Febrile neutropenia and septic shock

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Why Do Patients With Cancer Visit Emergency Departments? Results of a 2008 Population Study in North Carolina

Deborah K. Mayer, Debbie Travers, Annah Wyss, Ashley Leak, and Anna Waller

Table 2. 2008 NC DETECT Categorized Chief Complaints for Visits (N = 37,760)

Chief Complaint	No.	Overall Rank
Pain	9,000	1
Chest pain	2,429	
Abdominal pain	3,044	
Back pain	900	
Extremity	888	
Other	1,971	
Respiratory	5,856	2
Respiratory distress/SOB	4,711	
Cough	591	
Hemoptysis	120	
Fever/possible pneumonia	282	
COPD	137	
Other	229	
GI	3,280	3
Nausea/vomiting	2,543	
Diarrhea	568	
Constipation	187	
Bowel obstruction	55	
Other	243	
Malaise	2,577	4
Neurologic	2,218	5
Bleeding	2,164	6
Fever	2,000	7
Injury	1,930	8
Falls	1,262	
Lacerations	81	
Bites	38	
MVA	133	
Other	447	
Cancer	1,724	9
Syncope	1,071	10
Blood clots	115	11
Allergic reaction	111	12
Psychiatric	99	13

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La fièvre chez les patients se présentant aux urgences d'un hôpital cancérologique : place de la neutropénie fébrile

Febrile neutropenia at the emergency department of a cancer hospital

C. Debey[1,2], A.-P. Meert[1], T. Berghmans[1], J.-M. Thomas[2] et J.-P. Sculier[1]

[1]Unité des Soins Intensifs médico-chirurgicaux et Urgences oncologiques & Oncologie Thoracique, Institut Jules Bordet, Centre des Tumeurs de l'ULB, [2]Département de Médecine générale, ULB

- Period from 1/1/2008 to 31/12/2008
- 2130 consultations at the emergency department of Institut Bordet
- 408 consultations for fever
  - 88 (21.6%) for febrile neutropenia

Debey et al, Rev Med Brux 2011: 74

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Definitions

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Febrile neutropenia

Fever > 38°C twice or > 38.5°C

AND

Neutropenia

– Value below normal (1400/mm³)
– Significative < 1000/mm³
< 500/mm³
< 100/mm³

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Sepsis, severe sepsis and septic shock

Sepsis (SIRS + infection)	Systemic reaction to infection. The systemic reaction is defined by two or more of the following: –Temperature >38°C or <36°C –Heart rate >90/min –Respiration rate >20/min or $PaCO_2$<32 mmHg –Leukocytes >12,000/µl or <4000/µl or shift to the left >10%
Severe sepsis	Sepsis with new signs of organ dysfunction or a decrease in organ perfusion (lactate acidosis, oliguria (<30 ml/h or <0.5 ml/kg/h), hypotension (<90 mm Hg or decrease of >40 mm Hg), mental alteration
Septic shock	Severe sepsis and hypotension persistent despite adequate fluid substitution and exclusion for other reasons for hypotension

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Epidemiology

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Febrile neutropenia frequency

- Occurrence of FN is function of
  - Type of tumour:
    - solid tumour
    - haematological malignancy
    - allograft
  - Type of chemotherapy

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Cancer	CT	N Pts.	Neutropenia (Grade 4) (%)	FN (%)
Lymphoma	MOPP	123	22	—
	ABVD	115	3	—
	CHOP	216	22	—
	CHOP-R	33	58	18
	VAPEC-B	39	72	44
	ESHAP	122	500/µl median	30
	DHAP	90	53	48
NSCLC	Cis/VNR	206	59	10
	Cis/Pac(24hr)	288	57	16
	Cis/Gem	288	39	4
	Cis/Doc	289	48	11
	CBDCA/Pac	290	43	4
	Doc(75mg/m^2)	276	—	12.7
	Pemetrexed	265	—	1.9
Breast	Doc (100)	161	78.6	5.7
	AC	215	88(3+4)	10
	AT	214	97(3+4)	33
	TAC	54	100(3+4)	34
	CapDoc	255	11	16
	Doc	256	12	21

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Incidence of severe sepsis/septic shock in febrile neutropenia

- Prospective studies are not available.
- Most patients with FN fulfilled the definition of sepsis
- Few data on the frequency of septic shock in neutropenic patients → up to 40% in selected series

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Infections in neutropenic patients in the ICU

- During a one year period at the Bordet ICU
- 144 infections at admission or during ICU stay
- 32 (22%) occurred in neutropenic patients
  - Half had positive blood cultures

Berghmans et al, J Supp Cancer Care

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Is febrile neutropenia a major complication in cancer patients?
Is it a life-threatening complication?

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Infection is a major cause of death in cancer patients

Death aetiology	N	%
Infection	380	47
Organ failure	201	25
Infarction	90	11
Haemorrhage	62	7
Cancer	83	10
Overall	816	100

Inagaki et al; Cancer 33(2): 568-73; 1974

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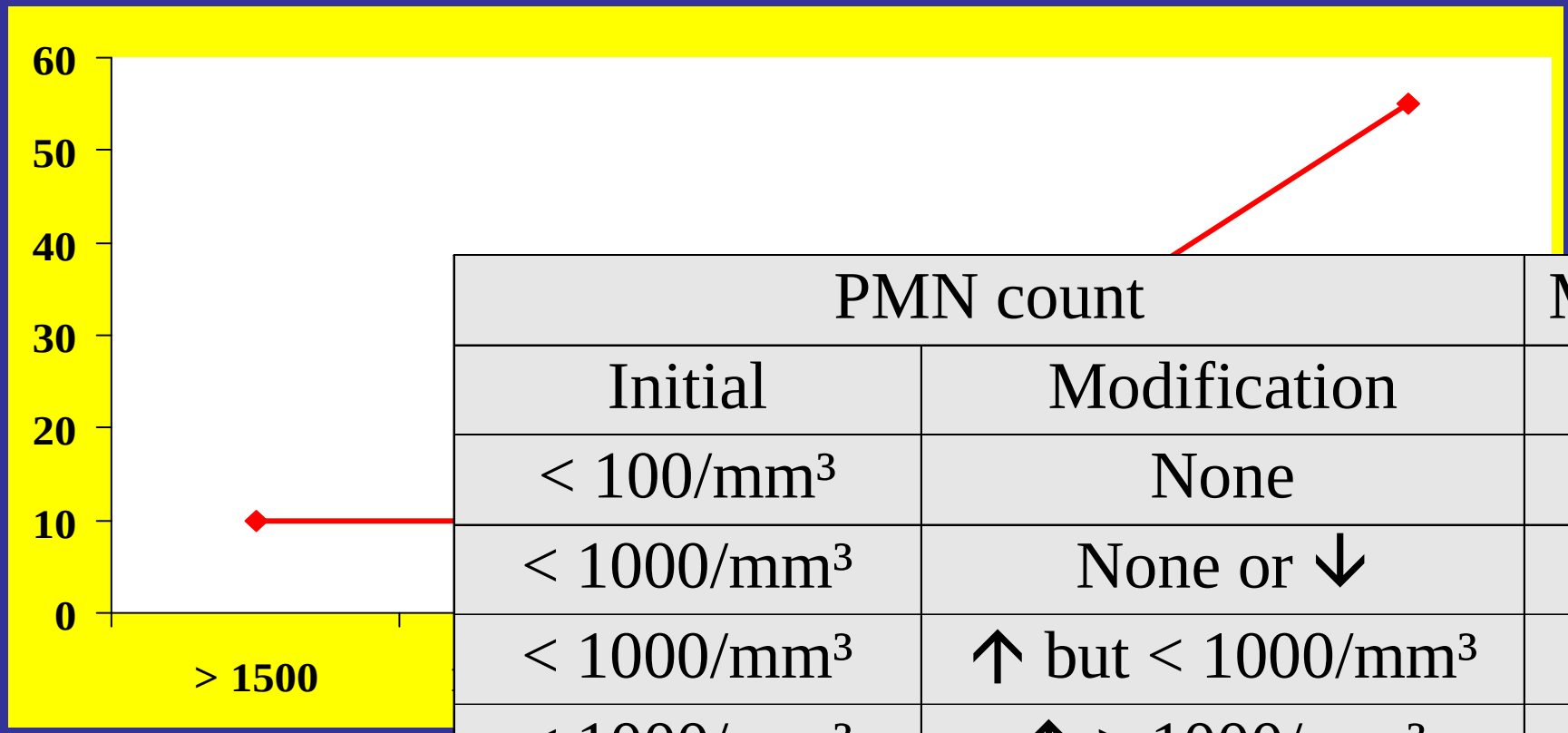
Risk of FN, neutrophil count and mortality

(Bodey et al, 1966)



PMN count		Mortality
Initial	Modification	
< 100/mm³	None	80%
< 1000/mm³	None or ↓	59%
< 1000/mm³	↑ but < 1000/mm³	40%
< 1000/mm³	↑ > 1000/mm³	27%
> 1000/mm³	↑	32%

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FEBRILE NEUTROPENIA IS A LIFE-THREATENING COMPLICATION IN CANCER PATIENTS

- Years 1960
  - **Mortality 90%**
  - Antibiotherapy only in case of positive microbiological documentation

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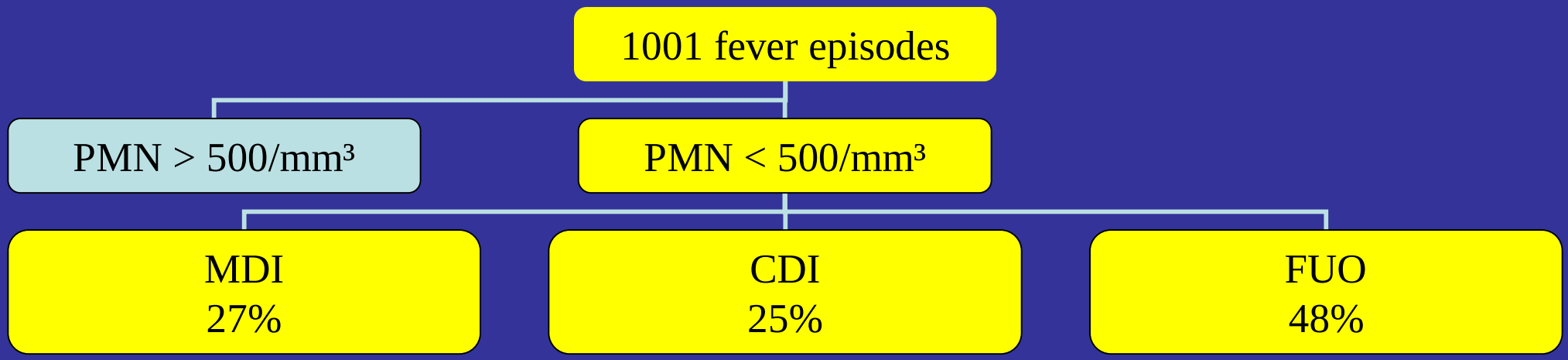
Microbiology



MDI: microbiologically documented infection

CDI: clinically documented infection

Pizzo et al, Medicine 1982

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And now ?

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The concept of empirical therapy

- Concept developed by Schimpff in 1971

⇨ mortality << 10%

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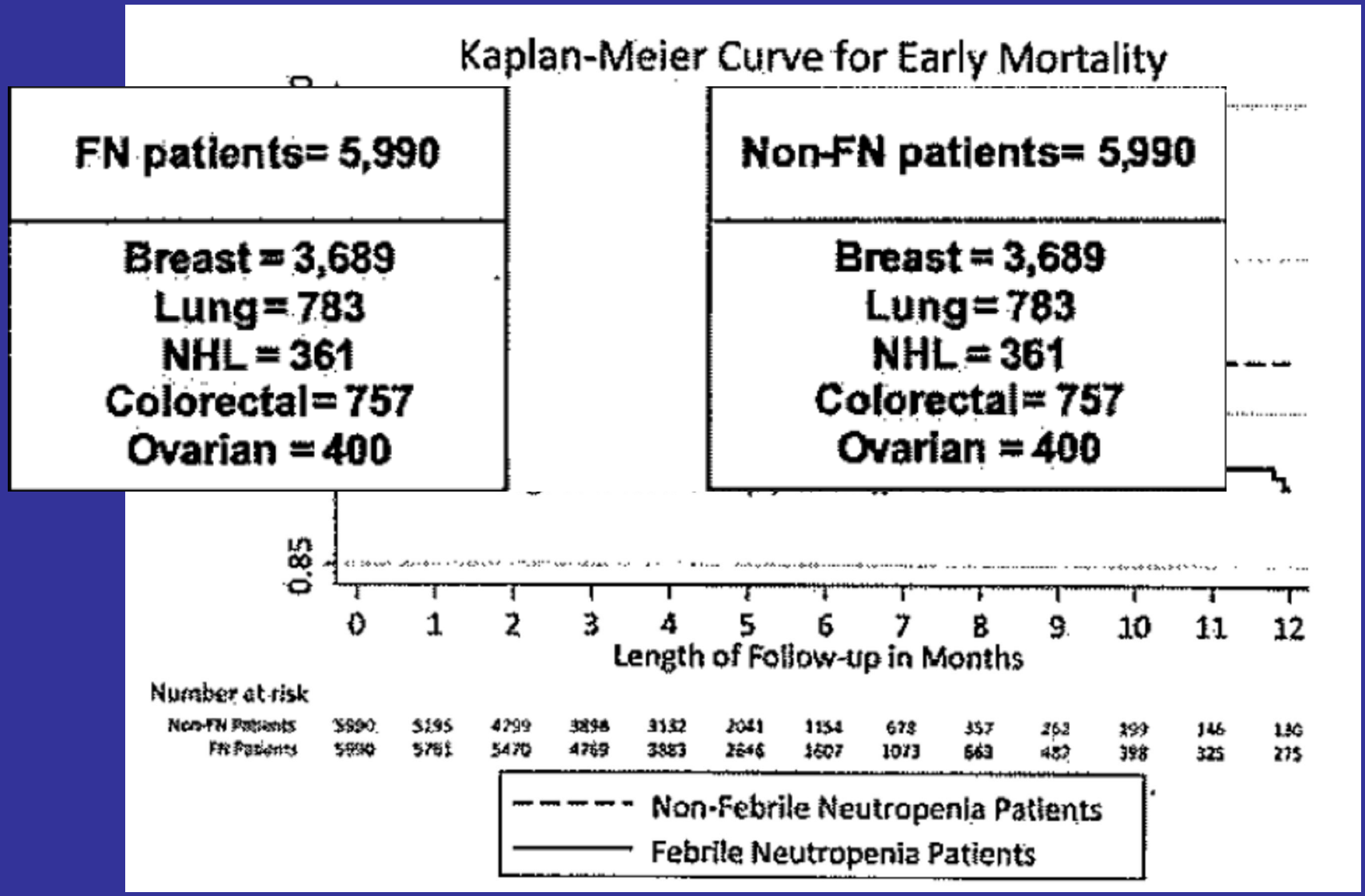
FN remains associated with increased mortality



Lyman et al, Cancer 2010

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Can we assess the risk of complication in patients presenting with febrile neutropenia ?

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Factors associated with a reduced risk of complication

- PMN > 100/mm³
- Monocytes > 100/mm³
- Neutropenia <7days
- Medullar recovery

- No co-morbidities
- Cancer in remission

- No catheter infection
- T° < 39°C
- No neurological signs
- No abdominal pain
- No symptoms
- Normal chest X-ray
- Normal renal and hepatic functions

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MASCC Score(JCO 2000)

Characteristic	Points
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No COPD	4
Solid tumour or no previous infection in haematological tumour	4
Outpatient status	3
No dehydration	3
Age <60 years	2

- Reduced risk for a score ≥ 21:

Positive predictive value 91% with specificity 68% and sensitivity 71%

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MASCC score in routine practice

Tableau 3 : Examens biologiques en salle d'urgences.

	Neutropénies fébriles (N = 88)	Non neutropéniques (N = 320)
Médiane globules blancs	919,5 (10-18.300)	8.405 (1.040-110.000)
Médiane neutrophiles absolus	175 (0-498)	6.135 (530-42.280)
Médiane CRP (mg/l)	58,3 (1-333,5)	68,3 (1,1-341,1)
CRP < 10 mg/l	7 (8 %)	25 (8 %)
Score MASCC :		
• ≥ 21	78 (88,6 %)	NA
• < 21	10 (11,4 %)	NA

Debey et al, Rev Med Brux 2011: 74

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Which empirical treatment ?

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Microbiological results in FN

Table 1. Type and frequency of 164 pathogens isolated

Microorganism	Absolute number (%)
S. aureus	23 (14)
CoNS	19 (11.6)
Enterococcus spp.	13 (7.9)
Streptococcus pneumoniae	2 (1.2)
Group G *Streptococcus* (*viridans*)	4 (2.4)
Clostridium difficile	3 (1.8)
Eubacterium lentum	1 (0.6)
Diphteroides spp.	1 (0.6)
Nocardia spp.	1 (0.6)
E. coli	38 (23.2)
Enterobacteriaceae other than *E. coli*	18 (11)
P. aeruginosa	13 (7.9)
Stenotrophomonas maltophilia	4 (2.4)
Acinetobacter baumannii	2 (1.2)
Alcaligenes xylosoxidans	1 (0.6)
Moraxella catarrhalis	1 (0.6)
Bacteroides spp.	1 (0.6)
Campylobacter jejunii	2 (1.2)
Rhizobium radiobacter	1 (0.6)
Cytomegalovirus	1 (0.6)
Leishmania spp.	1 (0.6)
Candida spp.	5 (3)
Mucor spp.	2 (1.2)
Aspergillus spp.	5 (3)
Fusarium spp.	1 (0.6)
Pseudoallescheria boydii	1 (0.6)

Cattaneo JAC 2008

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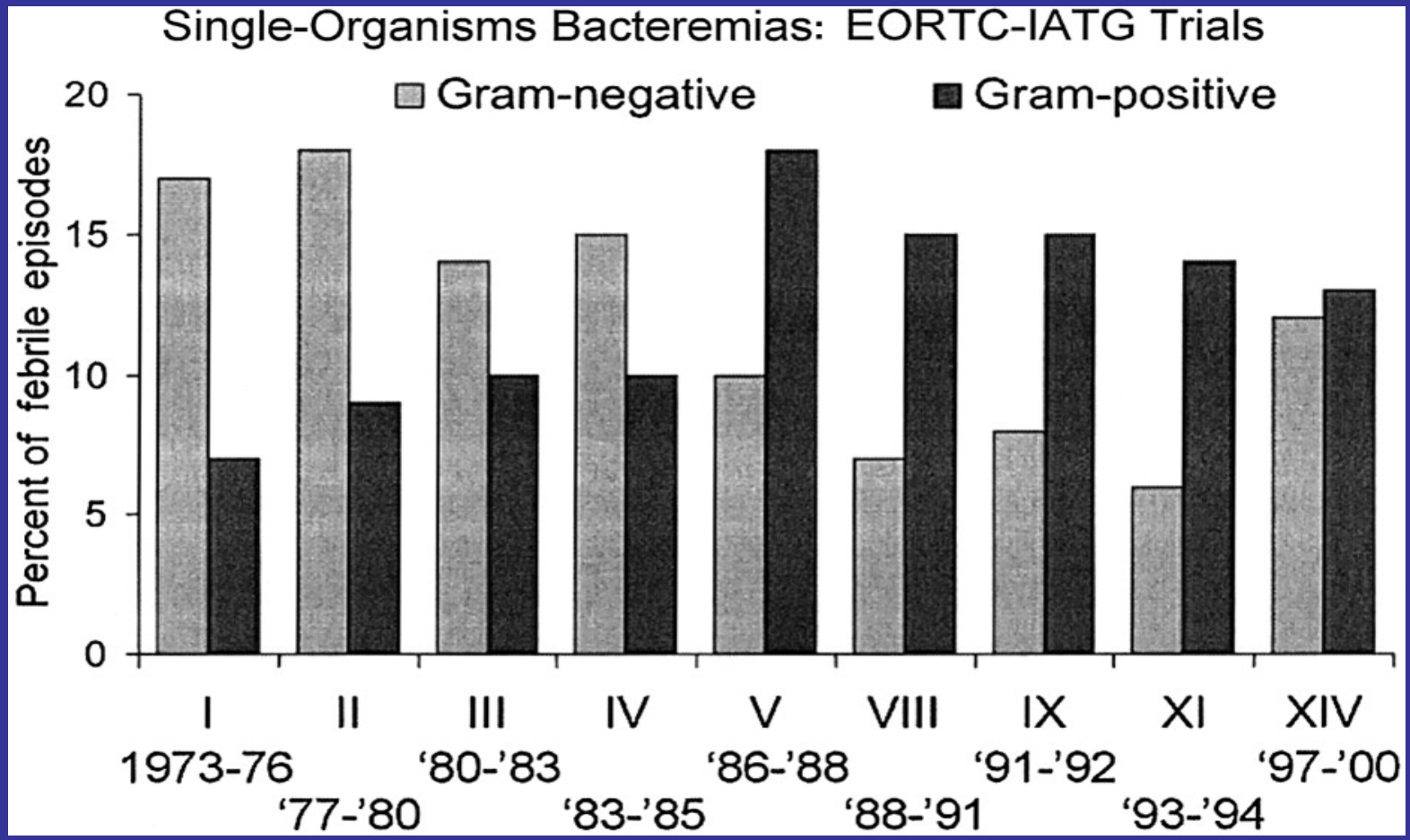
Evolving epidemiology of bacteraemia



Viscoli et al CLIN INFECT DIS 40(S4):S240-S245.

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Which empirical treatment ?

- Active against Gram negative bacilli ➔ *Pseudomonas aeruginosa*
- Active against Gram positive bacteria ➔ Streptococcus, methicillin sensitive Staphylococcus

➔ β LACTAME ANTI-PSEUDOMONAS + AMINOGLYCOSIDE

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Is an oral treatment possible ?

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Oral antibiotherapy is adequate in selected patients

Vidal et al The Cochrane Library 2008

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality	9	1392	Relative Risk (Fixed) 95% CI	0.95 [0.54, 1.68]
02 Treatment failure	18	2763	Relative Risk (Fixed) 95% CI	0.95 [0.85, 1.07]
03 Treatment failure - per protocol analysis	18	2547	Relative Risk (Fixed) 95% CI	0.98 [0.86, 1.13]
04 Adverse events requiring discontinuation of antibiotics	12	1577	Relative Risk (Random) 95% CI	1.80 [0.58, 5.60]
05 Gastrointestinal adverse events ('post-protocol' analysis)			Relative Risk (Fixed) 95% CI	Subtotals only
06 Lost to follow-up	15	2432	Relative Risk (Fixed) 95% CI	0.82 [0.61, 1.11]
07 Treatment failure not dt modification in update	18	2763	Relative Risk (Fixed) 95% CI	0.95 [0.85, 1.06]

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Which patient for an oral antibiotherapy?

- 1. The patient must swallow
- No Nausea or vomiting
- No stomatitis
- 2. To be at poor risk of complications:
- MASCC score ≥ 21
- 3. This is not implying a direct return at home

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Which combination ?

Study	Oral antibiotics n/N	IV antibiotics n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) CI
Test for overall effect z=0.38 p=0.7					
02 Quinolones in combination with augmentin, ampicillin-sulbactam, penicillin V or					
Freifeld 1999	60/142				64, 1.06]
Innes 2003					0.84 [0.42, 1.69]
Kern 1999				27.1	0.91 [0.64, 1.29]
Niho 2004		4/19		2.4	0.43 [0.09, 2.10]
Rolston 1995	9/89	12/90		6.6	0.76 [0.34, 1.71]
Rubenstein 1993	14/49	6/47		3.4	2.24 [0.94, 5.33]
Samonis 1997	12/97	15/98		8.2	0.81 [0.40, 1.64]
Velasco 1995	3/55	8/53		4.5	0.36 [0.10, 1.29]
Subtotal (95% CI)	**708**	**700**		**100.0**	**0.86 [0.72, 1.03]**
Total events: 157 (Oral antibiotics), 181 (IV antibiotics)					
Test for heterogeneity chi-square=7.51 df=7 p=0.38 I^2 =6.8%					
Test for overall effect z=1.66 p=0.1					

Amoxycillin-clavulanic acid + Ciprofloxacin
Moxifloxacin ?

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And in routine practice ?

Tableau 3 : **Examens biologiques en salle d'urgences.**

	Neutropénies fébriles (N = 88)	Non
Médiane globules blancs	919,5 (10-18.300)	
Médiane neutrophiles absolus	175 (0-498)	
Médiane CRP (mg/l)	58,3 (1-333,5)	
CRP < 10 mg/l	7 (8 %)	
Score MASCC :		
• ≥ 21	78 (88,6 %)	
• < 21	10 (11,4 %)	

Tableau 6 : **Traitement instauré en salle d'urgences.**

	Neutropénies fébriles (N = 88)	Non neutropéniques (N = 320)	P
Type de traitement :			< 0,00001
• Antibiothérapie	83 (94,3 %)	201 (63,2 %)	
• Autre	5 (5,7 %)	117 (36,8 %)	
Voie d'administration des antibiotiques :			0,036
• Orale	43 (51,8 %)	77 (38,3 %)	
• Intraveineuse	40 (48,2 %)	124 (61,7 %)	

Debey et al, Rev Med Brux 2011: 74

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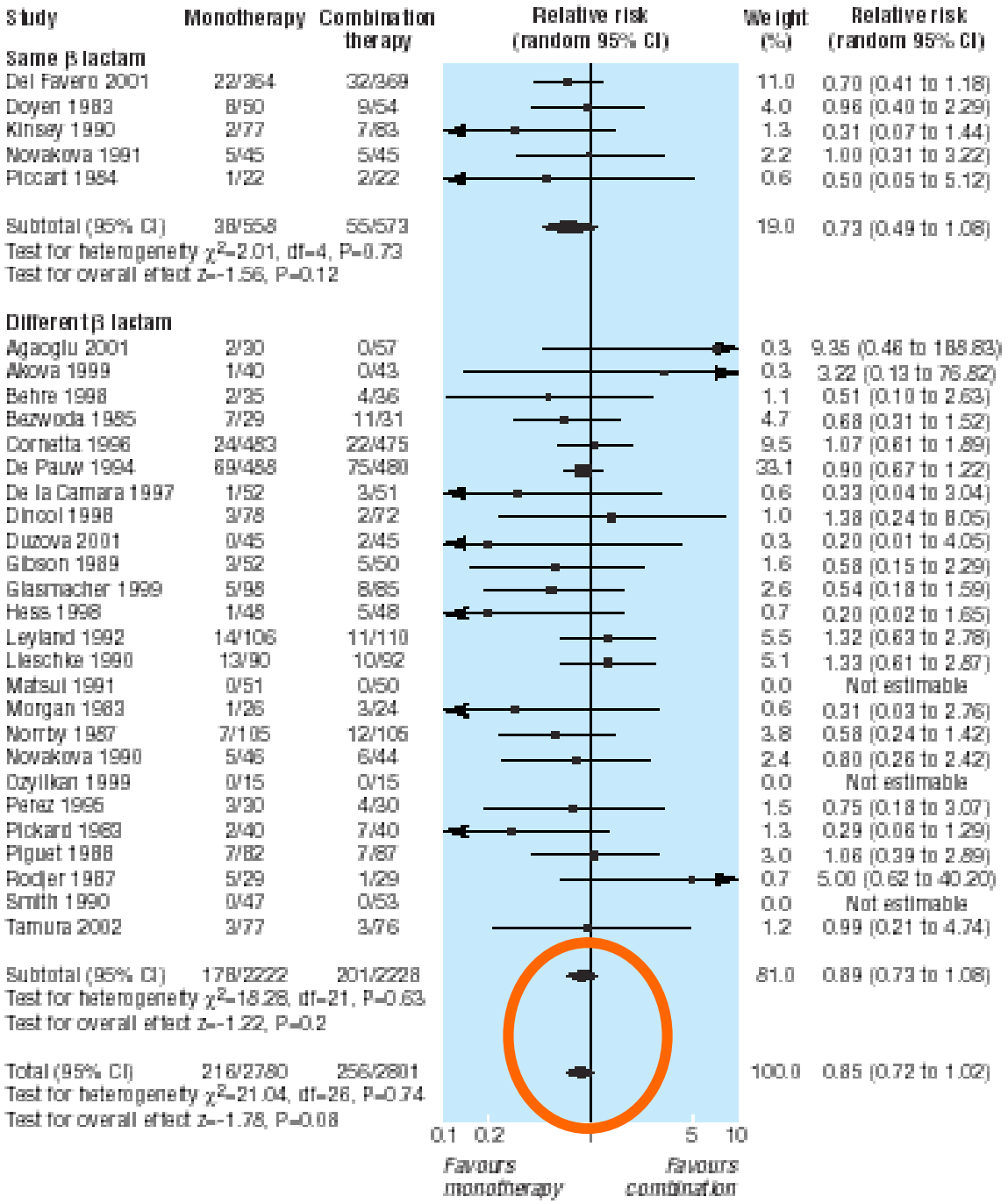

Fig 2 All cause fatality

Systematic addition of an aminoside to a beta-lactame does not modify the evolution

→ Aminoside to be reserved in case of

✧severe sepsis/septic shock

✧known « resistant » bacteria

BMJ 2003

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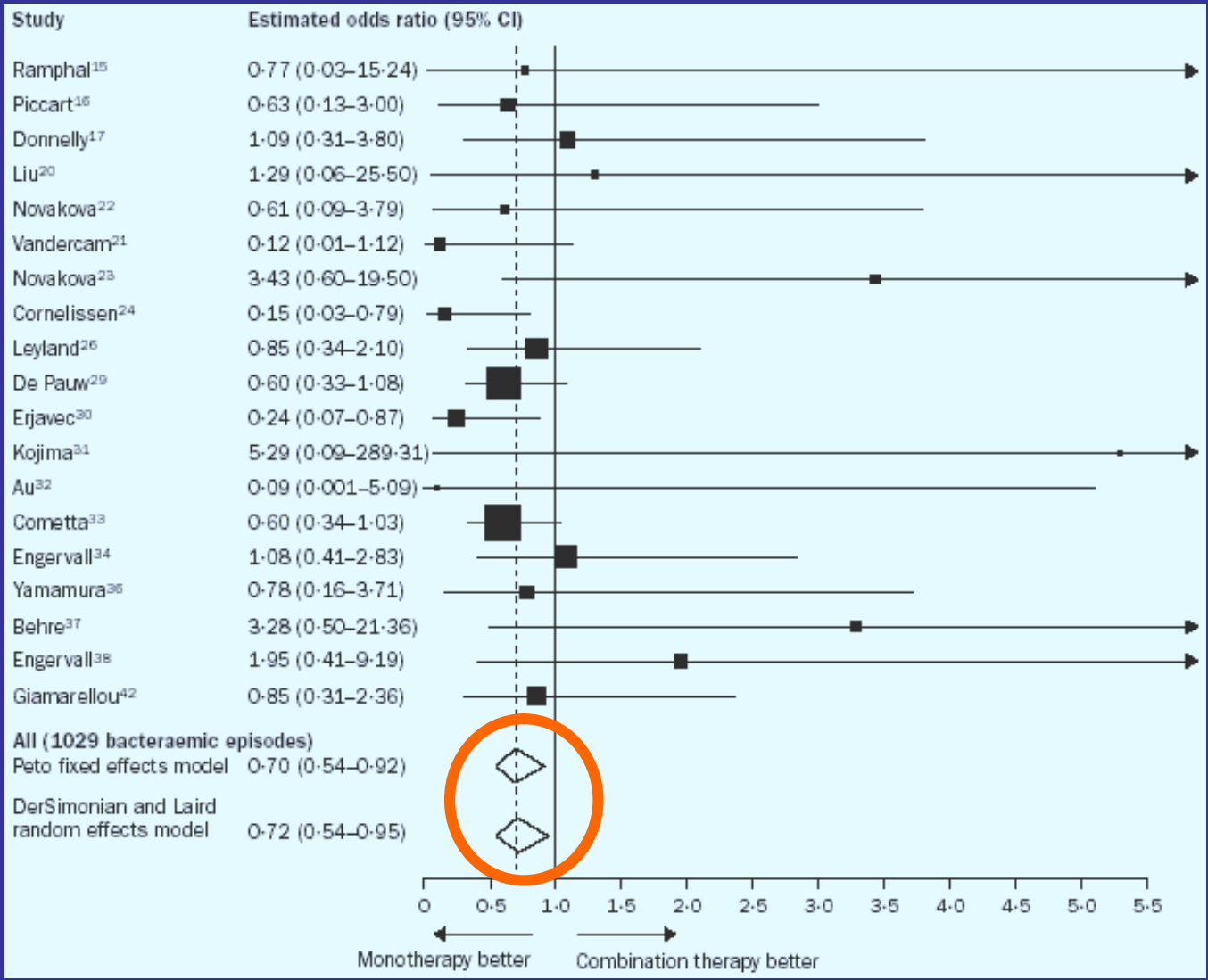
What about bacteremia ?

Furno et al Lancet Infect Dis 2002



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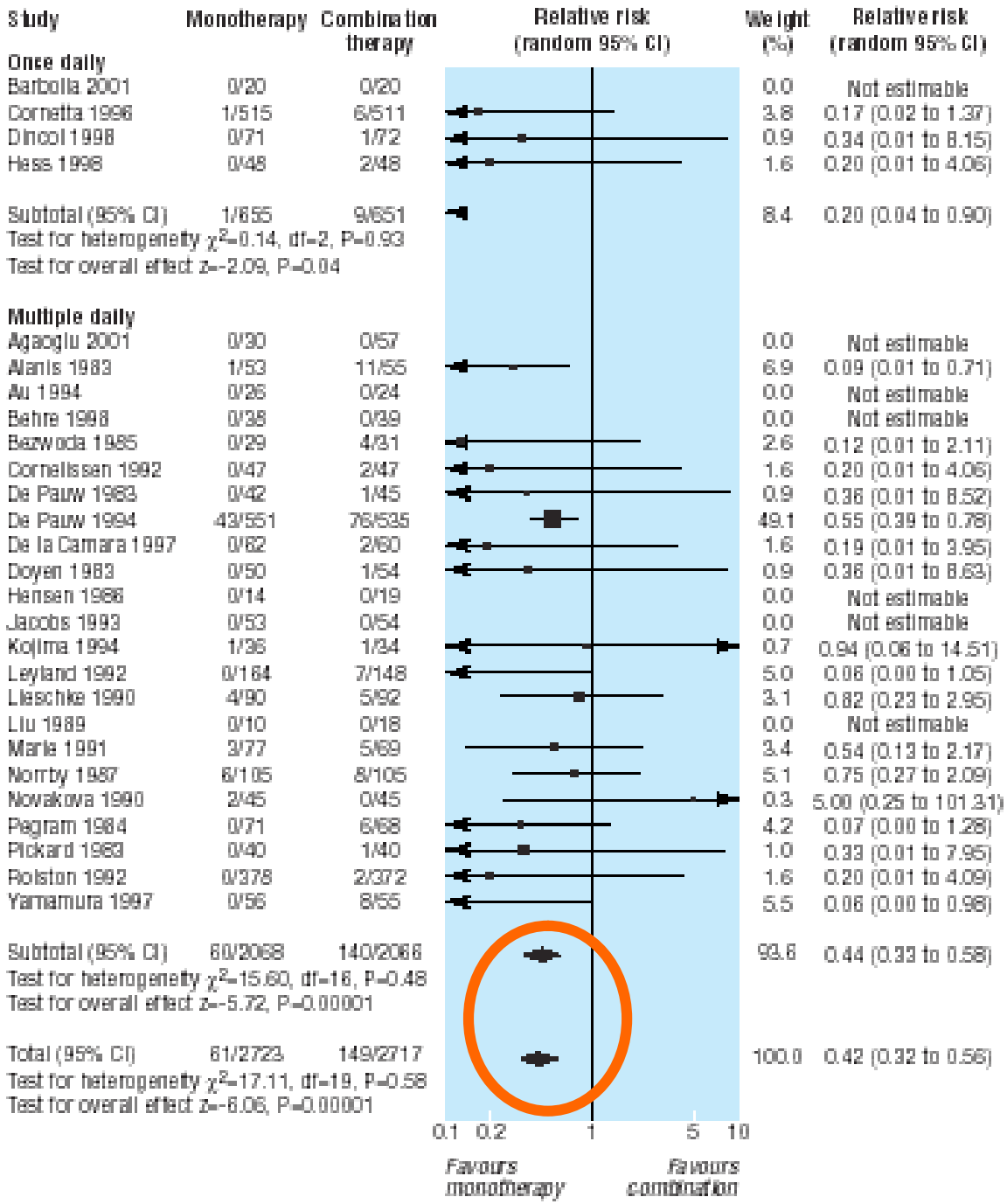

Fig 6 Nephrotoxicity

Systematic addition of an aminoside does not impact on final resolution of FN

BUT

Results in increased renal toxicity

→ CAVE with other nephrotoxic drugs (e.g. cisplatin, glycopeptides, iodine contrast …)

BMJ 2003

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Which beta-lactame ?

Cochrane review 2010

Comparison 3. Piperaciilin-tazobactam vs. other

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	8	1314	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.34, 0.92]
1.1 cefepime	3	755	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.32, 1.34]
1.2 carbapenem	4	398	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.22, 0.95]
1.3 ceftazidime	1	161	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.05, 13.36]

Comparison 4. Carbapenem vs. other

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	22	4431	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.87, 1.55]
1.1 ceftazidime	8	2028	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.54, 1.54]
1.2 cefepime	8	1570	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.52, 1.37]
1.3 cefoperazone-sulbactam	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.42, 3.34]
1.4 piperacillin-tazobactam	4	398	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.06, 4.57]
1.5 aztreonam	1	300	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [1.07, 13.23]

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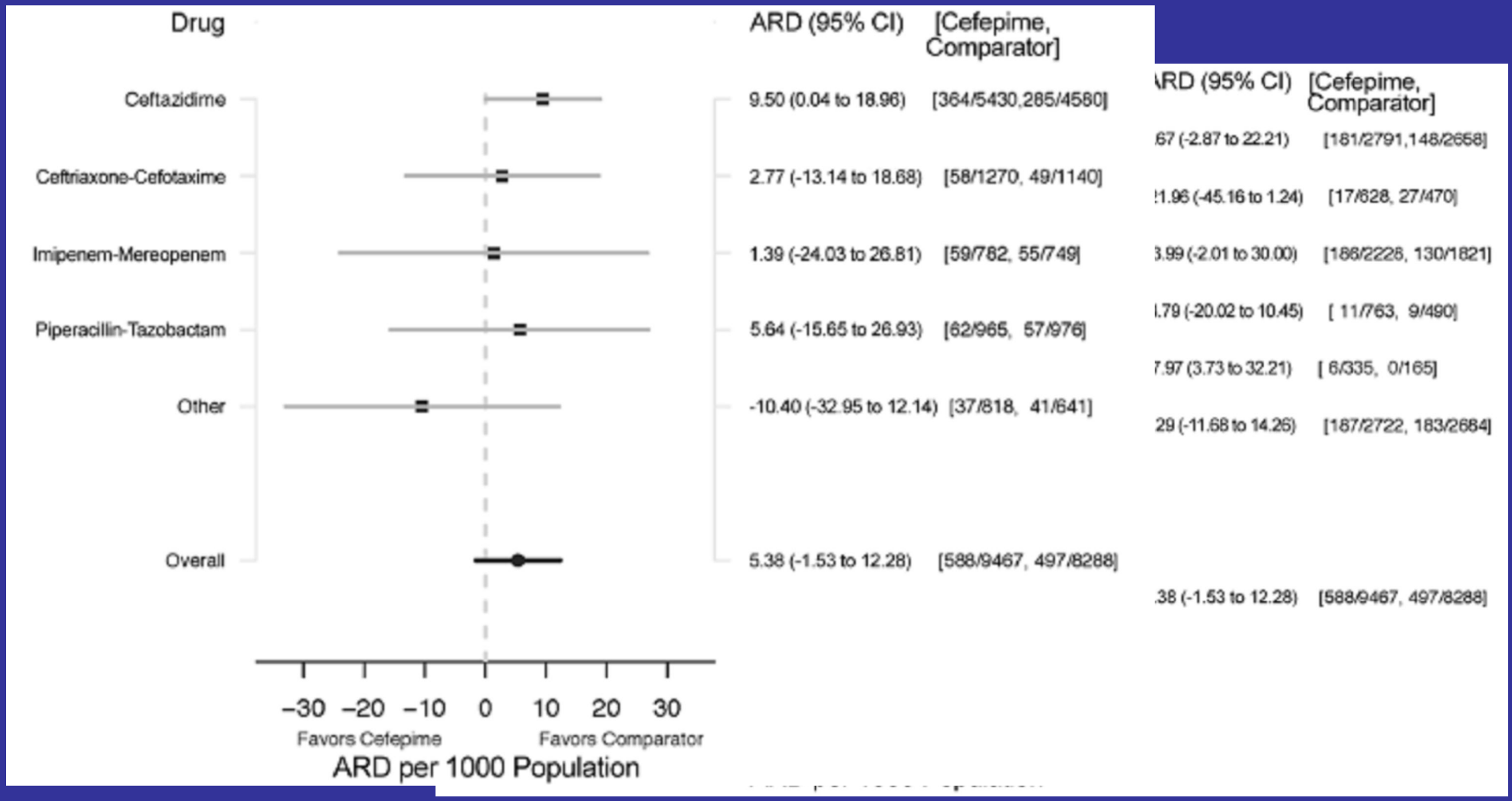
Which beta-lactame ?

Kim et al, Clin Infect Dis 2010



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No systematic administration of an aminoside
And a glycopeptide ?

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Addition of a glycopeptide ?

Vardakas et al Lancet 2005

- Success without treatment modification

  OR = 1.63 (95% CI 1.17–2.28)

  – *MDI*

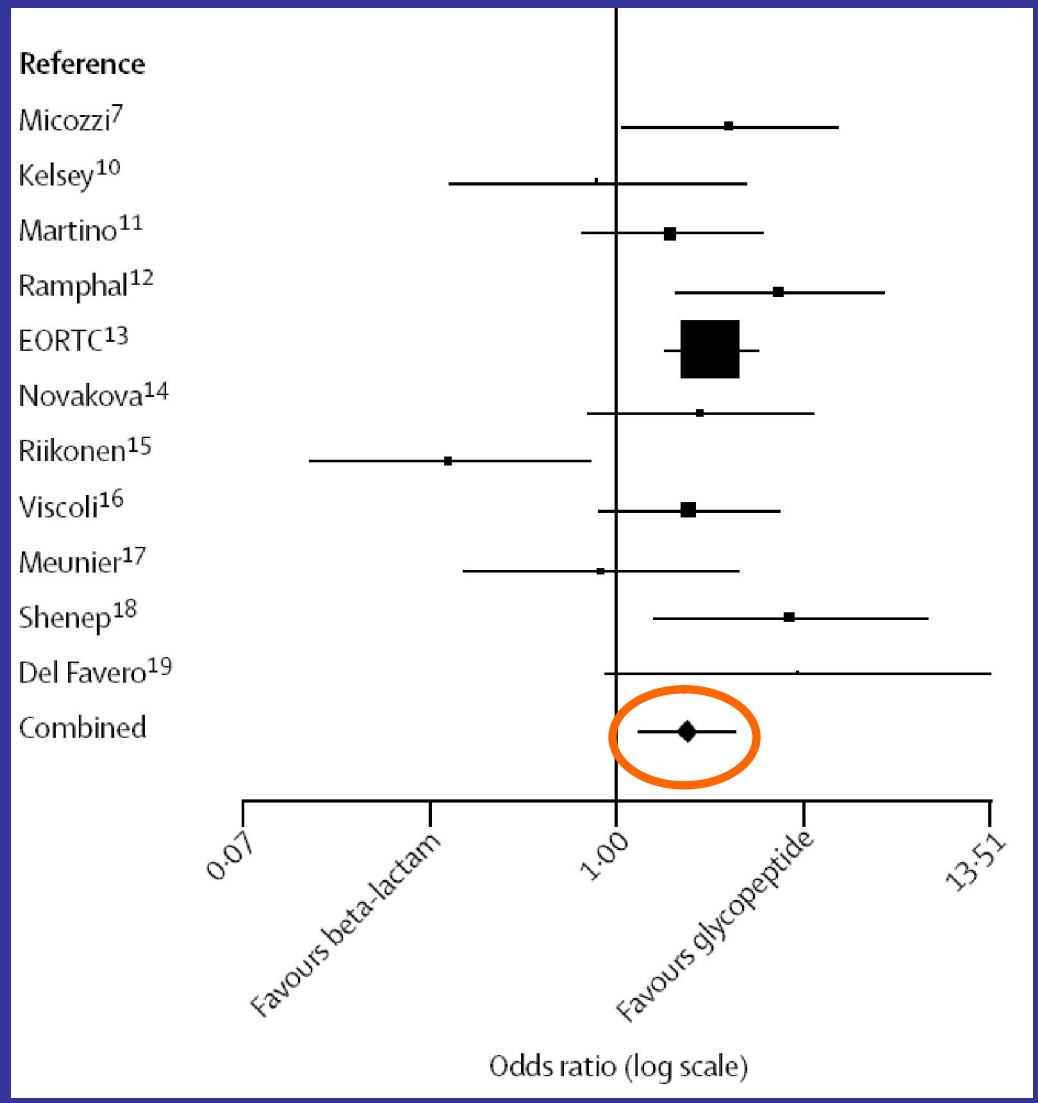
  OR = 2.03 (95% CI 1.39–2.97)

  – *Bacteraemia*

  OR = 1.80 (95% CI 1.23–2.63)

  – *Neutropenia < 100/mm³*

  OR = 2.24 (95% CI 1.15–4.39)



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Addition of a glycopeptide ?

Vardakas et al Lancet 2005

- Mortality

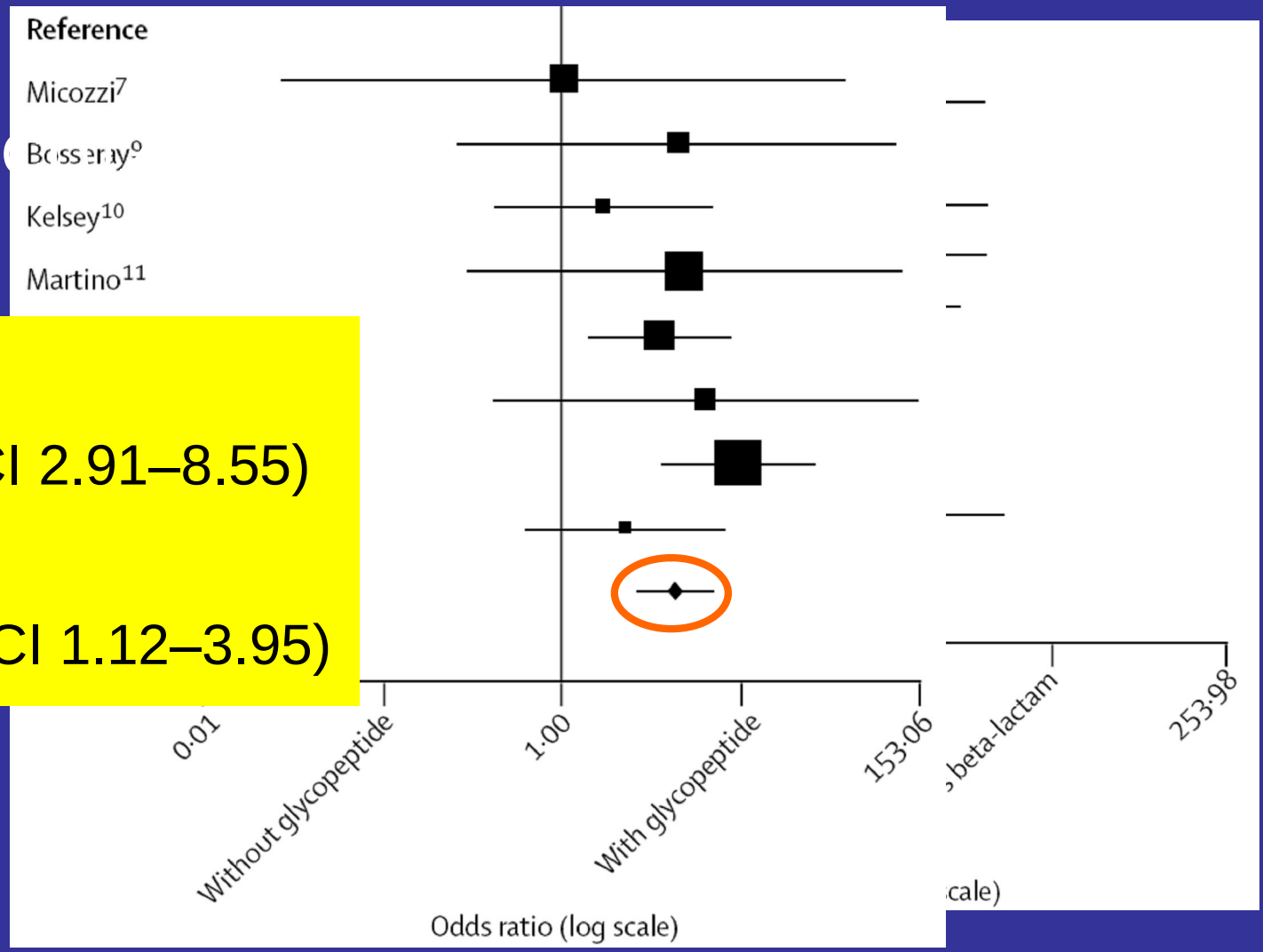
  OR = 0.67 (95% C
  1.05)

- Adverse events

  OR = 4.98 (95% CI 2.91–8.55)

- Nephrotoxicity

  OR = 2.10 (95% CI 1.12–3.95)



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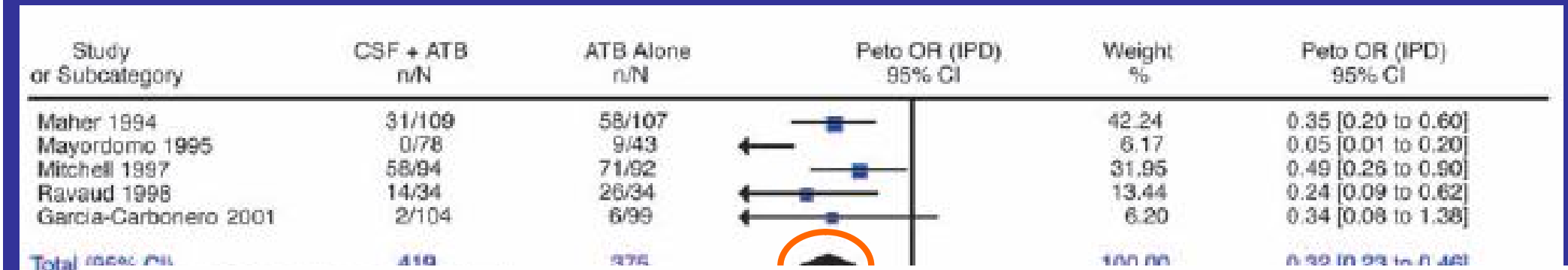
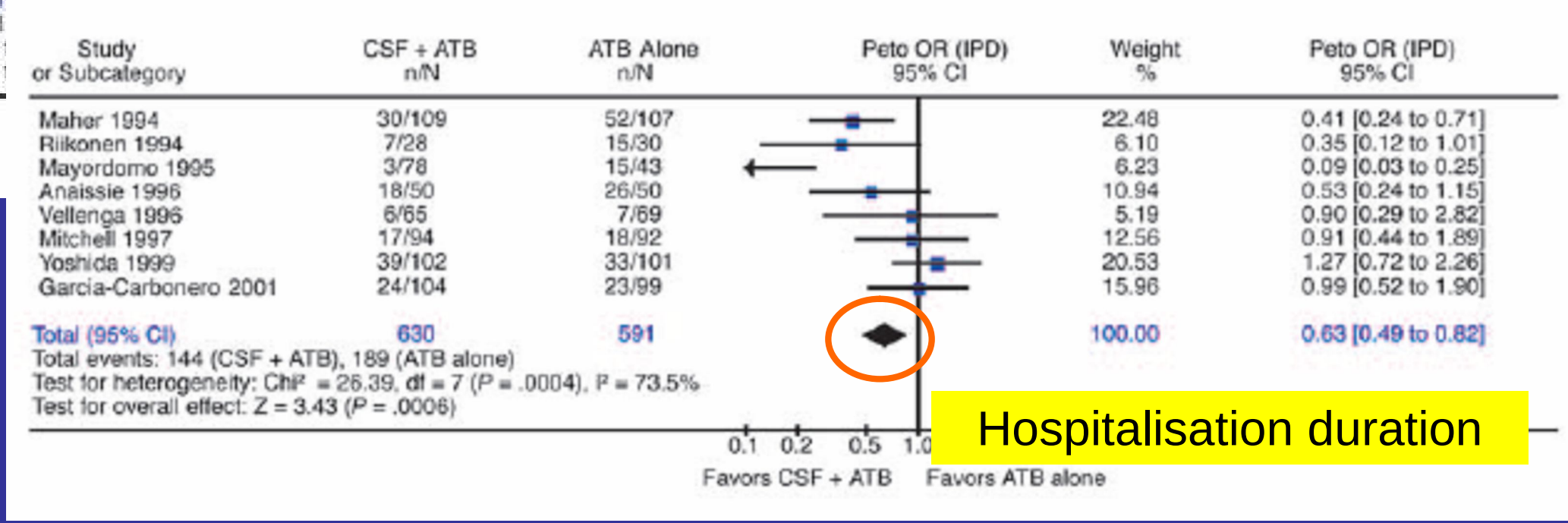
Usefulness of colony-stimulating factors ?

Clarke et al J Clin Oncol 2005



Study or Subcategory	CSF + ATB n/N	ATB Alone n/N	Peto OR (IPD) 95% CI	Weight %	Peto OR (IPD) 95% CI
Maher 1994	31/109	58/107		42.24	0.35 [0.20 to 0.60]
Mayordomo 1995	0/78	9/43		6.17	0.05 [0.01 to 0.20]
Mitchell 1997	58/94	71/92		31.95	0.49 [0.26 to 0.90]
Ravaud 1998	14/34	26/34		13.44	0.24 [0.09 to 0.62]
Garcia-Carbonero 2001	2/104	6/99		6.20	0.34 [0.08 to 1.38]
Total [illegible]	419	376		100.00	0.32 [0.23 to 0.46]



Study or Subcategory	CSF + ATB n/N	ATB Alone n/N	Peto OR (IPD) 95% CI	Weight %	Peto OR (IPD) 95% CI
Maher 1994	30/109	52/107		22.48	0.41 [0.24 to 0.71]
Riikonen 1994	7/28	15/30		6.10	0.35 [0.12 to 1.01]
Mayordomo 1995	3/78	15/43		6.23	0.09 [0.03 to 0.25]
Anaissie 1996	18/50	26/50		10.94	0.53 [0.24 to 1.15]
Vellenga 1996	6/65	7/69		5.19	0.90 [0.29 to 2.82]
Mitchell 1997	17/94	18/92		12.56	0.91 [0.44 to 1.89]
Yoshida 1999	39/102	33/101		20.53	1.27 [0.72 to 2.26]
Garcia-Carbonero 2001	24/104	23/99		15.96	0.99 [0.52 to 1.90]
Total (95% CI)	630	591		100.00	0.63 [0.49 to 0.82]

Total events: 144 (CSF + ATB), 189 (ATB alone)
Test for heterogeneity: $Chi^2 = 26.39$, df = 7 ($P = .0004$), $I^2 = 73.5\%$
Test for overall effect: $Z = 3.43$ ($P = .0006$)

Hospitalisation duration

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Overall mortality

Berghmans et al Support Care Cancer 2002

Référence	*CSF*	*ATB*	*ATB+CSF*	*RR*	*IC 95%*
Anaissie (1)	GM	3/50	3/50	1.00	0.21-4.72
Arnberg (2)	GM	0/15	1/14	10.71	0.02->100
Mayordomo (9)	GM	2/43	2/39	1.10	0.16-7.46
Riikonen (13)	GM	0/30	0/28	1.00	0->100
Vellenga (17)	GM	2/69	1/65	0.53	0.05-5.72
Aviles (3)	G	15/58	5/61	0.32	0.12-0.82
Maher (7)	G	15/107	12/108	0.79	0.39-1.61
Mayordomo (9)	G	2/43	4/39	2.21	0.43-11.38
Mitchell (11)	G	0/92	0/94	1.00	0->100
Total				0.71	0.44-1.15
Sous-groupe	G			0.66	0.39-1.13
Sous-groupe	GM			0.97	0.34-2.79

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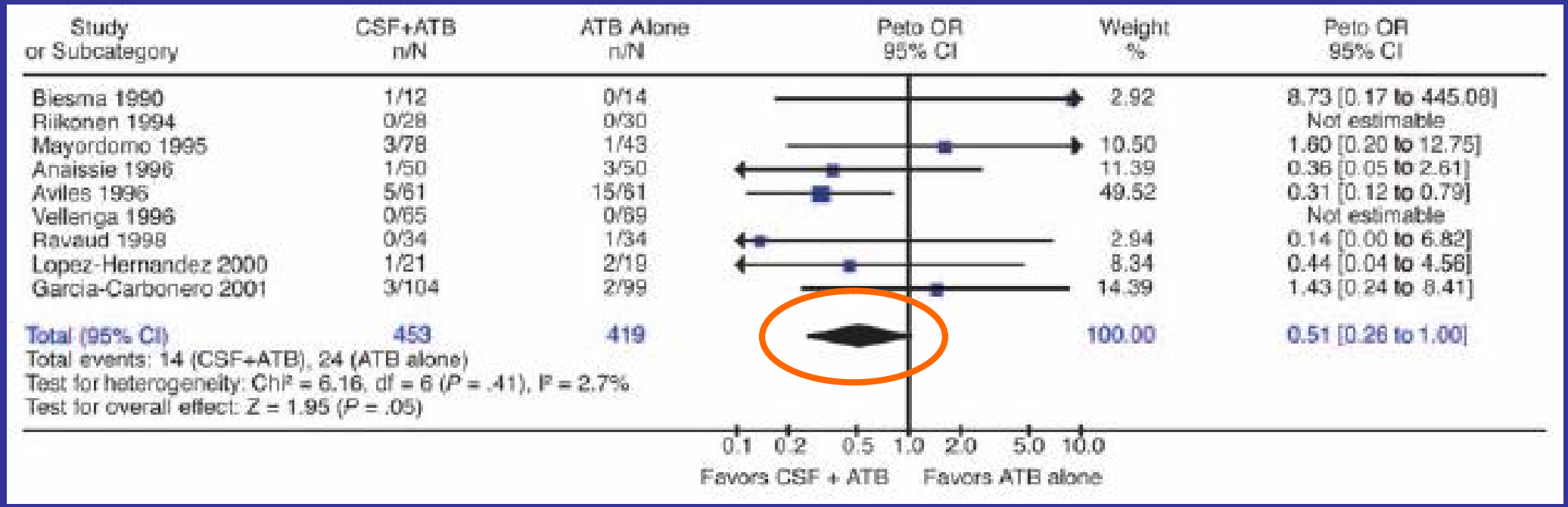
Mortality due to infection

Clarke et al J Clin Oncol 2005



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Other therapeutics ?

- Immunoglobulins
  - No data supporting the systematic use of immunoglobulins in case of febrile neutropenia
- White blood cell transfusions
  - Few data
  - No data supporting their systematic use in case of febrile neutropenia

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Summary of therapeutic attitude for febrile neutropenia at the emergency department

- FN must be rapidly treated
- Low risk:
  - consider oral antibiotherapy (amoxyclav-ciprofloxacin)
- High risk:
  - IV antibiotherapy
  - Large spectrum beta-lactame/peneme
- Severe sepsis/septic shock:
  - add aminoside

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Any specificity for severe sepsis/septic shock in neutropenic patients?

Ann Hematol (2006) 85: 424–433
DOI 10.1007/s00277-006-0096-2

ORIGINAL ARTICLE

Olaf Penack · Thomas Beinert · Dieter Buchheidt · Hermann Einsele · Holger Hebart · Michael G. Kiehl · Gero Massenkeil · Xaver Schiel · Jan Schleicher · Philipp B. Staber · Stefan Wilhelm · Hans Wolf · Helmut Ostermann

Management of sepsis in neutropenia: guidelines of the infectious diseases working party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

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AGIHO guidelines

- The decision to initiate intensive care treatment has to take into account the prognosis of the underlying disease.

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The ICU prognosis is function of the gravity of the complication

	Results of multivariate analyses	
ICU mortality	ICM scoring system APACHE II score	OR = 2.24 (95% CI 1.60-3.13; p < 0.001) OR = 1.10 (95% CI 1.04-1.16; p< 0.001)
Hospital mortality	ICM scoring system SAPS II score	OR = 2.31 (95% CI 1.69-3.16; p < 0.001) OR = 1.05 (95% CI 1.02-1.08; p< 0.001)
Survival after discharge from the hospital	ICM scoring system Cancer phase Type of cancer	HR = 1.67 (95% CI 1.22-2.30; p = 0.001) HR = 3.29 (95% CI 1.58-6.81; p = 0.001) HR = 0.35 (95%CI 0.13-0.90; p = 0.03)

Berghmans et al; J Supp Care Cancer

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AGIHO guidelines

- Antimicrobial treatment must be started immediately to improve tissue oxygenation, restore cardiovascular function, and improve other organ functions.

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AGIHO guidelines

- To restore adequate cardiac filling pressures and to maintain adequate organ perfusion, crystalloid fluids or colloids can be useful.
- If a sufficient mean arterial pressure (>65 mmHg) cannot be achieved by volume substitution in a reasonable time frame, treatment with vasopressors is indicated.

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AGIHO guidelines

- The AGIHO does not recommend the routine additional use of G-CSF or GM-CSF to standard treatment of sepsis in neutropenia.
- There are not enough data to recommend the routine use of additional immunoglobulins in the treatment of sepsis in neutropenia.

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AGIHO guidelines

- The recommendations for substituting platelets or packed red blood cell in neutropenic patients can be applied to those patients developing sepsis as well.
- However, the cut- off for substitution is often set to a higher value (platelets 20,000/µl instead of 10,000/µl).
- Although there are no prospective randomized studies showing a clinical benefit, haemoglobin levels should be kept above 9 g/dl to optimize tissue oxygenation.

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Situation in France
Febrile neutropenia at emergency departments of tertiary teaching and general community hospitals

André et al, Crit Care 2010

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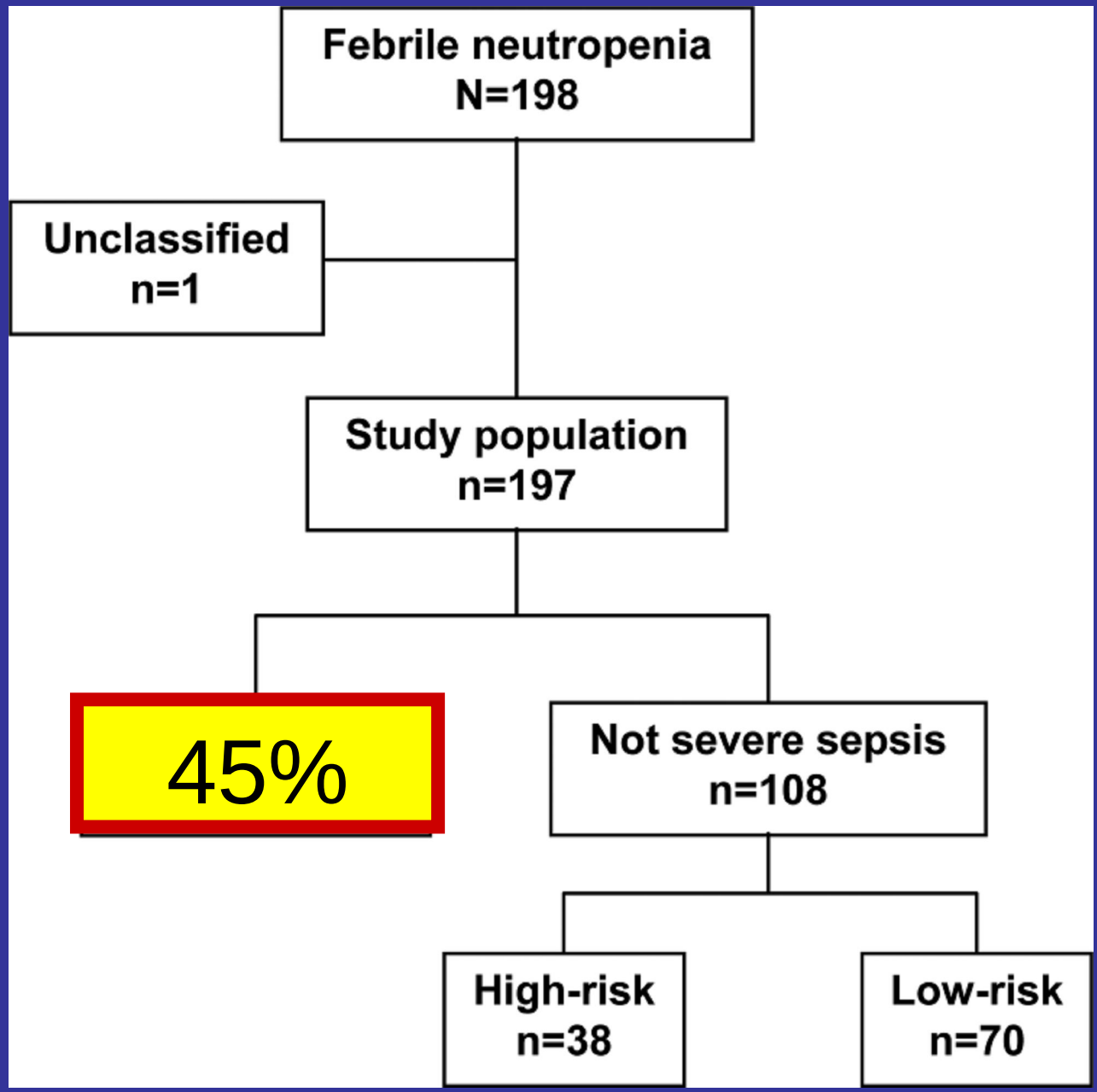
Prospective study
4/02 → 04/08/2008
47 centres
198 FN/ 777,876 visits
➢1/3930 visit



André et al, Crit Care 2010

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Some patients' characteristics

	Total	Severe sepsis	No severe sepsis	p
N	198	89	108	
Age (mean)	61	65	57	< 0.001
PS (median)	70	70	80	0.06
Haematologic tumours	45%	44%	45%	0.84
Solid tumours Lung Breast	55% 20% 13%	56% 27% 10%	55% 14% 16%	
Metastasis or uncontrolled	67%	78%	58%	0.004
MASCC < 20	53%	75%	35%	< 0.001

André et al, Crit Care 2010

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Exemple of attitude at emergency department: a French prospective study

- Implementation of guidelines for FN therapy at an emergency department during the first 90 minutes:
- Severe Sepsis/septic shock
  - 1st wide IV spectrum ATB dose
  - Fluid challenge (500 mL) if TAm < 65 mmHg
  - Lactate measurement
  - At least one blood culture
  - Hospitalisation
- Other patients
  - High risk according to MASCC score: IV ATB; no G-CSF; hospitalisation.
  - Low risk according to MASCC score: oral ATB; no de G-CSF; back home

André et al, Crit Care 2010

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How are these guidelines implemented ?

Table 6 Characteristics of the management of febrile neutropenia in patients with or without severe sepsis

Management in the ED	Patients with severe sepsis (n = 89)	Patients without severe sepsis	
		High risk (n = 38)	Low risk (n = 70)
Adequate antimicrobial therapy	28 (32)	30 (81)	31 (44)
Supportive treatment			
Fluid challenge	43 (49)	5 (14)	6 (9)
Vasoactive drugs	6 (7)	0 (0)	0 (0)
Laboratory data			
Lactate concentration	29 (33)	1 (3)	11 (16)
Blood cultures	87 (99)	36 (100)	63 (93)
New prescription of G-CSF	12 (14)	4 (11)	12 (17)
Adequate orientation	88 (99)	35 (95)	6 (9)
Global adequate management	6 (7)	26 (68)	1 (1)

André et al, Crit Care 2010

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