Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria

Khoa Hô Hấp 1

BS: Lê Thị Kiến Trúc

Contents

1. Overview of nosocomial pneumonia
2. Advantages and disadvantages of IV- Colistin.
3. Evidences of aerosolized colistin in MDR nosocomial.
4. Recommendations for the use of AS-Colistin
5. Conclusions.

The major HAIs

CDC 2015:

- Catheter-associated urinary tract infections (CAUTI; 40%)
- Ventilator-associated and healthcare-associated pneumonia (25%),
- Catheter-associated bloodstream infections (CABSI; 10%),
- And surgical site infections (SSI)

Agents of nosocomial pneumonia

- Ps. aeruginosa
- MRSA
- Acinetobacter baumanii
- Stenotrophomonas maltophila

Agents of nosocomial pneumonia CDC 2015

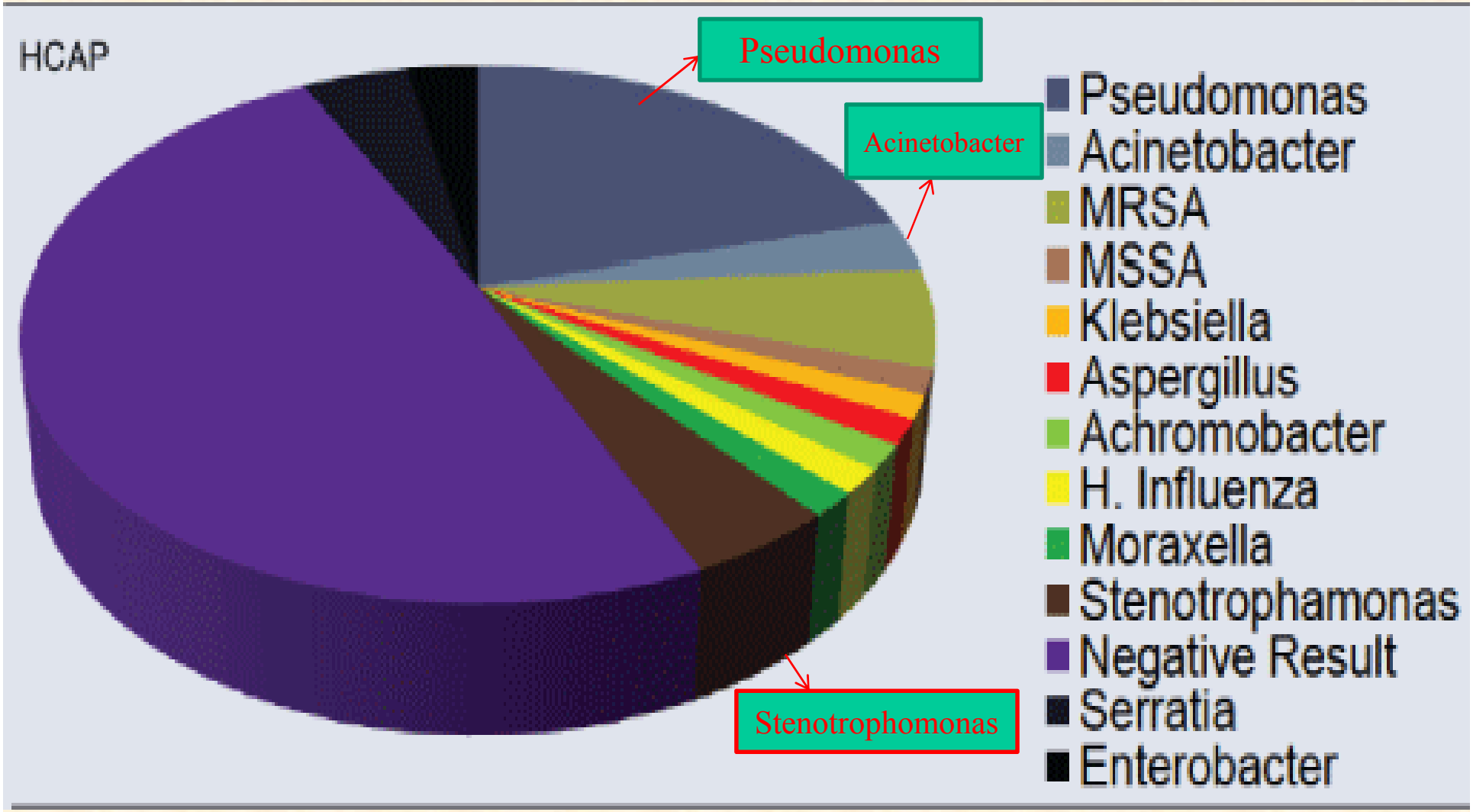
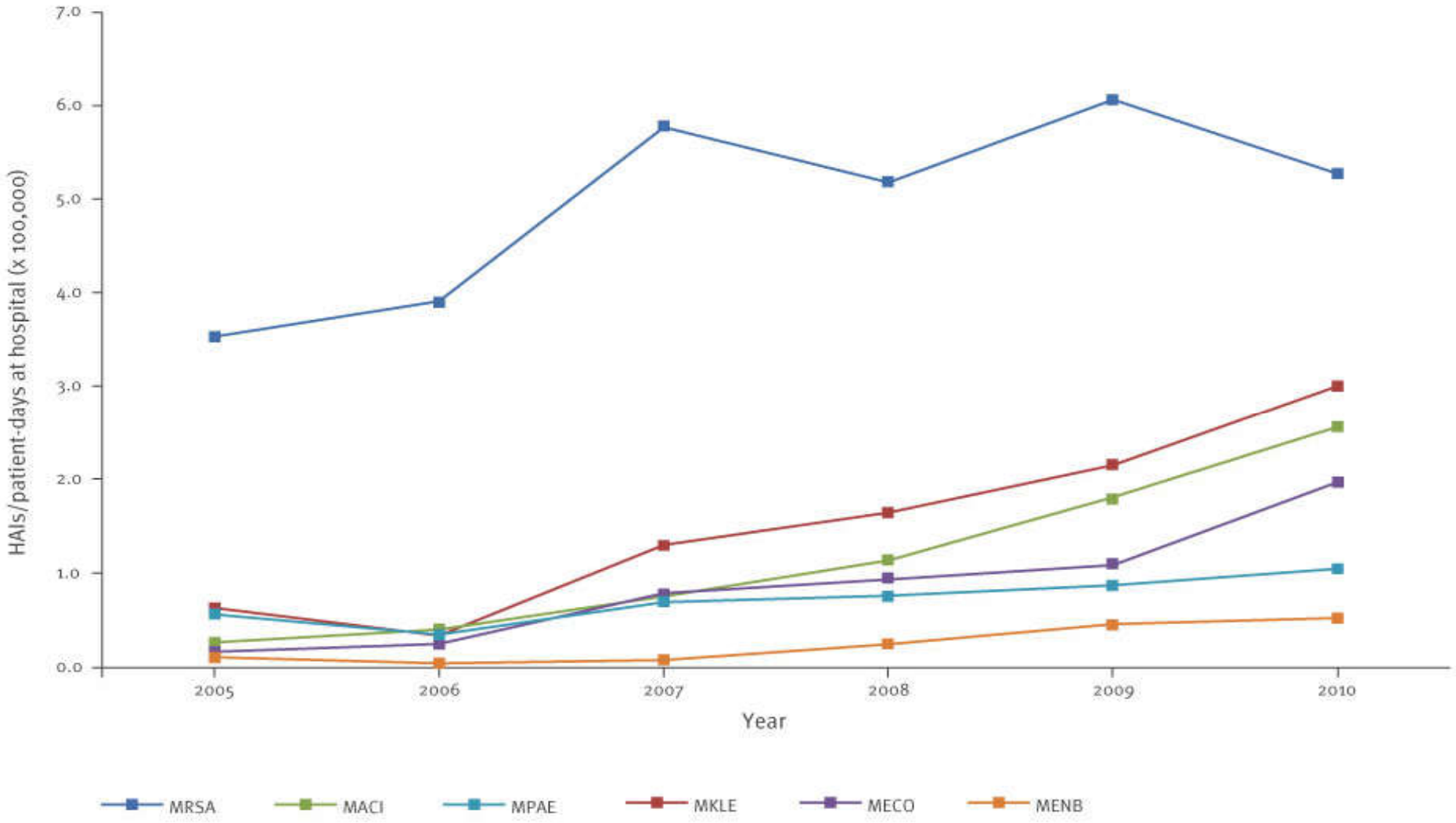


FIGURE 1

Annual incidence rates of reported hospital-acquired infections due to multidrug-resistant organisms in Hungary, 2005–10 (n=8,732)



HAI: healthcare-associated infection; MACI: multidrug-resistant *Acinetobacter baumannii*; MECO: multidrug-resistant *Escherichia coli*; MENB: multidrug-resistant *Enterobacter* sp.; MKLE: multidrug-resistant *Klebsiella* sp; MPAE: multidrug-resistant *Pseudomonas aeruginosa*; MRSA: methicillin-resistant *Staphylococcus aureus*.

NATIONAL SUMMARY DATA

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least **2,049,442** illnesses,

23,000 deaths

**bacteria and fungus included in this report*

+

Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least **250,000** illnesses,

14,000 deaths

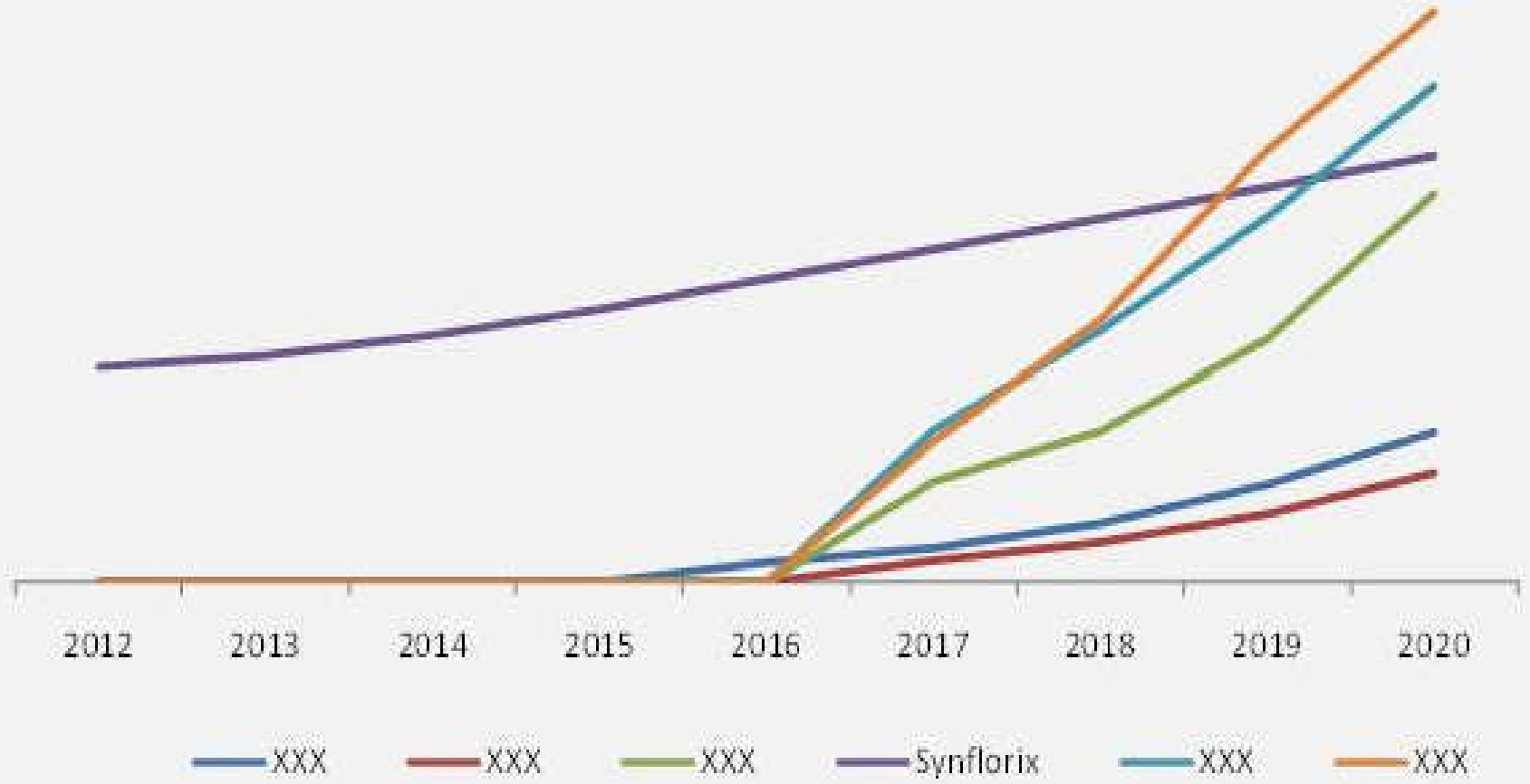
WHERE DO INFECTIONS HAPPEN?

Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community; however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Pathogen	Mortality
P.aerug or Acinetobacter	71%
Other organisms	41%

Global Pipeline Analysis for Hospital Acquired Pneumonia Drugs Market Revenue, 2012 – 2020 (USD Million)

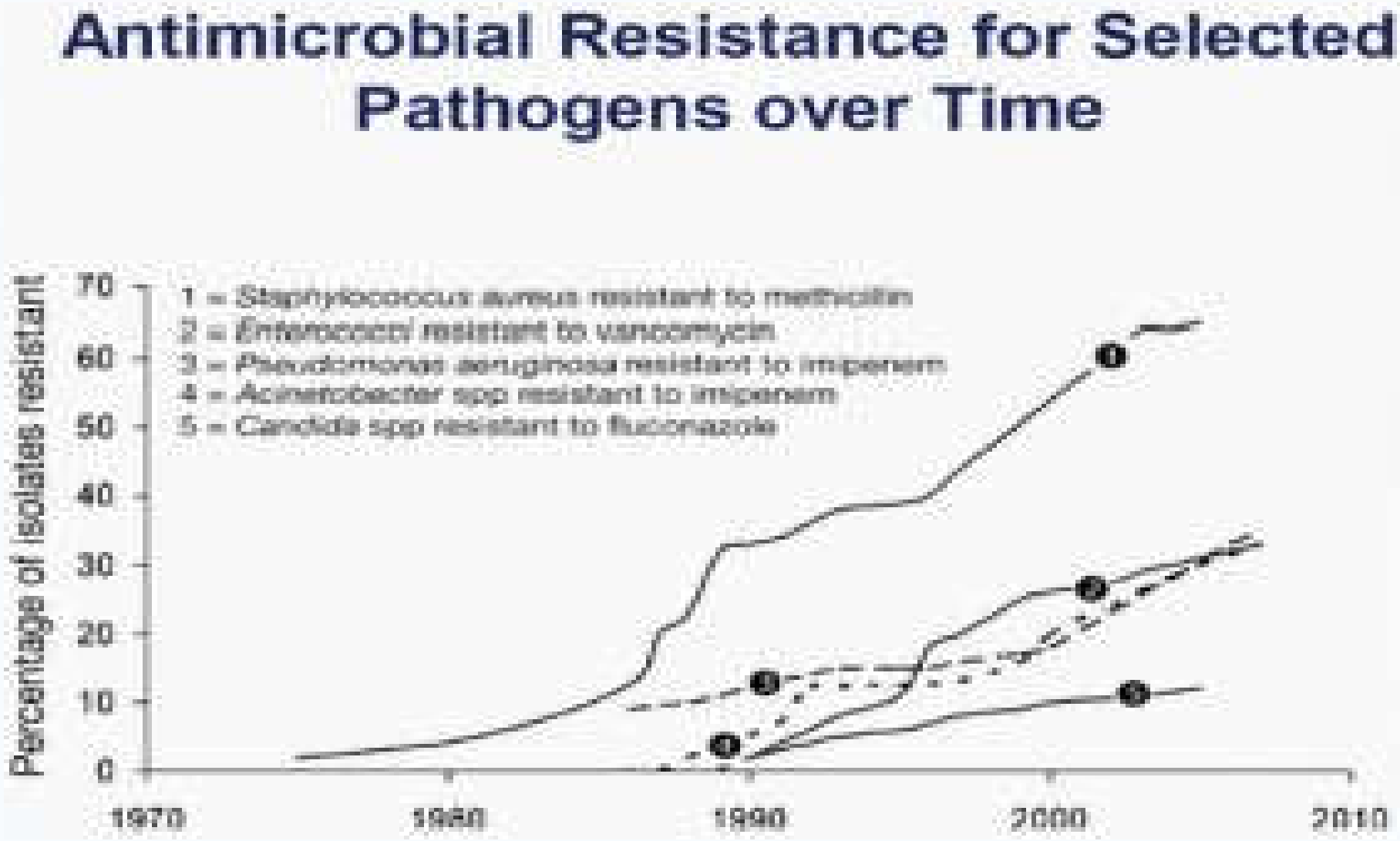


Source: KOL Opinions, Company Annual Reports, Expert Interviews, Biotechnology Journals, Investing Publications, Press Releases & TMR Analysis

Consequence ?

- 0.5 – 2% of hospitalized patients.
- #1 cause of death due to nosocomial infections.
- Mortality 25 – 50%
- Antimicrobial resistance increasing

MDR situation in nosocomial pneumonia



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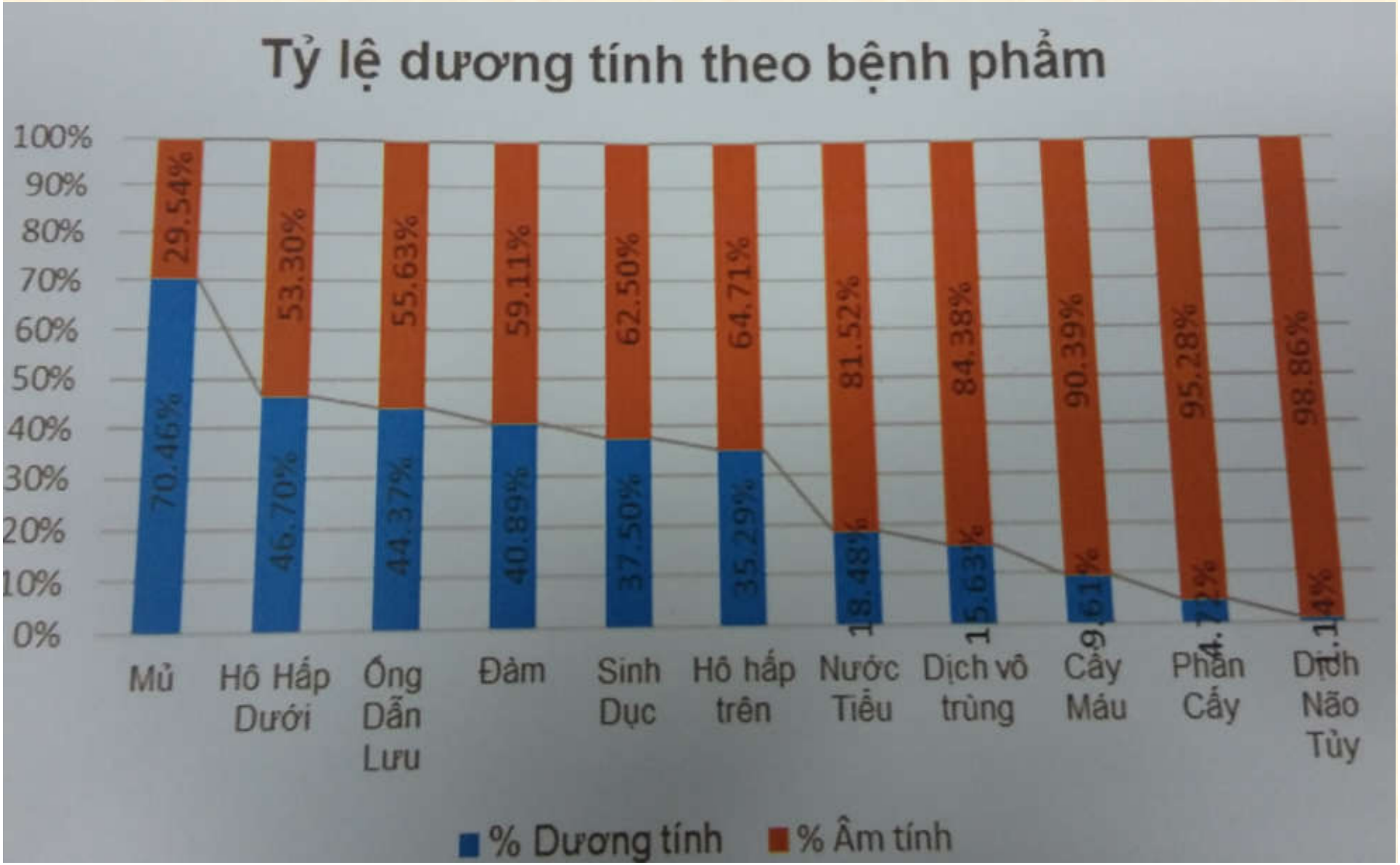
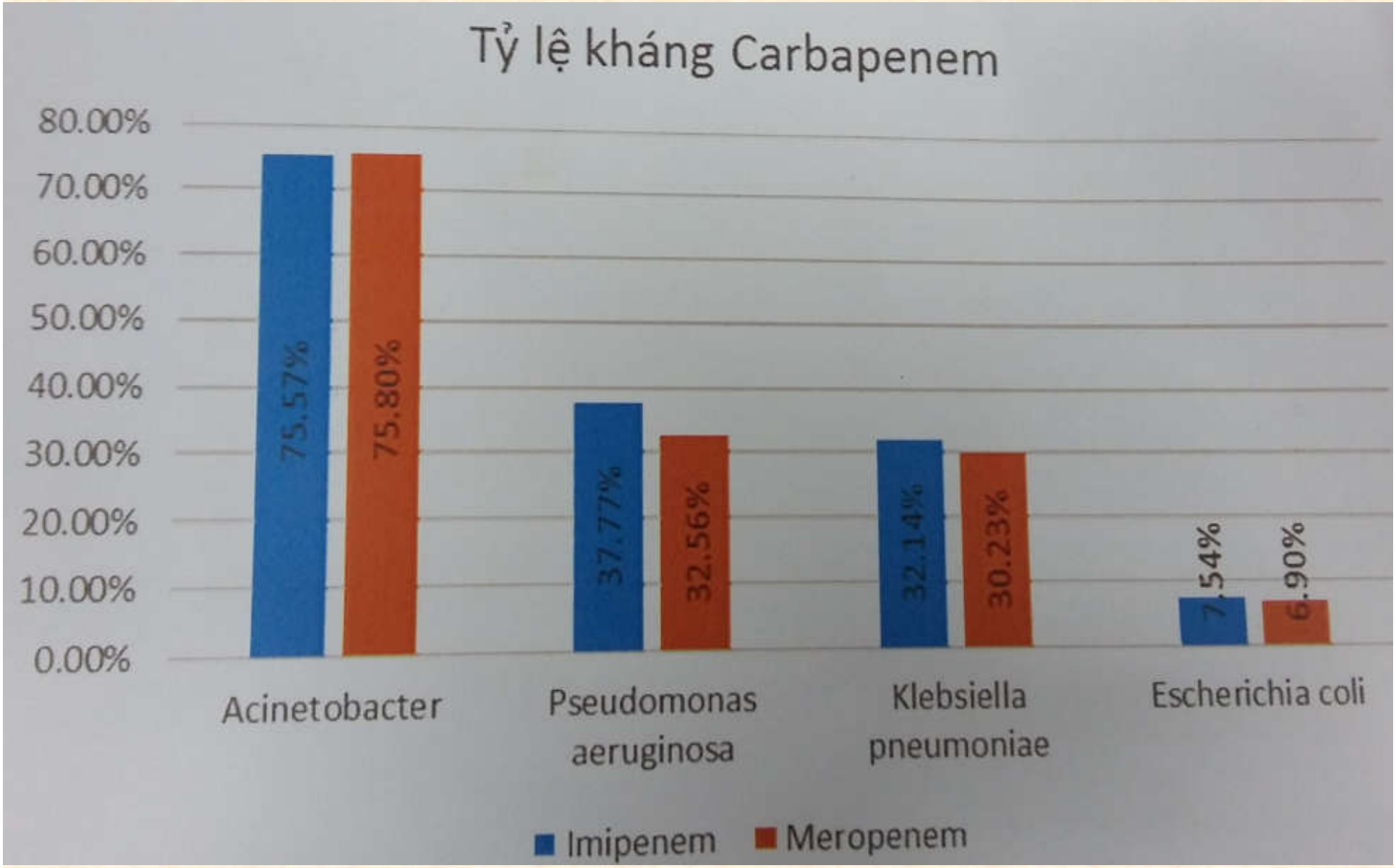



Tỷ lệ phân bố các vi khuẩn gây bệnh thường gặp
20%
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
18.56%
12.87%
11.52%
9.57%
7.91%
7.15%
6.59%
5.18%
5.13%
1.35%
1.27%
1.10%
1.01%
0.70%
Klebsiella pneumoniae
Acinetobacter spp
Burkholderia cepacia
Escherichia coli
Staphylococcus aureus
Candida albicans
Staphylococci coagulase âm
Pseudomonas aeruginosa
Streptococcus pneumoniae
Salmonella OMA
Haemophilus influenzae
Moraxella catarrhalis

Thông kê 6 tháng đầu năm 2016 tại BV Nhi Đồng 2

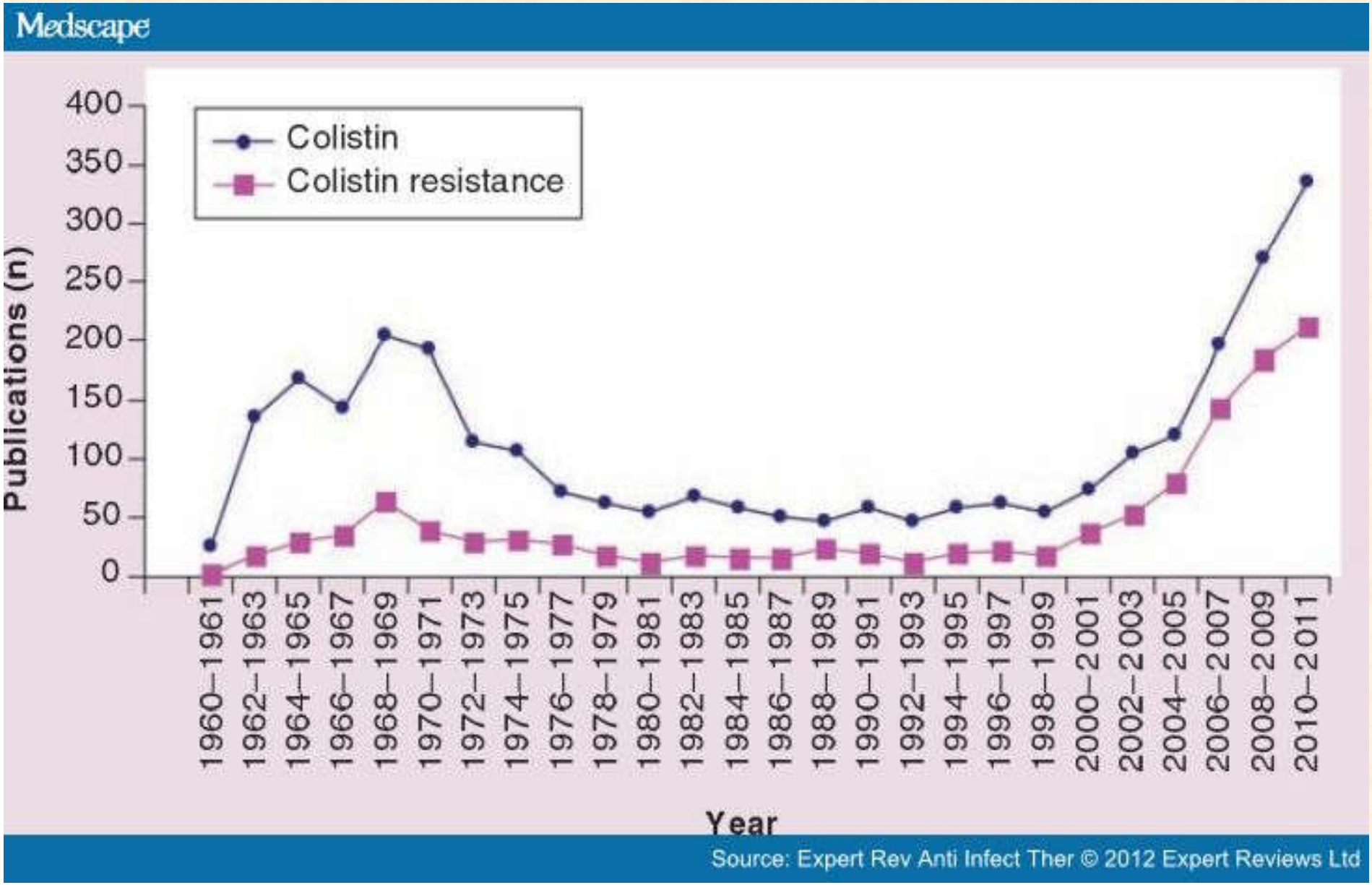


Thống kê 6 tháng đầu năm 2016
tại BV Nhi Đồng 2

BẢNG ĐỀ KHÁNG KS CỦA CÁC VI KHUẨN THƯỜNG GẶP 6 THÁNG ĐẦU NĂM 2016

Tỉ lệ đề kháng KS của các VK từ 01/12/2015 – 30/05/2016	Ampicillin	Penicillin	Oxacillin (Cefoxitin)	Amox-clavulanic	Ampi-sulbactam	Pipe-tazobactam	Ticar-clavulanic	Cefo-sulbactam	Cefepime	Cefotaxime/Ceftriaxone	Ceftazidime	Cefuroxime	Imipenem	Meropenem	Gentamicin	Amikacin	Ciprofloxacin	Levofloxacine	Trime-sulfametho	Chloramphenicol	Erythromycin	Clindamycin	Vancomycin	Fosfomycin	Colistin
Tổng số chủng VSV phân lập được/ Tổng số mẫu: 5146/25721=20.01%																									
Escherichia coli	97.34 (377)			79.40 (369)	59.87 (476)	16.00 (475)	37.68 (475)	10.56 (369)	73.16 (477)	90.10 (485)	83.08 (473)	89.81 (373)	7.54 (477)	6.90 (478)	53.54 (480)	3.11 (481)	71.45 (480)	70.79 (476)	69.93 (479)					1.08 (369)	0.00 (362)
Klebsiella pneumoniae	100 (526)			91.79 (524)	81.19 (734)	41.88 (733)	64.80 (733)	40.64 (524)	74.00 (727)	87.99 (733)	86.20 (732)	88.59 (526)	32.14 (731)	30.23 (731)	62.39 (734)	11.71 (734)	51.08 (734)	43.98 (732)	80.10 (734)					4.39 (523)	1.63 (732)
Salmonella OMA + OMB	67.27 (55)									24.00 (50)			0.00 (54)				7.27 (55)		38.18 (55)	60.00 (55)					
Elizabethkingia meningoseptica						11.85 (194)		13.47 (193)								51.81 (193)	19.07 (194)		56.70 (194)		45.87 (194)	57.73 (194)	23.58 (195)		
Acinetobacter spp.					60.55 (554)	71.14 (555)		49.29 (426)	78.14 (659)	80.31 (442)	79.93 (658)		75.57 (655)	75.80 (653)	73.59 (659)	61.45 (659)	67.78 (655)	61.06 (655)	75.15 (652)					12.64 (435)	0.6 (659)
Pseudomonas aeruginosa						6.97 (258)		18.29 (246)	21.07 (261)		29.27 (263)		37.77 (270)	32.56 (261)	24.52 (261)	18.00 (261)	22.59 (270)	24.32 (259)						9.88 (253)	0.00 (272)
Burkholderia cepacia							95.02 (563)				11.17 (564)			12.35 (536)				1.95 (563)	1.77 (564)	4.61 (520)					
Stenotrophomonas maltophilia							5.08 (236)				61.44 (236)							5.50 (236)	8.86 (237)	6.37 (204)					
Coag-Negative Staphylococcus spp.		97.60 (209)	86.19 (210)												52.91 (206)		44.67 (197)		57.14 (210)	22.50 (203)	92.10 (38)	71.05 (38)	0.00 (210)		
Staphylococcus aureus		99.75 (400)	82.33 (402)												34.96 (389)		37.19 (242)		17.16 (402)	11.02 (263)	82.92 (328)	82.31 (328)	0.00 (402)		
Streptococcus pneumoniae		54.83 (31)																5.18 (155)	95.78 (166)		90.37 (135)	84.44 (135)	0.00 (166)		
Enterococcus spp.	74.03 (104)	75.96 (104)															75.00 (72)	68.05 (72)					16.34 (104)		
Streptococcus spp.		10.52 (19)							15.78 (19)	30.00 (10)										11.11 (18)	54.54 (11)	45.45 (11)	0.00 (19)		

MDR situation in nosocomial pneumonia



Advantages of IV Colistin

Disadvantages of IV Colistin

- After parenteral administration, colistin achieves low protein binding, approximately 50%.
- About two thirds of CMS is eliminated as unchanged mainly by the renal route within 24 h.
- Containing colistin >4 μg/ml killed bacteria.
- Poorly distributed to the bones, cerebrospinal fluid, lung parenchyma, and pleural cavity.
- Nephrotoxicity and Neurotoxicity

- Evidence of aerosolized colistin in MDR nosocomial

The Cochrane Central Register of Controlled Trials (CENTRAL) 2014 Issue 1

Title	Re-emerging of colistin for treatment of nosocomial pneumonia due to gram negative multi-drug resistant pathogens in critically ill patients. Links Export Central Citation
Author(s)	Amin M, Rashad A, Fouad A, Abdel Azeem A
Source	Egyptian Journal of Chest Diseases and Tuberculosis
Date of Publication	2013
Volume	62
Issue	3
Pages	447-51
Publisher Name	Egyptian Society Of Chest Diseases And Tuberculosis (Egypt)
City of Publication	Egypt
Abstract	Background: Gram-negative (G-ve) bacilli, particularly Pseudomonas aeruginosa and Acinetobacter baumannii, are important opportunistic multidrug-resistant (MDR) pathogens in hospitalized patients, contributing to their morbidity and mortality. These organisms may still keep their sensitivity to colistin and allowed its use for these selective therapeutic indications. Objectives: The aim of the present study is to evaluate and compare the effectiveness and safety of both combined intravenous (i.v.) colistin with aerosolized colistin versus i.v. colistin alone in nosocomial pneumonia due to MDR G-ve pathogens in critically ill patients. Methods: 40 Patients were hospitalized in ICU due to different etiologies. These patients experienced nosocomial pneumonia. The pathogenic organisms were G-ve MDR bacilli and only susceptible to colistin. The first group received both i.v. colistin with aerosolized colistin versus (vs.) the second group who received i.v. colistin alone. Results: Mortality was less in patients who received i.v. plus inhaled colistin. Conclusion: Colistin is a reasonable safe last-line therapeutic alternative for pneumonia due to MDR G-ve pathogens. Aerosolized colistin may be considered as a useful adjunctive to i.v. colistin. 2013.

Age, years (mean ± SD)	55.6 ± 21.9	60.5 ± 4.5	>0.05
Sex (male) n/N (%)	15/28 (54%)	7/12 (58%)	>0.05
Apache II score (mean ± SD)	18.1 ± 5	19.1 ± 7	>0.05
Co morbidity n/N (%)			
Cardiovascular	11/28(40%)	5/12(39)	>0.05
Pulmonary	6/28(20%)	3/12(22%)	>0.05
DM	9/28 (30%)	4/12 (29%)	>0.05
Hepatic injury	2/28 (5%)	1/12 (8%)	>0.05
Hematological	3/28 (8%)	1/12(8%)	>0.05
Neurological	6/28(20%)	3/12(18%)	>0.05
Previous hospitalization n/N (%)	6/28(20%)	3/12 (18%)	>0.05
Previous antibiotic use n/N (%)	9/28 (30%)	4/12 (33%)	>0.05
Duration of hospitalization until the1st day of colistin (mean ± SD)	15.3 ± 9.5	13.5 ± 7.5	>0.05
Duration of ICU stay till 1st day of colistin, (mean ± SD)	9.8 ± 4.5	11.5 ± 3.8	>0.05
Duration of MV till the 1st day of colistin	7.6 ± 4.3	8.1 ± 6.1	>0.05
Special treatment n/N (%)			
Blood transfusion	16/28 (60%)	10/12 (80%)	<0.05
L-thyroxin	3/28 (10%)	2/12(16%)	>0.05
Urinary catheter n/N (%)	28/28(100%)	12/12(100%)	>0.05
Tracheostomy n/N (%)	14/28(50%)	7/12(58%)	>0.05
Bronchoscopy n/N (%)	6/28(20%)	2/12 (18%)	>0.05
i.v. colistin, days (mean ± SD)	15.3 ± 8.7	14.1 ± 9.4	<0.05
Dosage of i.v. colistin, IU (mean ± SD)	9.2 ± 16	8.4 ± 20	>0.05
Responsible pathogens, n/N (%)			
Acinetobacter baumannii	18/28 (65%)	8/12 (70%)	>0.05
Pseudomonas aeruginosa	7/28 (25%)	3/12 (25%)	>0.05
Klebsiella pneumonia	3/28 (10%)	1/12 (12%)	>0.05
Outcomes; n/N (%)			
Cure	22/28 (78%)	7/12 (60%)	<0.05
Mortality	8/28 (28%)	5/12 (41%)	<0.05

Conclusion: Colistin is a reasonable safe last-line therapeutic alternative for pneumonia due to MDR G-ve pathogens. Aerosolized colistin may be considered as a useful adjunctive to i.v. colistin.

CHEST

Original Research

CRITICAL CARE

Effect of Aerosolized Colistin as Adjunctive Treatment on the Outcomes of Microbiologically Documented Ventilator-Associated Pneumonia Caused by Colistin-Only Susceptible Gram-Negative Bacteria

Mario Tumbarello, MD; Gennaro De Pascale, MD; Enrico Maria Trecarichi, MD, PhD; Salvatore De Martino, MD; Giuseppe Bello, MD; Riccardo Maviglia, MD; Teresa Spanu, MD; and Massimo Antonelli, MD

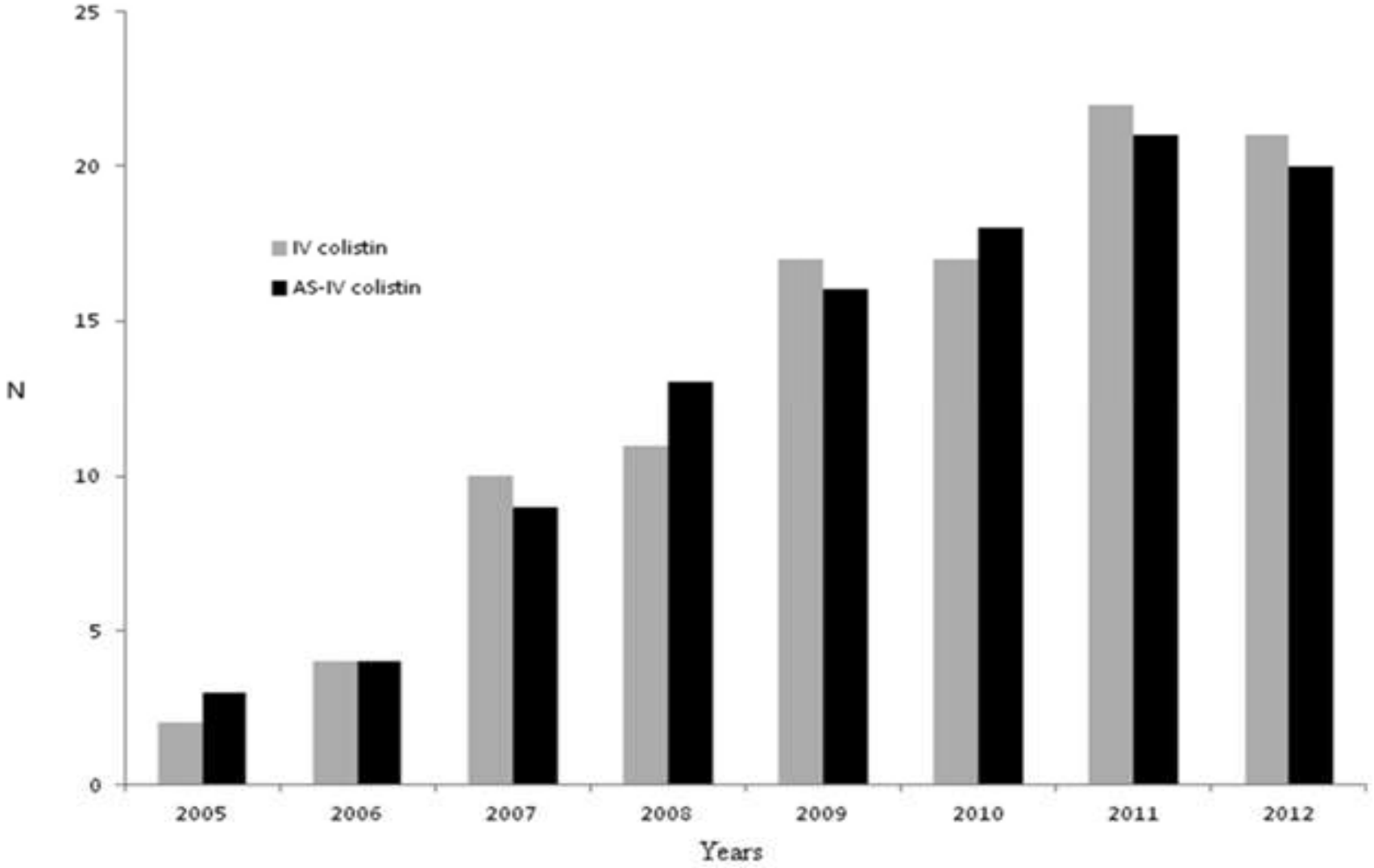


Figure 1. Temporal distribution of patients treated with IV colistin (IV cohort) and those who received IV and AS colistin (AS-IV cohort) in the study period. AS = aerosolized.

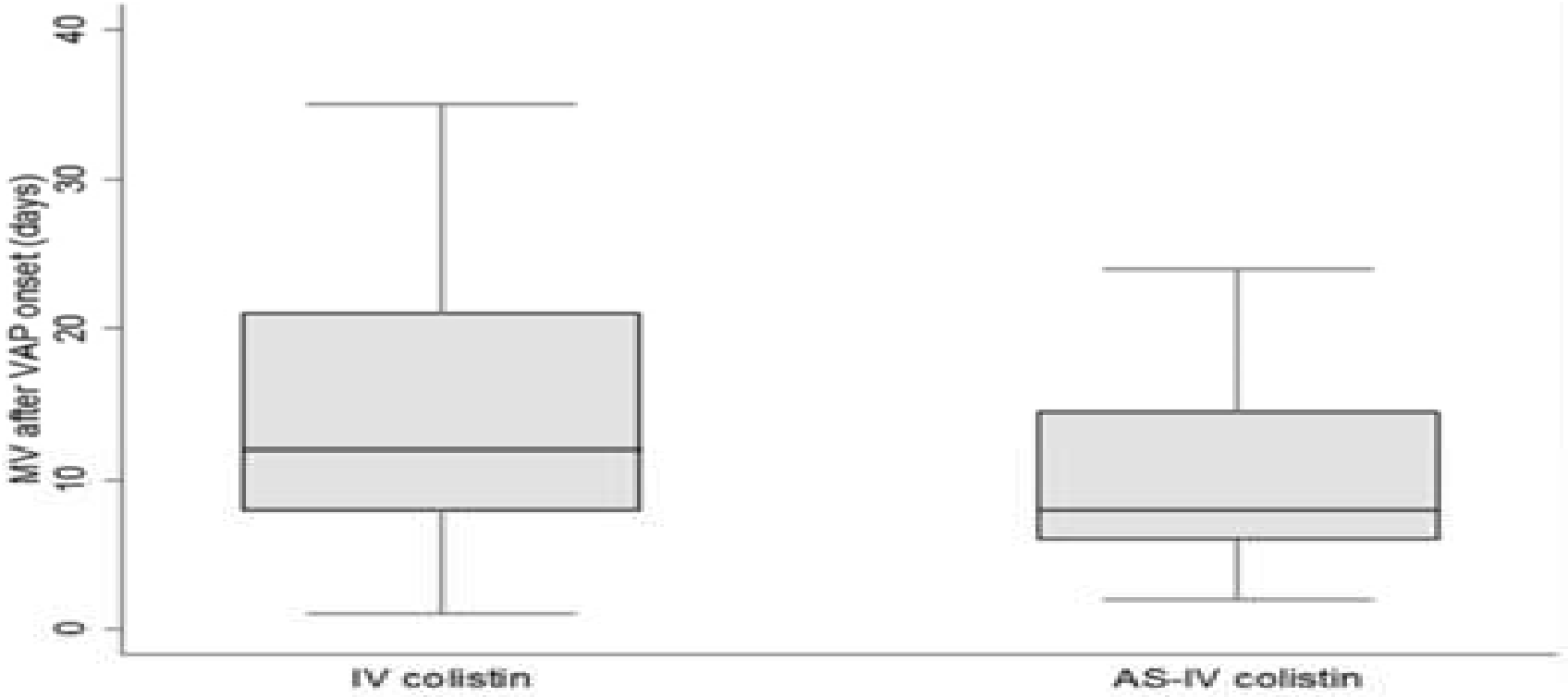


Figure 2. Box and whisker plots showing days of MV after onset of VAP in patients treated with IV colistin (IV cohort) and those who received IV and AS colistin (AS-IV cohort). MV duration was significantly shorter in the latter cohort ($P = .001$). Boxes represent interquartile ranges (lower border, 25th percentile; upper border, 75th percentile) and median (50th percentile) (horizontal line within the box); whiskers indicate minimum and maximum values. MV = mechanical ventilation; VAP = ventilator-associated pneumonia. See Figure 1 legend for expansion of other abbreviation.

Table 1—*Demographic and Clinical Characteristics of the 208 Patients With VAP Included in the Study*

Variable	Treatment Cohorts: AS-IV Colistin (n = 104)	IV Colistin (n = 104)	*P* Value
Patient characteristics on ICU admission			
Male sex	74 (71.1)	58 (55.8)	.02
Age, median (IQR), y	64 (48.5-76.5)	66 (49-77)	.78
Comorbidities on admission			
Diabetes mellitus	21 (20.2)	19 (18.3)	.72
Chronic renal failure	7 (6.7)	14 (13.5)	.11
Cancer	11 (10.6)	16 (15.4)	.30
Cardiovascular diseases	41 (39.4)	42 (40.4)	.89
COPD	21 (20.2)	28 (27.2)	.24
Immunosuppression*	25 (24)	22 (21.2)	.62
Type of ICU admission			
Medical	65 (62.5)	71 (68.3)	.38
Surgical	14 (13.5)	13 (12.59)	.84
Trauma-related	25 (24)	20 (19.2)	.40
SAPS II on ICU admission, median (IQR)	45.5 (34-56)	46.5 (33-55)	.90
Total days in ICU, median (IQR)	24.5 (13.5-44)	26 (16.5-39)	.73
Characteristics of VAP			
Late onset*	85 (81.7)	84 (80.7)	.85
CPIS at onset, mean SD	7.8 1.2	7.9 1.3	.87
SOFA score at onset, median (IQR)	7 (6-12)	8 (5-11)	.75
Causative organisms			
Acinetobacter baumannii	72 (69.2)	56 (53.8)	.02
Pseudomonas aeruginosa	24 (23.1)	28 (26.9)	.52
Klebsiella pneumoniae	8 (7.7)	20 (19.2)	.01
Presenting features			
ARDS	12 (11.5)	11 (10.5)	.82
Septic shock	46 (44.2)	46 (44.2)	1.00
Concomitant bacteremia	24 (23.1)	29 (27.9)	.43
CRRT at VAP onset	23 (22.1)	18 (17.3)	.38
Treatment of VAP			
Inadequate initial antibiotic therapy	91 (87.5)	87 (83.6)	.43
Duration of colistin treatment, median (IQR), d	7 (5-14)	10 (5.5-15)	.12
Daily dose of IV colistin, mean SD, IU	(7.0 2.6) × 10*	(7.3 2.4) × 10*	.29
Outcomes			
Clinical cure	72 (69.2)	57 (54.8)	.03
Microbiologic cure*	52 (63.4)	42 (50)	.08
Days of MV after pneumonia onset, median (IQR)	8 (6-14.5)	12 (8-21)	.001
Days in ICU after pneumonia onset, median (IQR)	12 (7-22.5)	14 (8-22)	.09
Death in ICU	45 (43.3)	48 (46.1)	.67
AKI during colistin therapy	26 (25)	23 (22)	.62

	IV Colistin	AS-IV Colistin	p
Clinical cure rate	54.8%	69.2%	0.03
Days of MV after pneumonia onset, median	12 days	8 days	0.001
Eradication of the causative organism	50%	63.4%	0.08
Septic shock at VAP onset	70.9%	27.9%	0.001
AKI during Colistin therapy	25%	22%	0.62 → No different
ICU mortality	No different		

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Review

Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and meta-analysis

Dong Liu [a], Jing Zhang [b], Hai-Xia Liu [a], Ying-Gang Zhu [a], Jie-Ming Qu [a,c,*]

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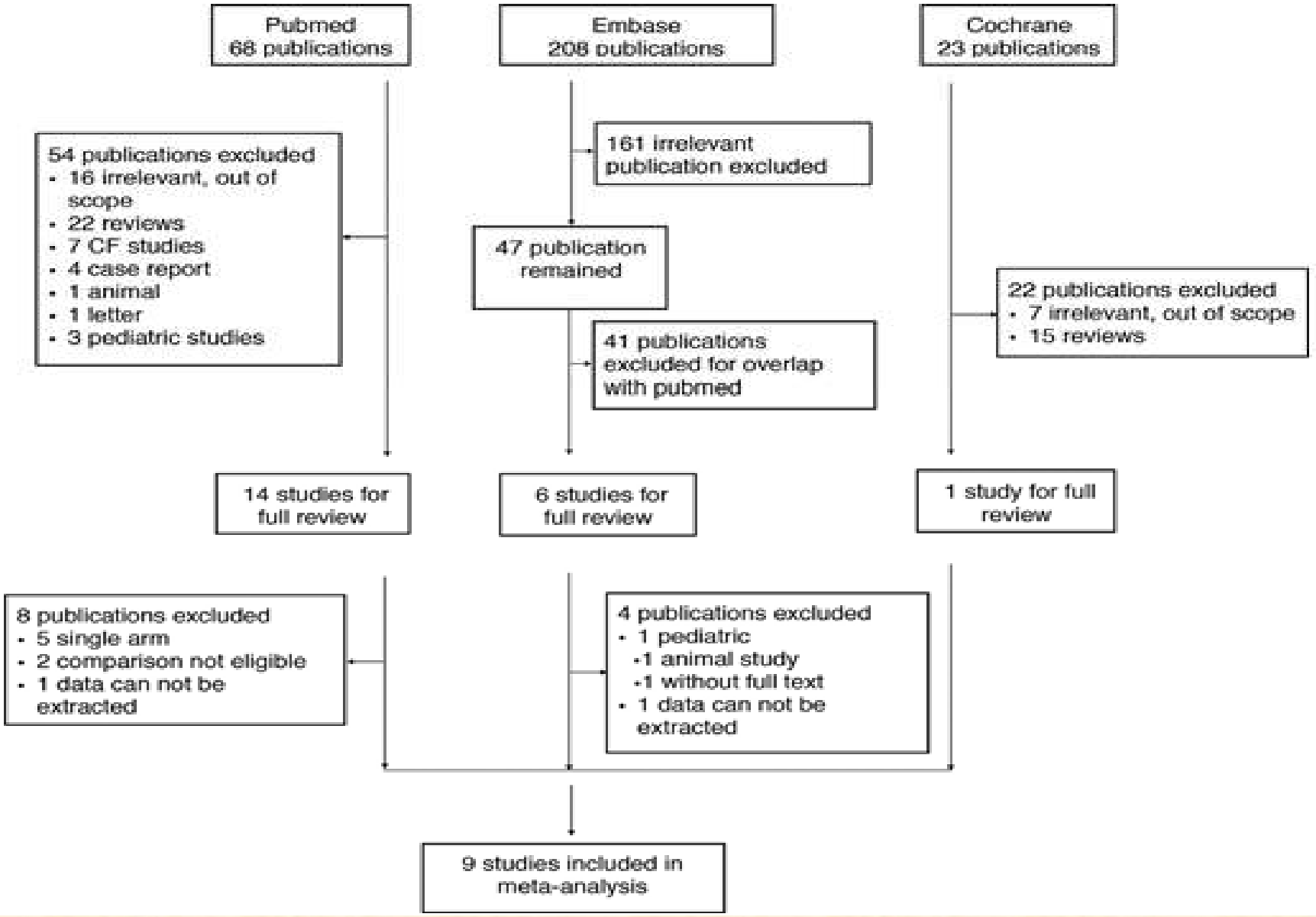
Pubmed
68 publications
Embase
208 publications
Cochrane
23 publications
54 publications excluded
• 16 irrelevant, out of scope
• 22 reviews
• 7 CF studies
• 4 case report
• 1 animal
• 1 letter
• 3 pediatric studies
161 irrelevant publication excluded
47 publication remained
41 publications excluded for overlap with pubmed
22 publications excluded
• 7 irrelevant, out of scope
• 15 reviews
14 studies for full review
6 studies for full review
1 study for full review
8 publications excluded
• 5 single arm
• 2 comparison not eligible
• 1 data can not be extracted
4 publications excluded
• 1 pediatric
•1 animal study
•1 without full text
• 1 data can not be extracted
9 studies included in meta-analysis

Table 1
Characteristics of studies included in the systematic review and meta-analysis.

Author/year	Study type	Country	Infectious disease	Pathogen	Colistin manufacturer	Concomitant antibiotics	Conclusion
Bogovic et al., 2014 [19]	Retrospective	Croatia	ICU with VAP	Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae	N/A	Yes, concurrently	IV-AS benefits microbiological outcome
Doshi et al., 2013 [20]	Retrospective	USA	ICU with NP	A. baumannii, P. aeruginosa, K. pneumoniae	N/A	Yes, concurrently	IV-AS was not better than IV
Tumbarello et al., 2013 [14]	Retrospective, case–control	Italy	ICU with VAP	A. baumannii, P. aeruginosa, K. pneumoniae	N/A	Yes, prior	IV-AS is better
Amin et al., 2013 [18]	Prospective	Egypt	ICU with NP	A. baumannii, P. aeruginosa, K. pneumoniae	N/A	Yes, prior	IV-AS is better
Kalin et al., 2012 [16]	Retrospective	Turkey	ICU with VAP	A. baumannii	Koçak Farma, Istanbul, Turkey	Yes, prior	Higher doses and AS had no advantages
Naesens et al., 2011 [17]	Retrospective	Belgium	ICU with NP	P. aeruginosa	Forest Laboratories, Kent, UK	Yes, concurrently	AS could be beneficial as adjunctive treatment
Pérez-Pedrero et al., 2011 [21]	Retrospective	Spain	ICU with NP, TB, CO	A. baumannii	N/A	N/A	IV had the poorest effect compared with IV-AS or AS alone
Kofteridis et al., 2010 [15]	Retrospective, case–control	Greece	ICU with VAP	A. baumannii, P. aeruginosa, K. pneumoniae	Norma, Greece	Yes, prior	Addition of AS did not provide benefit
Korbila et al., 2010 [13]	Retrospective	Greece	ICU with VAP	A. baumannii, P. aeruginosa, K. pneumoniae	Forest Laboratories, Kent, UK; Norma, Greece	Yes, concurrently	IV-AS was better than IV alone

ICU, intensive care unit; VAP, ventilator-associated pneumonia; N/A, not available; IV-AS, aerosolised and intravenous colistin; NP, nosocomial pneumonia; IV, intravenous colistin; AS, aerosolised colistin; TB, tracheobronchitis; CO, colonisation.

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Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: A systematic review and meta-analysis

Wan-Jie Gu[a], Fei Wang[b], Lu Tang[b], Jan Bakker[c], Jing-Chen Liu[a,*]

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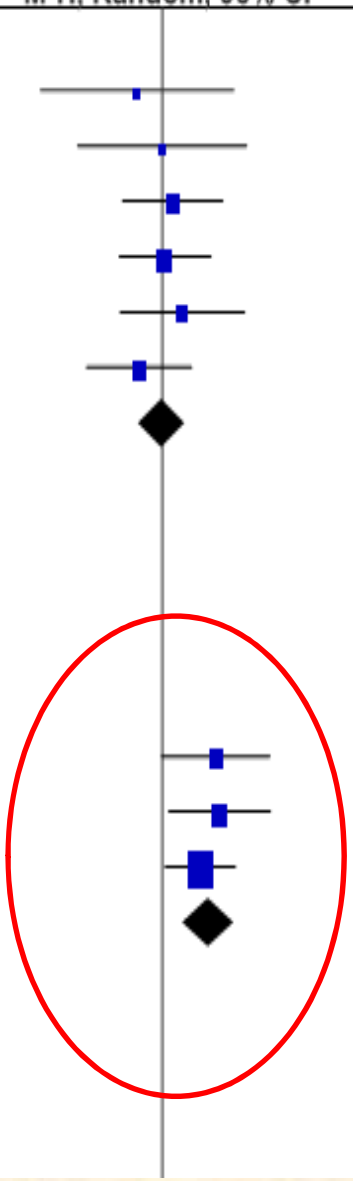
[b] Department of Anaesthesiology, General Hospital of Jinan Military Command, Jinan, China
[c] Department of Intensive Care Adults, Erasmus MC University Medical Center, Rotterdam, The Netherlands

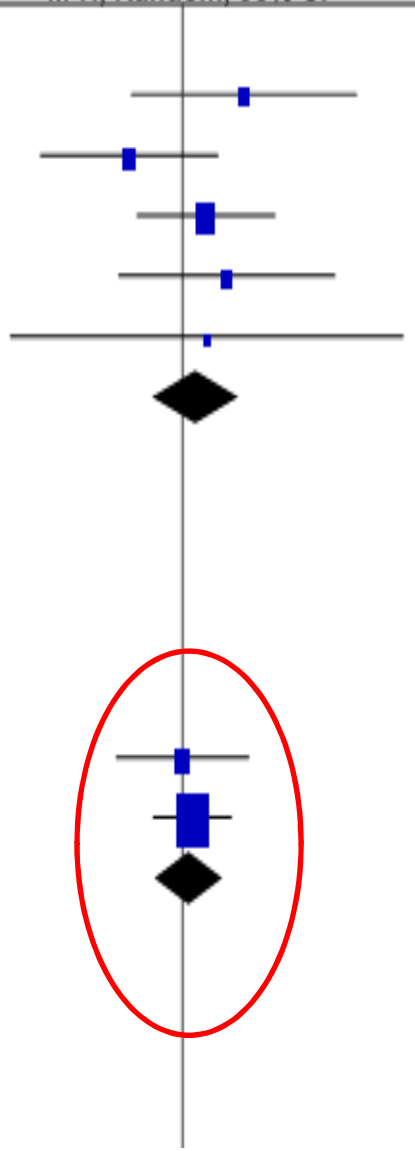
Forest plot depicting clinical cure

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Colistin vs. β-lactam antibiotics						
Betrosian 2008 [8]	9	15	9	13	6.1%	0.67 [0.14, 3.19]
Garnacho-Montero 2003 [5]	12	21	8	14	8.0%	1.00 [0.25, 3.92]
Kallel 2007 [6]	45	60	43	60	22.9%	1.19 [0.53, 2.67]
Lu 2012 [16]	29	43	81	122	27.4%	1.05 [0.50, 2.20]
Rios 2007 [7]	17	31	14	30	14.8%	1.39 [0.51, 3.80]
Zalts 2013 [17]	31	66	18	32	20.8%	0.69 [0.29, 1.61]
Subtotal (95% CI)		**236**		**271**	**100.0%**	**1.00 [0.68, 1.47]**
Total events	143		173			
Heterogeneity: Tau² = 0.00; Chi² = 1.59, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.1.2 AS plus IV colistin vs. IV colistin alone						
Kofteridis 2010 [18]	23	43	14	43	22.2%	2.38 [0.99, 5.72]
Korbila 2010 [19]	62	78	26	43	25.1%	2.53 [1.11, 5.76]
Tumbarello 2013 [20]	72	104	57	104	52.7%	1.86 [1.05, 3.27]
Subtotal (95% CI)		**225**		**190**	**100.0%**	**2.12 [1.40, 3.20]**
Total events	157		97			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 3.57 (P = 0.0004)						

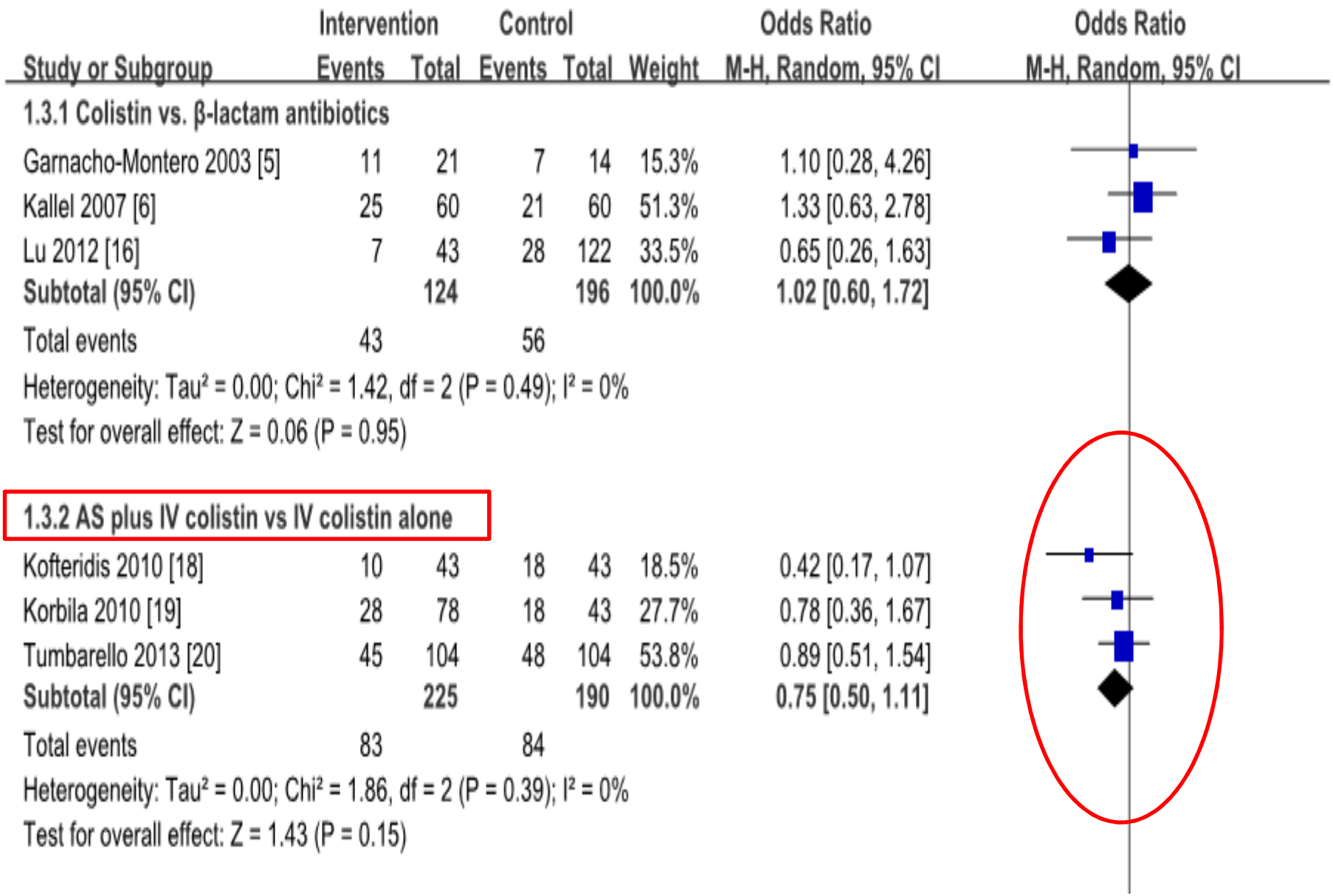


Forest plot depicting nephrotoxicity

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.6.1 Colistin vs. β-lactam antibiotics						
Betrosian 2008 [8]	5	15	2	13	15.0%	2.75 [0.43, 17.49]
Garnacho-Montero 2003 [5]	5	21	6	14	24.1%	0.42 [0.10, 1.79]
Lu 2012 [16]	5	43	10	122	39.8%	1.47 [0.47, 4.58]
Rios 2007 [7]	4	31	2	30	16.2%	2.07 [0.35, 12.27]
Zalts 2013 [17]	1	66	0	32	4.9%	1.49 [0.06, 37.56]
Subtotal (95% CI)		**176**		**211**	**100.0%**	**1.26 [0.62, 2.58]**
Total events	20		20			
Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 4 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.6.2 AS plus IV colistin vs. IV colistin alone						
Kofteridis 2010 [18]	8	43	8	43	25.9%	1.00 [0.34, 2.96]
Tumbarello 2013 [20]	26	104	23	104	74.1%	1.17 [0.62, 2.23]
Subtotal (95% CI)		**147**		**147**	**100.0%**	**1.13 [0.65, 1.96]**
Total events	34		31			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						



Forest plot depicting intensive care unit mortality



Recommendations for the use of AS-Colistin

The dosage recommended is:

- 40 mg (500,000 IU) every 12 h for patients with bodyweights of ≤40 kg
- 80 mg (1 million IU) every 12 h for patients with bodyweights of >40 kg

Thank you for your attention !