Management of hospital-acquired pneumonia in the Asian Pacific region

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Incidence of HAP

- Reported incidence

Country	Incidence		Remark
Korea	6.3	1,000 hospital admissions	National data (2000)
Philippines	6	1,000 hospital admissions	National data (2006)
Thailand	21.8	1,000 hospital admissions	
Taiwan	0.5 - 0.8	1,000 patient days	National data (2006)
China	1	1,000 patient days	
USA*	5 – 15	1,000 hospital admissions	National data*

- HAP : 25 % of all ICU infections (USA)

  90 % of ICU HAP – mechanical ventilation

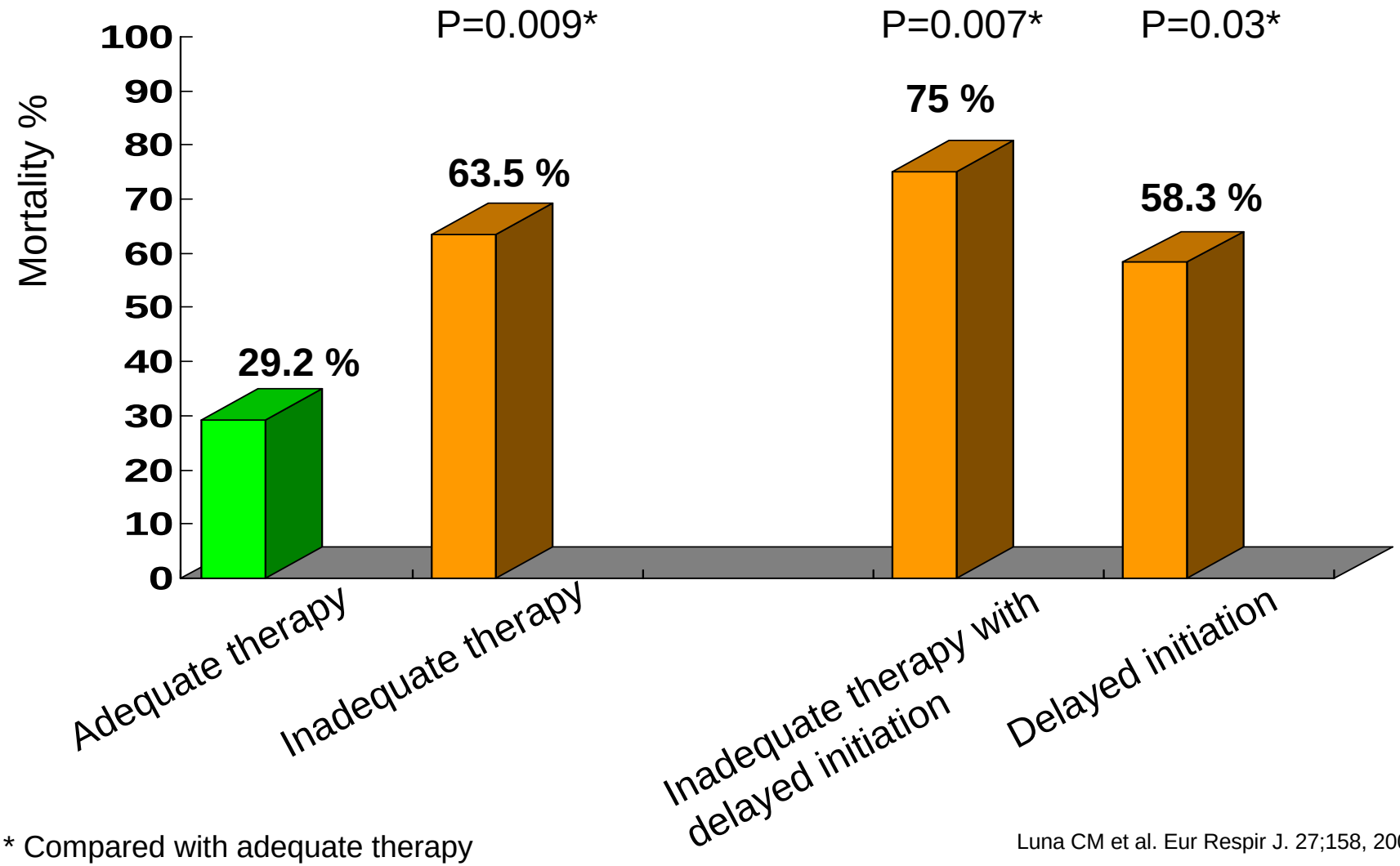
Song JH et al. Am J Infect Control. In press, 2007 ;
* ATS. Am J Respir Crit Care Med. 171;388-416, 2005

Mortality rate of HAP

Country	Mortality rate (%)
USA	Crude 30 – 70 % Attributable 33 – 50 %
India	37 – 47 %
Pakistan	58 %
China	25.8 %
Thailand	26 – 28 %
Philippines	42.4 %

Song JH et al. Am J Infect Control. In press, 2007

Impact of inappropriate therapy in HAP



* Compared with adequate therapy

Luna CM et al. Eur Respir J. 27;158, 2006

Impact of inappropriate therapy in HAP

Pathogen	Inappropriate therapy / Delayed initiation of appropriate therapy		Appropriate therapy	
	Total	Died	Total	Died
Acinetobacter	**19**	**13 (68 %)**	**7**	**3 (43 %)**
P.aeruginosa	**17**	**12 (71 %)**	**2**	**1 (50 %)**
K.pneumoniae	2	1 (50 %)	3	2 (67 %)
E. cloacae	2	2 (100 %)	-	-
E. coli	-	-	2	0 (0 %)
S. aureus				
MSSA	3	3 (100 %)	3	0 (0 %)
MRSA	13	6 (46 %)	6	2 (33 %)

Luna CM et al. Eur Respir J. 27;158, 2006

Need for treatment guidelines : Asian perspectives

- Clinical impact of HAP & VAP : high mortality
- Difficult diagnosis : etiologic diagnosis
- Antimicrobial resistance in major pathogens : Asia
- Frequent antibiotic abuse and misuse

  → antimicrobial resistance or treatment failure

⇨ Consensus guidelines for appropriate use of antibiotics in the treatment of HAP & VAP in Asia

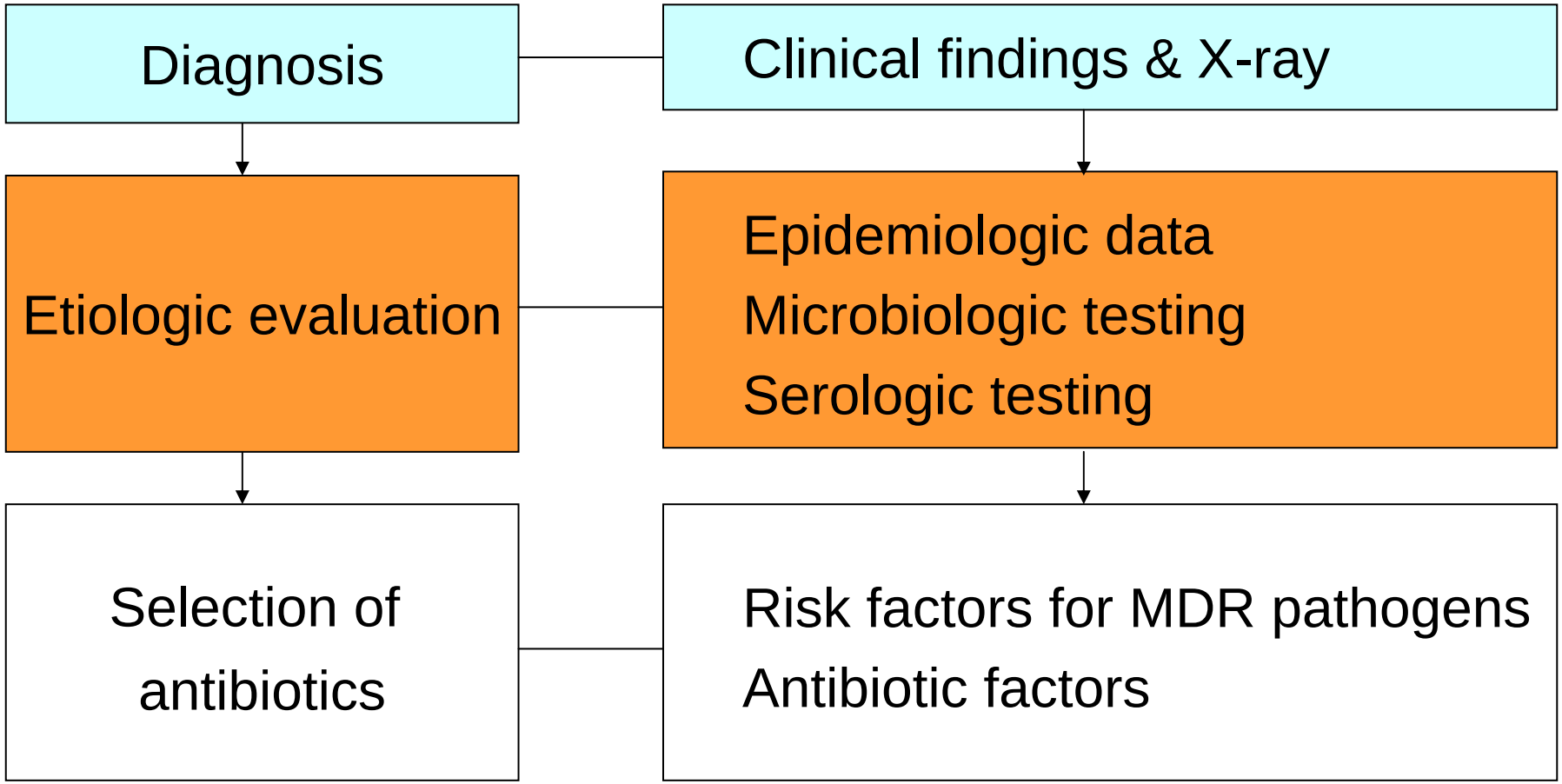
HAP : early vs late-onset

- Early onset
  - Occurring < 5 days after hospital admission
  - Commonly associated with antibiotic-sensitive bacteria
    : *H.influenzae,* oxacillin-sensitive *S. aureus,* and *S. pneumoniae*
  - No risk factors for infection due to potentially antibiotic-resistant bacteria :
    antibiotic treatment or prior health care facility exposure

- Late onset
  - Occurring ≥ 5 days after hospital admission
  - Usually antibiotic-resistant bacteria
    : MRSA, *P. aeruginosa, Acinetobacter* spp., and *Enterobacter* spp.

ATS. Am J Respir Crit Care Med. 171;388, 2005
Ibrahim EH, et al. Chest. 117:1434, 2000 ;
Trouillet JL, et al. Am J Respir Crit Care Med. 157;531, 1998

Approach to treatment of HAP



Major pathogens of HAP

Pathogen	%
S. aureus	18.1
P. aeruginosa	17.0
Enterobacter spp.	11.2
K. pneumoniae	7.2
E. coli	4.3
H. influenzae	4.3
Other pathogens	37.9

* NNIS Data (January 1992 to May 1999), USA

Am J Infect Control. 1999;27:520-532.

Etiology of HAP : Asian situation

Rank	Korea	China	Taiwan	Thailand	Malaysia	Philippines*	India	Pakistan
1	P. aerug (23 %)	P.aeru (18 %)	P.aeru (21 %)	A.baum (28 %)	A.baum (23 %)	P.aeru (42.1 %)	A.baum (38 %)	A.baum (58 %)
2	MRSA (23 %)	MRSA (16 %)	A.baum (20 %)	P.aeru (18 %)	P.aeru (17.6 %)	K.pn (26.3 %)	K.pn (23 %)	MRSA (18 %)
3	K. pn (11 %)	A.baum (16 %)	MRSA (16 %)	K.pn (7.7 %)	MRSA (11.8 %)	A.baum (13.1 %)	P.aeru (20 %)	P.aeru (18 %)
4	A.baum (9 %)	K.pn (14 %)	K.pn (9 %)	MRSA (7.6 %)	S.malto (11.8 %)		MRSA (5 %)	
5	E.cloa (8 %)	E.cloa (8 %)	E.coli (3.6 %)	E.coli (2.8 %)	K.pn (5.8 %)			

* Philippines : VAP data

Song JH et al. Am J Infect Control. In press, 2007

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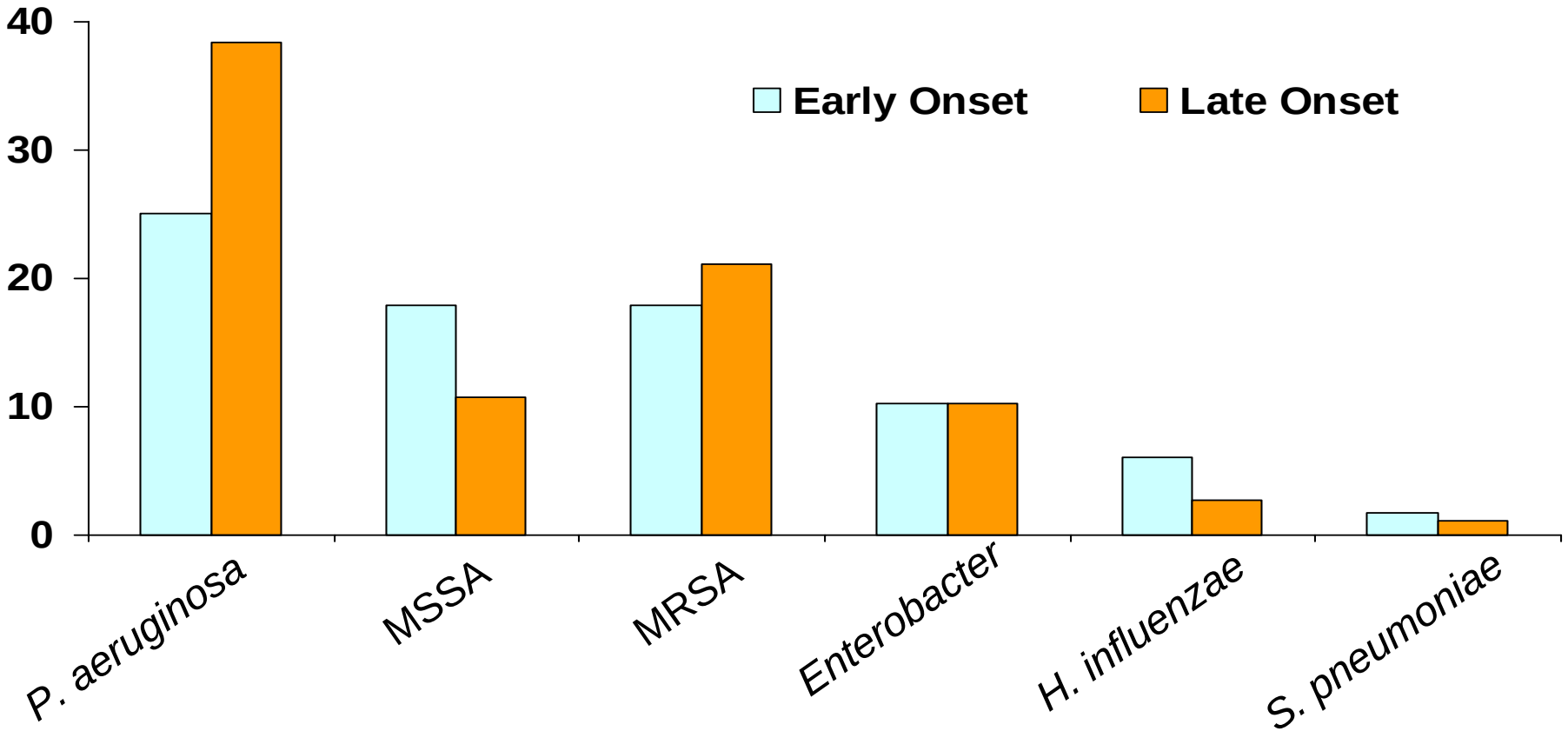
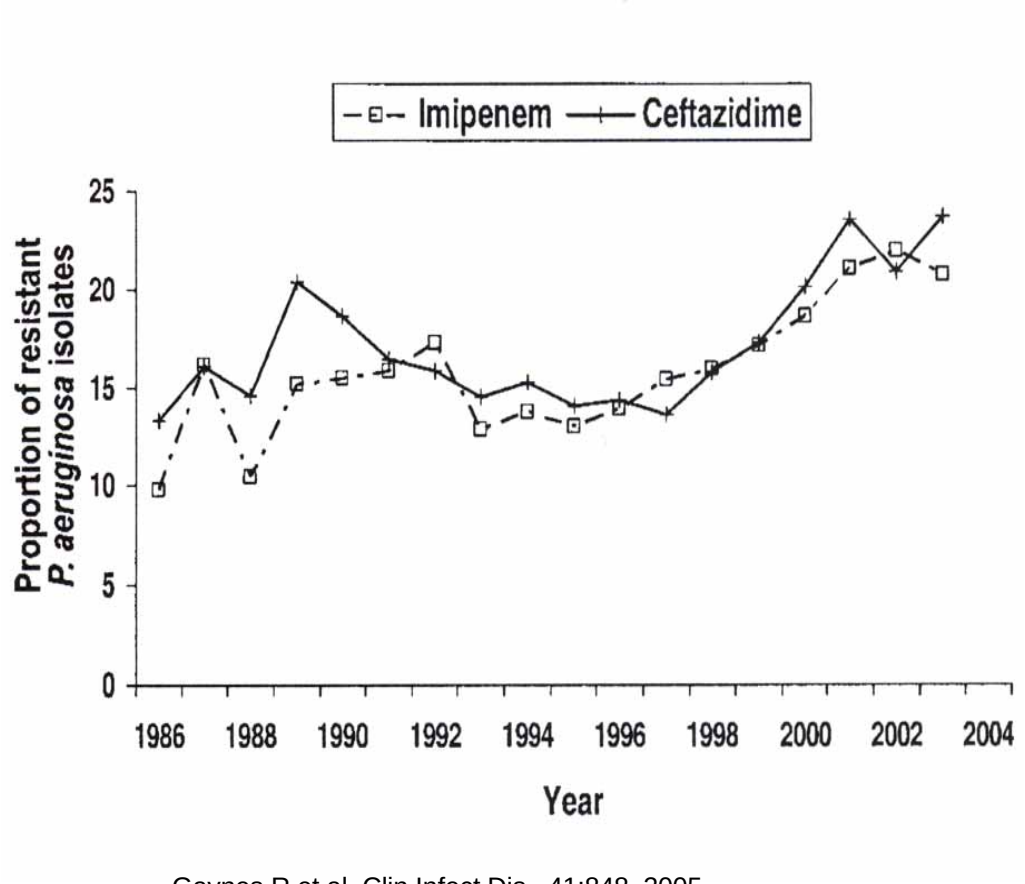
Microbiology of HAP : early vs late-onset



Ibrahim EH, et al. Chest. 117:1434, 2000

Antimicrobial resistance in *P. aeruginosa*

USA



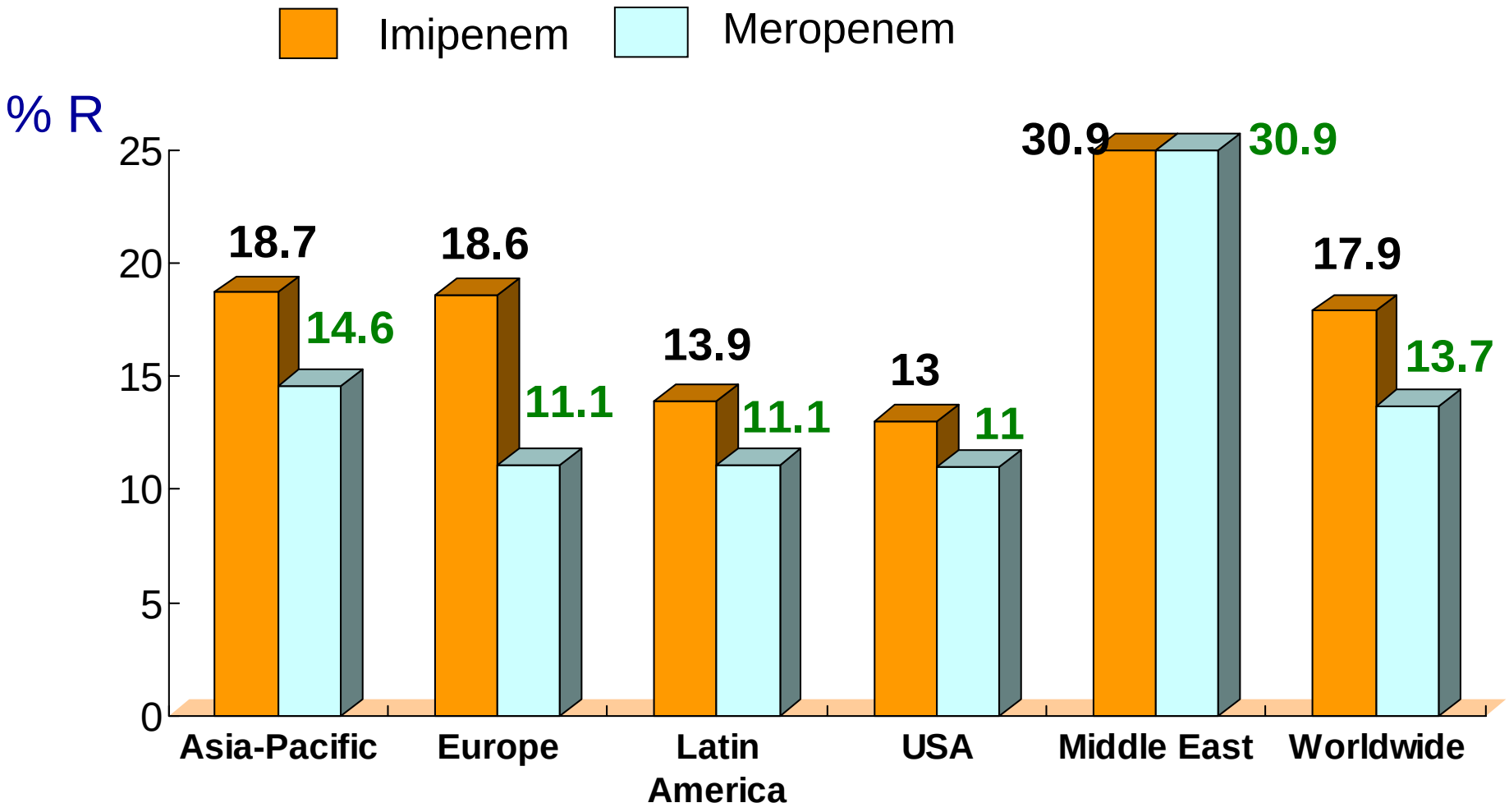
Gaynes R et al. Clin Infect Dis. 41;848, 2005

Antibiotics	Korea (2003)	SENTRY+ (2001-2004)
Ceftazidime*	19	18.7
Imipenem*	20	12.5
Ciprofloxacin	40	25.3

+ Global data (8,705 isolates)

Lee K et al. J Korean Med Sci. 19;8, 2004 ;
Lee K et al. Yonsei Med J. 47;43, 2006 ;
Gales AC et al. Clin Microbiol Infect 12;315;2006

Carbapenem resistance in *P. aeruginosa*



Paterson DL et al. J Antimicrob Chemother 55;965. 2005

Antimicrobial resistance in *P. aeruginosa*

- Multidrug-resistant *P.aeruginosa* (China)

1996	1998	1999	2000	2001	2002
11.5 %	11.5	11.7	16.3	14.9	20.5

- Emergence of pandrug-resistant *P.aeruginosa* (Taiwan)

  37 strains (2003) resistant to all available anti-pseudomonal agents

  clinical infections : pneumonia, catheter infection, abscess

  associated with increasing use of ciprofloxacin and imipenem

  associated with increased mortality

Wang H. et al. Diag Microbiol Infect Dis. 51;201, 2005 ;
Wang CY et al. Clin Microbiol Infect 12;63, 2006

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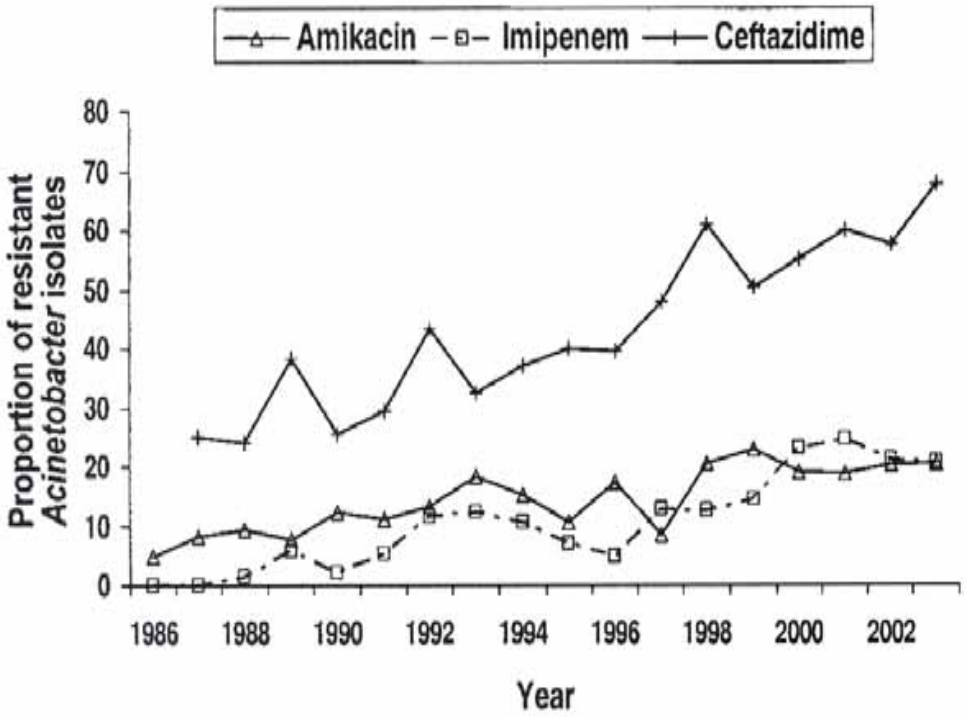
Antimicrobial resistance in *Acinetobacter* spp.

USA



Gaynes R et al. Clin Infect Dis. 41;848, 2005

Antibiotic	% resistance		
	Korea (2003)	Taiwan (2003)	SENTRY (2001-04)
Ceftazidime	55	48	48
Cefepime	41	46.5	37
Imipenem	13	24.2 (meropenem)	16
Ciprofloxacin	58	49	55
Amikacin	54	45	36
Amp/sulb	22	ND	31.6
Polymyxin B	ND	ND	**2.1**

Lee K et al. J Korean Med Sci. 19;8, 2004 ;
Lee K et al. Yonsei Med J. 47;43, 2006 ;
Gales AC et al. Clin Microbiol Infect 12;315;2006 ;
Hsueh PR et al. Int J Antimicrob Agents. 26;463, 2005

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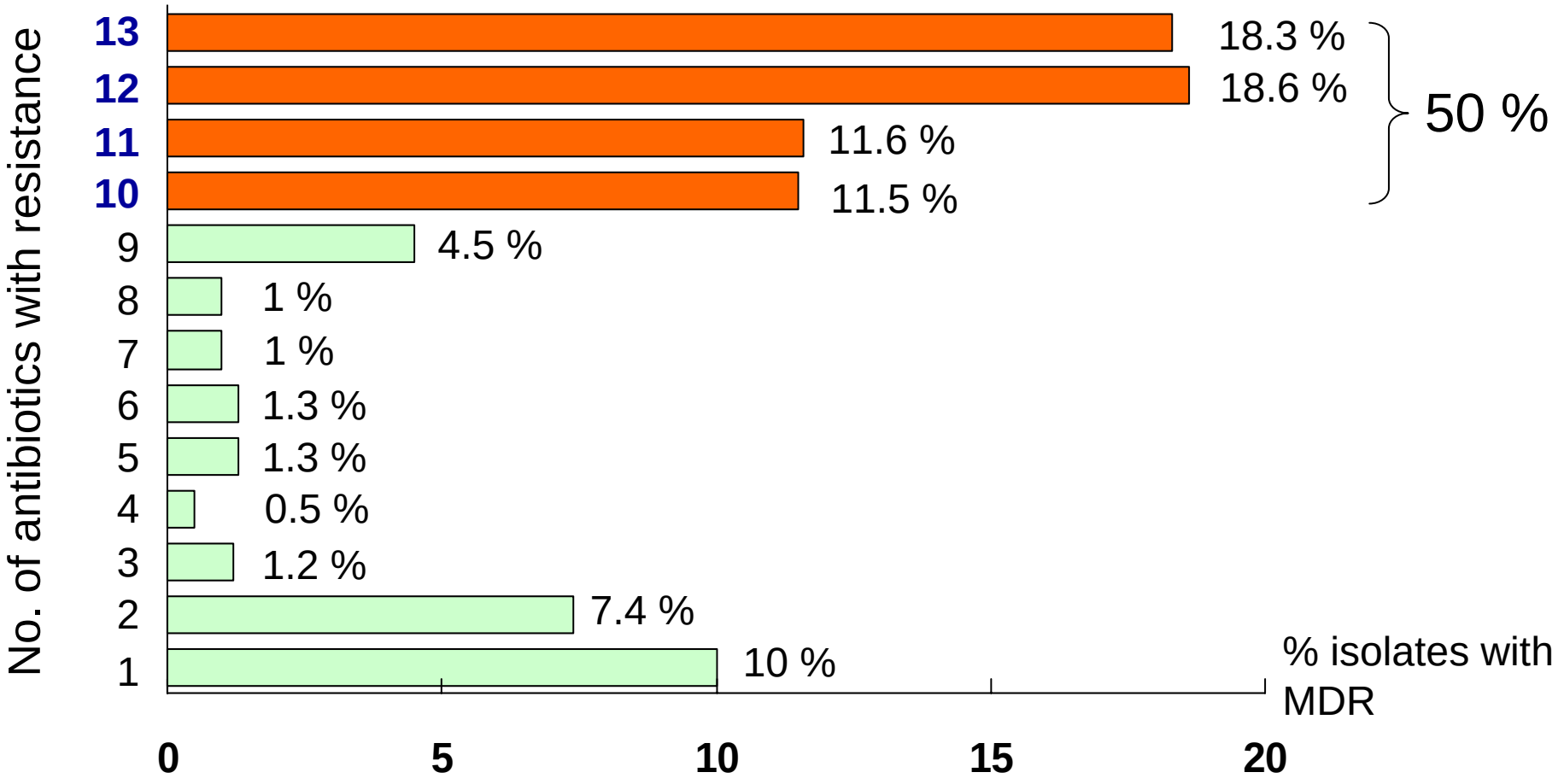
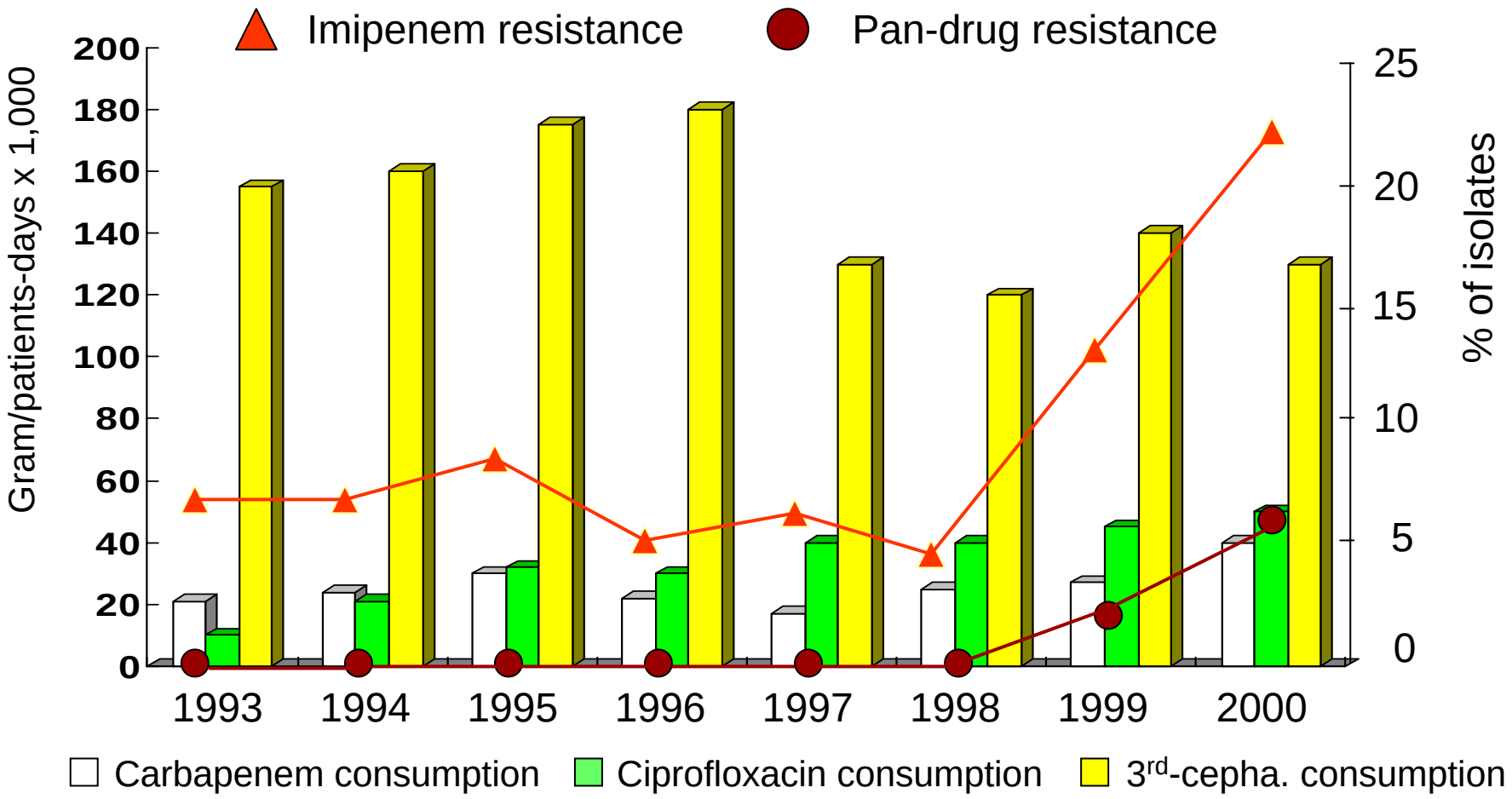
Multidrug resistance in *Acinetobacter* spp.



* Data from YUMC, Korea

Lee K et al. Yonsei Med J. 47;43, 2006

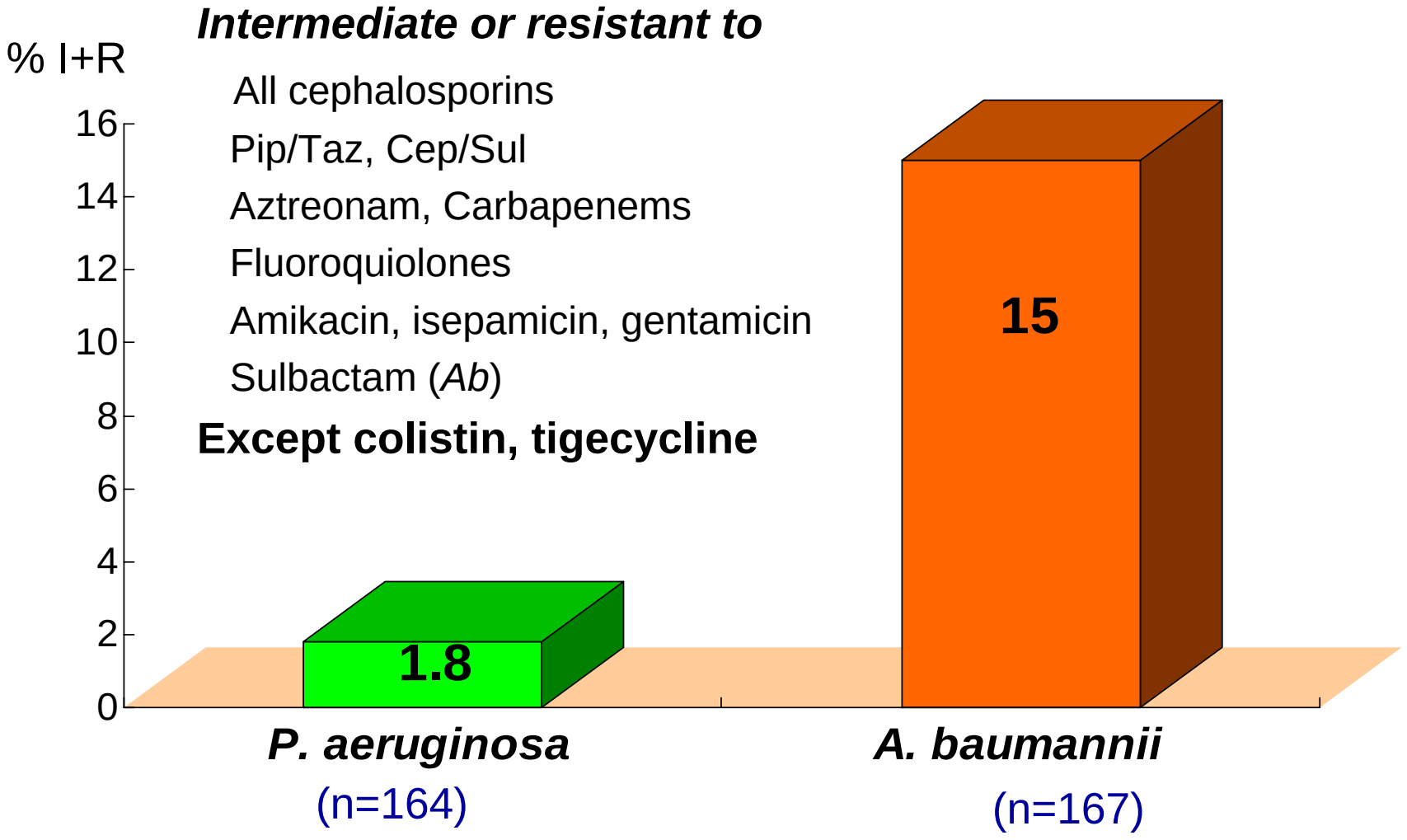
Pandrug resistance in *Acinetobacter* spp.



* Data from NTUH, Taiwan

Hsueh et al. Emerg Infect Dis. 8;827, 2002

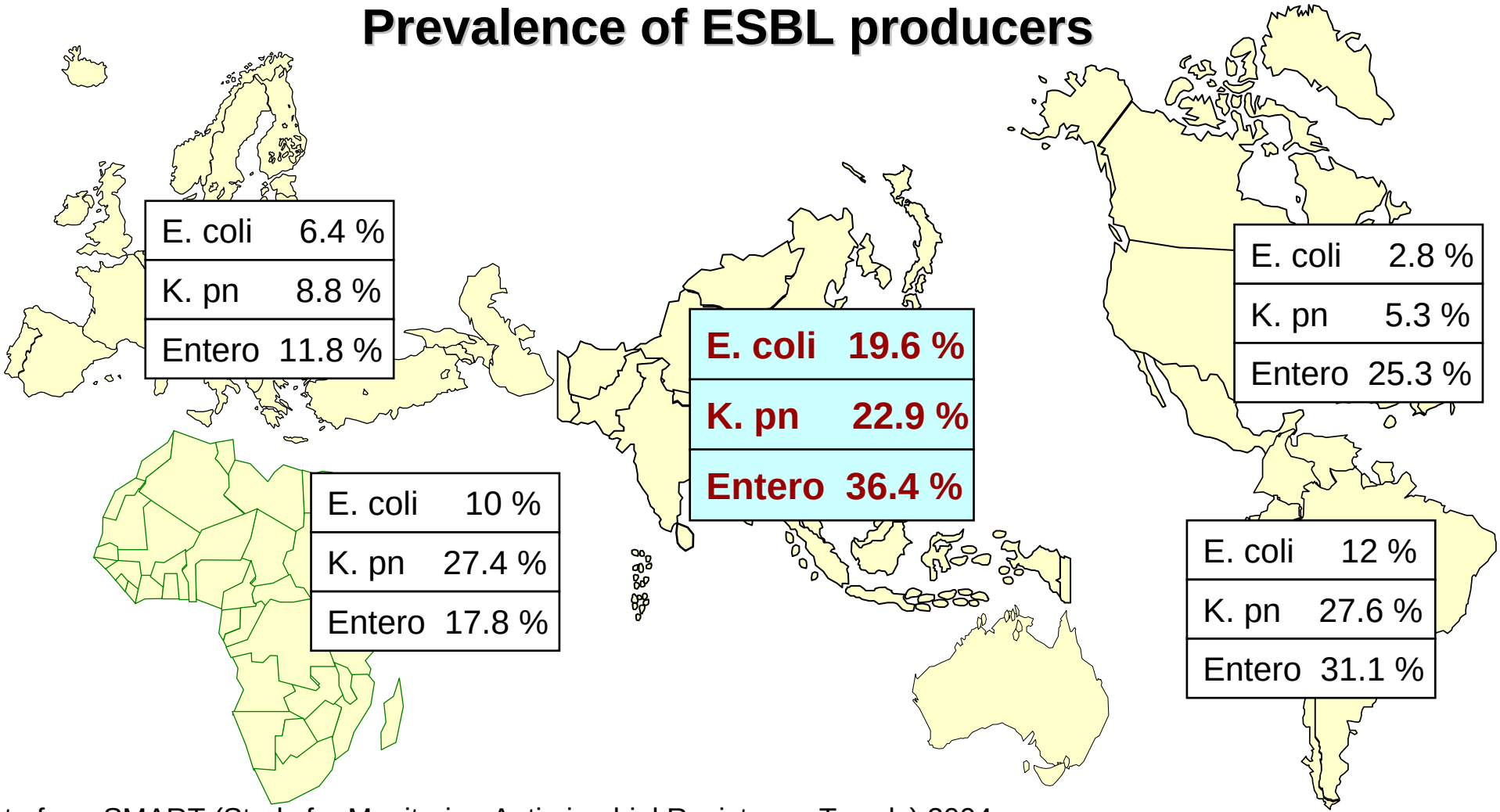
Pandrug resistance in *Acinetobacter* spp.



* SMART surveillance, ICUs (2004)

Data from Hsueh PR, ISAAR 2005

ESBL-producing Gram-negative bacilli



* Data from SMART (Study for Monitoring Antimicrobial Resistance Trends) 2004

Rossi F et al. J Antimicrob Chemother. 58;205, 2006

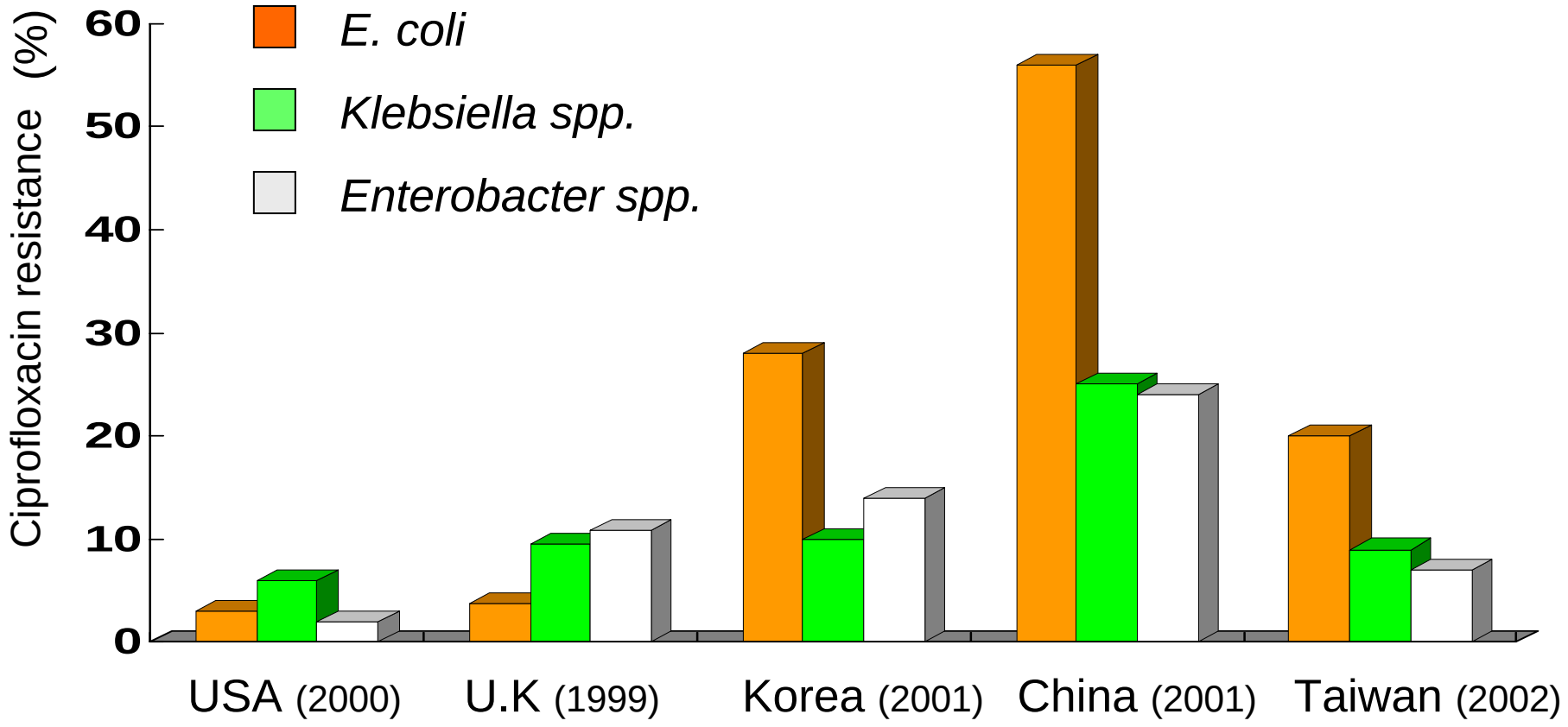
ESBL+ Gram-negative bacilli in AP region

Country	% of ESBL-producing strains	
	E. coli	*K. pneumoniae*
China	24.5	30.7
Hong Kong	14.3	11.6
Japan	2.4	10.0
Philippines	5.0	21.9
Singapore	11.3	35.6
Taiwan	5.6	13.5
Australia	0.5	3.7
Korea*	4.8 - 7.5	22.5 - 22.8

* SENTRY surveillance (1998-2002) except Korea

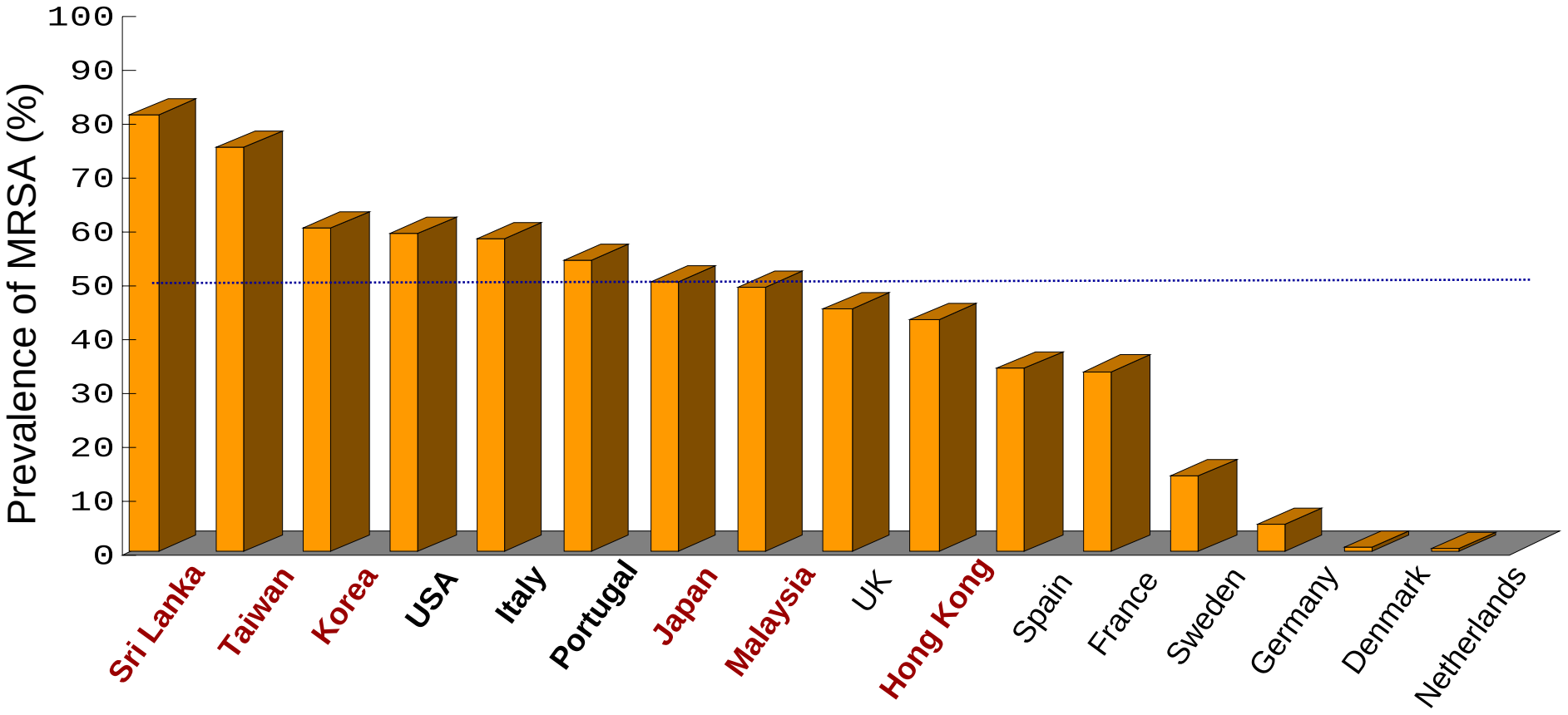
Hirakata Y et al. Diag Microbiol Infect Dis. 52;323, 2005;
Pai H*. Yonsei Med J. 39:514, 1998

Fluoroquinolone resistance in GNB



Pfaller et al. Diag Microbiol Infect Dis. 41;177, 2001; Livermore et al. Emerg Infect Dis. 8;473, 2002 ; Lee K et al. J Korean Med Sci. 16; 262, 2001; Hsueh PR et al. Emerg Infect Dis. 8;132,2002; Wang F et al. J Infect Chemother. 7;117, 2001

Worldwide prevalence of MRSA



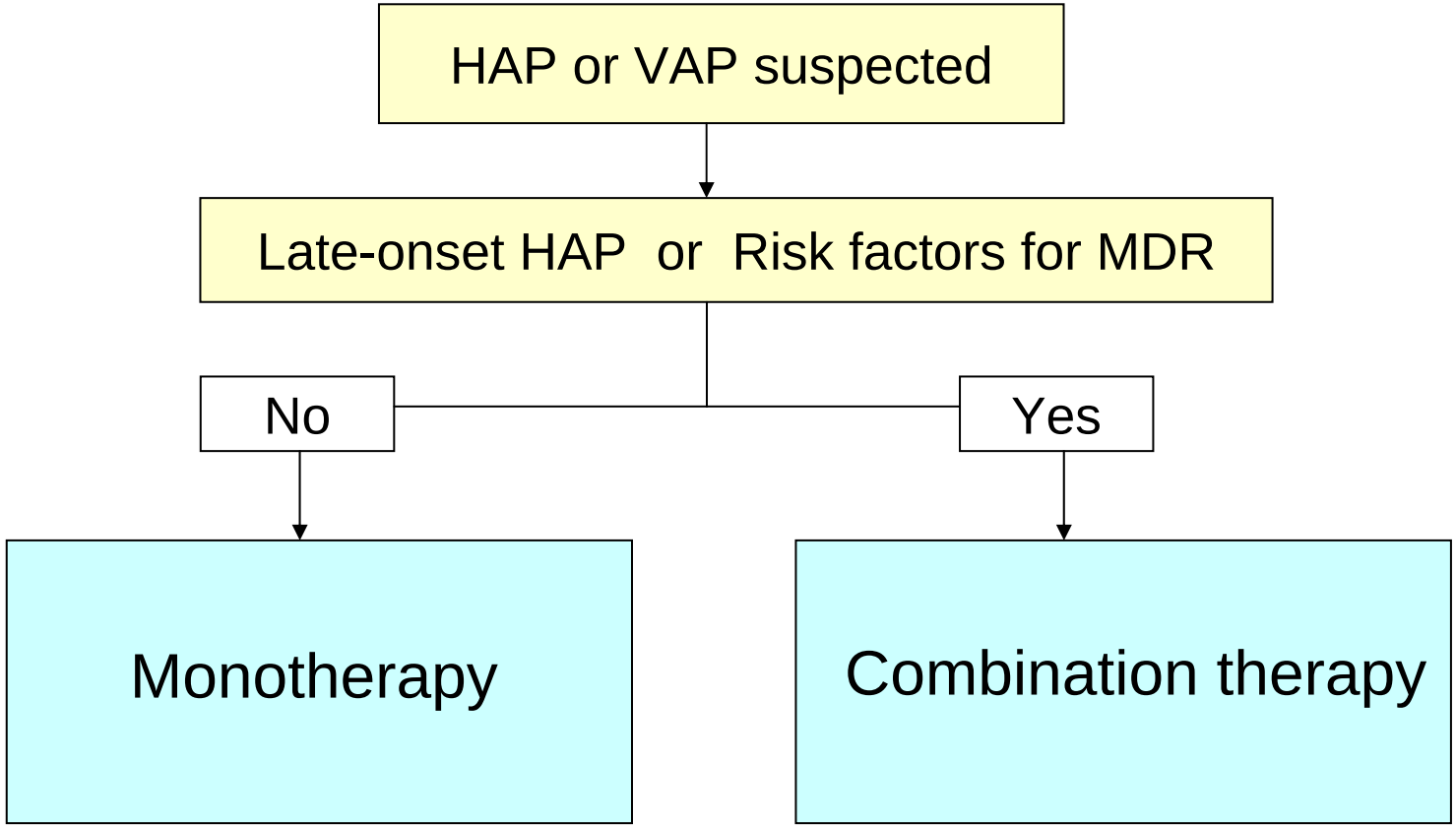
ANSORP surveillance (2005-2006); NNIS. Am J Infect Control. 32;470, 2004 ;
Hsueh PR et al. Int J Antimicrob Agents. 26;45-9, 2005 ; Bertrand X et al. Med mal Infect. 35;329, 2005

Risk factors for MDR pathogens in HAP

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of ≥ 5 days
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP :
  - hospitalization for ≥ 2 days in the preceding 90 days
  - residence in a nursing home
  - home infusion therapy
  - chronic dialysis within 30 days
  - home wound care
  - family member with MDR pathogens
- Immunosuppressive disease and/or therapy

ATS. Am J Respir Crit Care Med. 171;388-416, 2005

Initial empiric therapy : ATS / IDSA approach



ATS. Am J Respir Crit Care Med. 171;388-416, 2005

Initial empiric therapy for HAP

- Choice of specific agents should be dictated by local microbiology and resistance pattern, cost, availability, and formulary restriction -- "Best empiric therapy regimen"
- For patients who have recently received an antibiotic, a different antibiotic class is recommended
- Initial antibiotic therapy should be given promptly because delays may add to excess mortality

ATS. Am J Respir Crit Care Med. 171;388-416, 2005 ;
Song JH et al. Am J Infect Control. In press, 2007

Initial empiric therapy for HAP

- For patients with severe VAP or suspected MDR pathogens, patients should initially receive combination therapy which could be switched to a single agent after culture results
- Rationale for combination therapy for HAP
  - Synergy (against *P. aeruginosa*)
  - Prevention of the emergence of resistance
  - Broad coverage of potential pathogens
- If patients receive combination therapy with an aminoglycoside-containing regimen, aminoglycosides can be stopped after 5-7 days in responding patients

ATS. Am J Respir Crit Care Med. 171;388-416, 2005 ;
Song JH et al. Am J Infect Control. In press, 2007

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Initial empiric therapy : ATS / IDSA approach

HAP onset	MDR risk factors	Potential pathogens	Recommended antibiotics
Early	No	*S. pneumoniae* *H. Influenzae* MSSA Antibiotic-susceptible GNB	Ceftriaxone or Levofloxacin, Moxifloxacin, Ciprofloxacin or Ampicillin/sulbactam or Ertapenem
Late	Yes	MDR *P. aeruginosa* ESBL (+) *Klebsiella* MDR *Acinetobacter* MRSA	Cefepime, ceftazidime or Imipenem, meropenem or Piperacillin-tazobactam + Ciprofloxacin, Levofloxacin or Aminoglycosides + Linezolid or Vancomycin

ATS. Am J Respir Crit Care Med. 171;388-416, 2005

Initial empiric therapy : Asian perspectives

Type of HAP	Initial empiric regimen
Early-onset HAP	Same monotherapy regimens recommended by ATS / IDSA
Late-onset HAP	Same combination regimens recommended by ATS / IDSA
	Alternative options against MDR *Acinetobacter* spp.* - cefoperazone/sulbactam + FQs or AGs or ampicillin/sulbactam - FQs (cipro) + AGs +/- glycopeptides or linezolid

* These options are used in some Asian countries without evidence of clinical usefulness

Song JH et al. Am J Infect Control. In press, 2007

Specific treatment : *P. aeruginosa*

Current standard options

Cefepime or Ceftazidime

or

Piperacillin-tazobactam

or

Imipenem or Meropenem

+

Amikacin or Tobramycin

or

Ciprofloxacin

ATS. Am J Respir Crit Care Med. 171;388-416, 2005 ;
Song JH et al. Am J Infect Control. In press, 2007

Specific treatment : *Acinetobacter* spp.

Current options

- In vitro active agents : colistin, sulbactam, tigecycline, minocycline
- In vitro synergy : meropenem+sulbactam, cefepime+amp/sulb
  colistin+rifampin, colistin+meropenem,
  colistin+azithromycin, colistin+doxy
- Clinical data : colistin
  colistin+rifampin
  sulbactam, ampicillin/sulbactam, or sulperazone

Livermore DM. Ann Med. 35;226, 2003
Murray CK et al. Curr Opin Infect Dis. 18;502, 2005
Timurkaynak F et al. Int J Antimicrob Agents. 27; 224, 2006
Taccone FS. Eur J Clin Microbiol Infect Dis. 25;257, 2006

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Specific treatment : MDR non-fermenters

Colistin

- Polymixin B
  Polymixin E : Colistin -- Colistin sulfate, Colistimethate sodium
- In vitro active against MDR Gram-negative bacilli
- Promising clinical usefulness in the treatment of HAP / VAP caused by MDR GNB
- Adverse reactions : nephrotoxicity, neurotoxicity

Li J et al. Lancet Infect Dis. 6;589, 2006

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Colistin* for MDR non-fermenter infection

Author	Diseases (No. of patients)	Pathogens	Clinical cure (or improvement)
Reina	VAP (29), bacteremia (9), UTI (10), others (7)	P.aeruginosa (19) A.baumanii (36)	**15 %** (day 6 of treatment)
Michalopoulos	HAP (31), bacteremia (14)	P.aeruginosa (35) A.baumanii (8)	**69.8%**
Falagas	HAP (11), bacteremia (1) UTI (2)	P.aeruginosa (10) A.baumanii (4)	**52.6 %**
Levin	HAP (19), UTI (12), bacteremia (9)	P.aeruginosa (21) A.baumanii (28)	**58 %**
Garnacho	VAP (21)	A.baumanii (21)	**57 %**
Linden	HAP (18), bacteremia (8)	P.aeruginosa (23)	**61 %**
Markou	VAP (15), sepsis (4)	P.aeruginosa (18) A.baumanii (6)	**73 %**

* IV colistimethate sodium

Li J et al. Lancet Infect Dis. 6;589, 2006

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Specific treatment : MDR non-fermenters

Inhaled colistin therapy

- 21 patients with HAP and were treated with nebulized colistin sulphomethate
- *A. baumanii* 17, *P. aeruginosa* 4
- Treatment response :
  - Favorable response : 18 / 21 (**85.7 %)**
    - Favorable clinical & microbiological outcomes : 12 / 21 (**57.1 %**)
    - Favorable microbiologic outcome only : 6 / 21 (28.6 %)
    - Documented microbiologic eradication : 11 / 21 (61.1 %)
  - Death : 10 / 21 (47.6 %)
    - Attributable mortality : 3 / 21 (14.3 %)
    - 7 patients cured of MDR pneumonia and died of underlying diseases
- Adverse reactions : No nephrotoxicity or neurotoxicity

Kwa AL et al Clin Infect Dis. 41;754, 2005

Emergence of colistin resistance

Antibiotic	Total+		*A.baumanii* subgroup I*		*A.baumanii* subgroup II		*A.baumanii* subgroup III	
	R (%)	MIC90	R (%)	MIC90	R (%)	MIC90	R (%)	MIC90
Polymixin B	**18.1**	**8**	**2.1**	**2**	**38.9**	**8**	**72.2**	**32**
Colistin	**27.9**	**32**	**7.0**	**2**	**64.8**	**64**	**88.9**	**>64**
Ciprofloxacin	28.7	>64	45.1	>64	1.9	1	16.7	>64
Rifampin	2.3	8	1.4	8	3.7	4	0	4
Amikacin	30.2	>128	37.3	>128	18.5	128	11.1	>128
Imipenem	8.3	8	8.5	8	0	1	5.6	1
Ceftazidime	35.1	>64	45.8	>64	13	>64	16.7	>64
Pip/tazo	25.3	>256/4	43	>256/64	1.9	16/4	11.1	256/4
Amp/sulb	23.4	>64/32	40.1	>64/32	0	4/2	11.1	64/32
MDR	**33.2**		**45.1**		**13**		**16.7**	

+ 265 isolates of *A.baumanii* from 2 Korean hospitals

* Subgrouping based on *rpo*B gene sequence

Ko KS, Song JH et al. J Antimicrob Chemother. In press, 2007

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New antibiotic options against non-fermenters

Agent	Class	Company	Current status	Remark
Doripenem	Carbapenem	Johnson & Johnson	NDA	
Tigecycline	Glycylcycline	Wyeth	Marketed	No effect against Pseudomonas
Ceftobiprole	Cephalosporin	Johnson & Johnson	NDA	Equivalent to cefepime
Sitafloxacin	Fluoroquinolone	Daiichi	Phase III	

Rice L. Clin Infect Dis. 43;S100, 2006 ;
Mesaros N et al. Clin Microbiol Infect 13;560, 2007

Doripenem against non-fermenters

Antibiotics	*P. aeruginosa*		*Acinetobacter* spp.	
	MIC_{90}	% resistance	MIC_{90}	% resistance
Doripenem	8	NA	4	NA
Ertapenem	> 8	NA	> 8	NA
Imipenem	> 8	13.5	2	7.1
Meropenem	16	11.7	8	7.7
Cefepime	> 16	11.6	> 16	29.7
Ceftazidime	> 16	19.2	> 16	37.1
Piperacillin/Tazobactam	256	18.2	> 256	43.9

Fritsche TR et al. Clin Microbiol Infect. 11;974, 2005

Tigecycline against MDR *Acinetobacter* spp.

Organism		MIC90 (mg/L)	
S.aureus :	All	0.25 – 0.5	
	MRSA	**0.25 – 0.5**	√
	VISA / VRSA	0.5	
Enterococci :	All	0.12 – 0.5	
	VRE	0.25	
S.pneumoniae :	All	0.12 – 0.25	
	PRSP	0.12 – 0.25	
E.coli :	All	0.25 – 0.5	
	ESBL+	**0.5 – 1**	√
K.pneumoniae :	All	0.5 – 1	
	ESBL+	**1 – 2**	√
Acinetobacter spp.		**2**	√
B.fragilis		2 - 4	

Stein GE et al. Clin Infect Dis. 43;518, 2006

Tigecycline against MDR *Acinetobacter* spp.

Treatment	No. of cases	No (%) of patients		
		Clinical resolution	Microbial eradication	Microbial failure
Tigecycline	5	5 (100 %)	3 / 3 (100 %)	0 / 3 (0 %)
Tigecycline + Imipenem	9	9 (100 %)	4 / 4 (100 %)	0 / 4 (0 %)
Tigecycline + Imipenem + Colistimethate	4	3 (75 %)	2 / 3 (67 %)	1 / 3 (33 %)
Tigecycline + Colistimethate	7	4 (57 %)	3 / 5 (60 %)	2 / 5 (40 %)
Total	25	21 (84 %)	12 / 15 (80 %)	3 / 15 (20 %)

* 25 cases of VAP/bacteremia caused by MDR *A.baumanii*

Schafer JJ et al. Pharmacother. 27;980, 2007

Treatment of ESBL+ Gram-negative bacilli

Drug	% susceptibility		
	K. pneumoniae	*E. coli*	*P. mirabilis*
Imipenem	98 – 100	100	98
Meropenem	99 – 100	100	100
Amikacin	52 – 100	92 – 93	96
Gentamicin	31 – 47	49 – 80	32 – 71
Ciprofloxacin	37 – 95	20 – 49	25 – 57

Mulvey *et al*. AAC 2004; 48:1204 - Hernandez *et al*. AAC 2005; 49:2122 - Luzzaro *et al*. JCM 2006; 44:1659; Goossens & Grabein DMID 2005; 53:257 - Hirakata et *al*. DMID 2005; 52:323

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Treatment of ESBL+ Gram-negative bacilli

Antibiotic	Fact	Recommendation
Carbapenems	Best clinical efficacy	Yes
Tigecycline	Promising clinical usefulness	Yes
3rd & 4th generation cephalosporins	Documented clinical failures	No
4th generation cephalosporins	Inoculum effect	No
β-lactam / β-lactamase inhibitor	Variable in vitro and in vivo efficacy	No
Fluoroquinolones	Frequent coexistence of FQ resistance	No
Cephamycin	ESBL producers with AmpC	Not for serious infections

Specific treatment : MRSA

Category	Class	Antibiotic*
Current standard	Glycopeptides	Vancomycin
		Teicoplanin
Current alternatives on the market	Oxazolidinone	Linezolid
	Streptogramin	Quinupristin/Dalfopristin
	Lipopeptide	Daptomycin
	Glycylcycline	Tigecycline
New investigational options	Cephalosporin	Ceftobiprole
	Glycopeptides	Telavancin
		Dalbavancin
		Oritavancin

Summary

- Treatment of HAP is becoming more difficult with the emergence of antibiotic resistance in major pathogens
- MDR non-fermenters such as *P.aeruginiosa* and *A.baumanii* and MRSA are the most common pathogens of HAP in Asian countries
- Treatment recommendations should be prepared based on prospective multinational surveillance studies on etiologic pathogens and antimicrobial resistance in Asian countries

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