

Management of hospital-acquired pneumonia in the Asian Pacific region

Jae-Hoon Song, MD, PhD

Samsung Medical Center

Asian Network for Surveillance of Resistant Pathogens (ANSORP)

Asian-Pacific Research Foundation for Infectious Diseases (ARFID)



Incidence of HAP

- Reported incidence

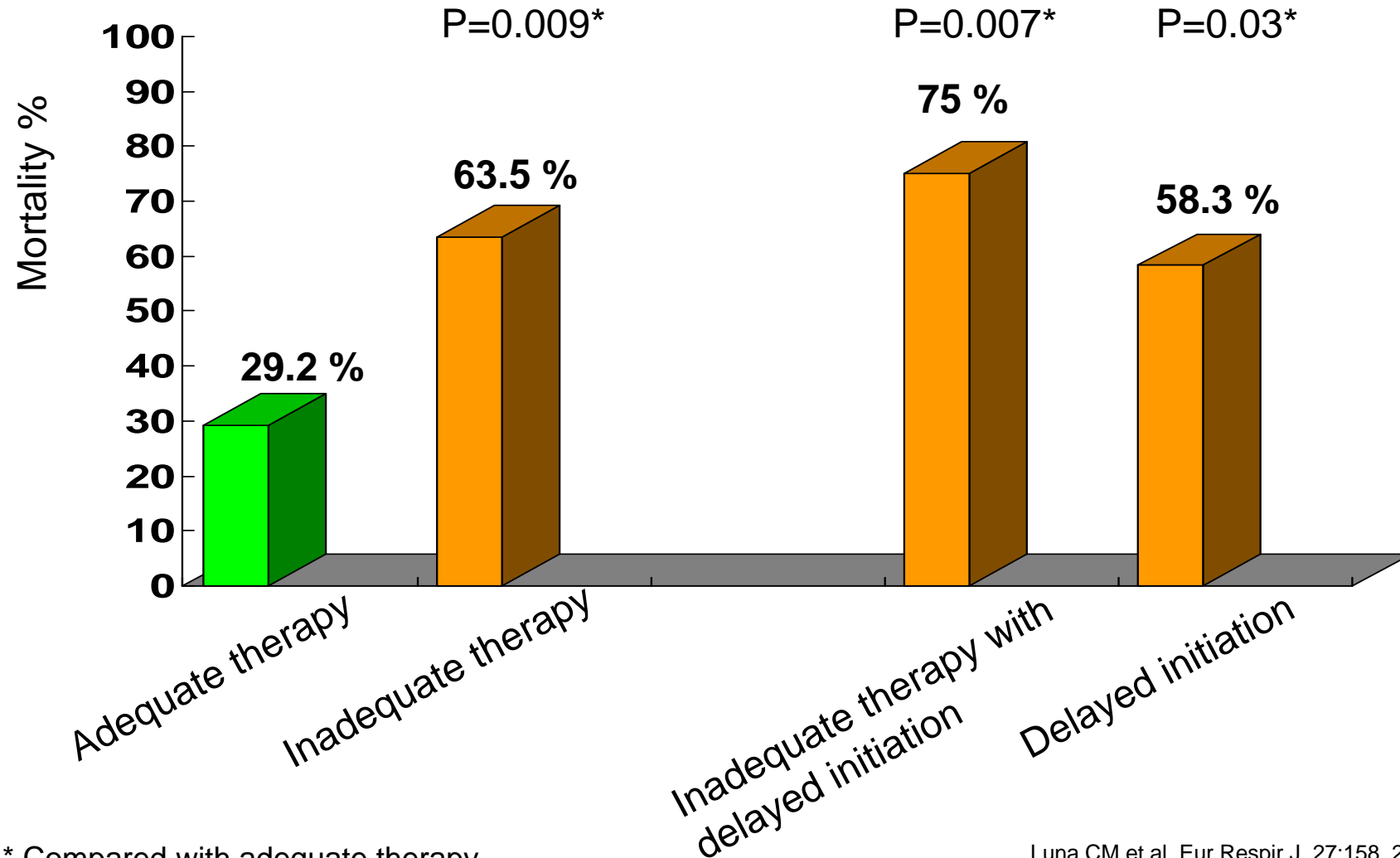
| Country | Incidence | | Remark |
|-------------|-----------|---------------------------|----------------------|
| Korea | 6.3 | 1,000 hospital admissions | National data (2000) |
| Philippines | 6 | 1,000 hospital admissions | National data (2006) |
| Thailand | 21.8 | 1,000 hospital admissions | |
| 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

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 % |

Impact of inappropriate therapy in HAP



* Compared with adequate therapy

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

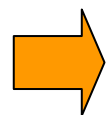


Impact of inappropriate therapy in HAP

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

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 \geq 5 days after hospital admission

Usually antibiotic-resistant bacteria

: MRSA, *P. aeruginosa*, *Acinetobacter* spp., and *Enterobacter* spp.

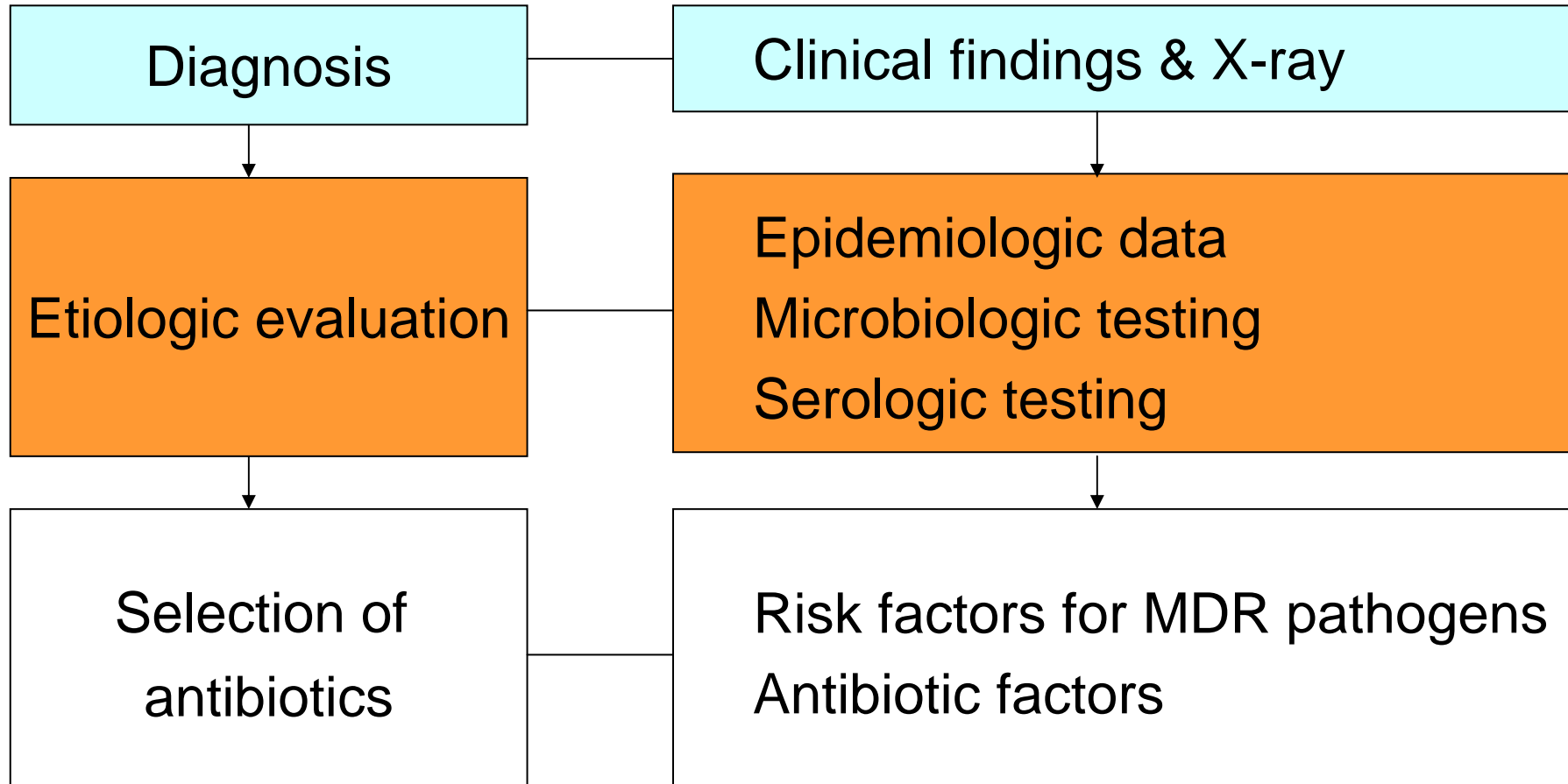
ATS. Am J Respir Crit Care Med. 171;388, 2005

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 | % |
|--------------------------|------|
| <i>S. aureus</i> | 18.1 |
| <i>P. aeruginosa</i> | 17.0 |
| <i>Enterobacter</i> spp. | 11.2 |
| <i>K. pneumoniae</i> | 7.2 |
| <i>E. coli</i> | 4.3 |
| <i>H. influenzae</i> | 4.3 |
| Other pathogens | 37.9 |

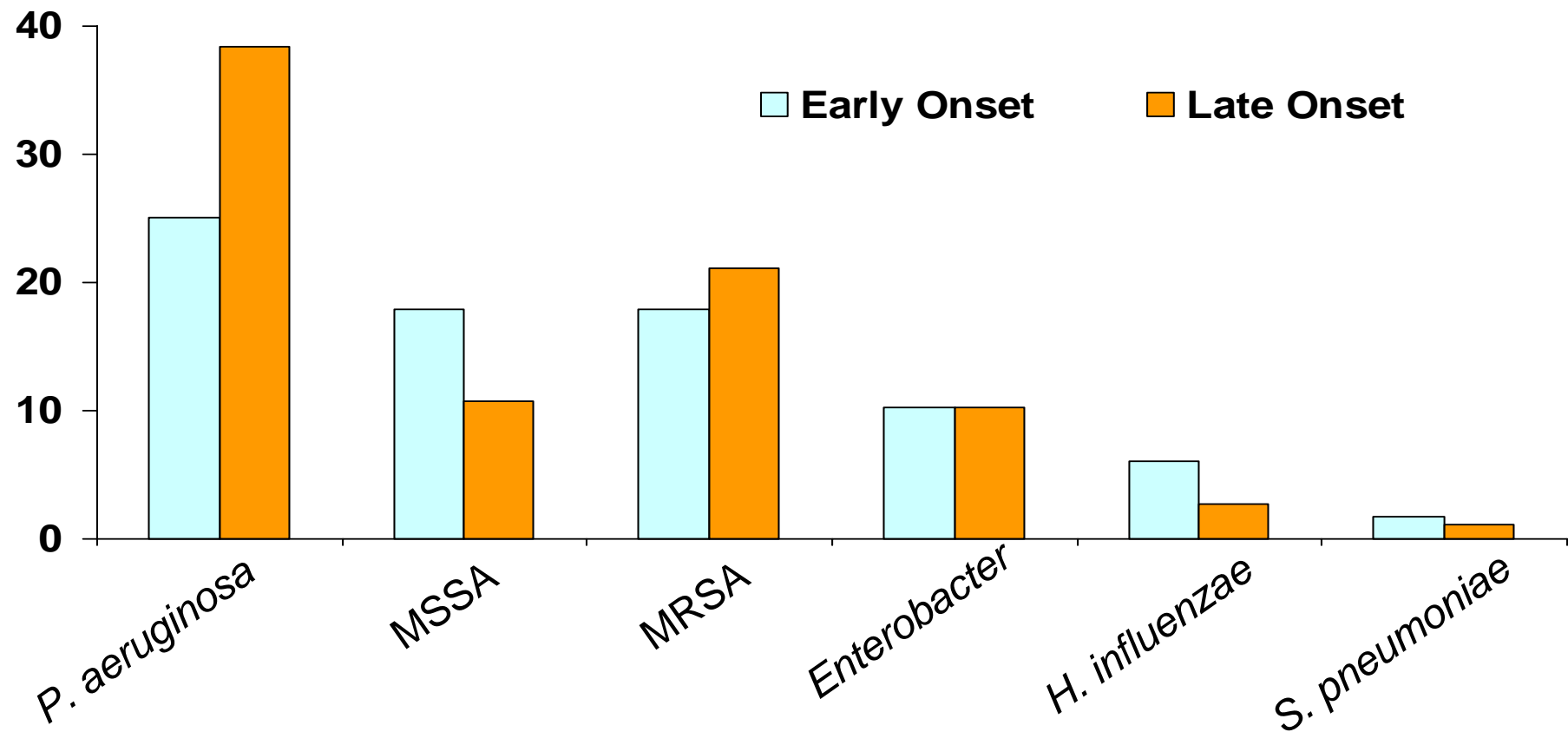
* NNIS Data (January 1992 to May 1999), USA

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 %) | | | |

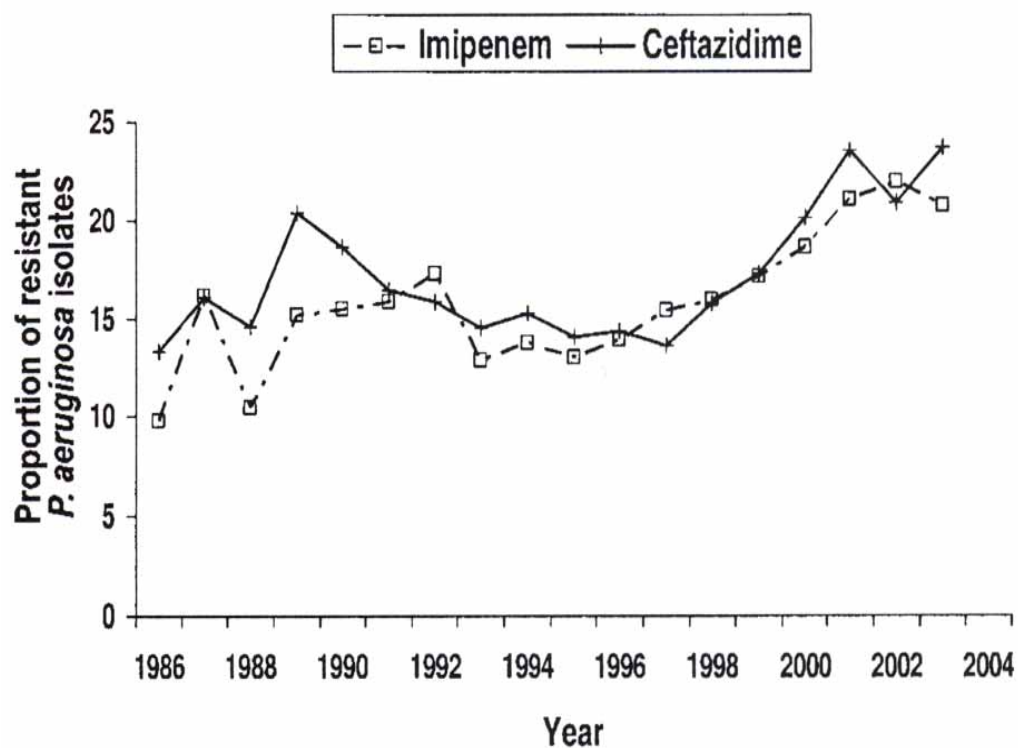
* Philippines : VAP data

Microbiology of HAP : early vs late-onset



Antimicrobial resistance in *P. aeruginosa*

USA



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

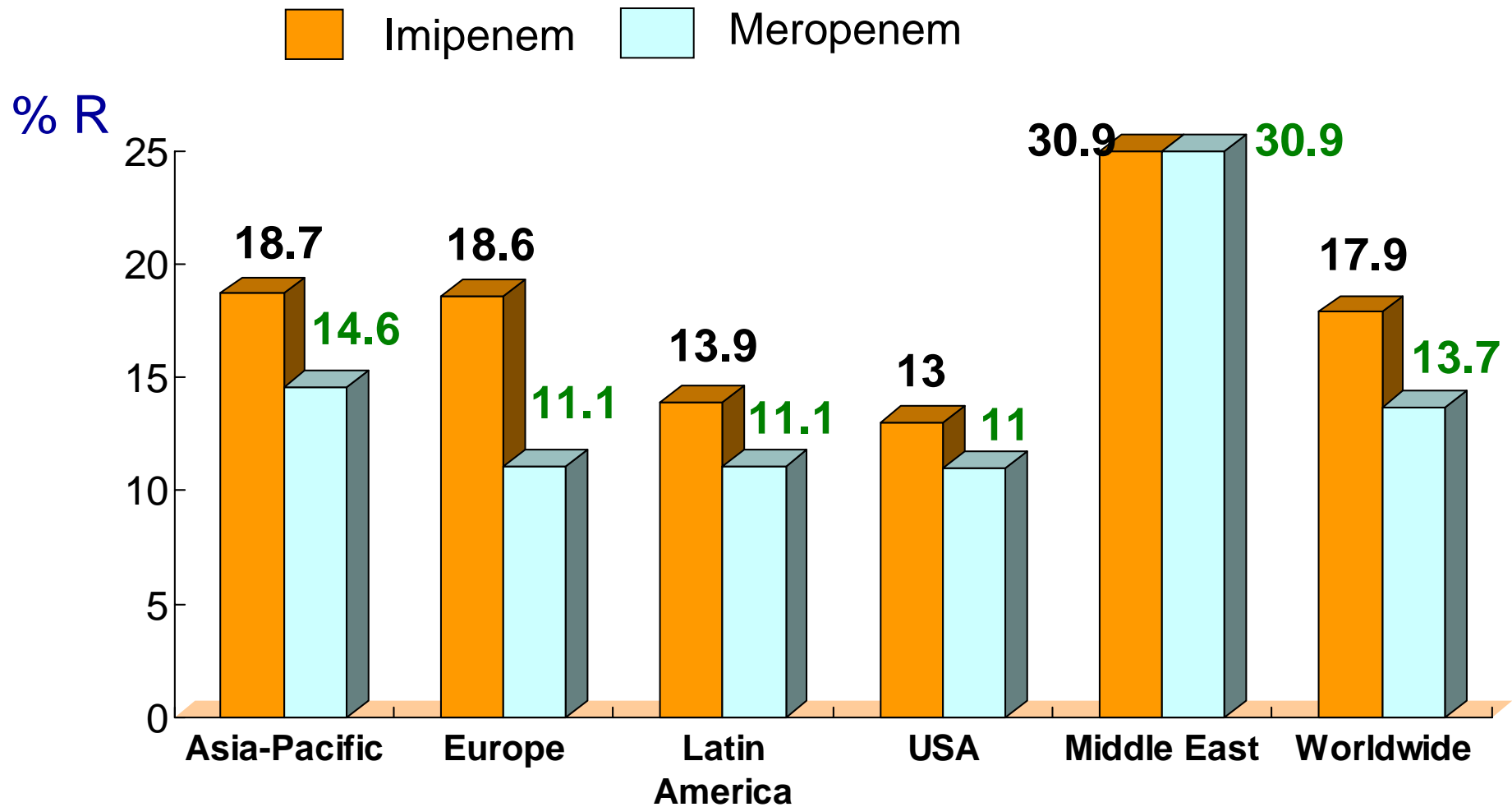
| Antibiotics | Korea (2003) | SENTRY+ (2001-2004) |
|---------------|--------------|---------------------|
| Ceftazidime* | 19 | 18.7 |
| Imipenem* | 20 | 12.5 |
| Ciprofloxacin | 40 | 25.3 |

+ 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*



Antimicrobial resistance in *P. aeruginosa*

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

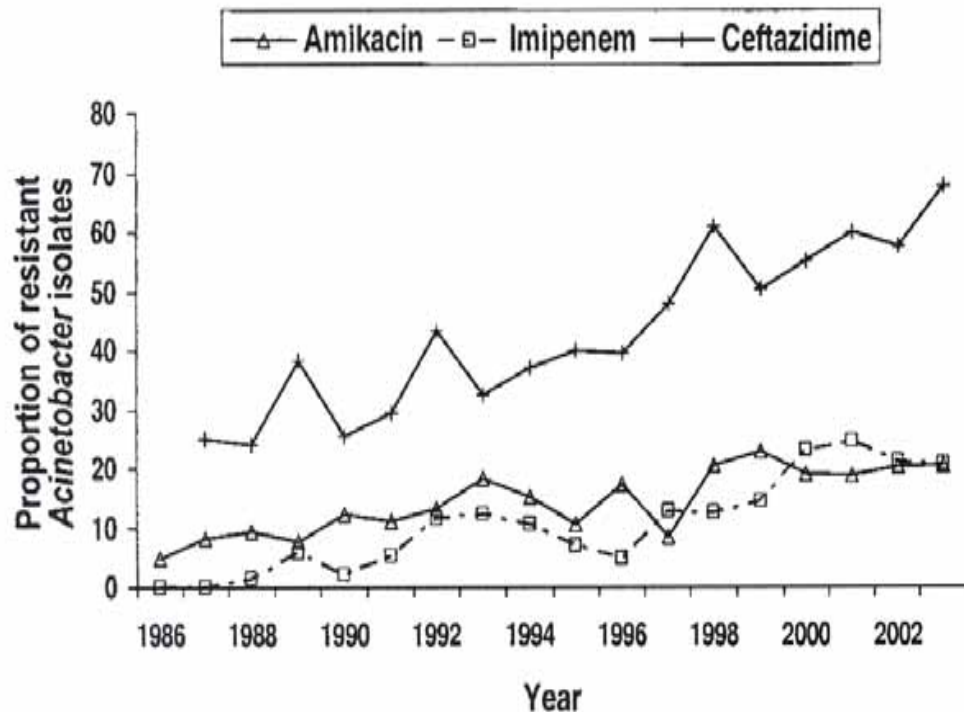
| 1996 | 1998 | 1999 | 2000 | 2001 | 2002 |
|--------|------|------|------|------|------|
| 11.5 % | 11.5 | 11.7 | 16.3 | 14.9 | 20.5 |

- 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

Antimicrobial resistance in *Acinetobacter* spp.

USA



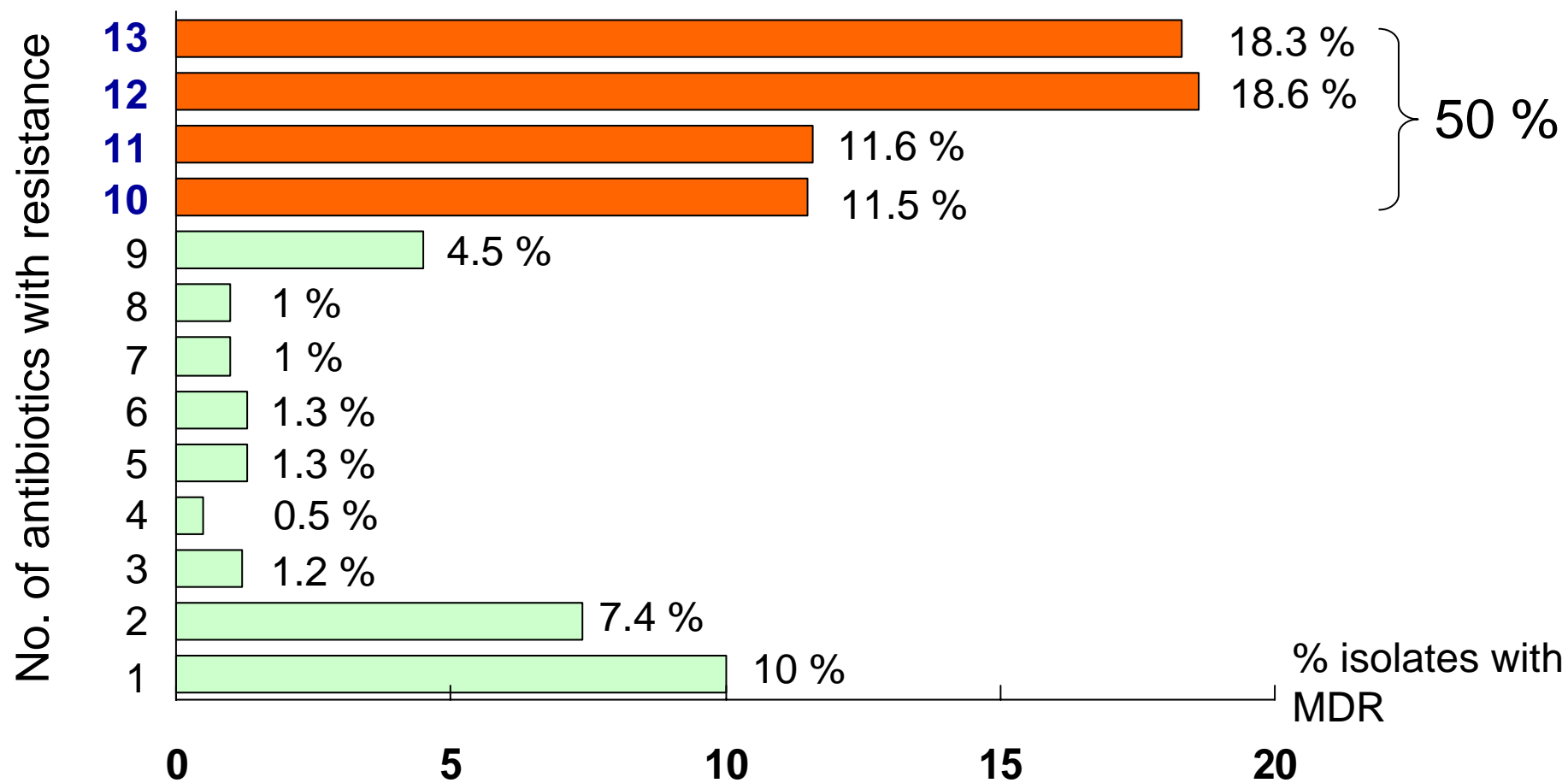
| Antibiotic | % resistance | | |
|---------------|--------------|---------------------|------------------|
| | Korea (2003) | Taiwan (2003) | SENTRY (2001-04) |
| Ceftazidime | 55 | 48 | 48 |
| Cefepime | 41 | 46.5 | 37 |
| Imipenem | 13 | 24.2 (meropenem) | 16 |
| Ciprofloxacin | 58 | 49 | 55 |
| Amikacin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

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

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



Multidrug resistance in *Acinetobacter* spp.

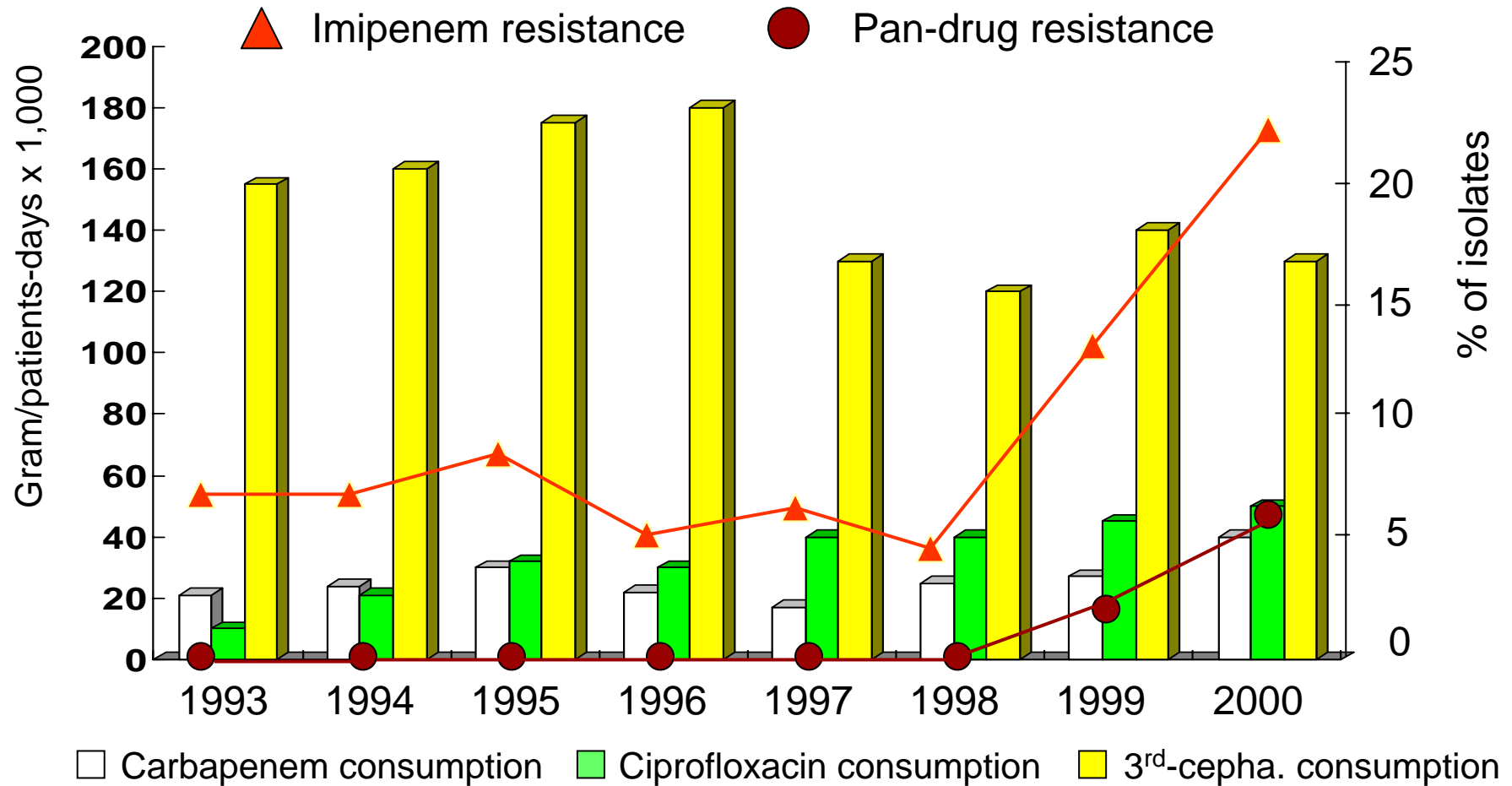


* Data from YUMC, Korea

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

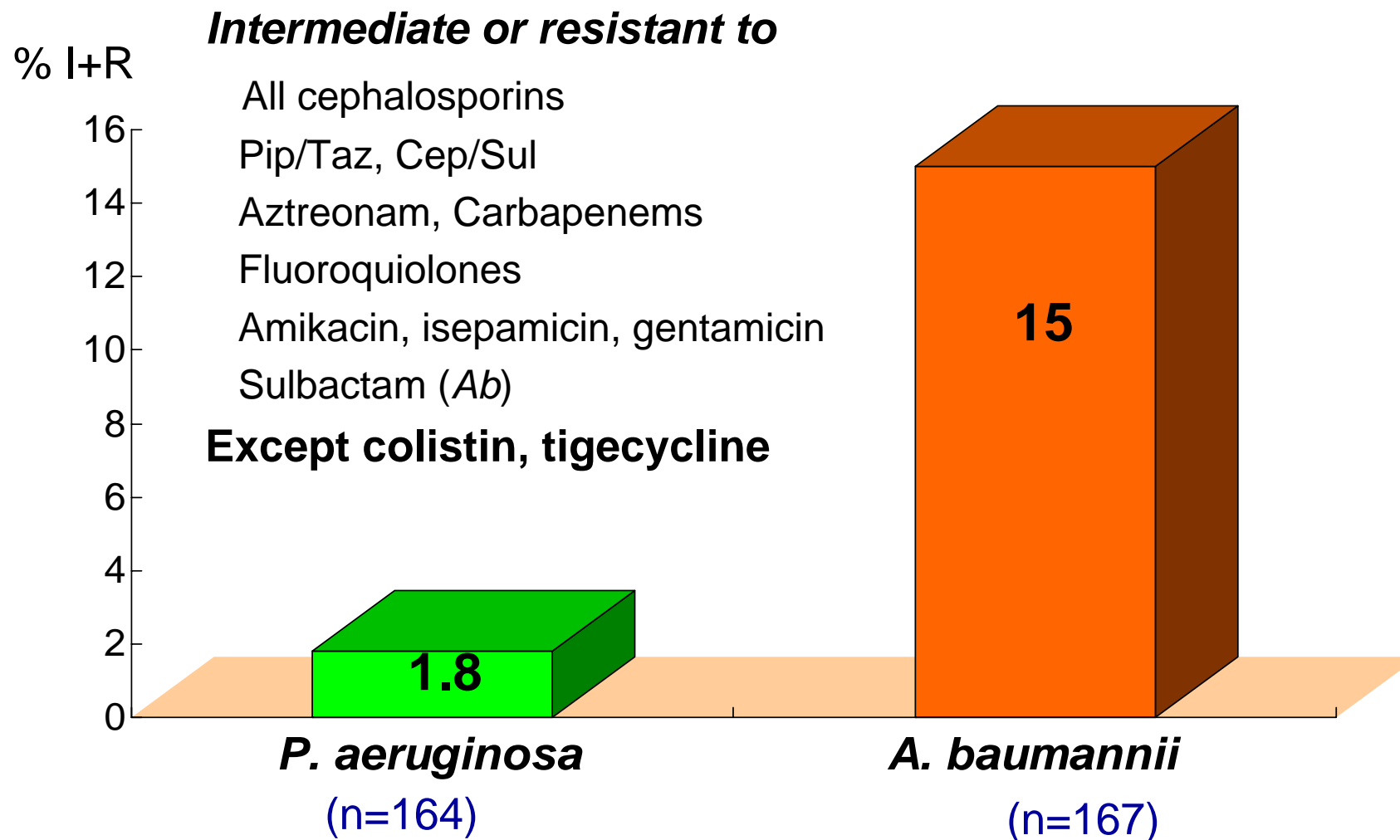


Pandrug resistance in *Acinetobacter* spp.



* Data from NTUH, Taiwan

Pandrug resistance in *Acinetobacter* spp.



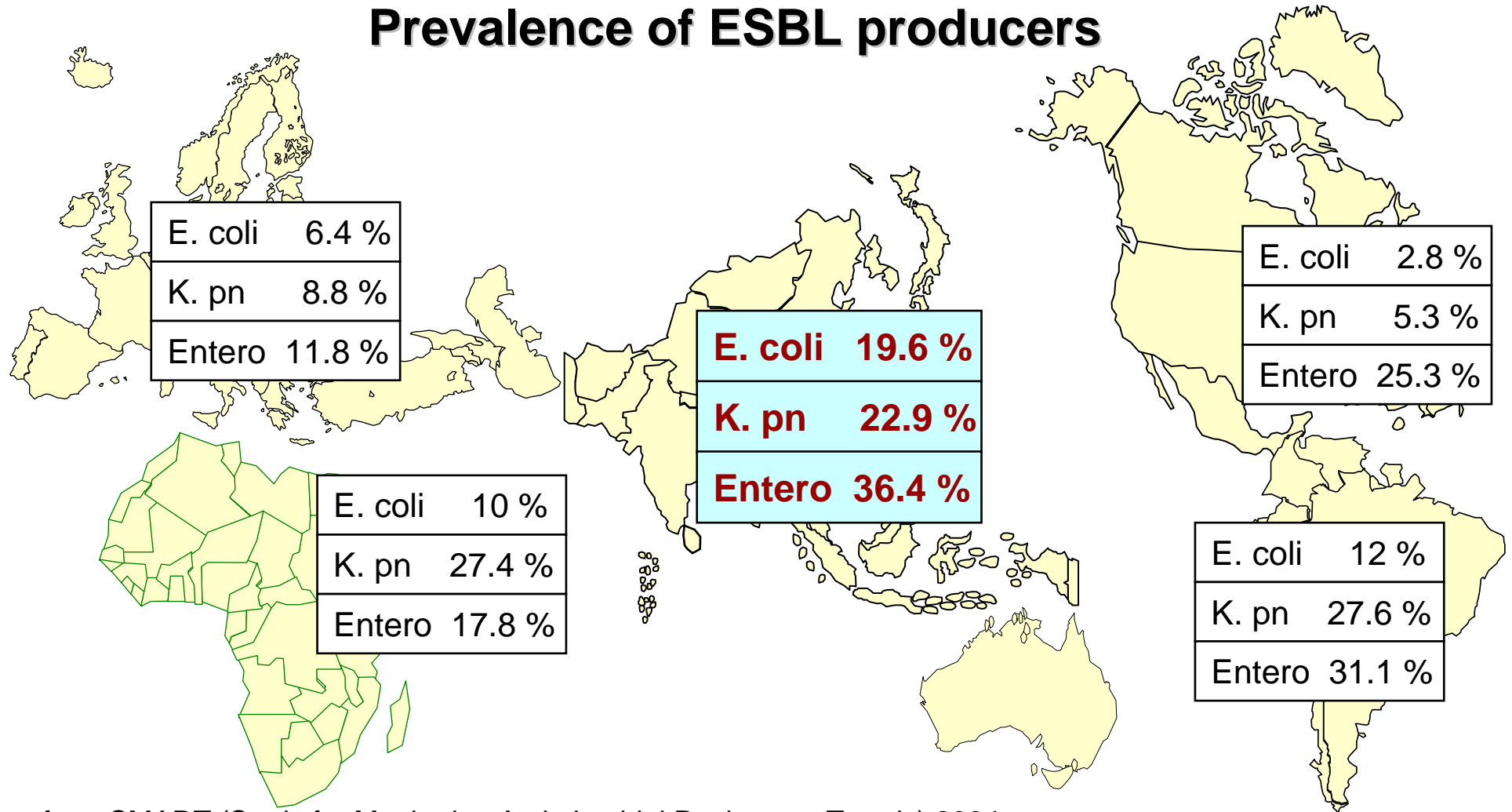
* SMART surveillance, ICUs (2004)

Data from Hsueh PR, ISAAR 2005



ESBL-producing Gram-negative bacilli

Prevalence of ESBL producers



* 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

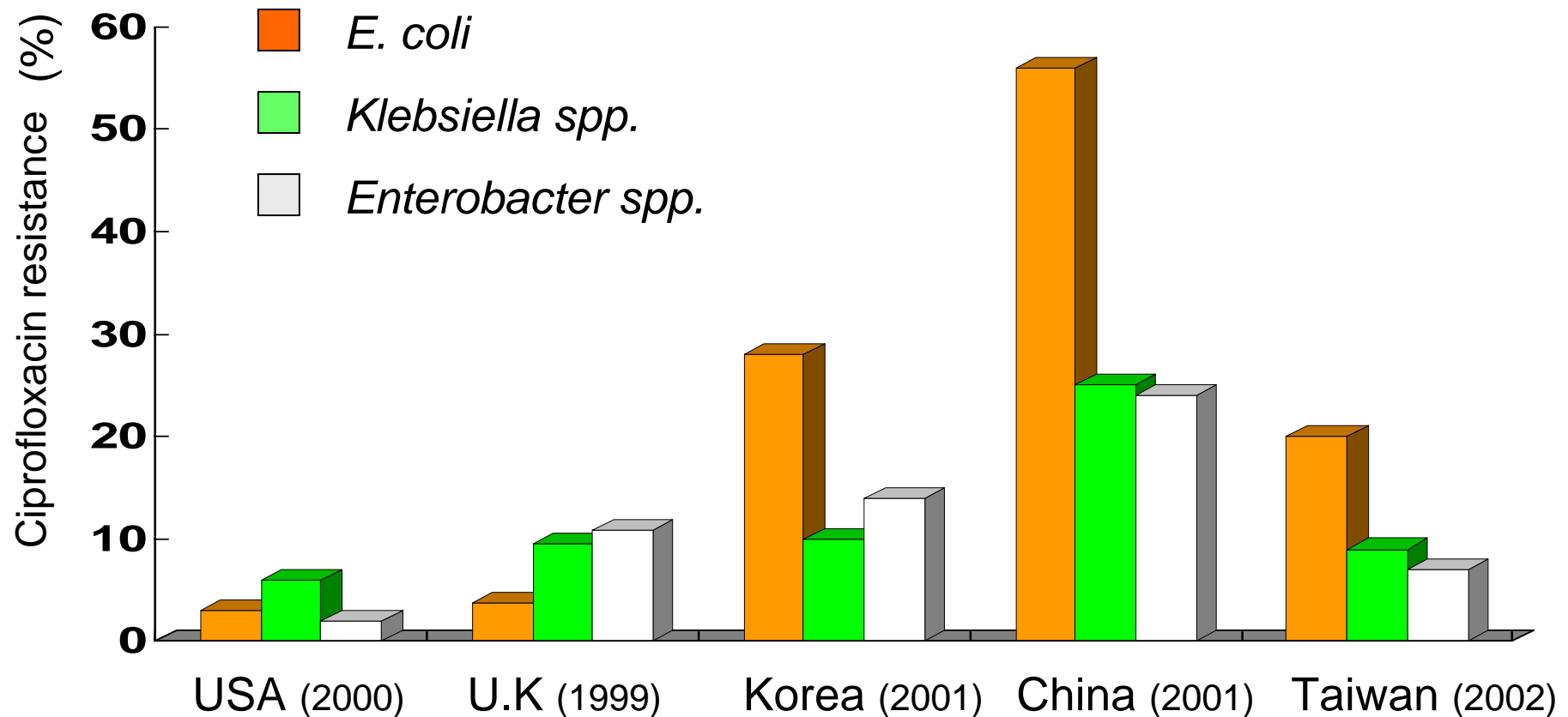
| Country | % of ESBL-producing strains | |
|-------------|-----------------------------|----------------------|
| | <i>E. coli</i> | <i>K. pneumoniae</i> |
| China | 24.5 | 30.7 |
| Hong Kong | 14.3 | 11.6 |
| Japan | 2.4 | 10.0 |
| Philippines | 5.0 | 21.9 |
| Singapore | 11.3 | 35.6 |
| Taiwan | 5.6 | 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



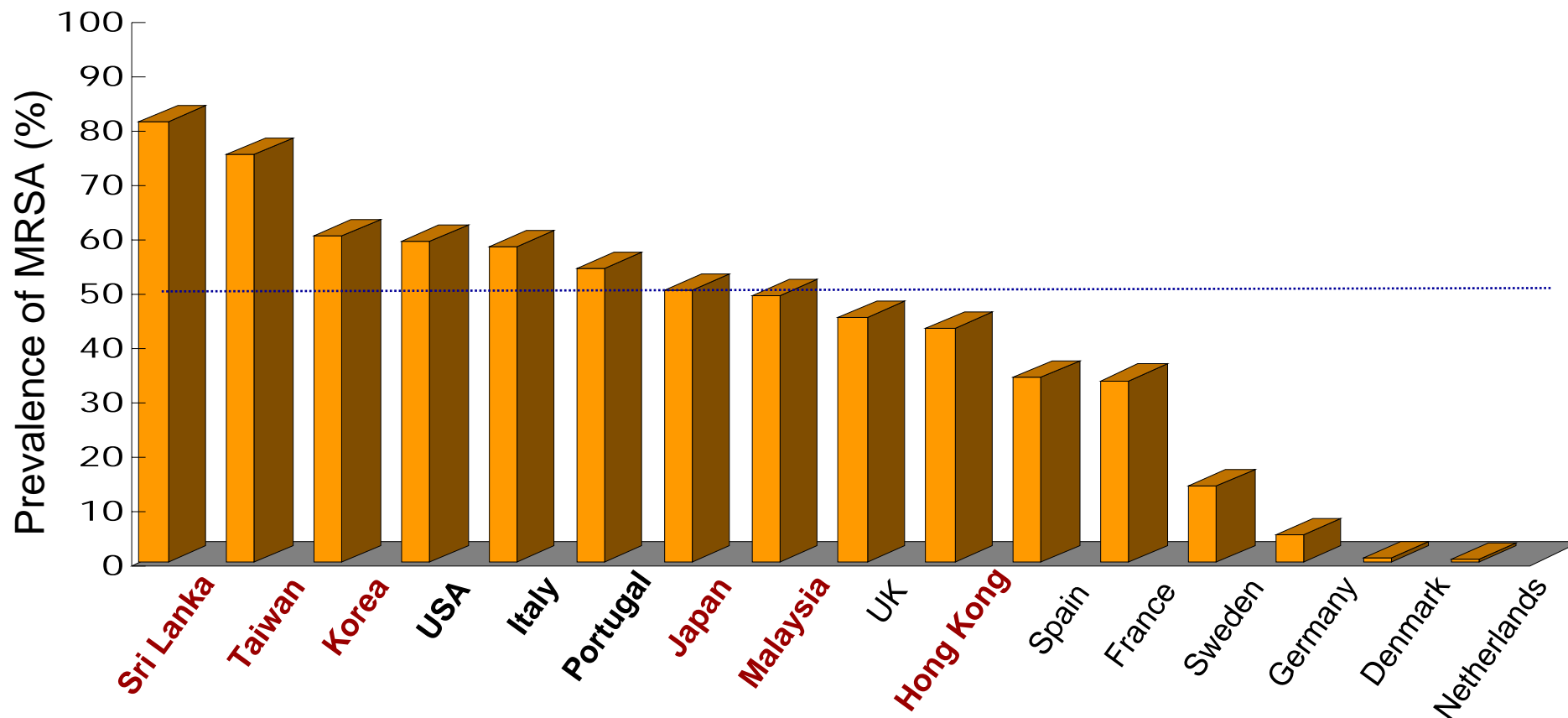
Fluoroquinolone resistance in GNB



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



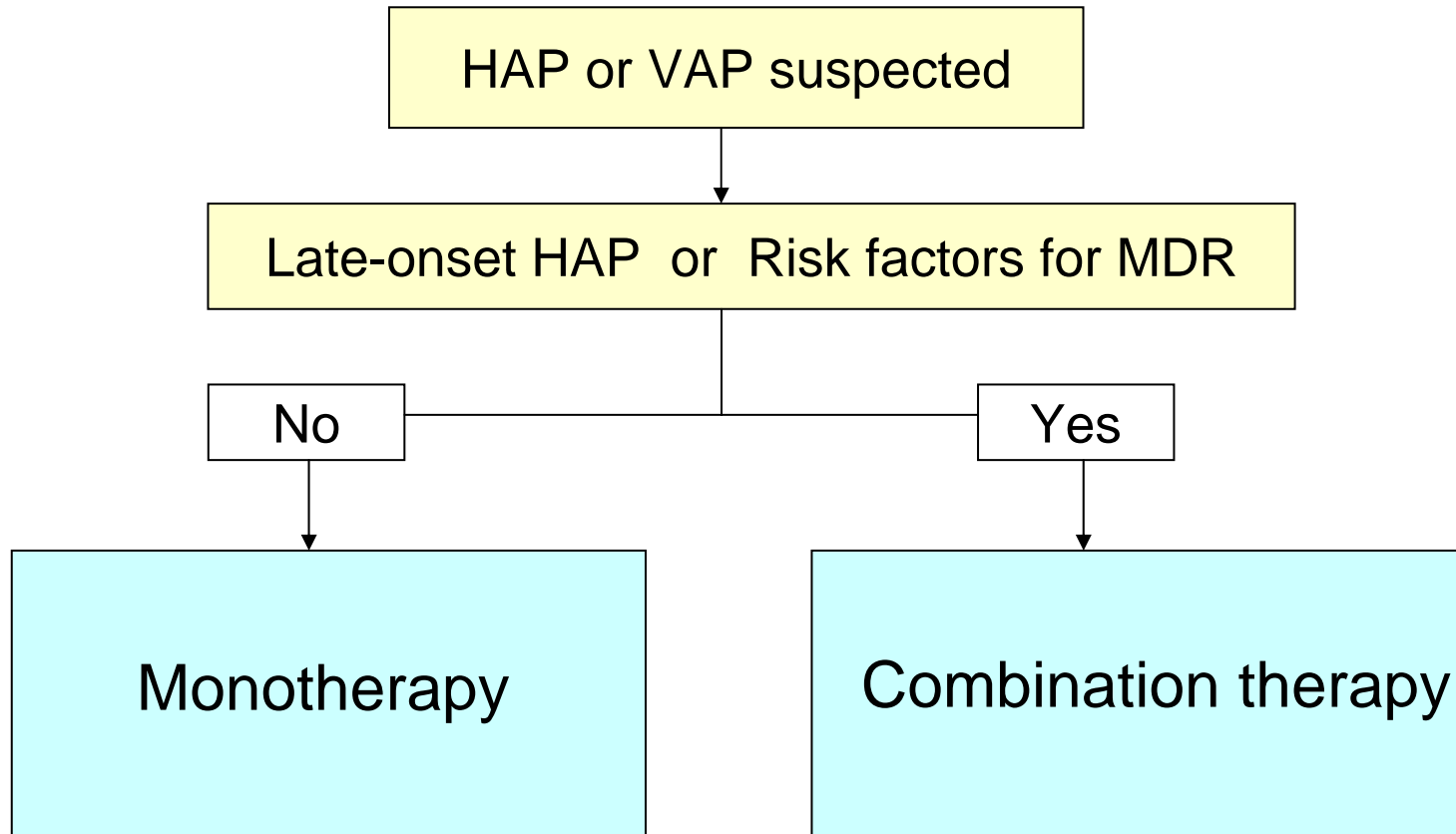
ANSORP surveillance (2005-2006); NNIS. Am J Infect Control. 32;470, 2004 ;
Hsueh PR et al. Int J Antimicrob Agents. 26;45-9, 2005 ; Bertrand X et al. Med mal Infect. 35;329, 2005



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

Initial empiric therapy : ATS / IDSA approach



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

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

Initial empiric therapy : ATS / IDSA approach

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

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 <i>Acinetobacter</i> spp.* <ul style="list-style-type: none">- 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

Specific treatment : *P. aeruginosa*

Current standard options

Cefepime or Ceftazidime

or

Piperacillin-tazobactam

or

Imipenem or Meropenem

+

Amikacin or Tobramycin

or

Ciprofloxacin

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

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

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.baumannii (36) | 15 % (day 6 of treatment) |
| Michalopoulos | HAP (31), bacteremia (14) | P.aeruginosa (35) A.baumannii (8) | 69.8% |
| Falagas | HAP (11), bacteremia (1) UTI (2) | P.aeruginosa (10) A.baumannii (4) | 52.6 % |
| Levin | HAP (19), UTI (12), bacteremia (9) | P.aeruginosa (21) A.baumannii (28) | 58 % |
| Garnacho | VAP (21) | A.baumannii (21) | 57 % |
| Linden | HAP (18), bacteremia (8) | P.aeruginosa (23) | 61 % |
| Markou | VAP (15), sepsis (4) | P.aeruginosa (18) A.baumannii (6) | 73 % |

* IV colistimethate sodium

Specific treatment : MDR non-fermenters

Inhaled colistin therapy

- 21 patients with HAP and were treated with nebulized colistin sulphomethate
- *A. baumannii* 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

Emergence of colistin resistance

| Antibiotic | Total ⁺ | | <i>A.baumannii</i> subgroup I* | | <i>A.baumannii</i> subgroup II | | <i>A.baumannii</i> 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.baumannii* from 2 Korean hospitals

* Subgrouping based on *rpoB* gene sequence

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



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 | |

Doripenem against non-fermenters

| Antibiotics | <i>P. aeruginosa</i> | | <i>Acinetobacter</i> 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 |

Tigecycline against MDR *Acinetobacter* spp.

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

✓

✓

✓

✓

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.baumannii*

Treatment of ESBL+ Gram-negative bacilli

| Drug | % susceptibility | | |
|---------------|----------------------|----------------|---------------------|
| | <i>K. pneumoniae</i> | <i>E. coli</i> | <i>P. mirabilis</i> |
| 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



Treatment of ESBL+ Gram-negative bacilli

| Antibiotic | Fact | Recommendation |
|---|--|----------------------------|
| Carbapenems | Best clinical efficacy | Yes |
| Tigecycline | Promising clinical usefulness | Yes |
| 3 rd & 4 th generation cephalosporins | Documented clinical failures | No |
| 4 th 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 |
| | | Telavancin |
| | | Dalbavancin |
| | Glycopeptides | Oritavancin |

Summary

- Treatment of HAP is becoming more difficult with the emergence of antibiotic resistance in major pathogens
- MDR non-fermenters such as *P.aeruginosa* and *A.baumannii* 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