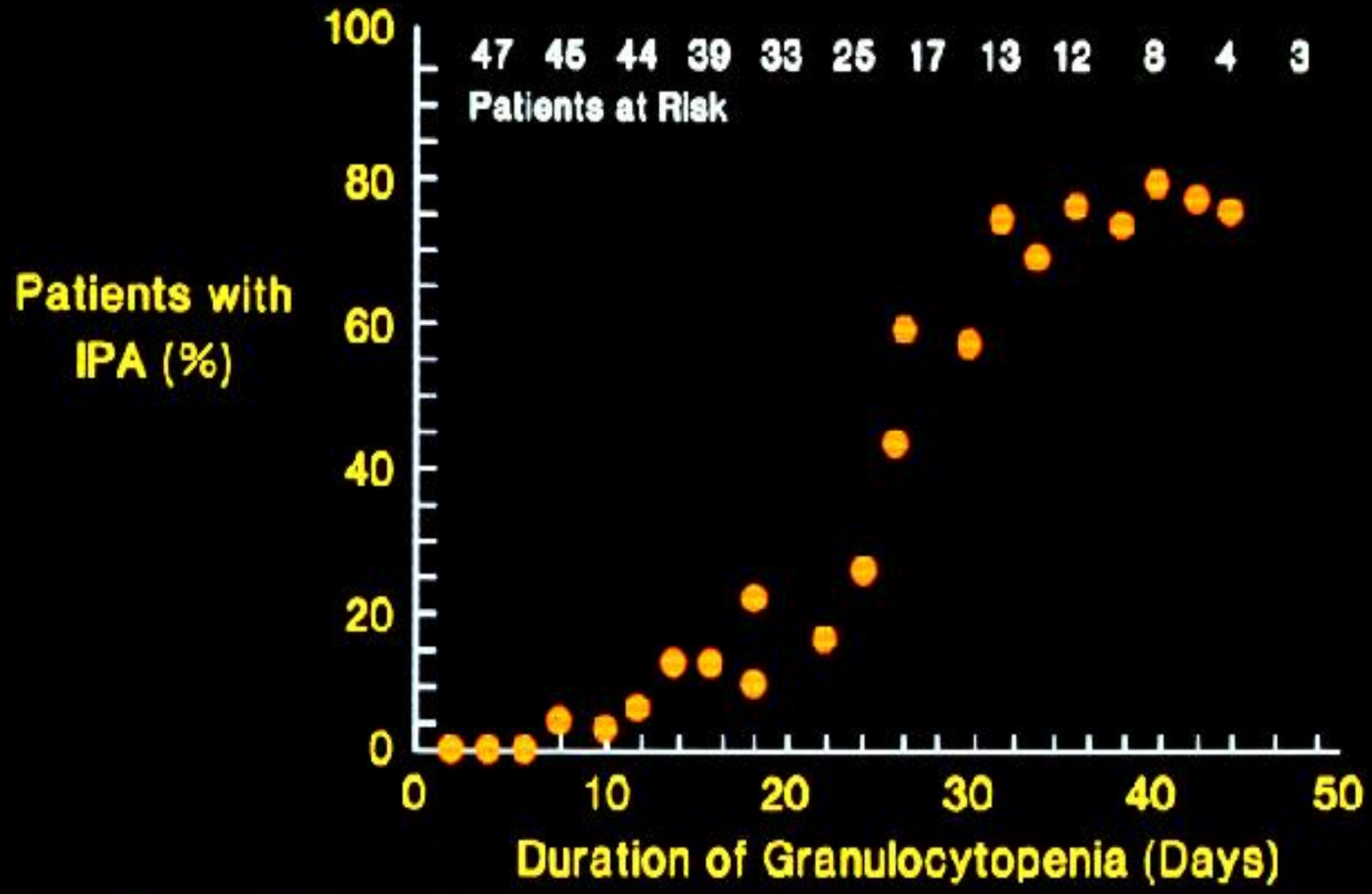
Multiresistant organisms

- ESBL or AmpC GNB
- Multiresistant P. aeruginosa

Fungi

- Aspergillus, Mucor, Fusarium

Aoun M. Médisphère 1999

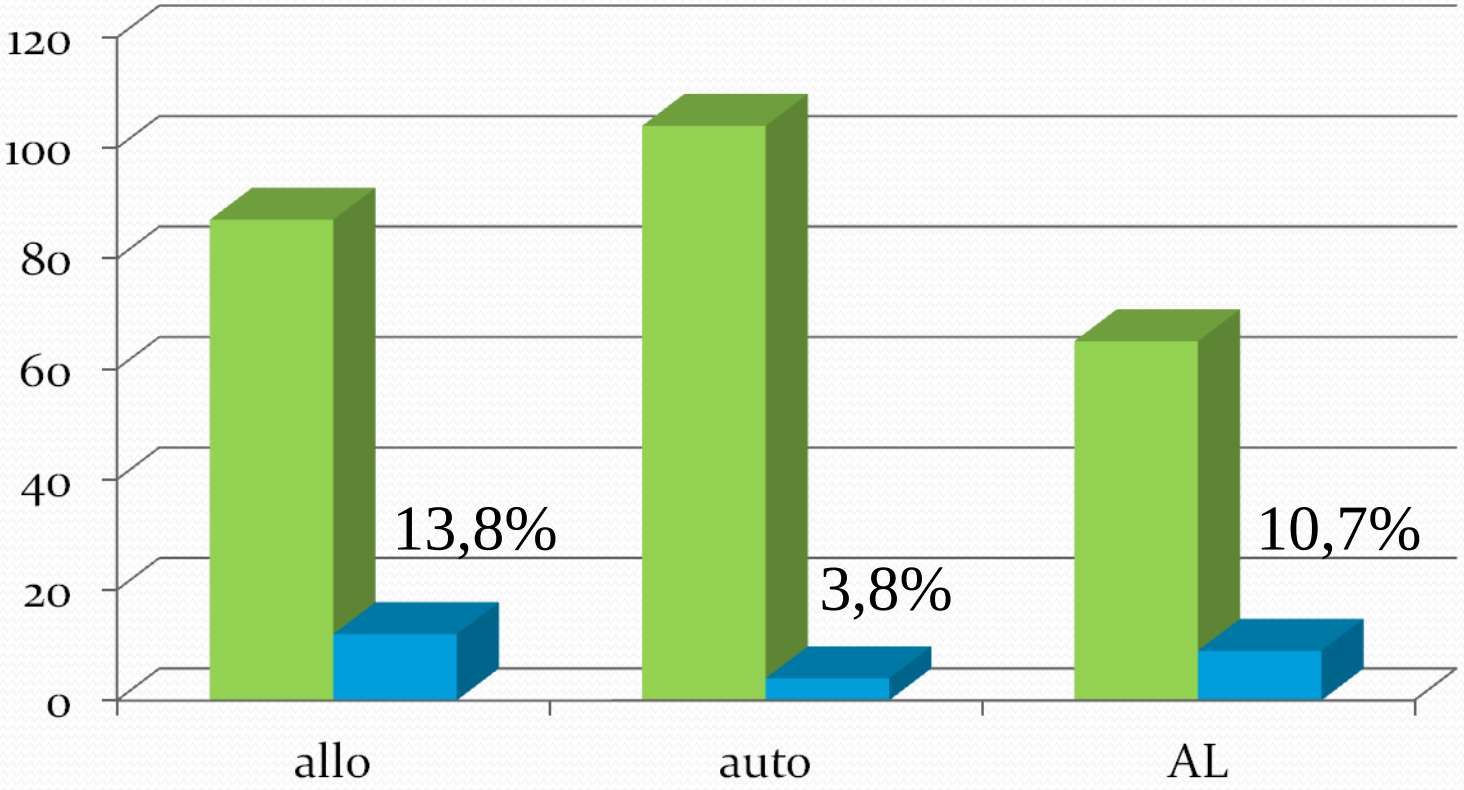


Percentage of all granulocytopenic patients who developed invasive pulmonary aspergillosis (IPA) as a function of duration of granulocytopenia. Two linear regression lines were calculated: one between the 1st and 22nd days, y = 1.0X-4.0; the other between the 22nd and 36th days, y = 4.3X• 73

Gerson et al., 1984

Proven or probable aspergillosis
Institut J. Bordet

April 2002 – December 2005

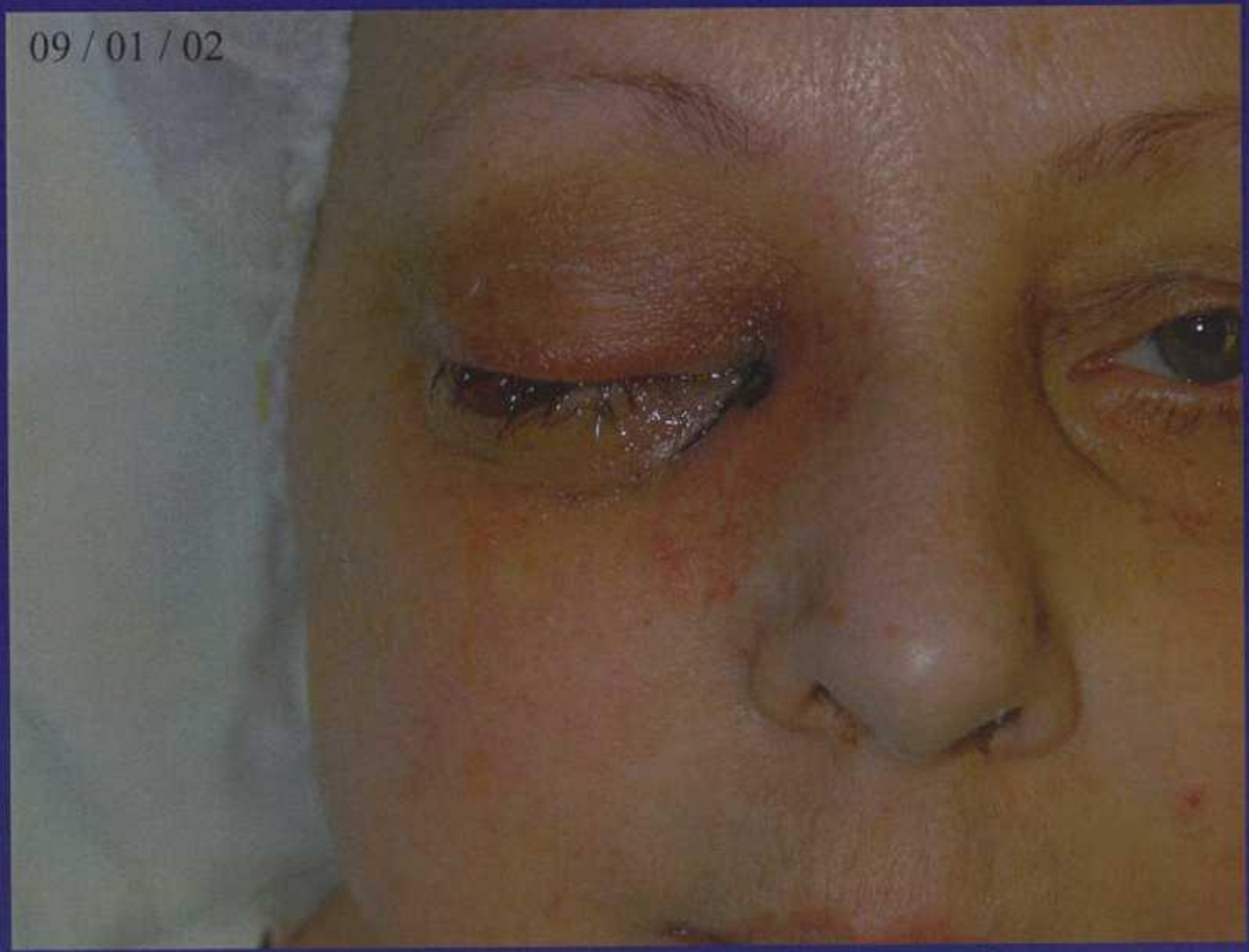


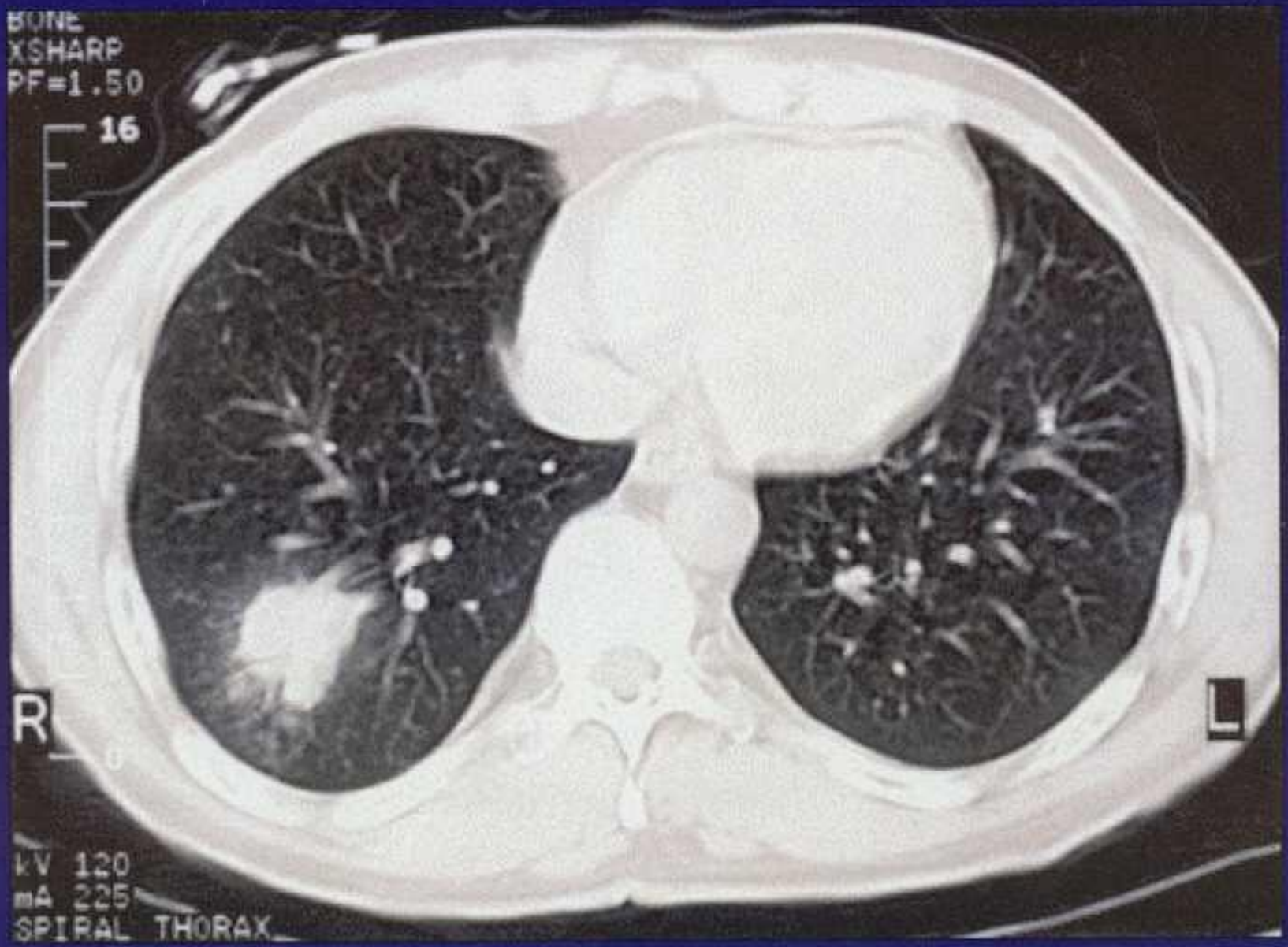
NF : 2/17 (11,7%)
F : 5/47 (10,6%)
Haplo : 5/23 (21,7%)

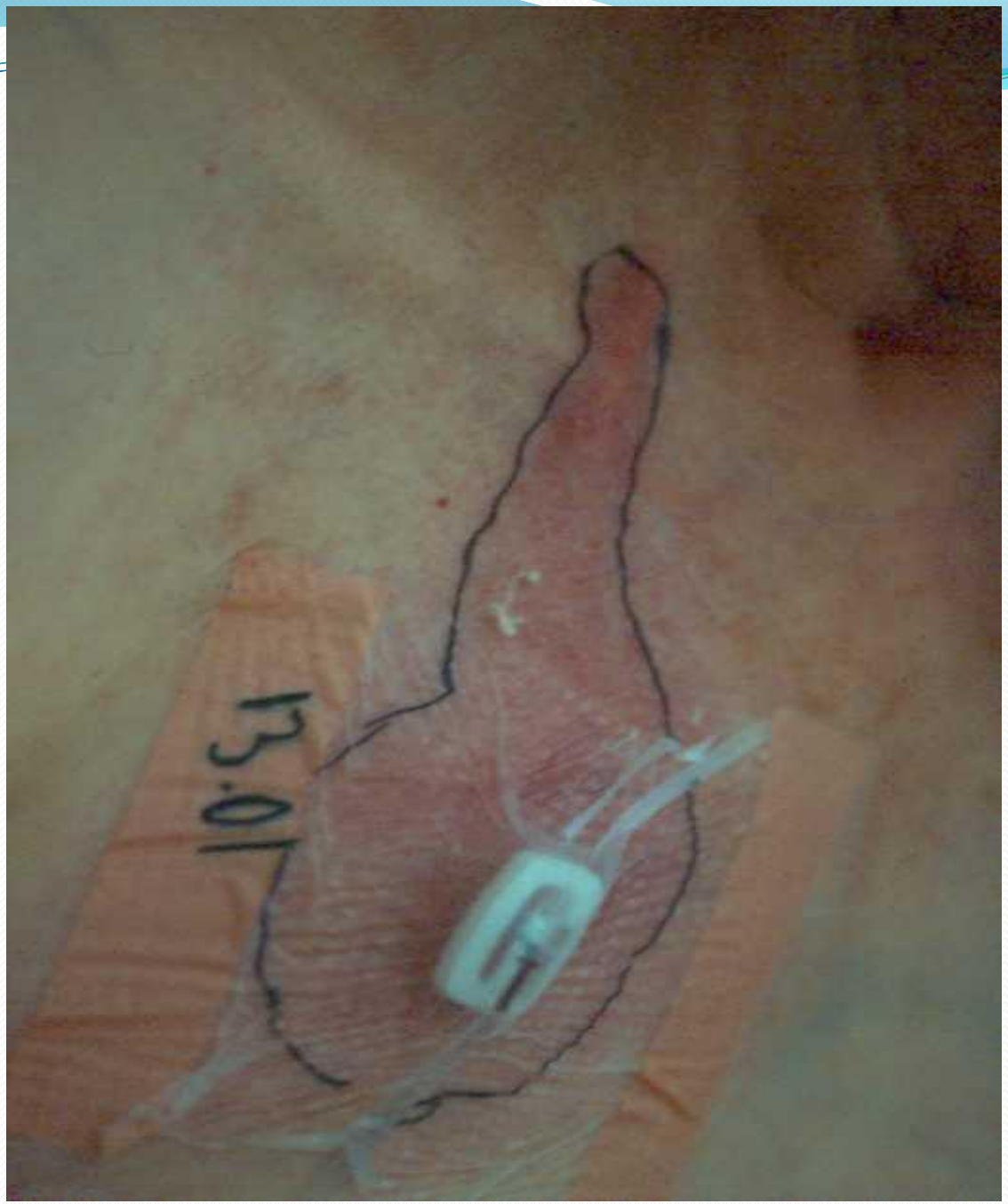
Invasive aspergillosis : clinical manifestations

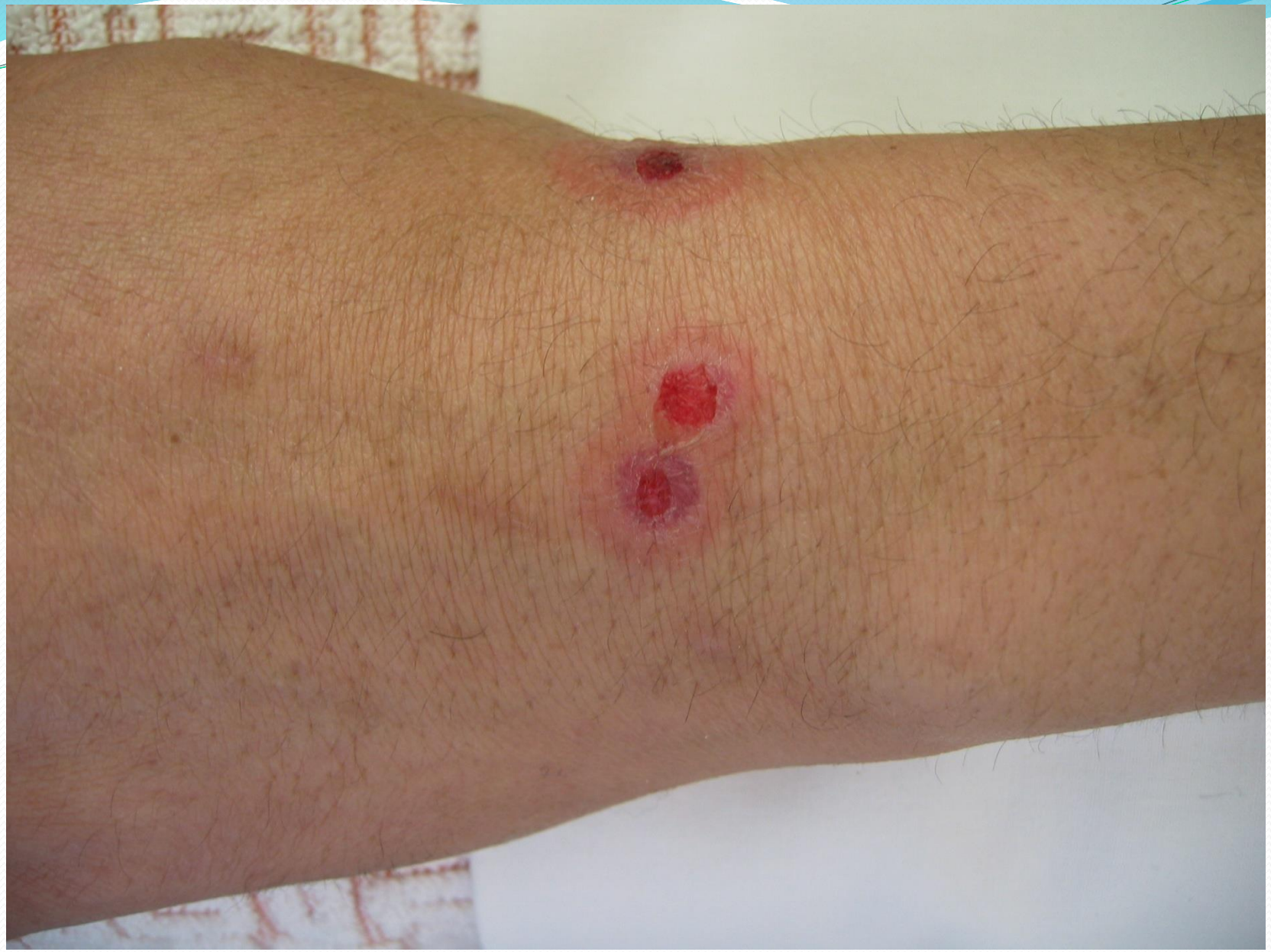
Persistent fever

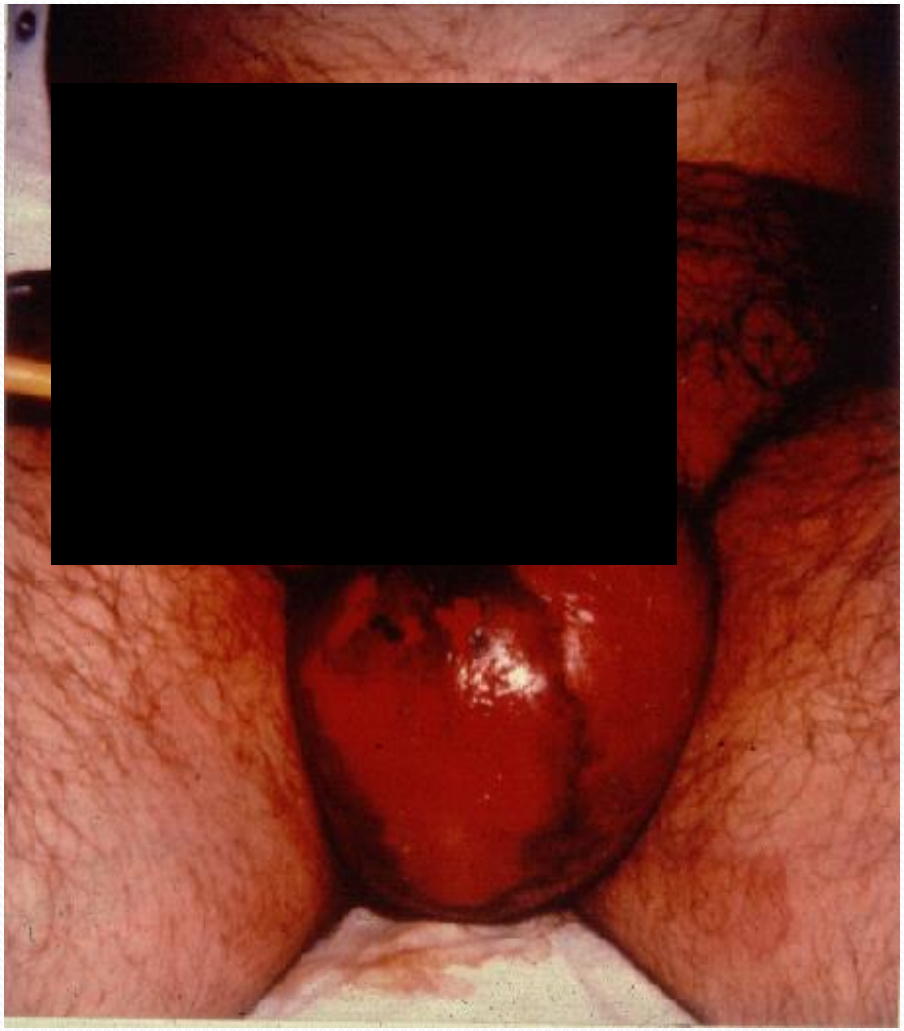
- Pneumonia : - Pleuritic chest pain
  - Cough
  - Dyspnea and hypoxia
- Sinusitis : - Nasal discharge
  - Epistaxis
  - Facial swelling and tenderness

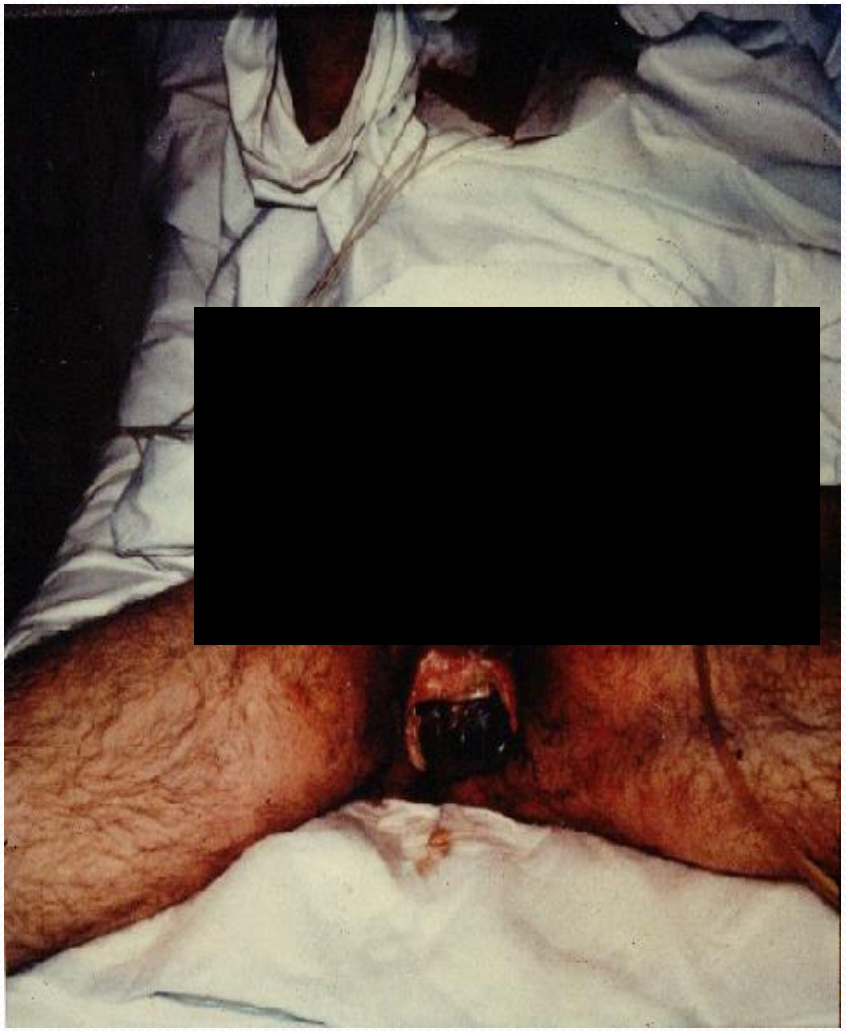

09 / 01 / 02

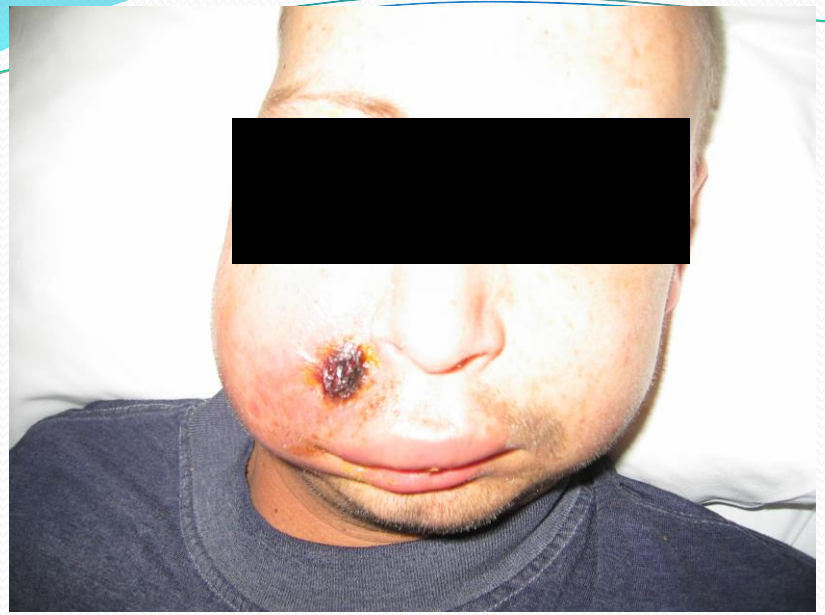

BONE
XSHARP
PF=1.50
16
R
L
kV 120
mA 225
SPIRAL THORAX

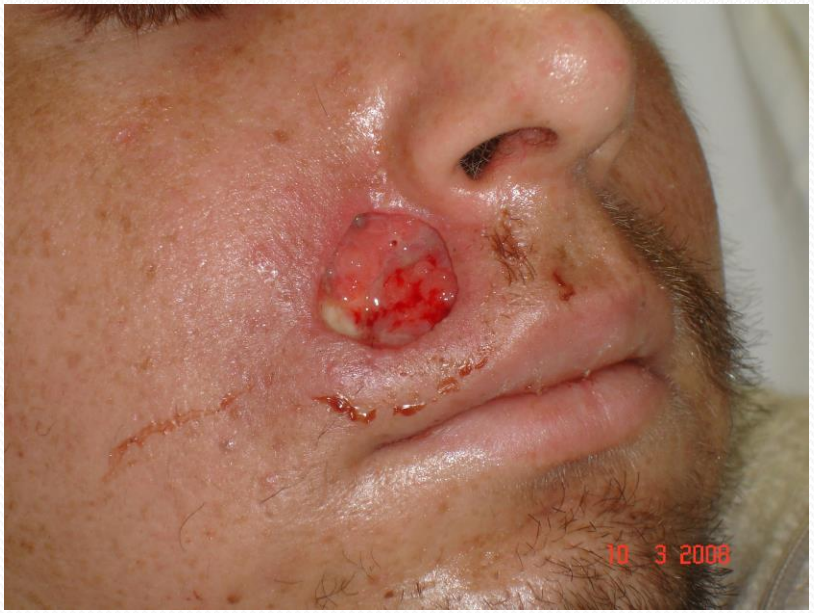










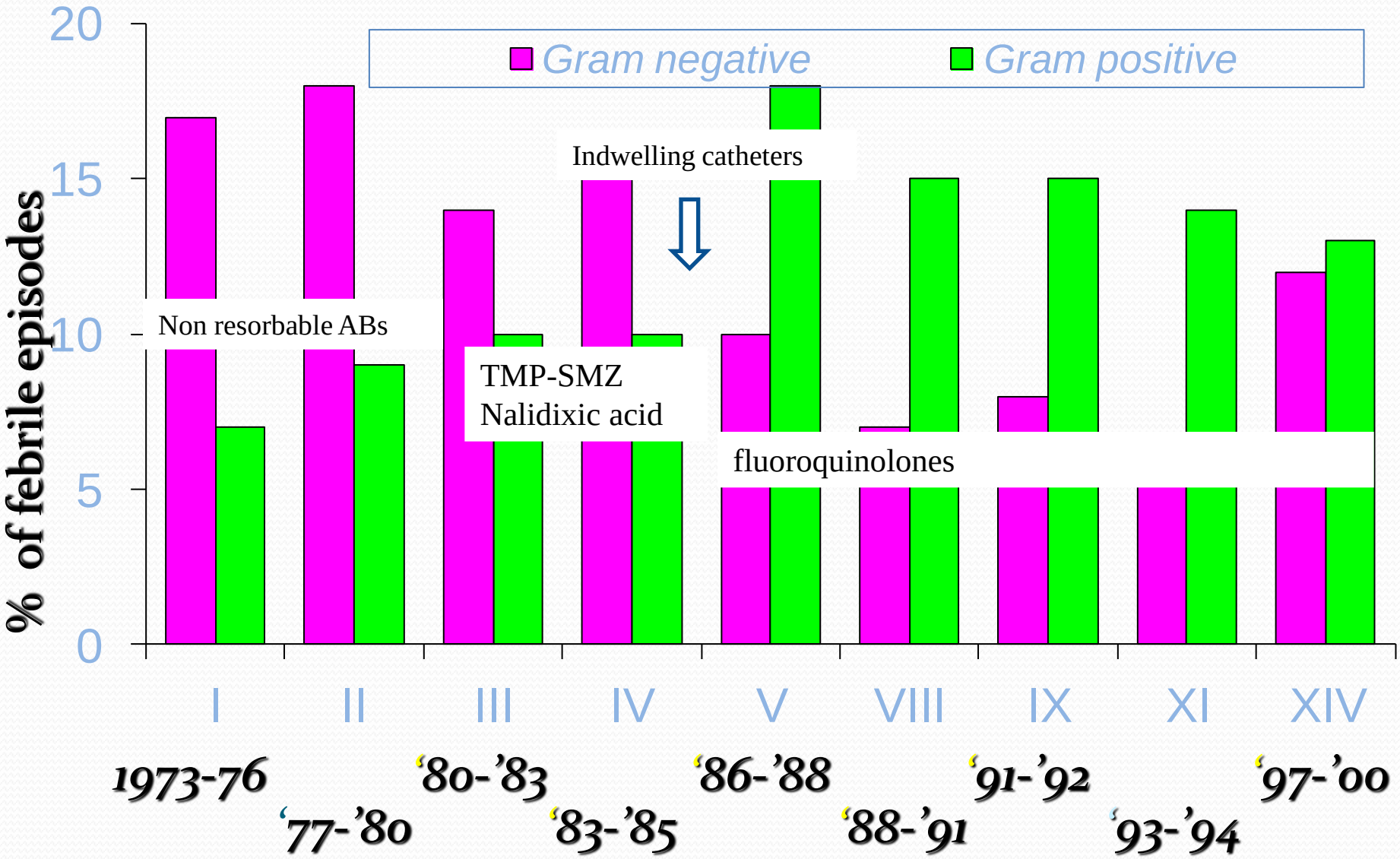

10 3 2008

Bloodstream infections in FN patients

- Incidence ~ 25 – 30 %
- Increased mortality :
  - Bacteremic vs non-bacteremic (10 vs 3 %)
  - GNB vs GPB (18 vs 5 %)
  - Polymicrobial (13 %)
  - Complex vs primary (12 vs 8 %)
- Common pathogens :
  - Common Gram-positive pathogens
    - CNS, MSSA or MRSA, Enterococcus spp , S. viridans group, S. pneumoniae, S. pyogenes
  - Common Gram-negative pathogens :
    - E. coli, Klebsiella spp, Enterobacter spp, P. aeruginosa, Citrobacter spp., Acinetobacter spp., S. maltophilia

Klastersky et al, Int J Antimicrob Agents 2007,308:S51-S59
Frere et al, Bone Marrow Transplant 2006; 37:411-418

Single-Organisms Bacteremias in EORTC-IATG Trials of empirical therapy of febrile neutropenia



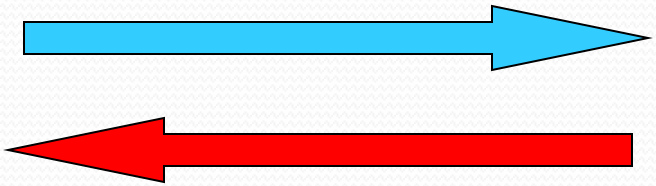
Major elements of standard care

- Empiric therapy
- Double coverage with β-lactam and an aminoglycoside
- β-lactam monotherapy
- Risk-adapted therapy

Single-drug therapy

First line

- Ceftazidime
- Cefepime
- Piperacillin/ tazobactam



Second line

Carbapenems :

- Imipenem
- Meropenem

Distribution of etiologic agent isolated from bacteremia in patients with cancer in published studies since 2008

Characteristic/agent	Irfan et al 2008	Cattaneo et al 2012	Kjellander et al 2012	Chong et al 2011	Kang et al 2012	Gudiol et al 2012
Study period	2001-2006	2004-2010	2002-2008	2006-2009	2006-2007 2008-2008	2006-2010
Country	Pakistan	Italy	Sweden	Japan	South Korea	Spain
Prophylaxis	Not reported	Not reported	No prophylaxis	No prophylaxis	No prophylaxis	No prophylaxis
Gram negative	41 %	57.3 %	46.9 %	48.1 %	55.6 %	49 %
P. aeruginosa	9.7 %	15 %	5.3 %	14.7 %	7.1 %	23 %
E. coli	36.6 %	NS	17.8 %	18.6 %	25 %	51 %
S. maltophilia	2 %	NS	0.8 %	NS	NS	1 %
Acinetobacter spp.	14.8 %	NS	0.1 %	NS	2.6 %	1 %
Klebsiella spp.	11.6 %	NS	9.8 %	9 %	16.2 %	22 %
Enterobacter spp.	8.5 %	NS	5.4 %	3.5 %	4.7 %	9 %
Citrobacter spp.	1.7 %	NS	1.3 %	NS	NS	NS
Gram positive	54 %	33.6 %	53.1 %	45.5 %	32.7 %	41 %
Staphylococcus spp.	55.2 %	NS	NS	33 %	NS	NS
Staphylococcus aureus	9.5 %	NS	6.9 %	1.3 %	9.8 %	12 %
Coagulase-negative staph.	NS	NS	14.7 %	23.1%	8.3 %	43 %
Enterococcus spp.	5.1 %	NS	9.5 %	5.8 %	9.2 %	23 %
Streptococcus spp.	5.5 %	NS	NS	6.4 %	3.4 %	NS
Streptococcus pneumoniae	3.5 %	NS	2.3 %	NS	2 %	6 %
Streptococcus viridans	NS	NS	14 %	5.8 %	NS	23 %

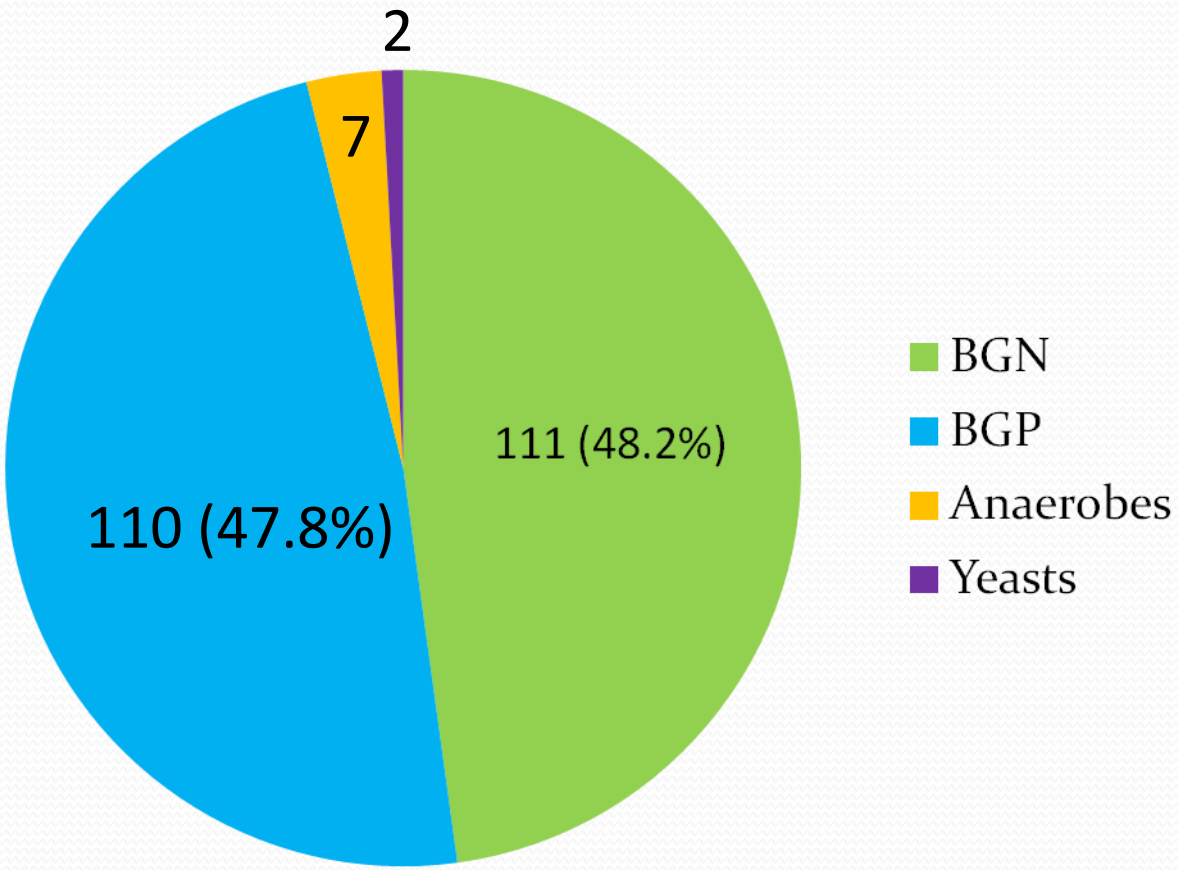
Montassier E, Eur J Clin Microbiol 2013;32:841-850

Neutropenic adult patient with hematological malignancies or HSCT
Institut Jules Bordet – bacteremias 2008-2012

Organism	Total	%
Single Gram-negative	83	40
E. coli	47	22.7
P.Aeruginosa	17	8.2
Klebsiella spp.	17	8.2
Enterobacter spp.	1	0.5
S. maltophilia	1	0.5
Single Gram-positive	83	40
Streptococcus viridans	34	16.4
Enterococcus sp.	17	8.2
Staphylococcus coagulase negative	20	9.6
Staphylococcus aureus	4	1.9
others	8	3.8
Polymicrobial *	32	15.5
anaerobes	7	3.4
yeasts	2	1

* Mixed GNB : 9; mixed GPB : 12; mixed GNB+GPB : 11

Neutropenic adult patient with hematological malignancies or HSCT
Institut Jules Bordet – bacteremias 2008-2012



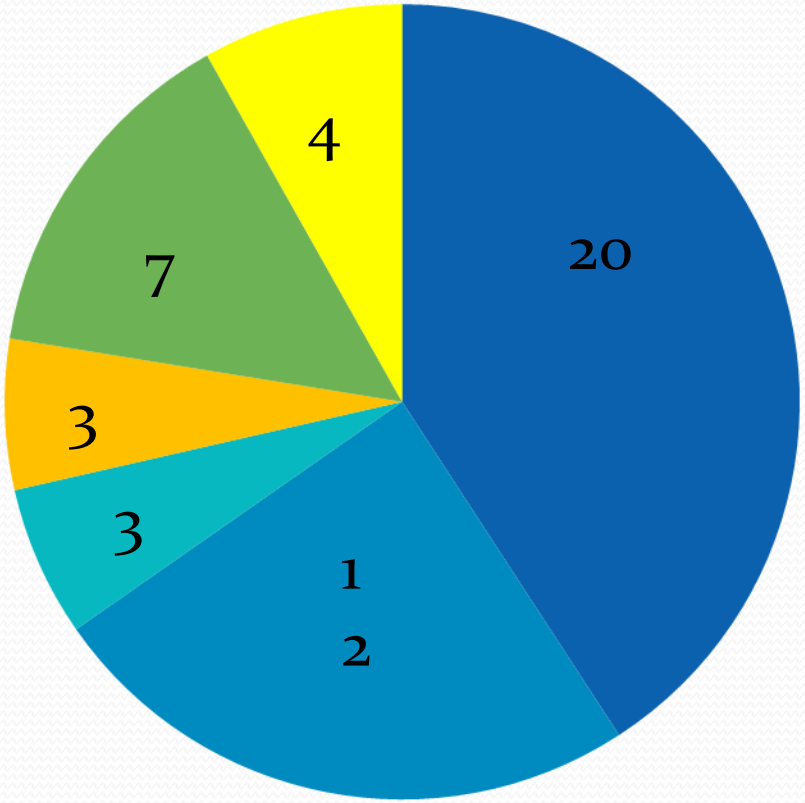
E	Enterococcus faecium
S	S. aureus
K	Klebsiella pneumoniae
A	Acinetobacter baumanii
P	P. aeruginosa
E	Enterobacter sp.

E	Enterococcus faecium
S	S. aureus (S. viridans)
C	Clostridium difficile
A	Acinetobacter sp.
P	P. aeruginosa
E	Enterobacteriaceae
S	S. maltophilia

Rice LB, JID 2008;197-1079

Bacteremia due to multidrug-resistant gram-negative bacilli in cancer patients : risk factors, antibiotic therapy and outcomes

- of 747 bacteremias (2006-2009), 372 were due to GNB
- 51 of 372 (13.7%) were caused by MDRGNB



MDRGNB risk factor for 30-day mortality (OR 3.5, 95% CI 1.4-9.1)

- ESBL-Enterobacteriaceae
- Amp-C-Enterobacteriaceae
- S. maltophilia
- A. baumannii
- P. aeruginosa
- other

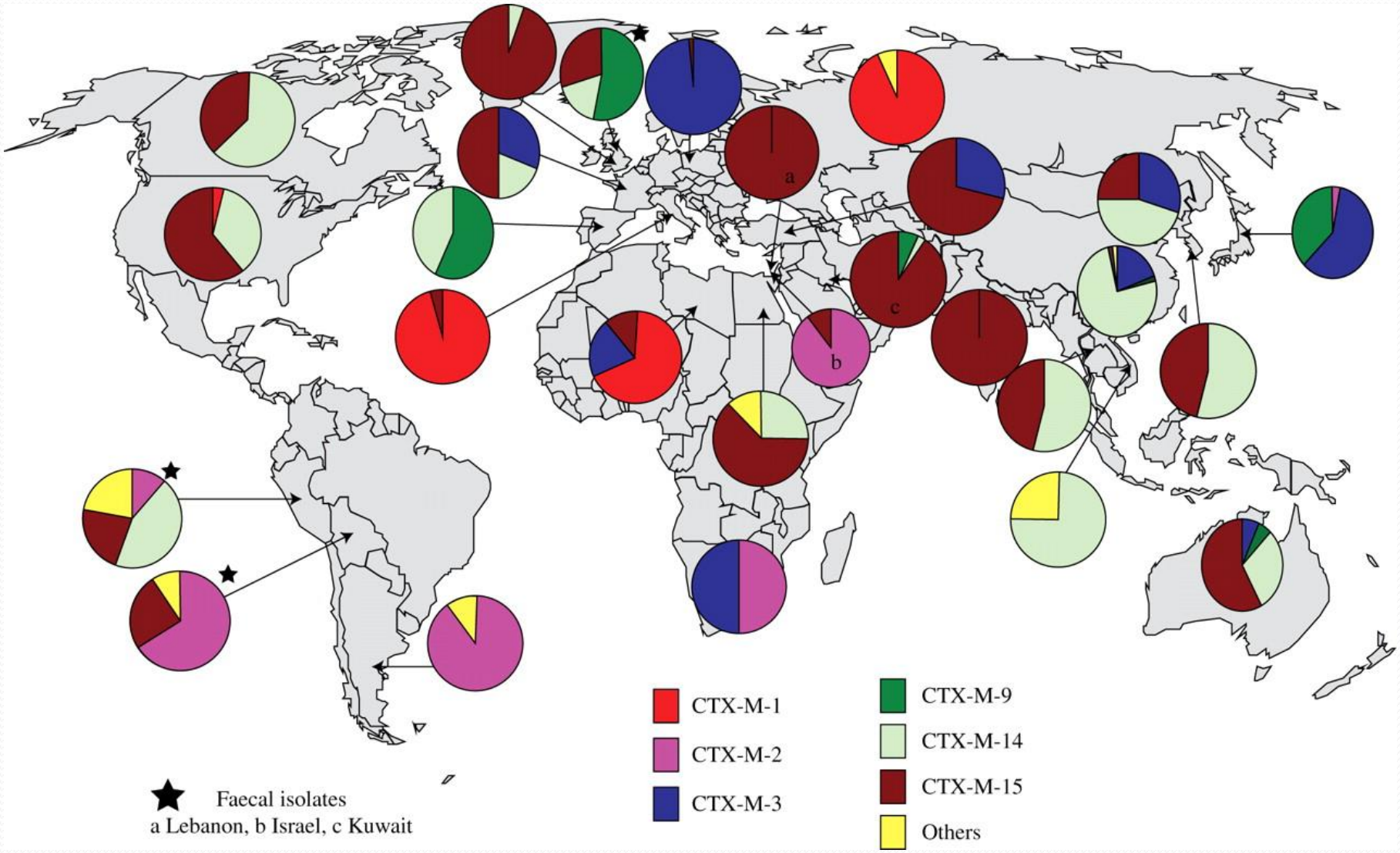
Gudiol C, J Antimicrob Chemother 2011

Institut Jules Bordet
Bacteremias 2008-2012
N=230 pathogens

	ESCAPES	rESCAPES
E.coli	60	11 (18.3 %)
Klebsiella sp.	26	7 (26.9 %)
Enterobacter sp.	3	2
P. aeruginosa	20	6
Acinetobacter sp	0	0
S. maltophilia	1	0
S. viridans	42	1 (pen R) 5 (pen I)
Enterococcus sp	25	1
S. aureus	4	0

Risk of resistant pathogen : 15.46%

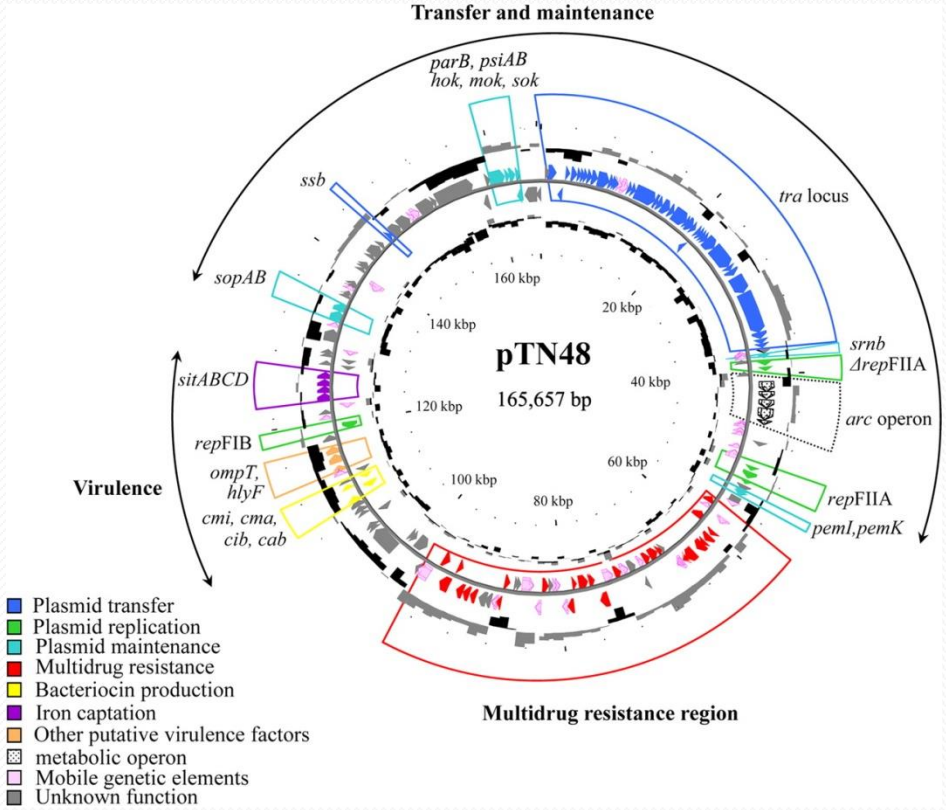
Global distribution of CTX-M genotypes.11,13,15,62–84.



Hawkey PM; JAC 2009;64 suppl 1:i3-i10

CTX-M ESBL

Classes	Genes
Aminoglycosides	*aac6' –lb-cr* *aadA5*
ß-lactams	$bla_{CTX\text{-}M\text{-}15}$, $bla_{OXA\text{-}1}$ $bla_{TEM\text{-}1}$
Chloramphenicol	*cat*B4
Macrolides	*mph*(A)
Fluoroquinolones	*aac6' –lb-cr*
Sulphonamides	*sul*I
Trimethoprim	$dhfr_{XVII}$
Tetracycline	*tet*(A)



Woodford N et al, AAC 2009:53-4472.

ESBL(s)
Klebsiella spp. and E. coli

- Prevalence varies with
  - Geographical area, institution, unit

Ortega	JAC 2009	Spain	E. coli 4 %
Gudiol	JAC 2010	Spain	E. coli 12.6%
Si-Hoyn Kim	Ann Hematol 2013	Korea	E. coli+K.pneumoniae 26 %
Chiol-In Kang	Ann Hematol 2012	Korea	E.coli+K.pneumoniae 23 %
Tumbarello	AAC 2006	Italy	K. pneumoniae 30 %
Trecarichi	J Infection 2009	Italy	E.coli 41%
Kara Ö	ICAAC 2010	Turkey	E.Coli 40%-K. pneumoniae 25%

Institut Jules Bordet
Bacteremias 2008-2012
N=230 pathogens

	ESCAPES	rESCAPES
E.coli	60	11 (18.3 %)
Klebsiella sp.	26	7 (26.9 %)
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S. viridans	42	1 (pen R) 5 (pen I)
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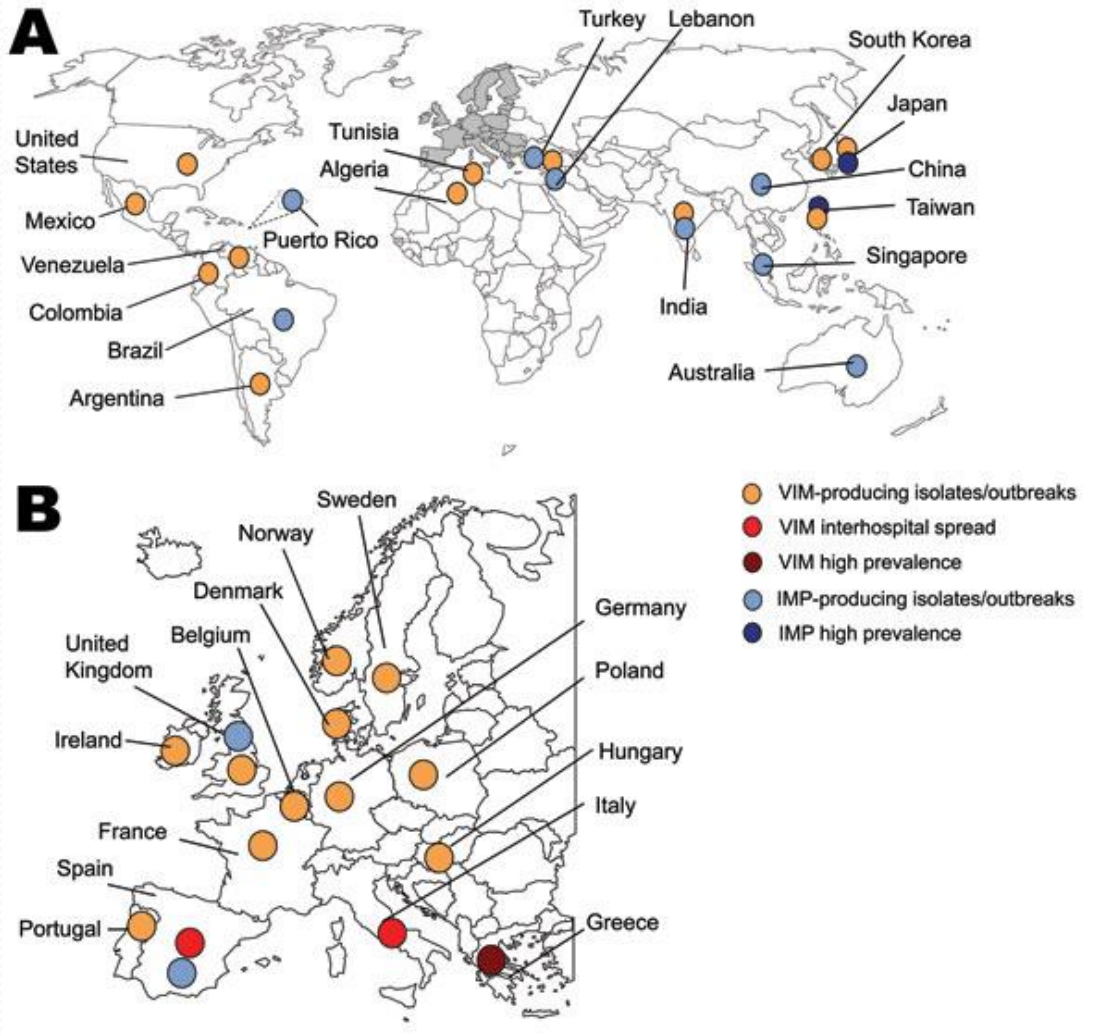
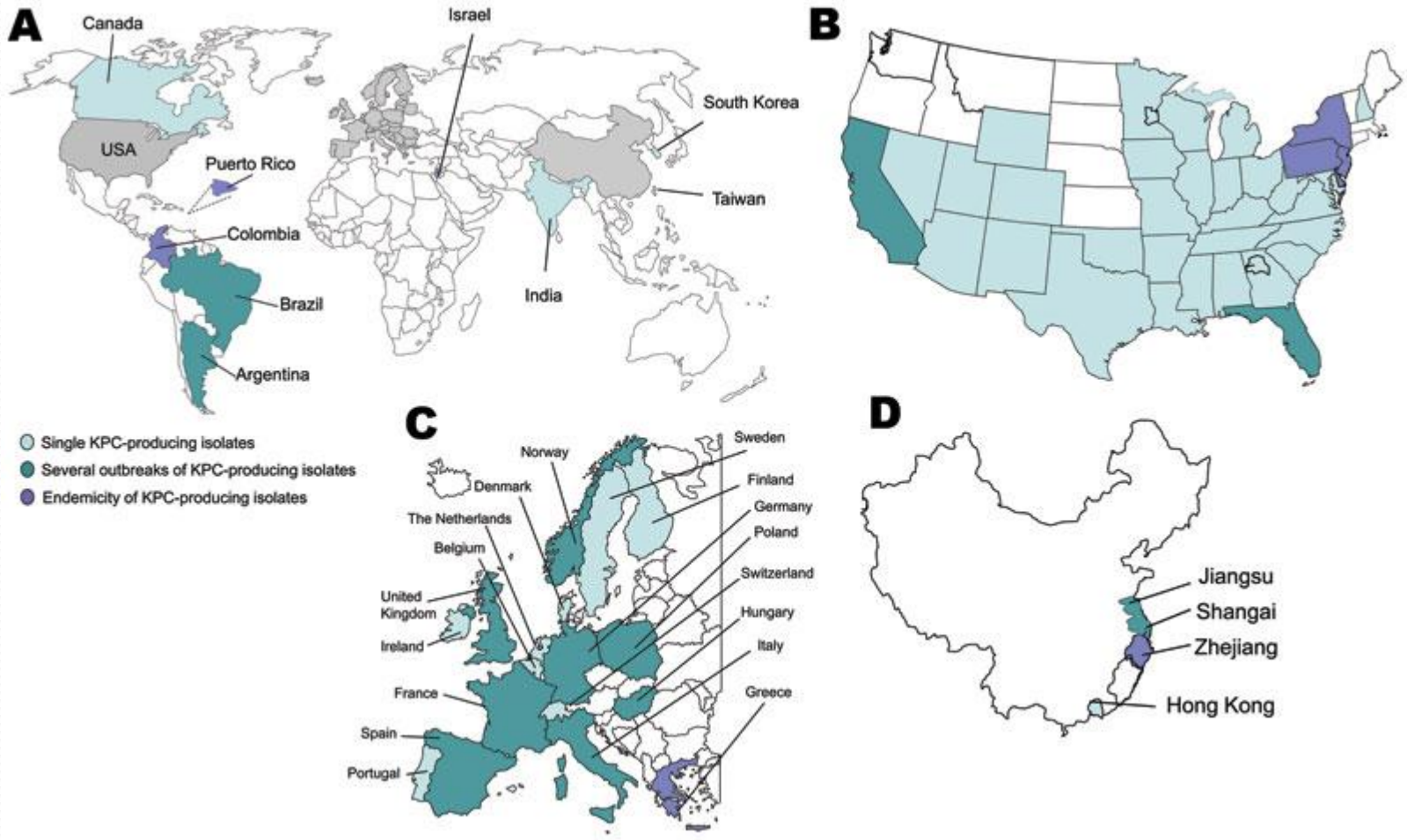
Risk of resistant pathogen : 15.46%

Worldwide and European geographic distribution of Verona integron–encoded metallo-β-lactamase (VIM) and IMP enterobact



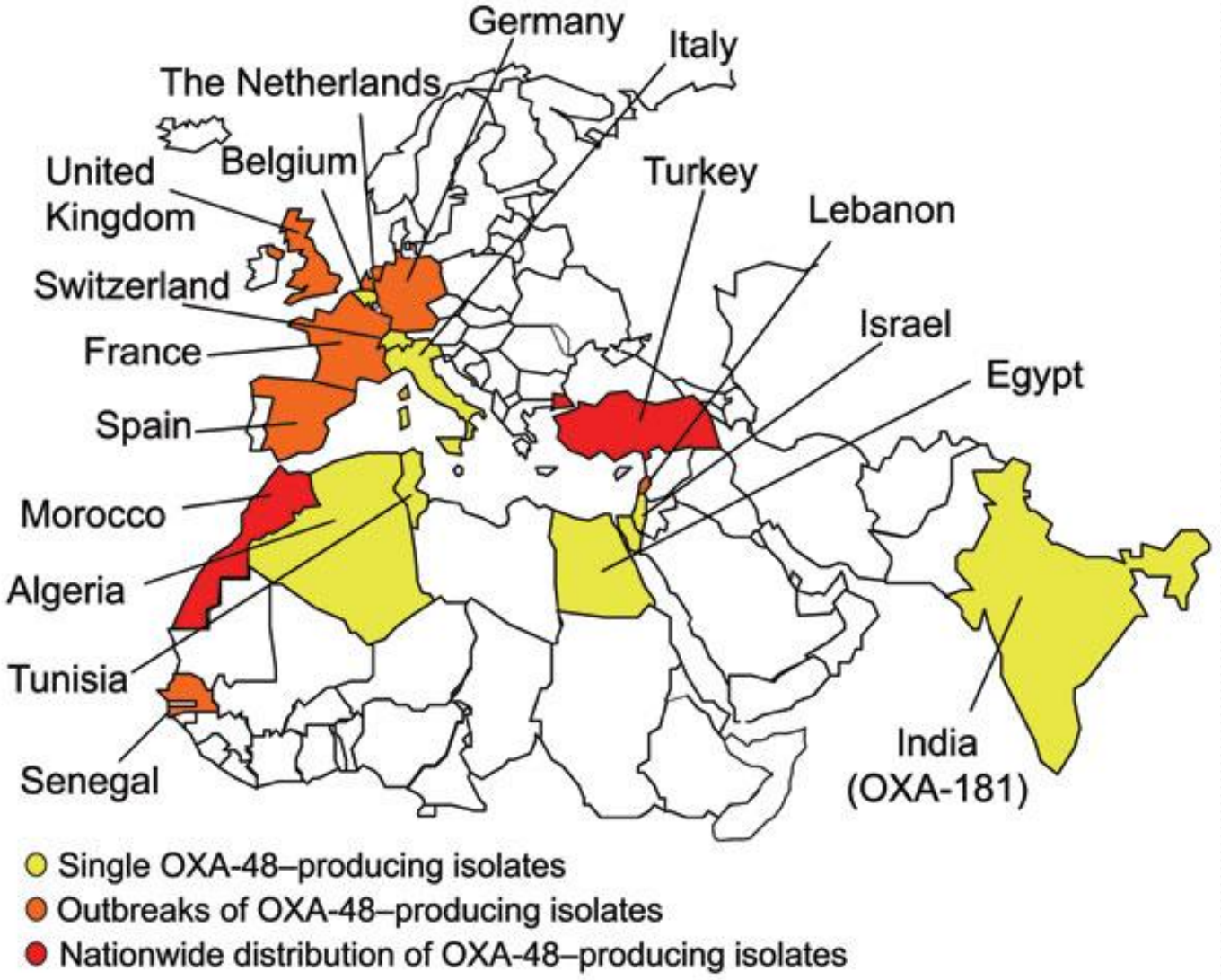
Nordmann P et al, Emerging Infectious Diseases 2011;17

Worldwide geographic distribution of Klebsiella pneumoniae carbapnemase (KPC)



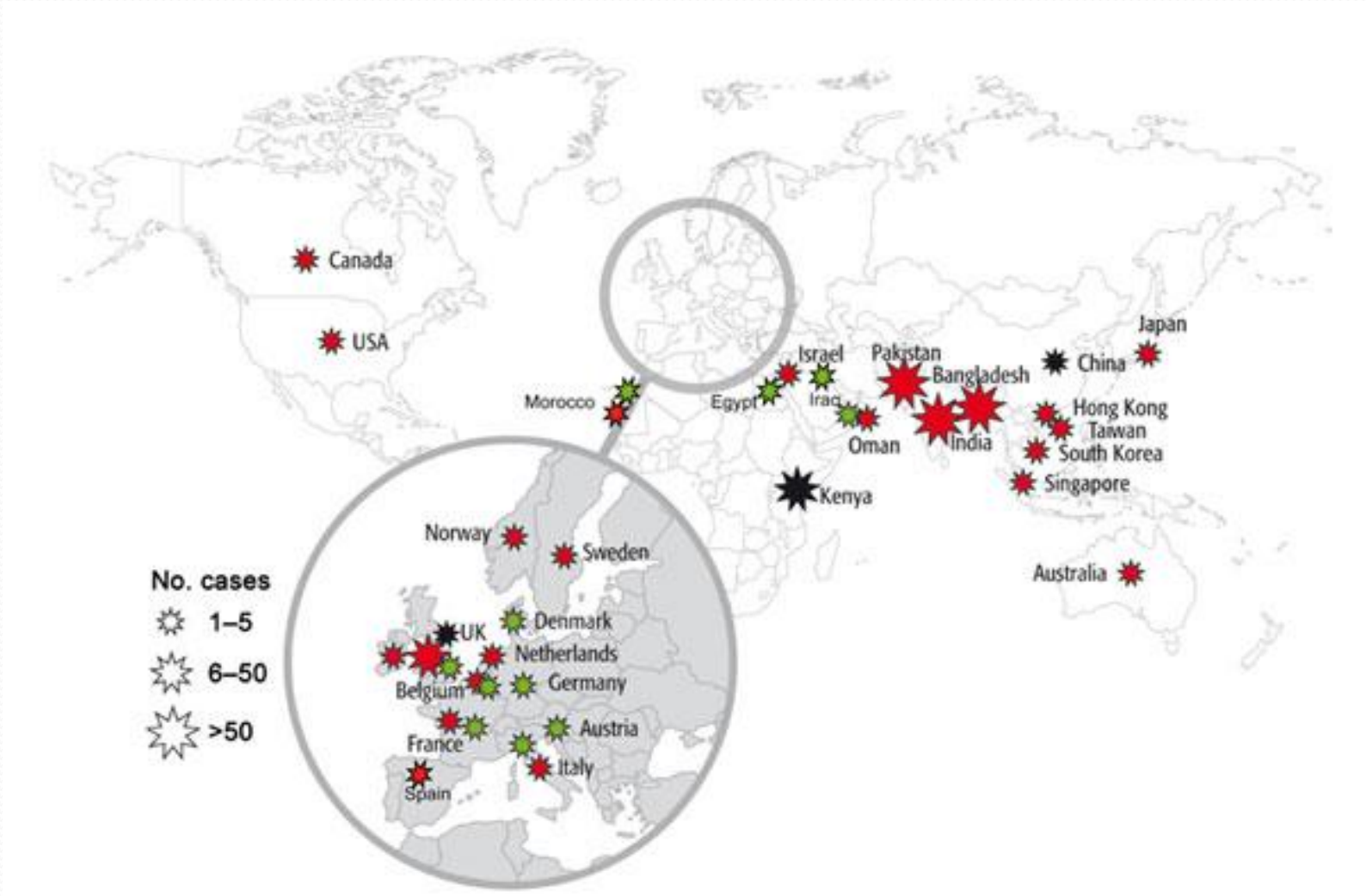
Nordmann P et al, Emerging Infectious Diseases 2011;17

Geographic distribution of oxacillinase-48 (OXA-48)



Nordmann P et al, Emerging Infectious Diseases 2011;17

Geographic distribution of New Delhi metallo-β-lactamase-1 (NDM-1)



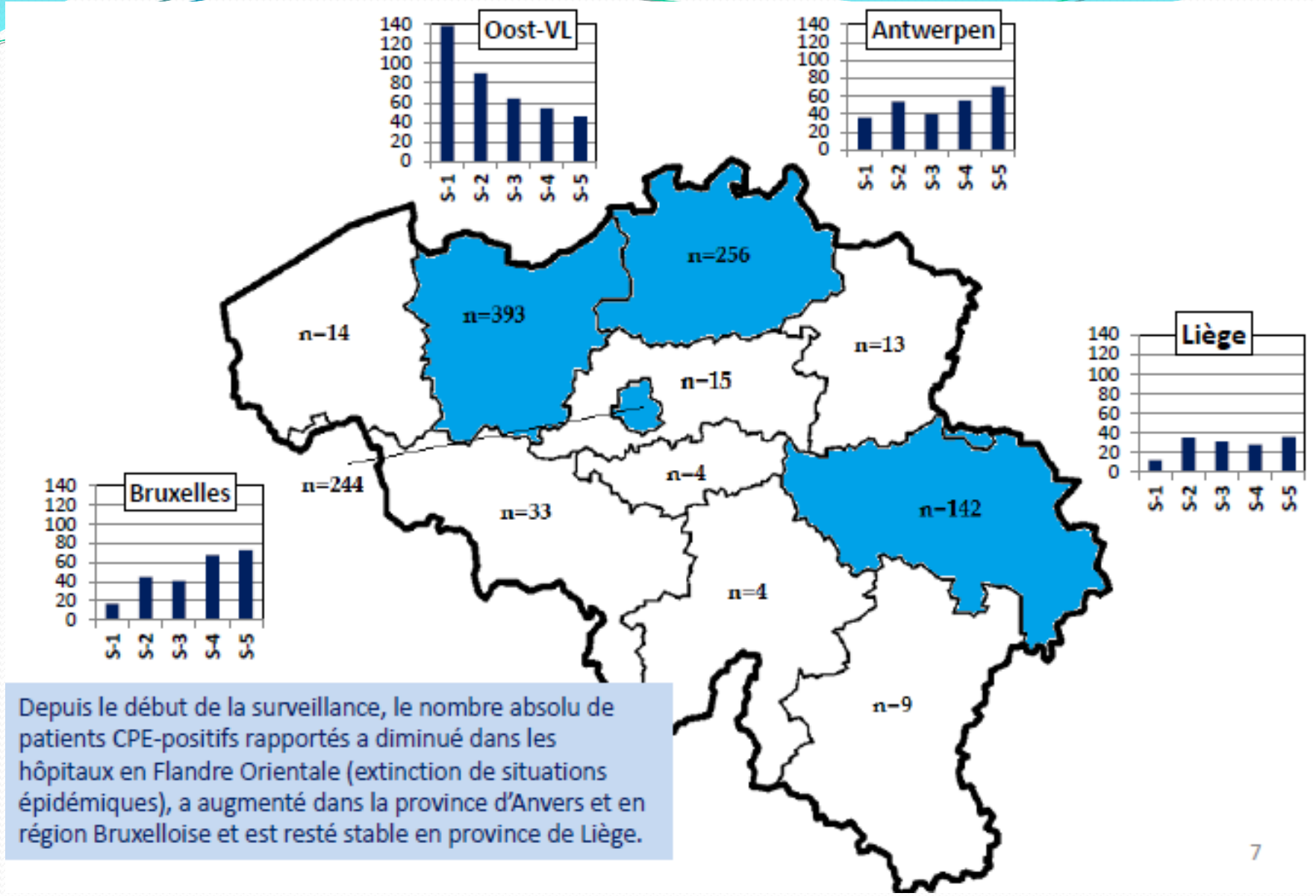
Nordmann P et al, Emerging Infectious Diseases 2011;17

Fecal carriage of NDM-1 in hospitalized and non hospitalized patient

- 122 healthy controls and 95 ICU patients
- Fecal carriage was seen
  - 9/122 (7.4%) of controls
  - 25/95 (27.4%) of ICU patients carbapenem resistance
  - Day 1- 3/95 (3.2%)
  - Day 4- 13/97 (13.7%)
  - 8/95 (8.4%) showed colonisation on both days
  - Mainly E. coli, Mainly NDM-1

- 7.4 % controls
- ICU
  - Day 1-3.2%
  - Day 4-13.7%

HISICON 2013 abtract OC 17
G. Mittal et al, Vardhaman Mahavir Medical College & Safdarjung Hospital, Delhi



Depuis le début de la surveillance, le nombre absolu de patients CPE-positifs rapportés a diminué dans les hôpitaux en Flandre Orientale (extinction de situations épidémiques), a augmenté dans la province d'Anvers et en région Bruxelloise et est resté stable en province de Liège.

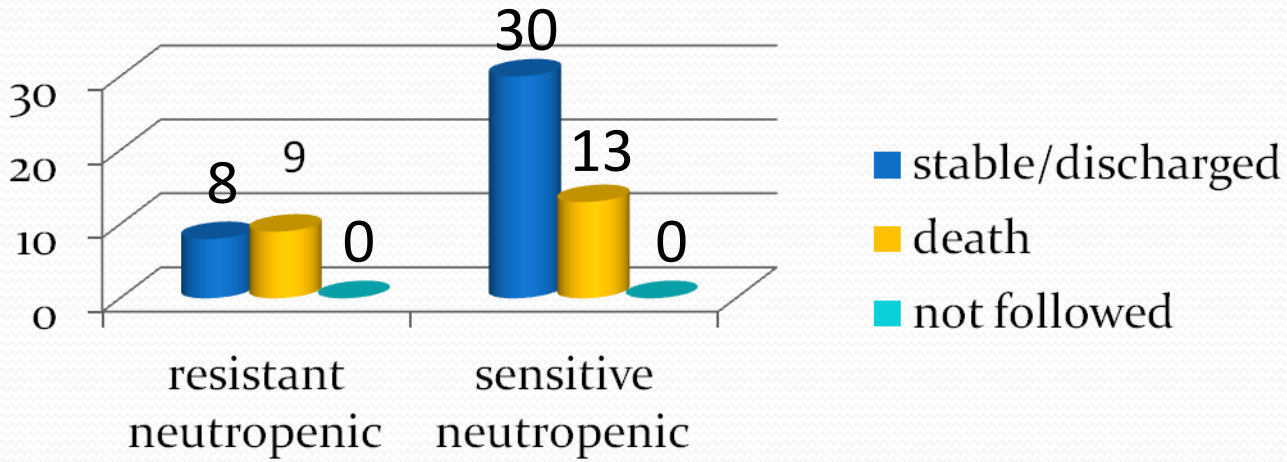
Epidemiology of CR K. pneumoniae in oncology patients in Hacettepe

- June 2009-December 2010
- Active surveillance in neutropenic patients
- 43.312 rectal swabs
  - 100 colonized patients
  - 9 were infected with CRKP
- Records available for 93 patients colonized
  - 55.4 % immunosuppressed
  - 40 % hospitalized during the past 6 months
  - All had antibiotics during past month
  - 32.3 % died
- Beta-lactamases in 50 isolates
  - 38 OXA-48 and 39 CTX-M producers

Eser O et al, ECCMID 2013, Berlin

Clinical study on carbapenem sensitive & carbapenem resistant bacteremia in neutropenic & non-neutropenic patients- The first series from India

Clinical outcome among neutropenic group



30 day mortality		Mortality p value
Resistant neutropenic	(52.94%)	- < 0.001
Sensitive neutropenics	(30.23%)	

Abdul Ghafur et al, ECCMID poster N°P1368, Berlin 2013

Distribution of etiologic agent isolated from bacteremia in patients with cancer in published studies since 2008

Characteristic/agent	Irfan et al 2008	Cattaneo et al 2012	Kjellander et al 2012	Chong et al 2011	Kang et al 2012	Gudiol et al 2012
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Country	Pakistan	Italy	Sweden	Japan	South Korea	Spain
Prophylaxis	Not reported	Not reported	No prophylaxis	No prophylaxis	No prophylaxis	No prophylaxis
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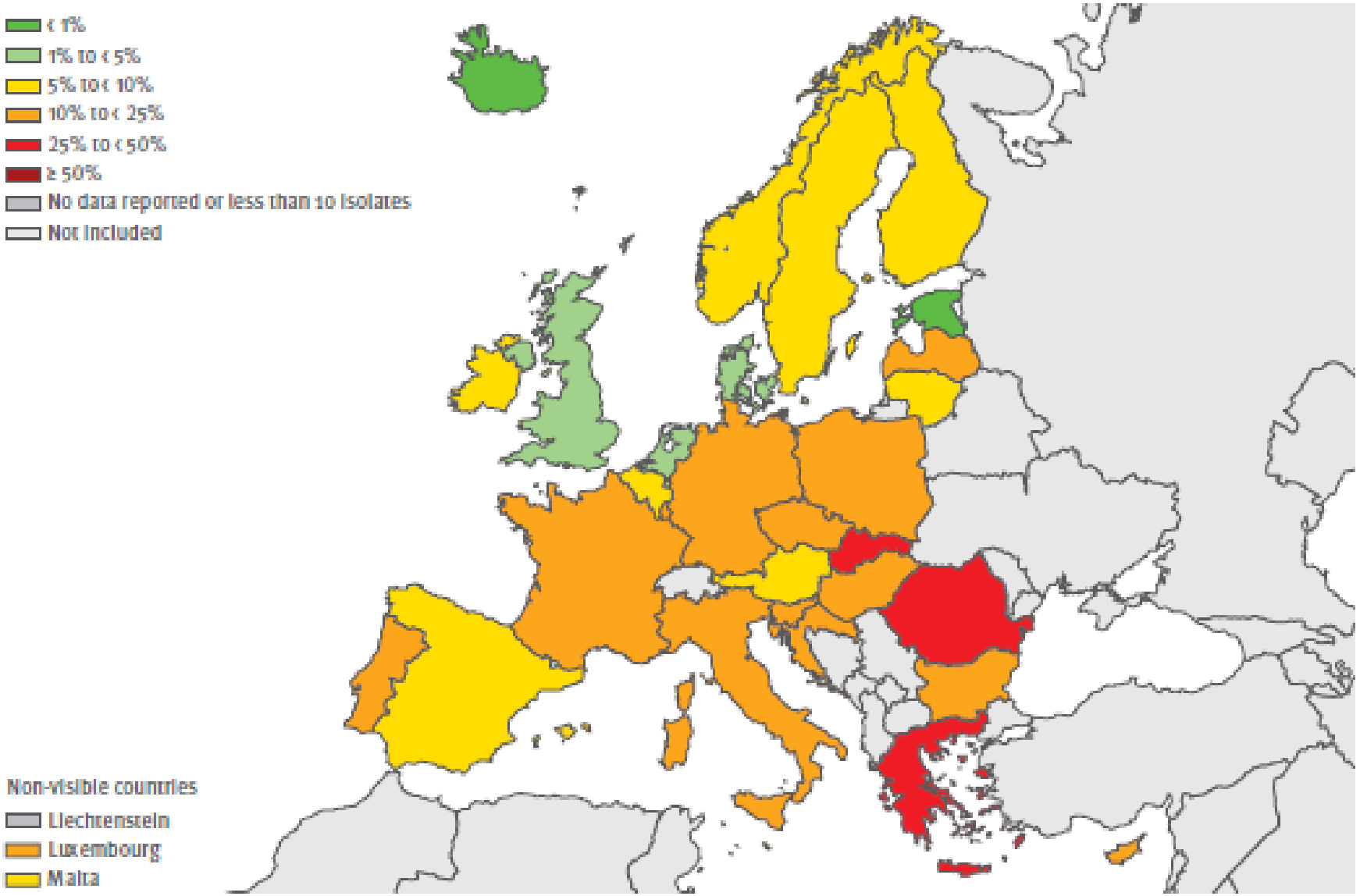
P. aeruginosa	**9.7 %**	**15 %**	**5.3 %**	**14.7 %**	**7.1 %**	**23 %**
E. coli	36.6 %	NS	17.8 %	18.6 %	25 %	51 %
S. maltophilia	**2 %**	**NS**	**0.8 %**	**NS**	**NS**	**1 %**
Acinetobacter spp.	**14.8 %**	**NS**	**0.1 %**	**NS**	**2.6 %**	**1 %**
Klebsiella spp.	11.6 %	NS	9.8 %	9 %	16.2 %	22 %
Enterobacter spp.	8.5 %	NS	5.4 %	3.5 %	4.7 %	9 %
Citrobacter spp.	1.7 %	NS	1.3 %	NS	NS	NS
Gram positive	54 %	33.6 %	53.1 %	45.5 %	32.7 %	41 %
Staphylococcus spp.	55.2 %	NS	NS	33 %	NS	NS
Staphylococcus aureus	9.5 %	NS	6.9 %	1.3 %	9.8 %	12 %
Coagulase-negative staph.	NS	NS	14.7 %	23.1%	8.3 %	43 %
Enterococcus spp.	5.1 %	NS	9.5 %	5.8 %	9.2 %	23 %
Streptococcus spp.	5.5 %	NS	NS	6.4 %	3.4 %	NS
Streptococcus pneumoniae	3.5 %	NS	2.3 %	NS	2 %	6 %
Streptococcus viridans	NS	NS	14 %	5.8 %	NS	23 %

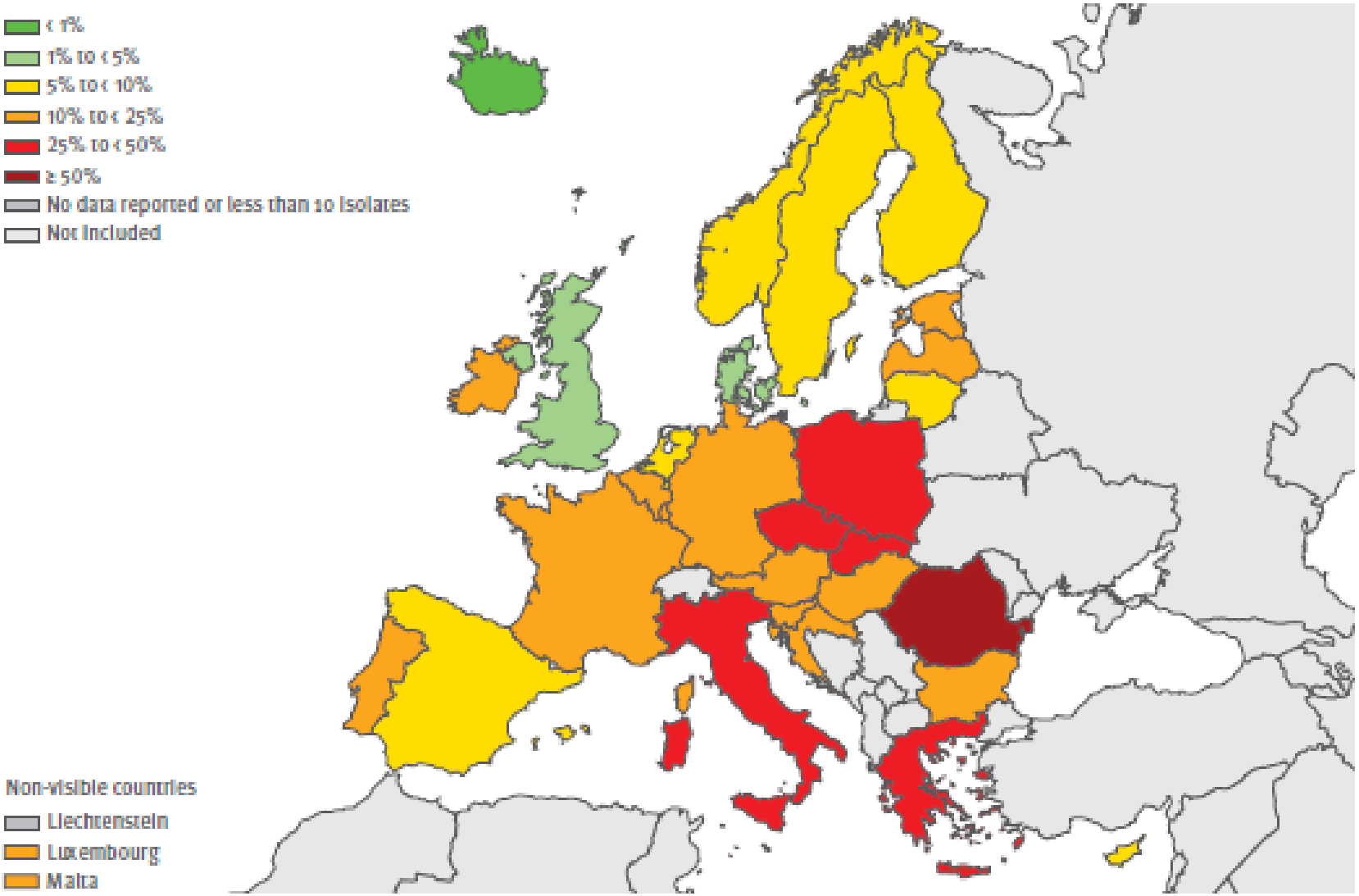
Montassier E, Eur J Clin Microbiol 2013;32:841-850

Figure 3.13. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to ceftazidime, by country, EU/EEA countries, 2013



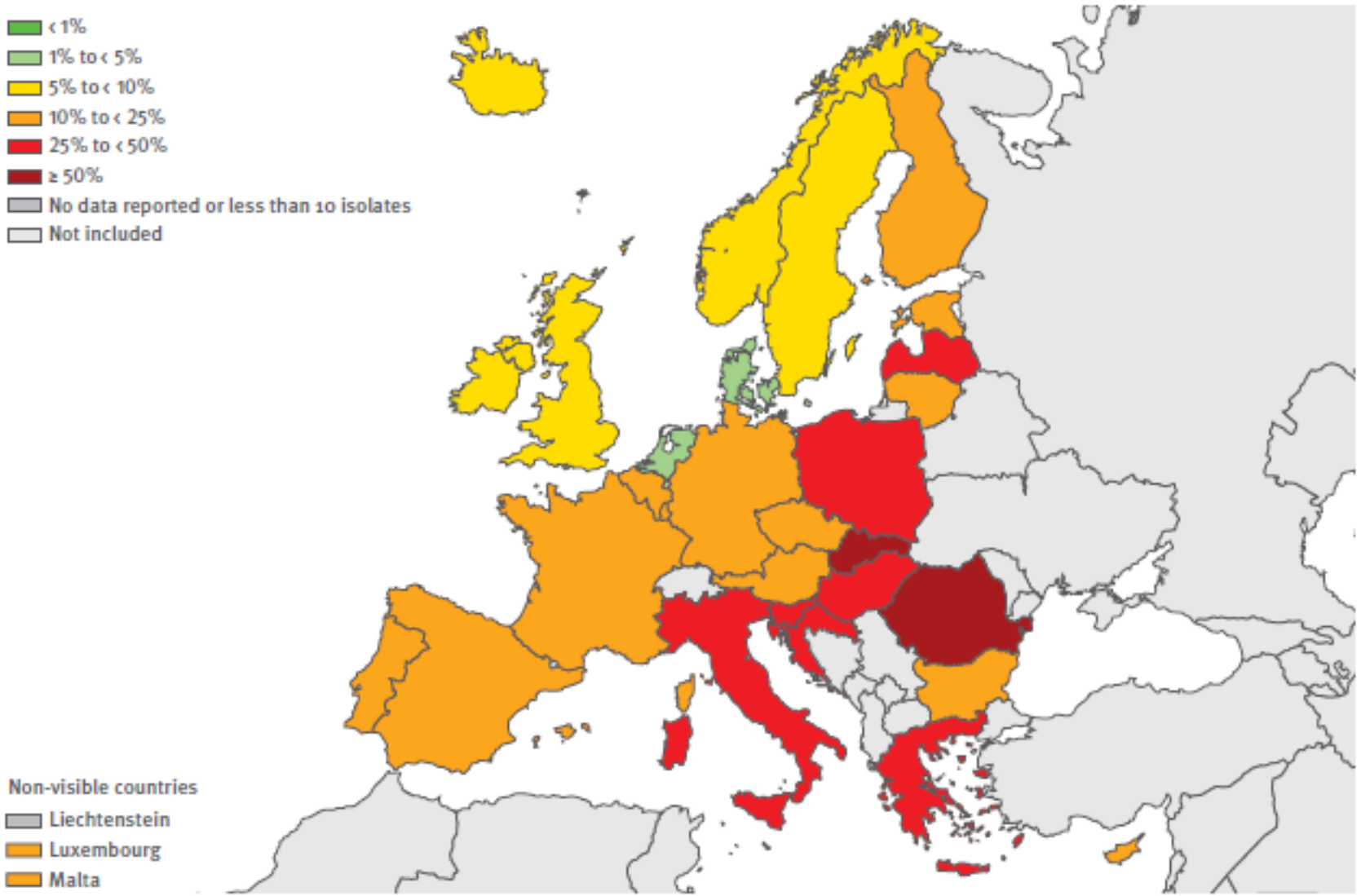
ECDC antimicrobial resistance surveillance in europe 2013

Figure 3.11. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to piperacillin + tazobactam, by country, EU/EEA countries, 2013



ECDC antimicrobial resistance surveillance in europe 2013

Figure 3.15. ***Pseudomonas aeruginosa*****. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2013**



ECDC antimicrobial resistance surveillance in europe 2013

Pseudomonas aeruginosa bacteremia among hematological patients

- 441 cases (2004-2010)
- 66 due to P. aeruginosa
- 22 (33%) due to MDR strains
- Mortality
  - Higher in MDR strains (37% vs 23%, P=0.26)
  - Higher if inadequate empiric therapy (83% vs 18.8%,P=0.01)

Cattaneo C et al, Ann Hematolo 2012:91:1299-1304.

Results of Multiple logistic regression analysis using control group 1

Variable	Univariate P value	Multivarirate		
		P value	OR	95% CI
Carbapenem use ≥7 defined daily dose	< 0.001	0.001	23.8	3.5-166.67
History of previous P. aeruginosa infection	< 0.001	0.12	13.7	1.79-111.1
Steroid use during prior 30 days	0.007			
Chronic obstructive pulmonary disease	0.04	0033	25.0	1.30-480.90
Leukemia	0.05			

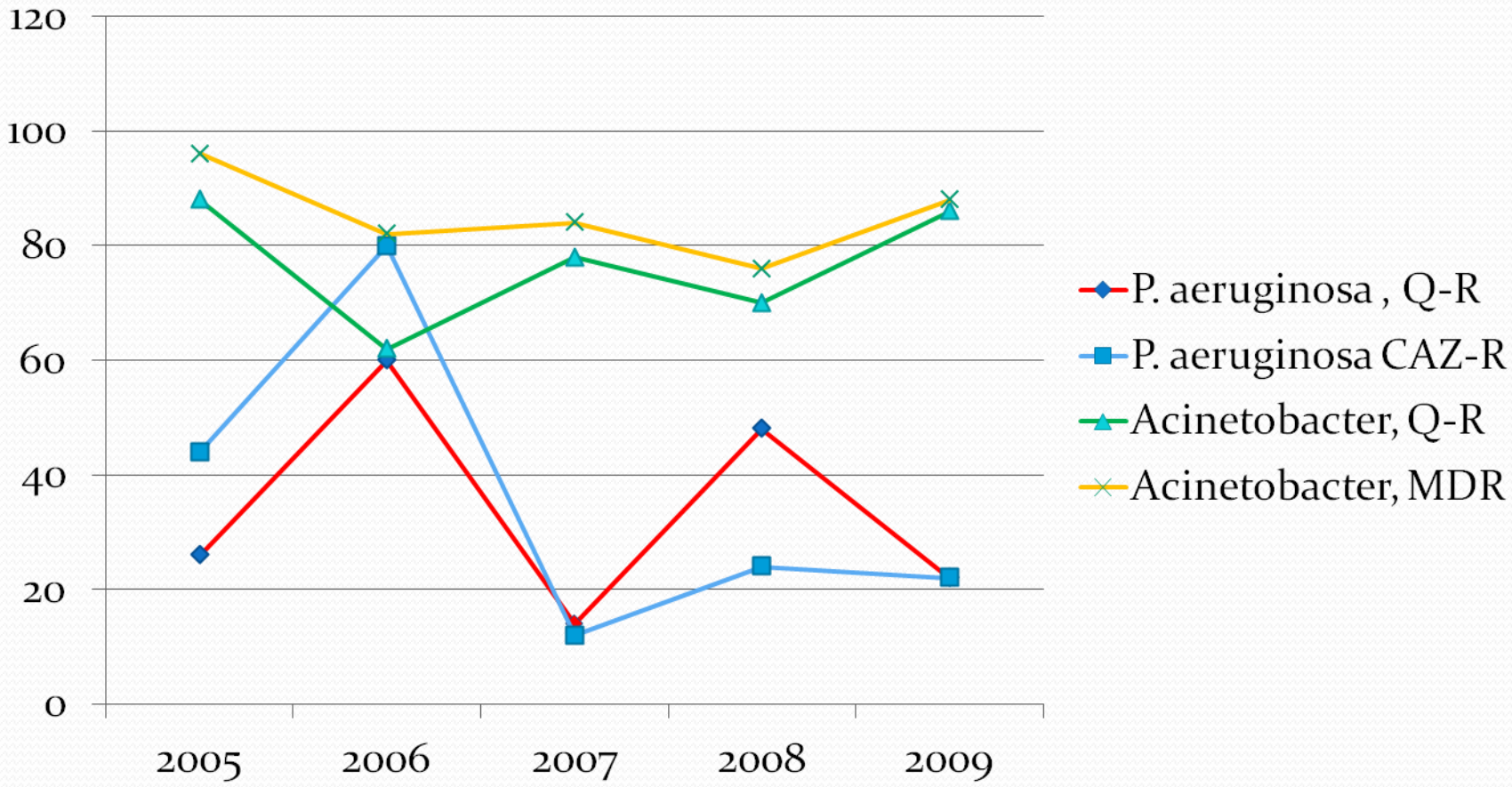
Ohmagari N et al; Cancer 2005;104:205-212

ESKAPE pathogens isolated in 1148 bacteremias in cancer patients (2006-2011)

Organism	ESKAPE N=382	rESKAPE N=54 (14.4%)
Enterococcus faecium	44	0 (0)
Staphylococcus aureus	93	13 (24)
Klebsiella pneumoniae	95	7 (13)
Actinetobacter baumanii	7 (1.8%)	4 (7)
Pseudomonas aeruginosa	106	18 (33)
Enterobacter spp.	47	12 (22)

Carratala J, ECCMID 2013 Berlin

Resistance patterns in P. aeruginosa and Acinetobacter spp in cancer patients



Kara ö, ICAAC 2010, Boston, USA

S. maltophilia

- Incidence very low but increased in some institutions
- Prolonged neutropenia
- Exposure to broad-spectrum antibiotics : selective pressure by carbapenems
- Mechanical ventilation
- TMP-SMZ : increase of resistance

Safdar A; Clin Infect Dis 2007;45 (12):1602-1609.

Addition of an anti-gram-positive (anti-GP) antibiotic to standard empirical antibiotics vs standard empirical antibiotics for cancer and febrile neutropenia

Outcome at 30 days	Number of trials	Weighted event rates		RRR (95% CI)	NNT (CI)
		Empirical with anti-GP	Empirical without anti-GP		
Overall mortality	7 (852)	10%	12%	18% (-20 to 44)	Not significant
Treatment failure (treatment modification counted)	10 (1779)	33%	44%	24% (15 to 32)	10 (7 to 14)
Overall treatment failure (treatment modification ignored	6 (943)	19%	19%	0% (-27 to 21)	Not significant
GP superinfection	9 (1688)	2.1%	8.1%	76% (60 to 86)	17 (13 to 25)

The addition of an anti-GP antibiotic should not be part or the initial empirical treatment of febrile neutropenia in patients with cancer (AI)

Borok et al , ACP Journal Club 2006;144:3

Addition of vancomycin to the initial regimen (IV)

CNS, Enterococci, Corynebacterium JK

- More indolent
- Few days delay not detrimental

Viridans streptococci, pneumococci and S. aureus :

- More fulminant

Risk for MRSA is determinant

- Patient previously colonized
- MRSA endemic in the unit
- Periporth cellulitis
- Furunculosis, folliculitis
- Breakthrough sepsis

Viridans group streptococci (VGS)

- Shock syndrome/ARDS : 7 - 39 %
- Mortality : 2 – 21 %
- Pen-R (MIC ≥ 2 μg/ml) : 4-14 % (Han SB et al, Infection 2013;41:917-924; Marron A et al, J Antimicrob Chemother 2001;47:87-91; Elting LS et al, Clin Infect Dis 1997;25:247-59; Bochud PY et al, Clin Infect Dis 1994;15:25-31)
- Remain susceptible to cefepime and Pip/Tz.
  A small proportion R to carbapenem
- S. mitis
  - Most constantly Pen-R : 50 – 86 %
  - More prevalent in children (Bruckner L; Semin Pediatr Infect Dis 2006;17:153-160)
  - Most commonly associated with VGSS/ARDS (Bruckner L; Semin Pediatr Infect Dis 2006;17:153-160)

Viridans group streptococci

- 569 cases (2000 – 2010)
- Factors associated with Pen-R (MIC ≥ 2 µg/ml)
  - ß-lactam use within 30 d
  - ß-lactam prophylaxis
  - In patient at onset of FN
- Patients lacking 3 criteria : 1% of Pen-R
  PPV : 34 %

Shelburne SA et al, Clin Infect Dis 2014;59:223-30

MRSA

- Considerable geographic variation
- Widespread presence in hospital and community setting
- Europe : 43 % of S. aureus isolates from blood are methicillin-resistant
- Neutropenic patients : 56 % of S. aureus blood isolates were MRSA

  14 centers – 8 countries – 2000's (range 18 – 100 %) (Mikulska M et al, J Infect 2014;68:321-331)
- Vancomycin MIC ≥ 2µg/ml (54 %)

  Higher failure rate

  Higher mortality (Mahajan SM et al 2012;17:1329-1336).

VRE in allo-HSCT

- MSKCC (2008-2009)
- 247 pts allo-HSCT
  - 43 pts with bacteremia < 30 days post transplant
  - 23 (53.5 %) due to VRE within 10 days post transplant
  - 13 (57 %) colonized on pretransplant screening
- Risk factors
  - VRE colonisation OR 3.88 (95% CI : 1.5-10.4; P=0.005)
  - T cell depletion OR 10.89 (95% CI : 1.30-91.35; P=0.028)
- Attributable mortality : 9 %

Kamboj M et al, Biol Blood Marrow Transplant 2010;16:1576-1581

Implications for outcome

Characteristics	MDRGNB, N=51 n (%)	Non-MDRGNB, N=312 n (%)	P
Inadequate initial empirical antibiotic therapy	35 (69)	29 (9)	<0.001
Time to adequate antibiotic therapy >48h	21 (41)	13 (4)	<0.001
ICU admission	7 (14)	14 (4)	0.023
Invasive mechanical ventilation	7 (14)	10 (3)	0.005
Early case fatality rate (7 days)	9 (18)	33 (11)	0.15
Overall case-mortality rate (30 days)	20 (39)	62 (20)	0.003

Gudiol C, J Antimicrob Chemother 2011

Risk factors for antibiotic resistant bacteremia in neutropenic patients

1. Colonization
   - Stool :
     - ESBL (RR 4.5, 95% CI 2.89-7.04)
     - VRE (RR 10.2, 95 % CI 7.87-13.32)
   - Nares, skin :
     - MRSA
2. Exposure to broad spectrum antibiotics
   - ESBL :
     - Prior fluoroquinolones
     - Prior use of third generation cephalosporins
   - P. aeruginosa, S. maltophilia
     - Prior use of carbapenems
3. Severe illness :
   - AML
   - Comorbidities
4. Urinary catheter

Ha YE et al, J Antimicrob Agents 2013;42:403-409; Kang CI et al, Ann Hematol 2012; 91:115-121; Gudiol C et al, J Antimicrob Chemother 2011;66:657-663; Liss BJ et al; Infection 2012:40:613-619; Ortega M et al, J Antimicrob Chemother 2009:63:568-574

Three-drug therapy for bloodstream infections from carbapenemase-producing Klebsiella pneumoniae

- Klebsiella bacteraemia 125 cases-retrospective analysis
- 60% of the empirical regimens to be inadequate
- Forty-six patients (37%) received monotherapy; 79 (63%) received two or more antibiotics
- 30 days mortality rate was significantly higher among monotherapy recipients than among combination therapy recipients (54% vs. 34%)
- **Mortality was lowest (13%) for patients who received combination therapy with colistin, tigecycline, and meropenem (P=0.01)**

Tumbarello M et al, CID 2012;5:943

Efficacy of antimicrobial regimens for carbapenemase-producing K.pneumoniae infections

Antibiotic regimen	N° of patients	Outcome success (%)	Failure (%)
Antibiotic regimen			
Colistin	64 (24.2)	35 (54.7)	29 (45.3)
Tigecycline	8 (4.7)	5 (62.5)	3 (37.5)
Aminogyloside	16 (6.8)	12 (75.0)	4 (25.0)
Carbapenem	23 (9.8)	18 (78.3)	5 (21.7)
Total	111 (47.5)	70(63.1)	41 (36.9)
Combination therapy			
Two or more active drugs (carbapenem not included)	52 (22.2)	38 (73.1)	14 (26.9)
Two or more active drugs (carbapenem included)	30 (12.8)	28 (93.3)	2 (6.7)
Total	82 (35.0)	66 (80.5)	16 (19.5)
'inappropriate' therapy	41 (17.5)	23 (56.1)	18 (43.9)
Total	234 (100)	159 (67.9)	75 (32.1)

Akova M et al; Clin Microbiol Infect 2012; 18,439

Anti-anaerobic coverage mandatory (IV)

- Severe mucositis
- Typhlitis
- Perianal abscess
- Allogeneic BMT

Lark LB, Clin Inf Dis 2001;33:338-343

Zahar JR, Clin Microb Infect 2005;11:724-729

Fanourgiakis P, Suppot Care Cancer 2003;11:332-335

Monotherapy versus combination therapy

Two metaanalysis :

- Furno, Lancet ID 2002; vol 2 issue 4: 231-242
- Paul, BMJ 2003; vol 326

$\rightarrow$ no advantage (AI)

MASCC survey (1997-2003)
Mortality

	Sepsis on admission	Breakthrough sepsis	No sepsis
Nb of pts	27	75	919
Death	5 (18.5 %)	31 (41.3 %)	20 (2.2 %)

Combination therapy β-lactam + aminoglycoside

- **Double coverage**
- **Therapeutic synergy**
- **Prevention of emergence of resistance**
- **Risk of nephrotoxicity**

Combination therapy ß-lactam + aminoglycoside for 3 days (IV)

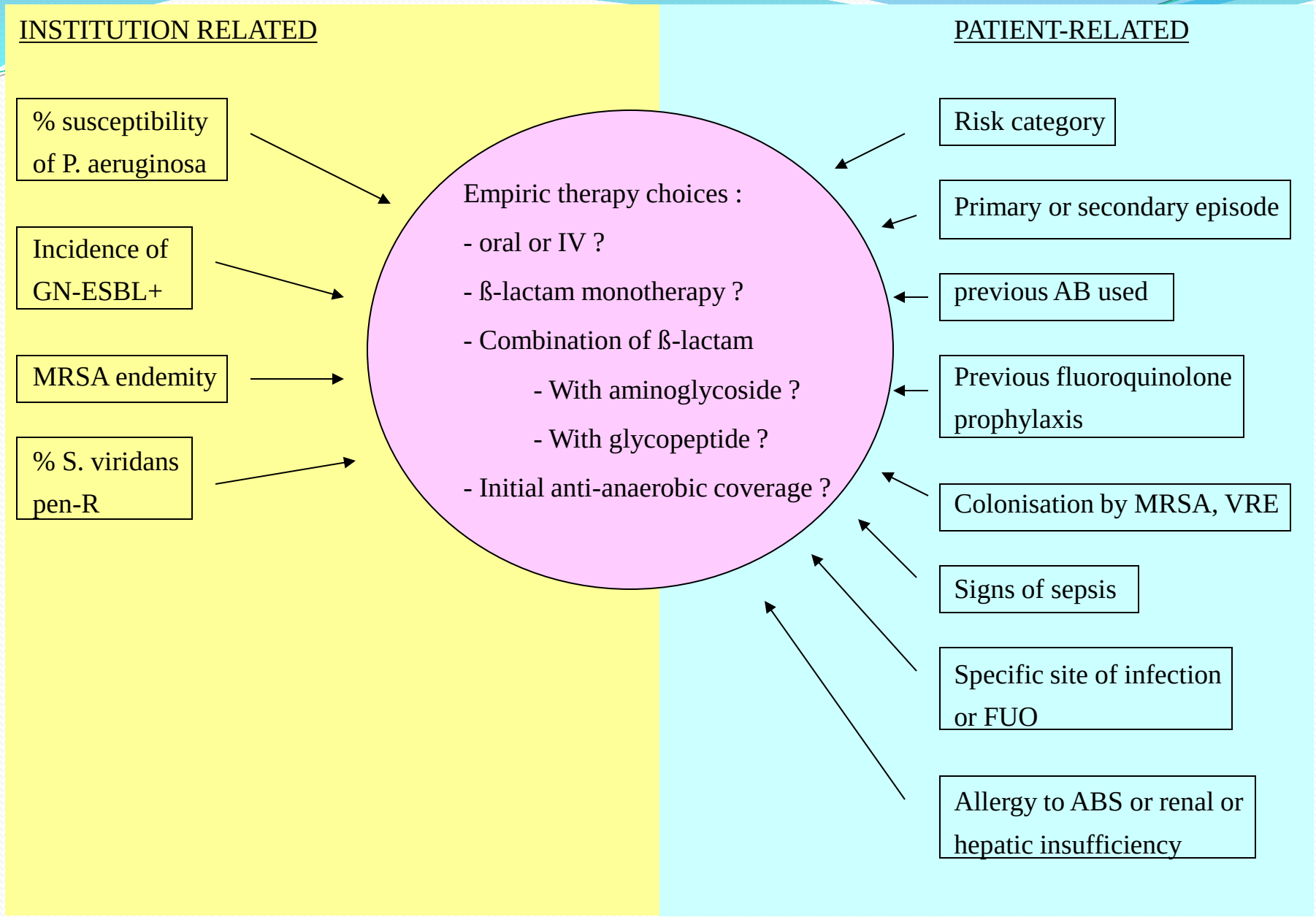
- Patient with sepsis or septic shock

  AND

- Patient at high risk of P. aeruginosa or GNB bacteremia

Modification of initial therapy in pts with persisting fever

- Patient hemodynamically stable :
  - Wait until day 5 (Cometta, Clin Infect Dis 2003;37:382-389)
  - After day 5 :
    - Shift to carbapenem (Kliasova, Abstract, Febrile Neutropenia 1997)
    - Perform chest and sinus CT scan
    - Galactomannan test
    - Add empiric antifungal ?
    - Work-up for viral (CMV, EBV, HHV6, …) and parasitic infection
- Patient deteriorating :
    - Hypotension
    - Tachypnea, tachycardia
    - Tissue hypoperfusion
  - Shift to carbapenem
  - Add glycopeptide
  - Add antifungal


INSTITUTION RELATED
% susceptibility of P. aeruginosa
Incidence of GN-ESBL+
MRSA endemity
% S. viridans pen-R
Empiric therapy choices :
- oral or IV ?
- ß-lactam monotherapy ?
- Combination of ß-lactam
- With aminoglycoside ?
- With glycopeptide ?
- Initial anti-anaerobic coverage ?
PATIENT-RELATED
Risk category
Primary or secondary episode
previous AB used
Previous fluoroquinolone prophylaxis
Colonisation by MRSA, VRE
Signs of sepsis
Specific site of infection or FUO
Allergy to ABS or renal or hepatic insufficiency

Is there a difference between 1st line molecules

Ceftazidime

Cefepime

Piperacillin/tazobactam

Shift towards Gram-positive

- Cefepime and pip/tazo more active on Streptococcus viridans and Staphylococcus aureus

  (Elting, Clin Inf Dis 1997;25:247-259)

- Less need for glycopeptide

  (Owens, Clin Inf Dis 2000;31:291)

- Emergence of ESBLs

  (Paterson, Clin Inf Dis 2004;38:S341-S345)
  (Johnson, J Inf Dis 1990;162:981-983)

Clinical evidence of monotherapy for primary episodes of febrile neutropenia in high-risk patients

- Meropenem
- Imipenem

(AI)
Relevance (epidemiology) : good
Relevance (population) : good

- Piperacillin/tazobactam : (AI)

Relevance (epidemiology) : moderate
Relevance (population) : good

- Cefepime : (AI)

Relevance (epidemiology) : moderate
Relevance (population) : good

Clinical evidence of monotherapy for primary episodes of febrile neutropenia in high-risk patients

- Ceftazidime : (AI)

  Relevance (epidemiology) : poor
  Relevance (population) : good

- Aztreonam : (AI)

  (+glycopeptide)

  Relevance (epidemiology) : poor
  Relevance (population) : poor
  Reserved to patients allergic to ß-lactams

New antimicrobials in development against GNB

-Inhibition of KPC

-Peptide mimetic

-Inhibitor of LPX-C

-Potent activity against P. aeruginosa

-No preexisting resistance

-No activity against

		Trial status
		Phase 3
		Phase 3
		Phase 3
		Phase 3
	Peptide	Phase 2
ACHN-975	LPX-C inhibitor	Phase 1
Monoclonal antibodies	Anti-Pseudomonas	Phase 1

In Conclusion

- Continuously and rapidly changing epidemiology
- Increase of GNB resistance is a major challenge for empiric therapy
- Better define risk factors of MDR
- Control measures
  - Hand hygiene
  - Limit underdosing and use of carbapenems
  - Antibiotic stewardship
  - Surveillance cultures

New Approach
Risk adapted strategy

- Accurate selection of patients at low-risk
- Oral antibiotics
- Out patient management

Score derived from the logistic equation of the MASCC predictive model *(1386 PATIENTS WITH FEBRILE NEUTROPENIA)*

Characteristic	Points
Burden of illness	
▪ No or mild symptoms	5
▪ Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection in hematological ca	4
Outpatient status	3
No dehydration	3
Age < 60 years	2

Threshold: score ≥ 21(maximum 26) predicting less than 5% of severe complications

J. Klastersky et al. (2001)

Flow-chart of study design

(unicentric study – Institut Jules Bordet)

Mascc risk-index score assessment

< 21 or ≥ 21
and not eligible for oral trt

Hospitalisation and IV treatment (piperacillin-tazobactam)

↓

Follow-up only

≥ 21
and eligible for oral trt

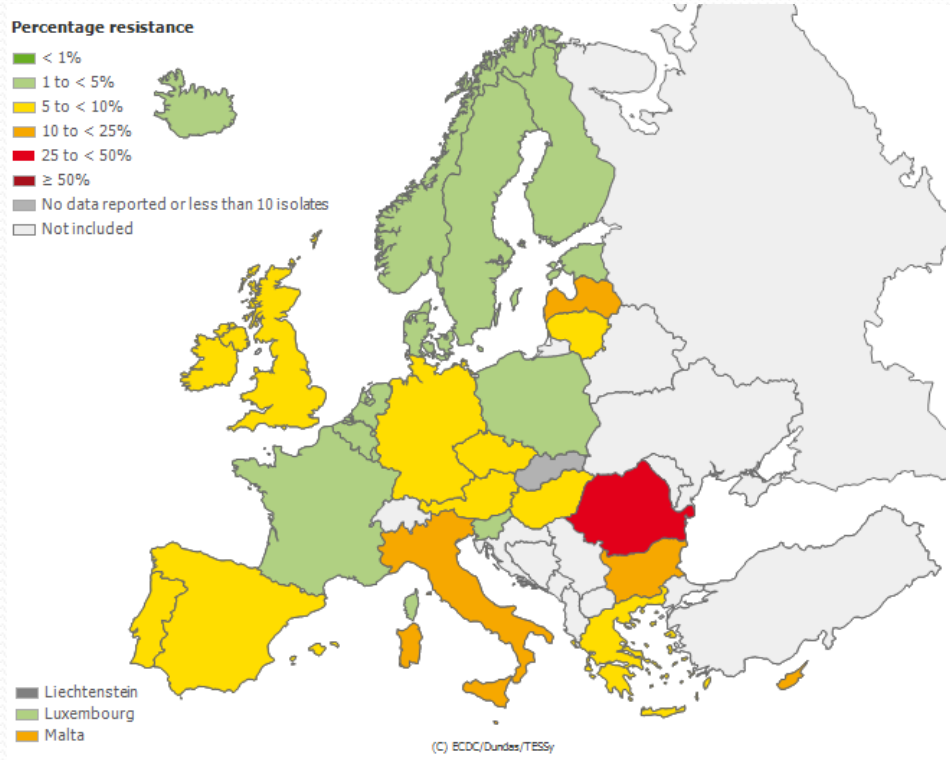
Oral treatment and treatment for 24 hours

↓

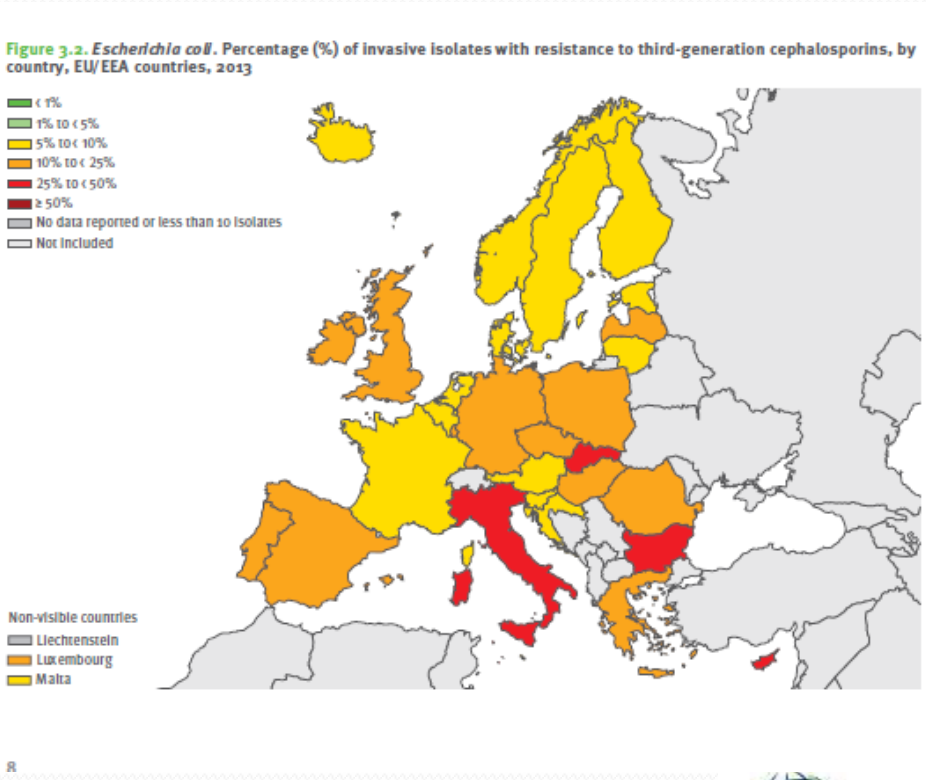
Early discharge if patient is stable and willing to go back home with daily phone contact

Proportion of 3rd gen. cephalosporins Resistant (R) Escherichia coli Isolates in Participating Countries

2007

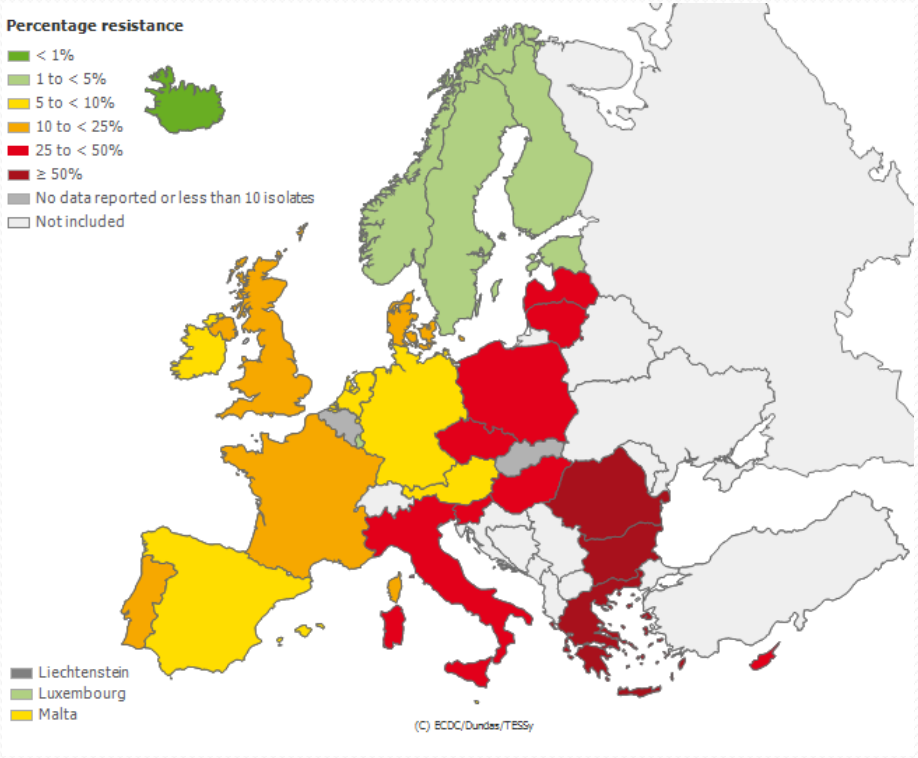


2013

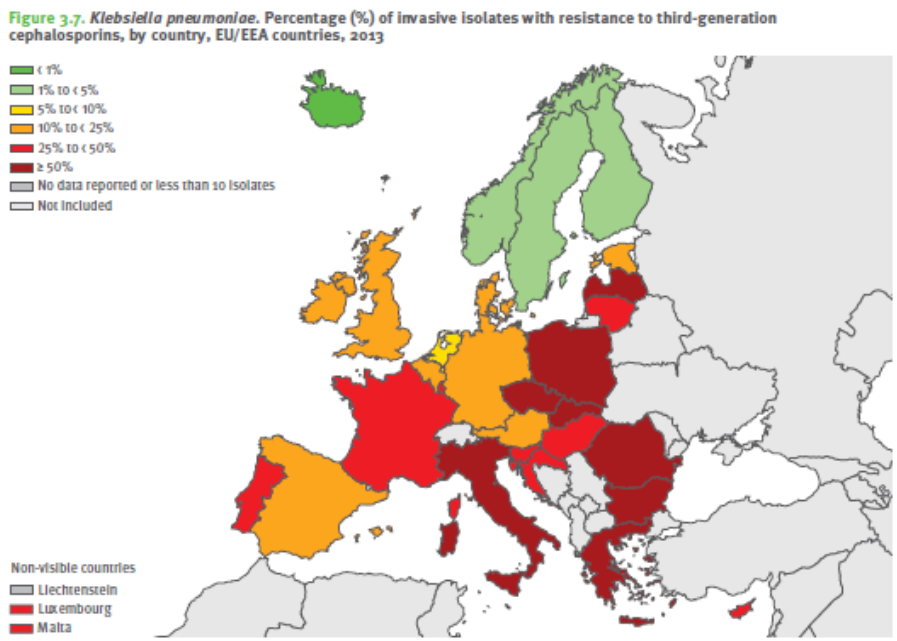


Proportion of 3rd gen. cephalosporins Resistant (R) Klebsiella pneumoniae Isolates in Participating Countries

2007



2013



Sites of infection among infectious febrile episodes in neutropenics (n=80)

Site of infection	Episodes	%
ORL	17	21.3%
Respiratory	12	15.0%
Gastro-intestinal	6	7.5%
Urinary tract	6	7.5%
Neurological	2	2.5%
Soft tissues	5	6.3%
Septic shock	5	6.3%
Primary bactereamia	15	18.8%
Secondary bactereamia	11	13.8%
other	1	12.5%

From Toussaint et al, Supp Care in Cancer 2006