Caso clinico, MP

- Maschio, 27 anni, LMA (maggio 2008)
- Proveniente dall'altro centro
- 1 ciclo di consolidamento agosto 2008
- Anamnesi infettivologica:
  - sepsi *A. baumanii e E. coli* nel 2008
  - *Influenza A 29/12/08*
  - *CVC gennaio 2009 in DH*
- Ricovero 6/01/09
- CBT 14/01/09

Caso clinico, MP

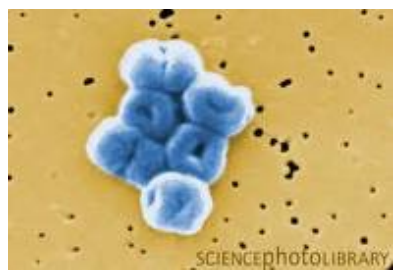
- CBT 14/01/09
- Screening di colonizzazione all'ingresso e quindi ogni settimana
- Profilassi con FQ
- Colonizzazione ingresso e +1: no VRE, flora normale
- +6 febbre > piperacillina/tazobactam (13,5g in 12 ore)
- +7 infezione severa > meropenem (3g infusione prolungata + amikacina 1g)
- +8 tampone faringeo del +5: *Acinetobacter* spp. possibile *Acinetobacter baumanii*

Caso clinico, MP

T. faringeo: *Acinetobacter* spp, possibile *A. baumanii*		
Amikacina	4	S
Ciprofloxacina	>4	R
Aztreonam	>64	R
Cefepime	>64	R
Ceftazidime	>64	R
Imipenem	>16	R
Meropenem	>16	R
Piperacillina	>128	R
Pip/taz	>128	R
Colistina	<0.5	S

Caso clinico, MP

- Meropenem + amikacina > colistina (3M UI x 3) + amikacina
- Permane febbre
- Decesso + 10
- Risultati colturali



Caso clinico, MP

Emocolture: +6, + 7, +8, +9, +10 *Acinetobacter baumanii* complex		
Amikacina	>64	R
Ciprofloxacina	>4	R
Aztreonam	>64	R
Cefepime	>64	R
Ceftazidime	>64	R
Imipenem	>16	R
Meropenem	>16	R
Piperacillina	>128	R
Pip/taz	>128	R
Tigeciclina		
Colistina	<0.5	S

Caso clinico, GI

- Donna, 25 anni
- Nefrectomia sn per rene policistico nel 2008
- LMA (luglio 2009)
- Allotrapianto sorella HLA-identica a Nov 2009
- Ricaduta di LMA
- 10/01/11-23/3/11 ricovero c/o Reparto di ematologia per ChT
  - 13/01/11 CVC
  - Tampone vaginale positivo per *K. pneumoniae* MDR
  - ChT (FLAG + Ida) 18-22/01/11

Caso clinico, GI

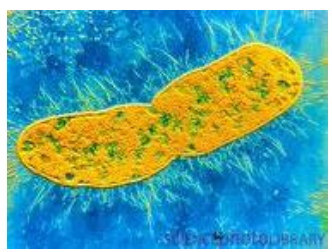
Tampone vaginale: *K. pneumoniae* KPC		
Amikacina	>64	R
Ciprofloxacina	>4	R
Amoxicillina/clavulanato	>32	R
Tobramicina	>16	R
Aztreonam	>64	R
Cefotaxime	>64	R
Ceftazidime	>64	R
Gentamicina	4	S
Imipenem	>16	R
Meropenem	>16	R
Piperacillina	>128	R
Pip/taz	>128	R
Colistina	<0.5	S

Caso clinico, GI

- ChT (FLAG + Ida) 18-22/01/11
- Sepsi in aplasia
  - Ipotensione
  - Emoftoe
  - Coagulopatia
  - Anasarca
  - 21-25/01 emocolture positive per MRSA
  - 28-31/01 emocolture positive per *K. Pneumoniae* MDR
  - 1/02/11 rimosso CVC
  - Terapia: daptomicina + colistina (3M UI x 3, aggiustamento x IRA) + gentamicina
  - Nefropatia con perdita di sali da tossicità tubulare, grave disioni, ipovolemia
  - 7-12/02 emocolture sempre positive per *K. Pneumoniae* MDR, prima emocoltura negativa il 14/02

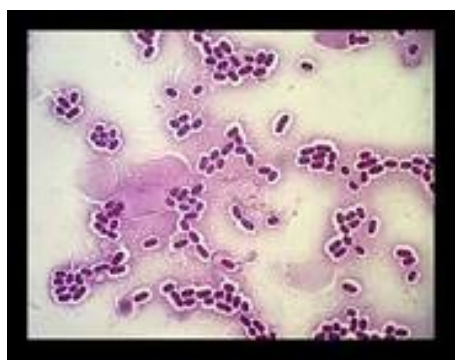
Caso clinico, GI

Tampone vaginale: *K. pneumoniae* KPC		
Amikacina	>64	R
Ciprofloxacina	>4	R
Amoxicillina/clavulanato	>32	R
Tobramicina	>16	R
Aztreonam	>64	R
Cefotaxime	>64	R
Ceftazidime	>64	R
Gentamicina	4	S
Imipenem	>16	R
Meropenem	>16	R
Piperacillina	>128	R
Pip/taz	>128	R
Colistina	<0.5	S



Caso clinico, GI

- Aprile 2011, valutazione pre-CBT (18/5/11)
- T. vaginale: K. Pneumoniae MDR + E. coli
- Non profilasi antibiotica con FQ
- 15/05/11 Febbre: meropenem + amikacina
- 16/05/11
  - Febbre, condizioni cliniche stabili
  - Meropenem + amikacina > meropenem + colistina
  - Dose di colistina (6 M UI dose di carico, quindi 4.5M UI x 2)
  - Monitorare funzionalità renale e ionogramma
  - Applicare le misure di isolamento
  - Emocolture del 15/05: bastoncini Gram-



Caso clinico, GI

- 17/05/11 isolamento *K. Pneumoniae*
  - Sera: peggioramento delle condizioni cliniche
- 18/05/11 Exitus

Caso clinico, GI

Tampone vaginale: *K. pneumoniae* KPC		
Amikacina	>64	R
Ciprofloxacina	>4	R
Amox/clav	>32	R
Tobramicina	>16	R
Aztreonam	>64	R
Cefotaxime	>64	R
Ceftazidime	>64	R
Gentamicina	4	S
Imipenem	>16	R
Meropenem	>16	R
Piperacillina	>128	R
Pip/taz	>128	R
Colistina	<0.5	S

Emocolture 15-17/05: *K. pneumoniae* KPC		
Amikacina	>64	R
Ciprofloxacina	>4	R
Amox/clav	>32	R
Tobramicina	>16	R
Aztreonam	>64	R
Cefotaxime	>64	R
Ceftazidime	>64	R
Gentamicina	>16	R
Imipenem	>16	R
Meropenem	>16	R
Piperacillina	>128	R
Pip/taz	>128	R
Colistina	>16	R

Management of Febrile neutropenia in 2011

- A little bit of history
- Classical antibiotic therapy
- The present situation
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INFECTION IN 55 ACUTE LEUKEMIA PATIENTS: 1953-57

Followed from diagnosis to death. Usually treated with 6 mercaptopurine or aminopterin; steroids for hemorrhage.

149 febrile episodes, defined as rectal temp. ≥ 38°C for 24 hrs.

47 not infection; 41 bacteremia, 20 pneumonia, 17 cellulitis.

Bacteremias: 21 *S. aureus*; 62% died. 4 *Pseudomonas*; all died.

Recovery was not felt to be related to absolute neutrophil count.

Recommendation: If profoundly ill or fever occurs late in therapy – start antibiotics before culture results are known.

If fever persists for 3-5 days without known cause, stop therapy.

Courtesy Gerald Bodey

Raab: Blood 16: 1609, 1960

PSEUDOMONAS BACTEREMIA: 1965 TO 1968

67 patients with bacteremia; 37% had severe neutropenia.

Survival with polymyxin 24%, inappropriate therapy 14%.

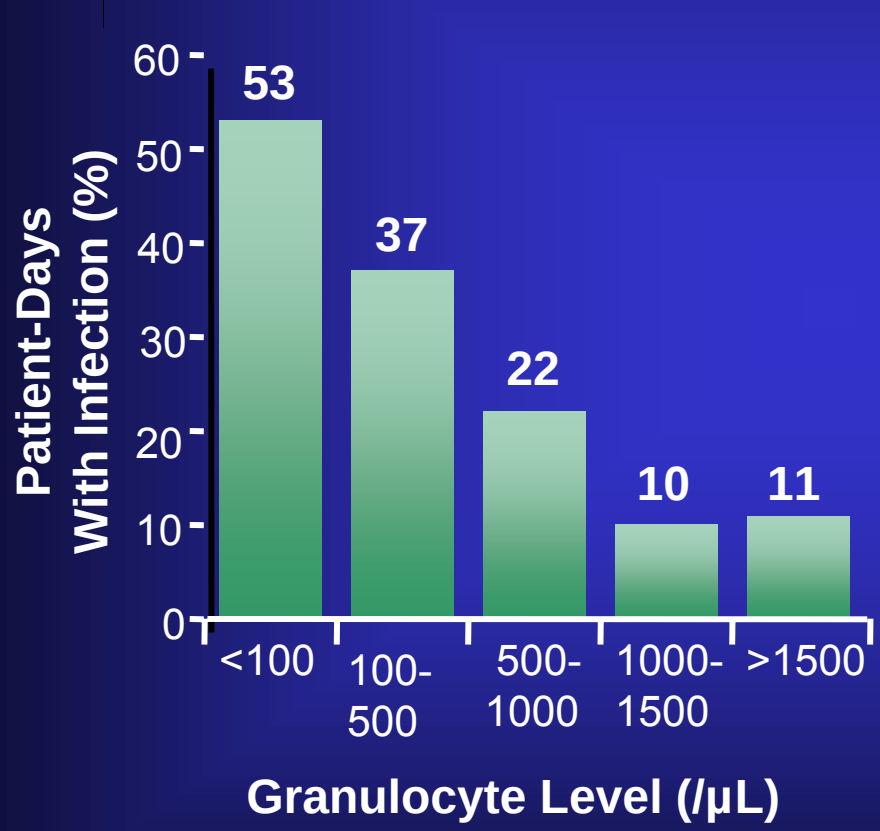
Among patients treated with polymyxins, 58% of neutropenic patients whose neutrophils increased survived compared to 8% of patients who became or remained neutropenic.

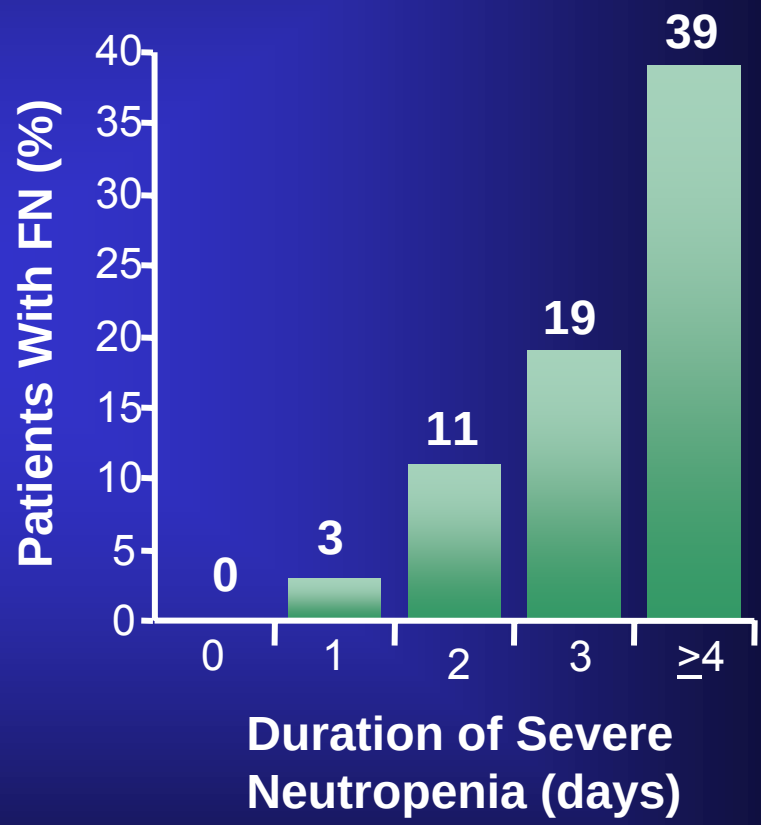
Major organ infection found in 86% of 42 autopsied cases.

Whitecar: Am J Med Sc 260: 216, 1970

Courtesy Gerald Bodey

Duration and severity of neutropenia





Courtesy Gerald Bodey

Bodey GP, et al. Ann Intern Med. 1966;64:328-340

FATALITY RATE OF SEVERE INFECTION RELATED TO PMN CHANGE

PMN Level / mm^3		
Initial	Change	Fatal Episodes (%)
< 100	None	80
<1000	None or Fall	59
<1000	Rise to > 1000	27
>1000	Any rise	27

Courtesy Gerald Bodey

Bodey: Ann Intern Med 64:328, 1966

? FIRST ANTIBIOTIC THERAPEUTIC TRIAL FOR CANCER PATIENTS (1958-59)

44 cancer patients (26 acute leukemia, 11 hematology cancers) with FUO (several febrile patterns included).

Randomized to placebo or tetracycline.

Documented infections on study: tetracycline 5 (one death), placebo 3.

Fevers not favorably affected by tetracycline, more severe infections developed, microbial flora unfavorably altered.

Trial of antibiotics unwarranted for FUO in cancer patients.

Courtesy Gerald Bodey

Boggs: Ann Int Med 53:754: 1960

FIRST PROSPECTIVE RANDOMIZED STUDY OF ANTIBIOTIC THERAPY FOR FEVER AND INFECTION IN NEUTROPENIC PATIENTS

Antibiotic therapy initiated promptly at temperature of 101°F

First study of double β-lactam combination: carbenicillin + cephalothin vs carbenicillin + kanamycin in 179 episodes of fever

Overall response rates: 48% C-K vs 49% C-C; for clinically documented infections 28% vs 30%

Response if organism susceptible in vitro: kanamycin 47%, cephalothin 69%

Response related to PMNs on day 4: <100/mm^3: 29%, 100-500/mm^3: 54%, > 500/mm^3: 80%

Courtesy Gerald Bodey

EORTC RANDOMIZED TRIAL OF ANTIBIOTIC REGIMENS FOR FEVER AND INFECTION IN NEUTROPENIC PATIENTS

	Carb-Ceph		Carb-Gent		Ceph-Gent	
	Cases	% Resp.	Cases	% Resp.	Cases	% Resp.
Doc. Inf.	135	72	156	71	162	68
GNB Inf.	50	50	83	63	64	52
Pseudo.	8	50	16	63	13	38
Kleb.	15	60	22	55	17	35
E. coli	18	44	30	73	27	67

Courtesy Gerald Bodey

EORTC: J Infect Dis 137:14, 1978

Ceftazidime Plus Amikacin Versus Ceftazidime Plus Vancomycin as Empiric Therapy in Febrile Neutropenic Children with Cancer

C. Viscoli, C. Moroni, L. Boni, P. Bruzzi, A. Comelli, G. Dini, A. Fabbri, V. Secondo, and A. Terragna

From the Departments of Infectious Disease and Pediatric Oncology, University of Genova, G. Gaslini Children's Hospital; and the Clinical Epidemiology Unit, National Institute for Cancer Research, Genova, Italy

Reviews of Infectious Disease 1991

Table 4. Response to therapy, by pathogen, in cases of bacteremia in febrile neutropenic children with cancer.

Pathogen	No. responding/no. treated (% responding) in indicated group		
	Ceftazidime/ amikacin	Ceftazidime/ vancomycin	Total
Gram-positive bacteria			
Staphylococcus aureus	1/4	4/10	5/14
Coagulase-negative staphylococci	4/5	2/2	6/7
Streptococcus species	1/4	2/5	3/9
Listeria monocytogenes	0/2	. . .	0/2
Clostridium species	. . .	0/1	0/1
Total	6/15 (40)	8/18 (44)	14/33 (42)
Gram-negative bacteria			
Escherichia coli	3/5	4/4	7/9
Klebsiella species	1/1	. . .	1/1
Pseudomonas aeruginosa	2/2	. . .	2/2
Haemophilus influenzae	1/1	. . .	1/1
Salmonella species	0/1	. . .	0/1
Pasteurella species	1/1	1/1	2/2
Acinetobacter species	1/1	. . .	1/1
Moraxella species	. . .	1/1	1/1
Total	9/12 (75)	6/6 (100)	15/18 (83)
Polymicrobial	0/2*	2/2†	2/4
Grand total	15/29 (52)	16/26 (62)	31/55 (56)

* *S. aureus* plus *Pseudomonas fluorescens* and *Streptococcus morbillorum* plus *E. coli*.

† *S. aureus* plus *Streptococcus milleri* and *Pseudomonas* species plus *Streptococcus faecalis*.

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Incidenza

Table 2. Incidence densities and rates of bloodstream infection (BSI) and pneumonia among 1899 patients who underwent allogeneic or autologous bone marrow or peripheral blood stem cell transplantation.

	Incidence density, episodes per 1000 neutropenic days		Rate, episodes per 100 patients	
Transplant source	BSI	Pneumonia	BSI	Pneumonia
All	14.0	5.9	20.8	8.8
Allogeneic	12.4	6.1	22.4	11.0
Autologous	18.9	5.6	18.2	5.4

- Dettenkofer et al. Clinical Infectious Diseases 2005; 40:926–31

Classic empirical therapy

- Ceftazidime or Pipera-tazobactam monotherapy
- Combination with aminoglycosides not superior to monotherapy
- Carbapenems second choice
- Empiric glycopeptides not indicated
- Fluoroquinolones for prophylaxis in high risk and oral monotherapy in low risk

STILL VALID?

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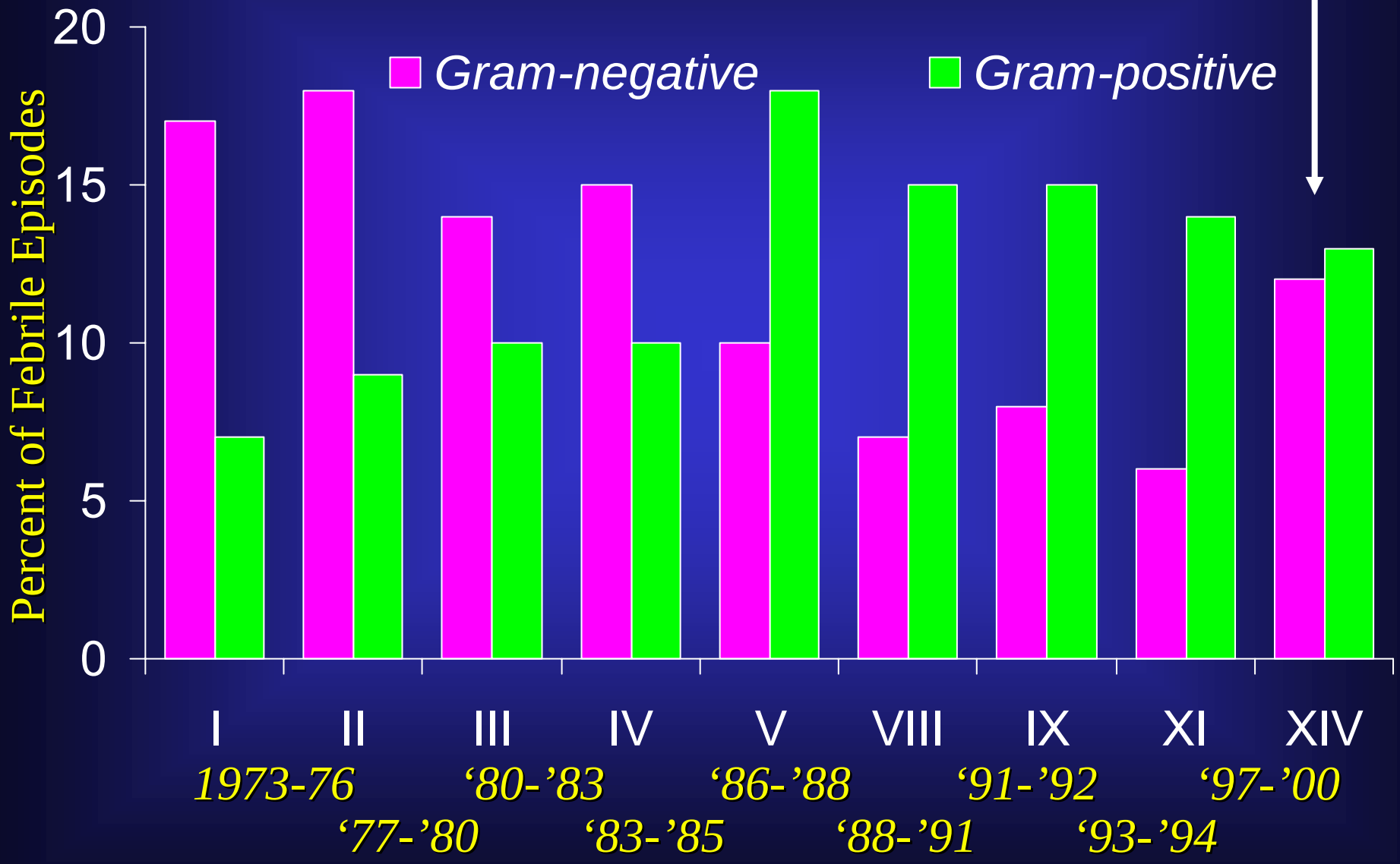
Single-Organisms Bacteremias
EORTC-IATG Trials



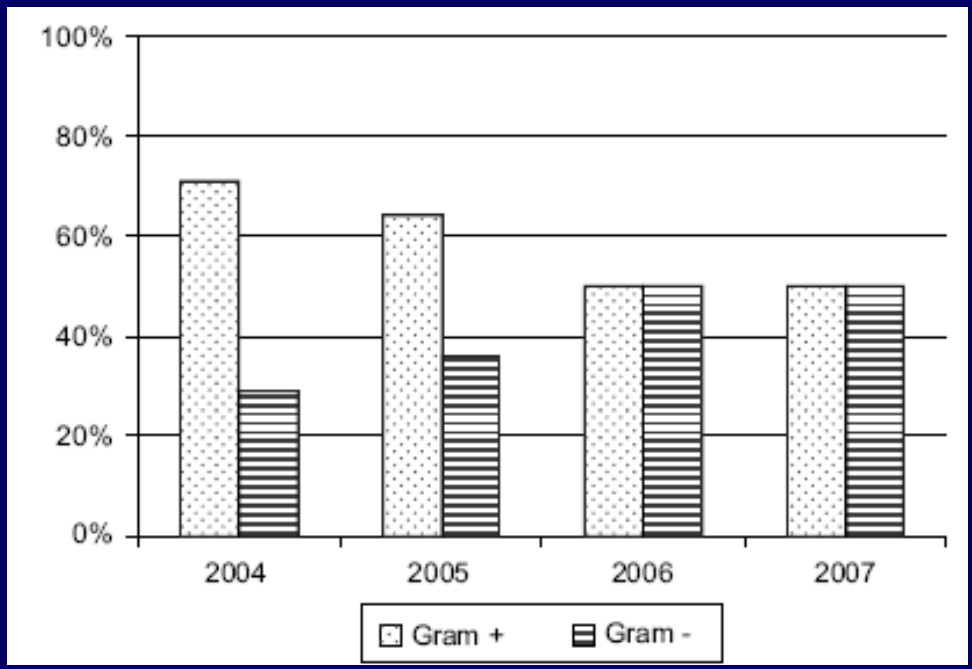
Neutropenia febbrile & Gram-

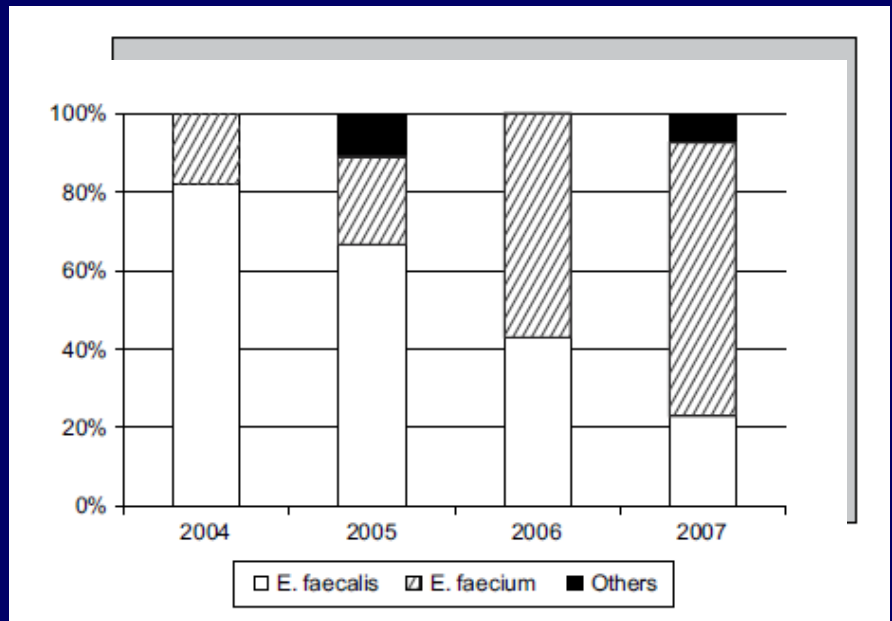
Blood Stream Infections in Allogeneic Hematopoietic Stem Cell Transplant Recipients: Reemergence of Gram-Negative Rods and Increasing Antibiotic Resistance

Malgorzata Mikulska,[1] Valerio Del Bono,[1] Anna Maria Raiola,[2] Barbara Bruno,[2] Francesca Gualandi,[2] Domenico Occhini,[2] Carmen di Grazia,[2] Francesco Frassoni,[2] Andrea Bacigalupo,[2] Claudio Viscoli[1]

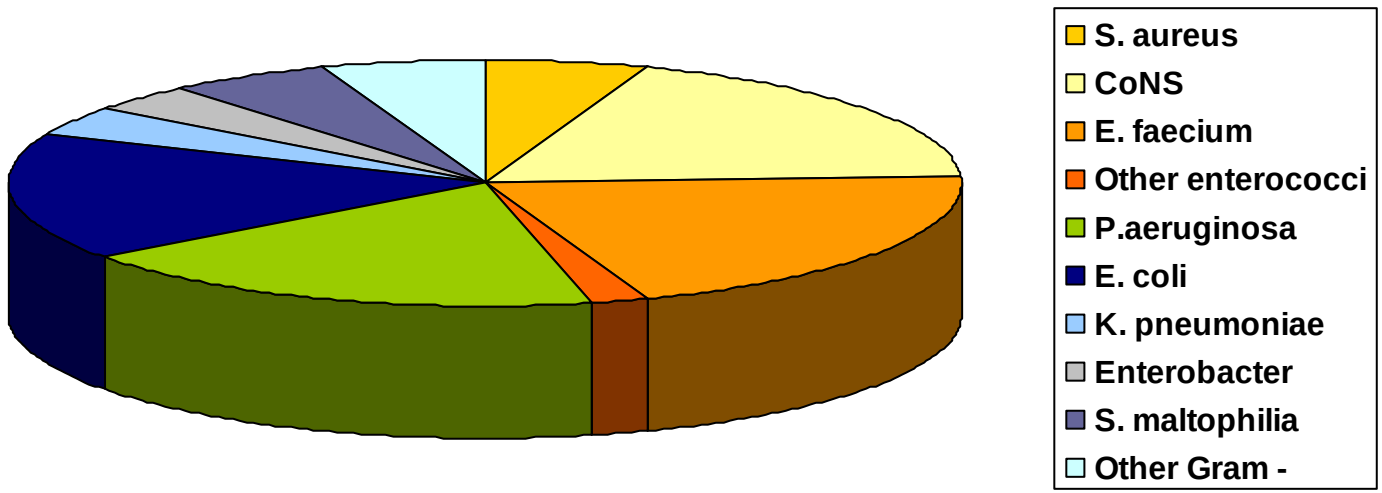
Biol Blood Marrow Transplant 15: 47-53 (2009)

168 episodes of BSI



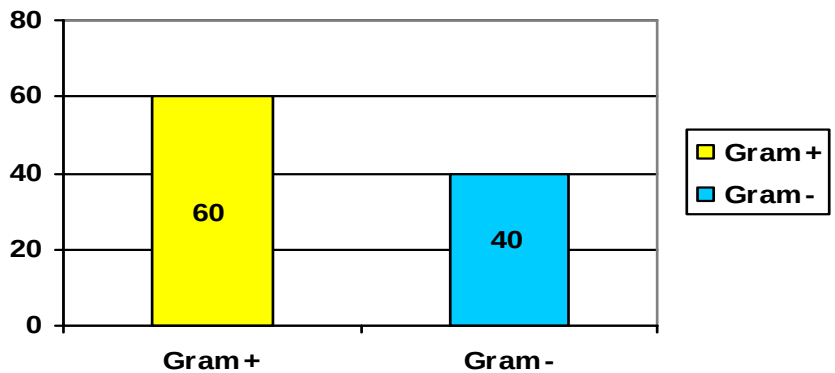


BSI 2010, isolates



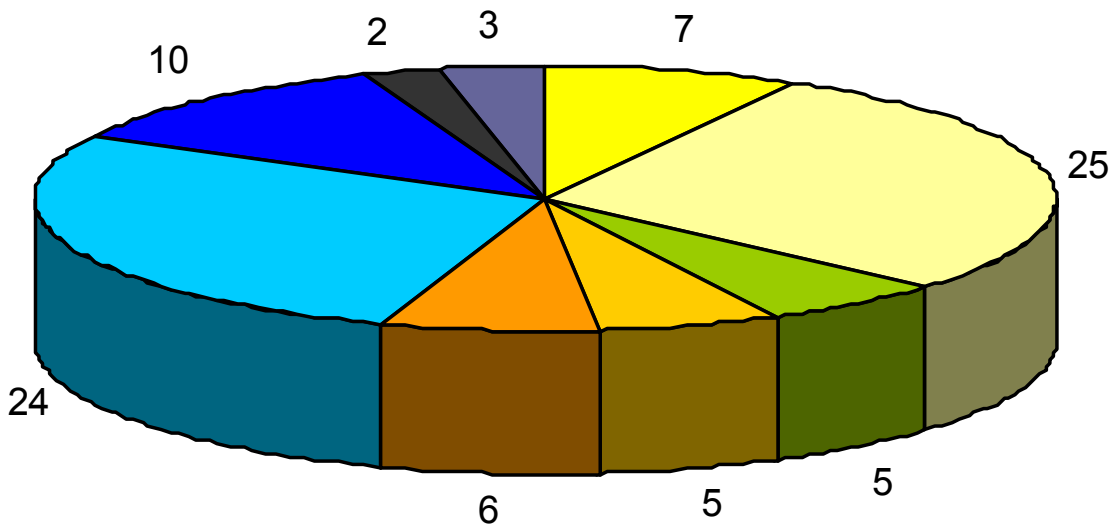
Published Data on Epidemiology of BSI Aetiology

- Data from 13 countries: Brazil, Denmark, Germany, India, Israel, Italy 8, Japan 3, Lebanon, New Zealand, Spain 4, Taiwan 2, Turkey 2, US 5, multicenter.
- Haematological, non HSCT: 21, Autologous HSCT: 17, Allogeneic HSCT: 18, Oncology: 9
- Observation period
  - Median 2001, range: 1987-2009
  - 5-year-period (range: 1-15)
- Number of BSI reported: median 197 (18-1307)
- G+ vs G- ratio: 60% (range: 26%-85%) vs 40% (range: 15%-74%)



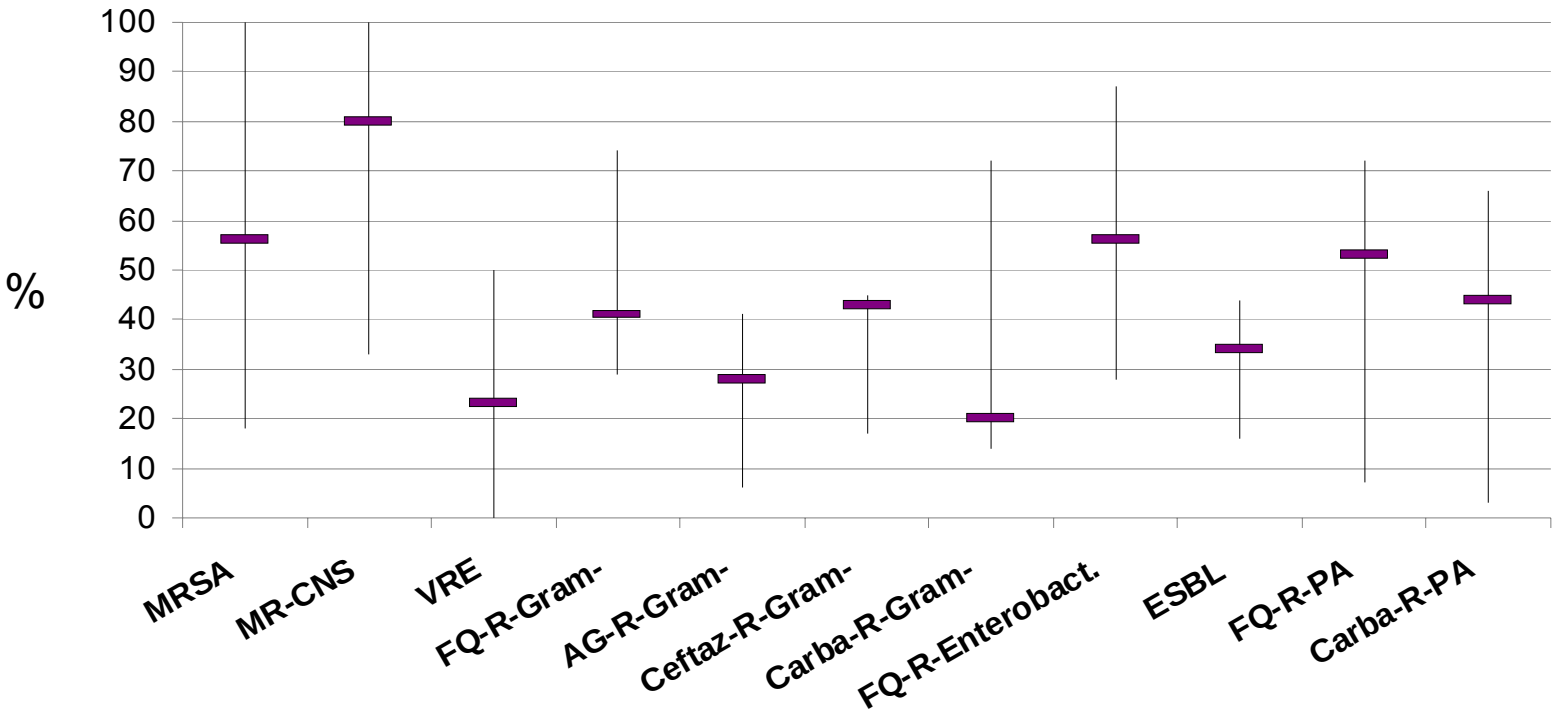
Detailed Aetiology of Bloodstream Infections

Median % of All BSI (Range)



- S. aureus, 7% (0-24%)
- CNS, 25% (2-60%)
- Viridans, 5% (0-16%)
- Enterococci, 5% (0-38%)
- Other Gram+, 6% (0-21%)
- Enterobacteriaceae, 24% (6-54%)
- P. aeruginosa, 10% (0-30%)
- Acinetobacter, 1% (0-12%)
- Other Gram-, 3% (0-11%)

Reported Rate of Resistance (Median) Among Given Species Causing BSI



Data from: 13 centres from 8 countries (Brazil, Germany, India, Italy 4, Japan 2, Taiwan 2, Turkey, US).
Data for given resistance reported from median 6 centres, range: 4-9.

Epidemiology in adults
Conclusions

- Gram negative bacteria almost = Gram positives in BSIs
- The most frequent resistance patterns: CNS resistant to methicillin and Gram-negatives resistant to FQ
- ESBL presence is regarded as an existing problem in two thirds of European centres
- Aetiology of BSI and rates and type of resistance varies importantly among the centres
- In haematology patients CNS, enterococci, *E. coli* and *Pseudomonas* are more resistant than isolates from non-haematology patients

The present situation

- Bad Bugs, No Drugs: No ESKAPE[1]
  - *Enterococcus faecium* (E), *Staphylococcus aureus* (S), *Klebsiella pneumoniae* (K), *Acinetobacter baumannii* (A), *Pseudomonas aeruginosa* (P), and *Enterobacter* spp. (E)
- The late-stage clinical development pipeline remains unacceptably lean[2]
  - Some important molecules for problematic pathogens such as MRSA
  - Few novel molecules for other ESKAPE pathogens
  - No new drugs for infection due to MDR Gram-negative bacilli (e.g., *A baumannii* and *P. aeruginosa*)
  - None represent more than an incremental advance over currently available therapies

[1]Rice LB. *J Infect Dis*. 2008;197:1079-1081.
[2]Boucher HW, et al. *Clin Infect Dis*. 2009;48:1-12.

Management of Febrile neutropenia in 2011

- A little bit of history
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Available drugs

- IIIrd generation cephalosporins
- Piperacillin-tazobactam
- Carbapenems
- Glycopeptides
- Aminoglycosides
- Fluoroquinolones
- Colimicin
- Linezolid
- Tigecycline
- Daptomycin
- Doripenem
- Fosfomycin

Inappropriate initial therapy is an independent factor for mortality

- Most studies in hemato-oncological patients indicate that failure to cover resistant pathogens, including ESBL-producers, significantly impairs outcome.

Trecarichi JI 09, Ortega JAC 09, Trecharichi Haemat 11, Tumbarello AAC 06, Martinez AAC 10, Ariffin Int J Infect Dis 99 Elting CID 97

Neutropenia febbrile & Gram-negativi

Journal of Infection (2009) 58, 299–307

Incidence and clinical impact of extended-spectrum-β-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with hematological malignancies

Enrico M. Trecarichi [a], Mario Tumbarello [a,*], Teresa Spanu [b], Morena Caira [c], Luana Fianchi [c], Patrizia Chiusolo [c], Giovanni Fadda [b], Giuseppe Leone [c], Roberto Cauda [a], Livio Pagano [c]

Aim: identify risk factors for mortality in patients with haematological malignancies with E. coli bacteremia
Retrospective, 8-year study

- 62 E. coli BSI
- ESBL production - 41.9%, fluoroquinolone resistance 62.9%
- 36 different ESBL genes were identified in 26 ESBL+ isolates
- 9 strains carried multiple ESBLs
- 30-day mortality rate was 20.9% (13/62)
- Predictors of mortality were: inadequate initial antimicrobial therapy, ESBL+ and prolonged neutropenia

IER
Diagnostic Microbiology and Infectious Disease 64 (2009) 320–326
www.elsevier.com/lo

Factors associated with mortality in bacteremic patients with hematologic malignancies

Mario Tumbarello[a,*], Teresa Spanu[b], Morena Caira[c], Enrico M. Trecarichi[a], Luca Laurenti[c], Eva Montuori[a], Luana Fianchi[c], Fiammetta Leone[b], Giovanni Fadda[b], Roberto Cauda[a], Livio Pagano[c]

[a]*Institute of Infectious Diseases, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy*
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Received 9 June 2008; accepted 17 February 2009

Table 3
Multivariate analysis of factors associated with death at 30 days among patients with hematologic malignancies and bacteremia

Variable	P	OR (95% CI)
Neutropenia ≥10 days at bacteremia onset	<0.001	6.07 (2.66–13.82)
Presentation with acute renal failure	0.002	5.62 (1.88–16.77)
Nosocomial bacteremia	0.009	4.22 (1.43–12.41)
Age >55 years	0.007	3.40 (1.40–8.24)
Monomicrobial bacteremia due to AR Gram negative organisms	0.009	3.15 (1.32–7.50)

The Impact of Antimicrobial-Resistant Gram-Negative Infections

- Resistance to antimicrobial agents is increasing among many gram-negative pathogens[1]
- Infection with resistant pathogens is associated with negative health outcomes[3,4]
  - Mortality/morbidity
  - Length of ICU and hospital stay
  - Healthcare costs
- No new antibiotic available[2]
  - Highlights the need to optimize existing classes of antimicrobials

1. Gaynes R, et al. *Clin Infect Dis.* 2005;41:848-854. 2. Spellberg B, et al. *Clin Infect Dis*. 2004;38:1279-1286. 3. Lautenbach E, et al. *Infect Control Hosp Epidemiol*. 2006;27:893-900. 4. Cosgrove, S et al. *Clin Infect Dis.* 2006;42:S82-S89. .

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Parameters for choosing a regimen

1) Bacterial epidemiology and resistance pattern in each given center
2) Patient's colonization or previous infection by resistant pathogens: especially with
   - MRSA and MRSE
   - MRSA and MRSE with VAN MIC ≥2
   - PEN-R and VAN-R *Enterococci*
   - ESBL-producers
   - MDR microorganisms (*A. baumannii*, carbapenemase-producing *Enterobacteriaceae, Pseudomonas* spp).
3) Patient-related factors:
   1) Presence of risk factors for infection due to resistant pathogens
   2) Clinical presentation

Therapeutic management in the light of spiralling resistance patters

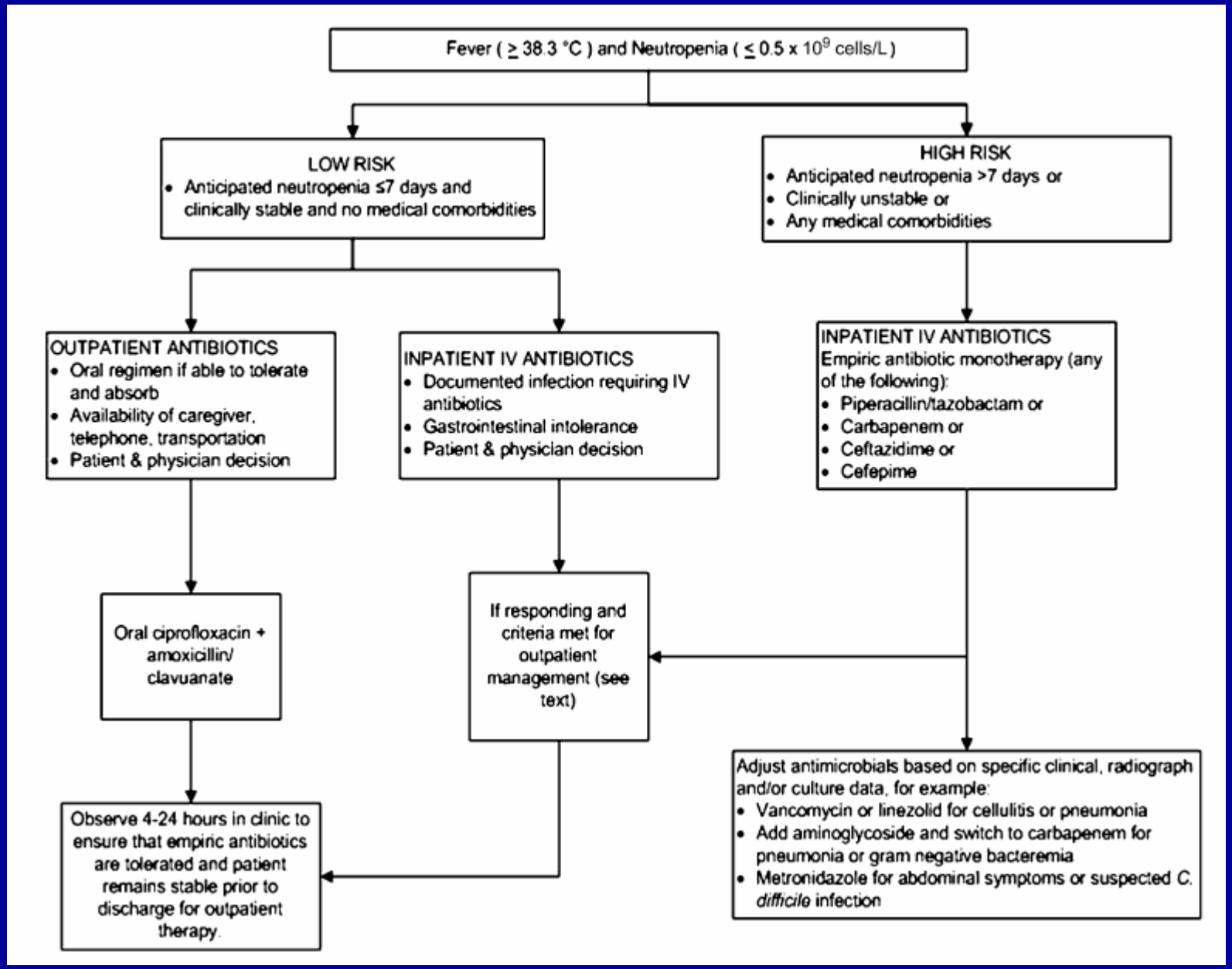
- **Severe sepsis/shock or pneumonia**
  - Meropenem + vancomycin because
    - half of our Gram neg are ESBL producers
    - MR resistance is very common
    - *Enterococcus faecium* frequent
  - Stop vanco if no Gram pos or Gram pos is PEN or MET S (in this latter case stop meropenem as well)
  - In general stop meropenem ASAP (carbapenemase induction)
  - Shift/add colymicin if MDR isolated
  - Consider amikacin, linezolid, daptomicin, ertapenem
- **Fever, no pneumonia, stable conditions**
  - Pip-tazo mono because
    - Likely there is time to change
    - *Pseudomonas* unlikely,
    - pip-tazo is active for many Gram pos.
  - Add vanco if MR Gram pos isolated
  - Consider amikacin, linezolid, daptomicin, ertapenem
  - Shift/add colymicin if MDR

THIS IS NOT A GUIDELINE; IT'S JUST WHAT WE DO

Viscoli C, Mikulska M
Present protocol at HSCT Unit, Genoa, Italy

Optimizing Antimicrobial Exposure

- Increase dose
  - Aminoglycosides, fluoroquinolones, beta-lactams
- Increase frequency
  - Beta-lactams, vancomycin
- Increase infusion duration
  - Beta-lactams via
    - Prolonged IV infusion (0.5 hr → 3hr)
    - Continuous IV infusion (loading dose followed by total daily dose over 24 hr period)


Fever (≥ 38.3 °C) and Neutropenia (≤ 0.5 x 10^9 cells/L)
LOW RISK
• Anticipated neutropenia ≤7 days and clinically stable and no medical comorbidities
HIGH RISK
• Anticipated neutropenia >7 days or
• Clinically unstable or
• Any medical comorbidities
OUTPATIENT ANTIBIOTICS
• Oral regimen if able to tolerate and absorb
• Availability of caregiver, telephone, transportation
• Patient & physician decision
INPATIENT IV ANTIBIOTICS
• Documented infection requiring IV antibiotics
• Gastrointestinal intolerance
• Patient & physician decision
INPATIENT IV ANTIBIOTICS
Empiric antibiotic monotherapy (any of the following):
• Piperacillin/tazobactam or
• Carbapenem or
• Ceftazidime or
• Cefepime
Oral ciprofloxacin + amoxicillin/ clavuanate
If responding and criteria met for outpatient management (see text)
Adjust antimicrobials based on specific clinical, radiograph and/or culture data, for example:
• Vancomycin or linezolid for cellulitis or pneumonia
• Add aminoglycoside and switch to carbapenem for pneumonia or gram negative bacteremia
• Metronidazole for abdominal symptoms or suspected *C. difficile* infection
Observe 4-24 hours in clinic to ensure that empiric antibiotics are tolerated and patient remains stable prior to discharge for outpatient therapy.

Clinical Practice Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G et al., Clin Infect Dis 2011; 52 (4):e56-e93

In patients with **unexplained fever** it is recommended that the initial regimen be continued until there are clear signs of marrow recovery; the traditional endpoint is an **increasing ANC that exceeds 500 cells/mm^3 B-II**

In clinically documented infection (**CDI**) or microbiologically documented infection (**MDI**): duration dictated by particular organism or site; appropriate antibiotics should continue for **at least the duration of neutropenia** (until ANC ≥ 500 cells/mm3) or longer if necessary **B-III**

Alternatively, if an appropriate treatment course has been completed and **all signs and symptoms of a CDI or MDI** have **resolved**, patients who remain neutropenic may **resume oral fluoroquinolone prophylaxis** until marrow recovery **C-III**

Duration of Empiric Antibiotic Therapy in Granulocytopenic Patients with Cancer

Pizzo PA et al., Am J Med, 1979; 67: 194-200

- Randomized study
- Neutropenic patients (high risk) with **FUO** becoming afebrile on empirical kefazolin + gentamicin + carbenicillin (KGC): n = 33
- **After 7 days** of antibiotic treatment and persisting neutropenia: stop vs. continuing KGC

Patients (n=33)	**Relapse of fever**	**Infection**	**Death**
Stop KGC (n=17) Duration of neutropenia median 13d (8-24)	**7 (41%)**	**5 (29%)** 1 cellulitis 1 pneumonia 2 *E. coli* bacteremia 1 cervical adenitis	**2 (12%)** 2 *E. coli* bacteremia
Continued KGC (n=16) Duration of neutropenia median 11d (8-25)	**1 (6%)**	**1 (6%)** pneumonia	**0**

Conclusion

- The phenomenon of resistance is posing new and dramatic problems
- We cannot rely anymore on our antibiotic armamentarium
- De-escalation therapy might be preferable in severe clinical presentations
- Certain aggressive therapies for hematological diseases might become impossible
- There is urgent need to conduct new trials of empirical therapy of fever during neutropenia; EMA is reconsidering febrile neutropenia as a possible indication and might approve new antibiotics for the use in this setting
- These trials might be powered on the expected rate of bacteremia and documented infections