Antimicrobial de-escalation for HAP/VAP :Pro

Saving carbapenem

울산의대 서울아산병원 호흡기 홍상범

Clinical Infectious Diseases Advance Access published July 14, 2016

Clinical Infectious Diseases

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

ERJ open research

Summary of the international clinical guidelines for the management of hospital-acquired and ventilator-acquired pneumonia

Antoni Torres[1], Michael S. Niederman[2], Jean Chastre[3], Santiago Ewig[4], Patricia Fernandez-Vandellos[5], Hakan Hanberger[6], Marin Kollef[7], Gianluigi Li Bassi[1], Carlos M. Luna[8], Ignacio Martin-Loeches[9], J. Artur Paiva[10,11], Robert C. Read[12], David Rigau[13], Jean François Timsit[14], Tobias Welte[15,16] and Richard Wunderink[17]

ERJ Open Res 2018; 4: 00028-2018

Intensive Care Med (2020) 46:245–265
https://doi.org/10.1007/s00134-019-05866-w

CONFERENCE REPORTS AND EXPERT PANEL

Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP)

PATHOGENESIS OF VAT AND VAP

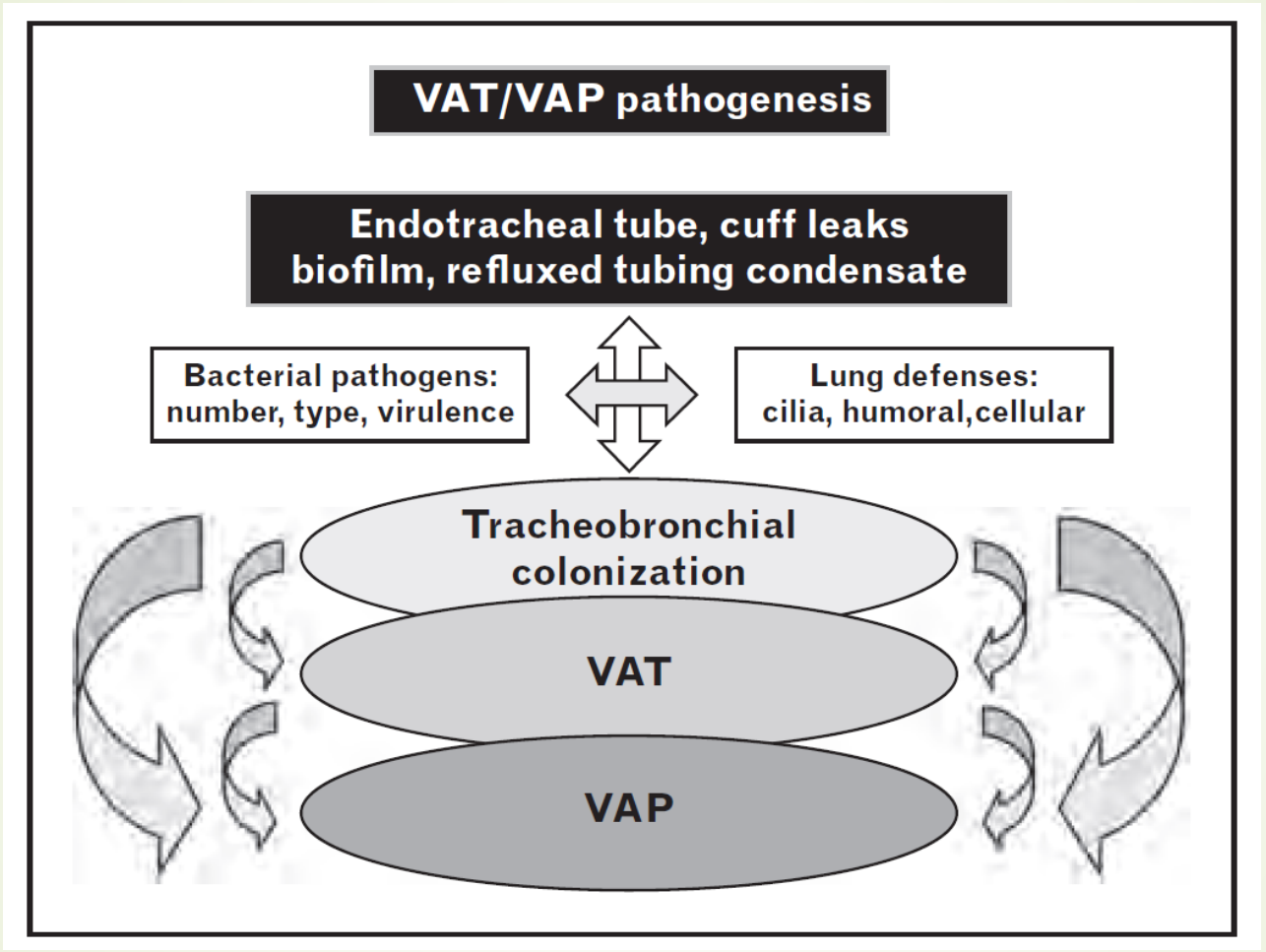
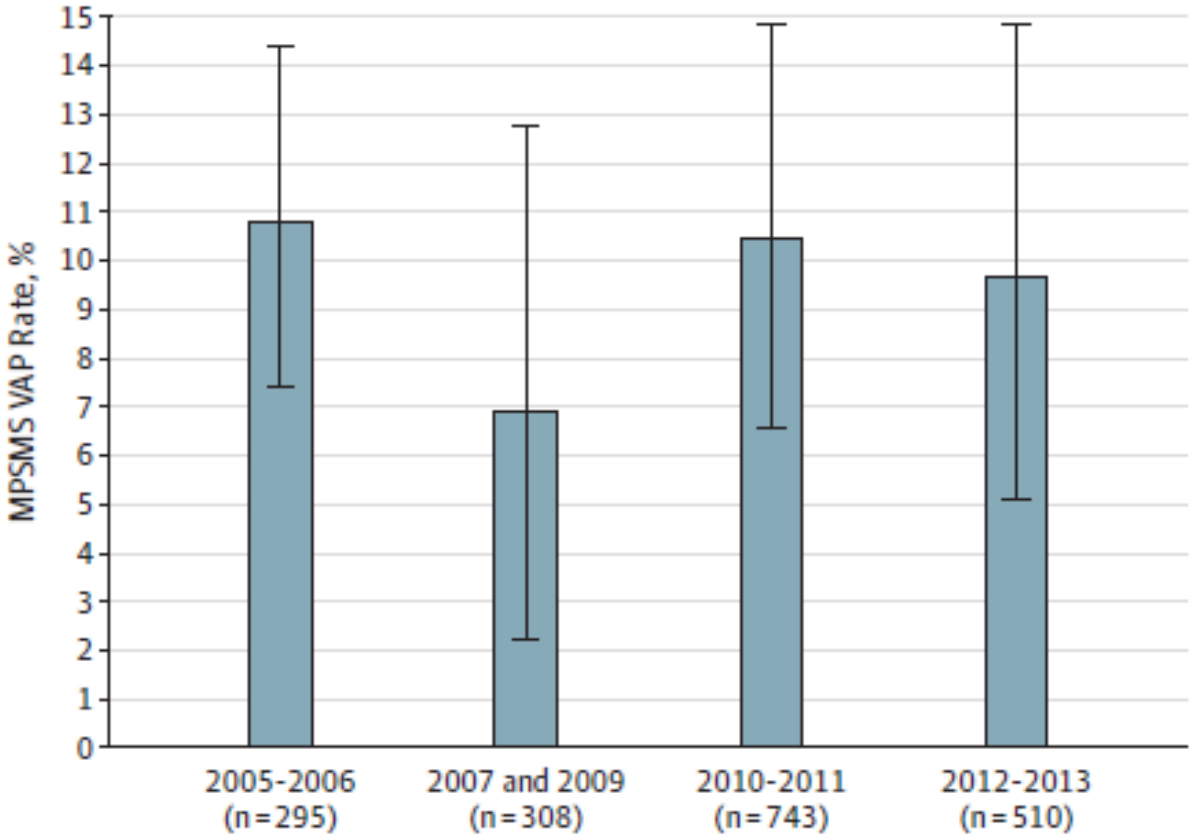


FIGURE 2. Pathogenesis of VAT and VAP

Interaction of bacterial pathogens with host lung defenses, resulting in colonization that may progress to VAT or VAP.

Figure. Adjusted Ventilator-Associated Pneumonia Rates Among Medicare Patient Safety Monitoring System Patients 65 Years and Older, 2005-2013, Based on Bootstrap Analysis



Error bars indicate 95% CIs.

SSC - Antibiotics

- **We recommend that administration of IV a ntimicrobials be initiated as soon as possib le after recognition and within 1 h for both sepsis and septic shock.**

(strong recommendation, moderate quality of evidence).

- **We recommend empiric broad-spectrum t herapy with one or more antimicrobials to cover all likely pathogens.**

(strong recommendation, moderate quality of evidence).

SSC : Antimicrobial Therapy
Antibiotic Stewardship

- We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
  - (BPS)
- We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated with sepsis and septic shock.
  - (Weak recommendation; low quality of evidence)
- We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.
  - (BPS)

Appropriate vs. antibiotics resistance

- Contemporary therapy for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)
- emphasizes the importance of prompt and appropriate antimicrobial therapy.

- Liberal use of antimicrobial combinations will encourage the
- emergence of multidrug resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant bacteria (PDR) and generate untreatable infections, including carbapenemase resistant infections.

Definition of ADE

Q1: What is the definition of antimicrobial de-escalation for critically ill patients receiving empirical antimicrobials for an infection?

1. Replacing broad-spectrum antimicrobials with agents of a narrower spectrum or a lower ecological impact. or

2. Stopping components of an antimicrobial combination. Two different situations can be included in this case

2.a. Stopping of an antimicrobial agent administered in combination therapy to provide double cover for certain pathogens

2.b. Stopping of an antimicrobial agent administered in the empirical regimen to cover pathogens that are not finally isolated in the clinical cultures

3. The early discontinuation of all antimicrobial therapy if infection is ruled out is not considered as de-escalation. (Definition, low quality of evidence.)

Q2: Does the panel recommend a numerical score to measure the ecological impact of the empirical antimicrobial regimen and can this score be used to guide antimicrobial de-escalation?

We recommend research is undertaken to develop multidimensional scores to measure the local ecological impact of empirical antimicrobial regimens and guide ADE. (Moderate recommendation; low quality of evidence.)

Effects of ADE

Q3: In critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on mortality and length of stay?

The ADE strategy is likely safe with regard to patients' outcomes. (Statement of fact; moderate quality of evidence.)

Q4: In critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on the total duration of antimicrobial therapy?

ADE is associated with a risk of increase in total duration of antimicrobial therapy. We recommend that ADE and duration of antimicrobial therapy are assessed separately but as part of the global stewardship strategy. (Statement of fact; low quality of evidence.)

Q5: In critically ill patients receiving antimicrobials for an infection, what are the effects of antimicrobial de-escalation compared to no de-escalation on the development of resistance to antimicrobials?

No recommendation can be made

Q6: In critically ill patients receiving antimicrobials for an infection, when is it recommended to perform de-escalation of the empirical antimicrobial regimen?

We recommend ADE is performed within 24 h of definitive culture results and antibiograms availability. (Strong recommendation; low quality of evidence.)

Q7: In critically ill patients receiving antimicrobials for an infection, are recommendations for or against antimicrobial de-escalation different for certain bacterial pathogens? For which?

Recommendations for or against ADE are similar for all bacterial pathogens except for difficult-to-treat pathogens in patients with a high risk of death. (Moderate recommendation, low quality of evidence.)

Q8: In critically ill patients receiving antifungal agents for invasive candidiasis, does the panel recommend antifungal de-escalation compared to no de-escalation?

We recommend ADE of antifungal agents after clinical and microbiological resolution of invasive candidiasis when the pathogens are susceptible to azole antifungal agents. (Strong recommendation; low-quality evidence.)

Q9: In critically ill patients receiving antimicrobials for a culture-negative infection, does the panel recommend antimicrobial de-escalation compared to no de-escalation?

We recommend that consideration is given to alternate non-infectious diagnosis and stopping all or part of the antibiotic regimen in critically ill patients with culture-negative infections. (Moderate recommendation; low-quality evidence.)

Q10: In neutropenic critically ill patients, does the panel recommend antimicrobial de-escalation compared to no de-escalation?

We suggest ADE can be applied in neutropenic critically ill patients. (Moderate recommendation, low quality of evidence.)

Q11: Are recommendations for or against antimicrobial de-escalation different depending on the source of infection?

We suggest that ADE can be applied in all sources of infection. (Weak recommendation; low quality of evidence.)

Q12: In critically ill patients receiving antimicrobials, does the panel recommend the use of biomarkers when considering antimicrobial de-escalation?

No recommendation can be made

Q13: In critically ill patients who are de-escalated, does the use of therapeutic drug monitoring (TDM) versus no TDM improve outcome?

No recommendation can be made

초기 항생제 선택 및 투여가 중요하다.

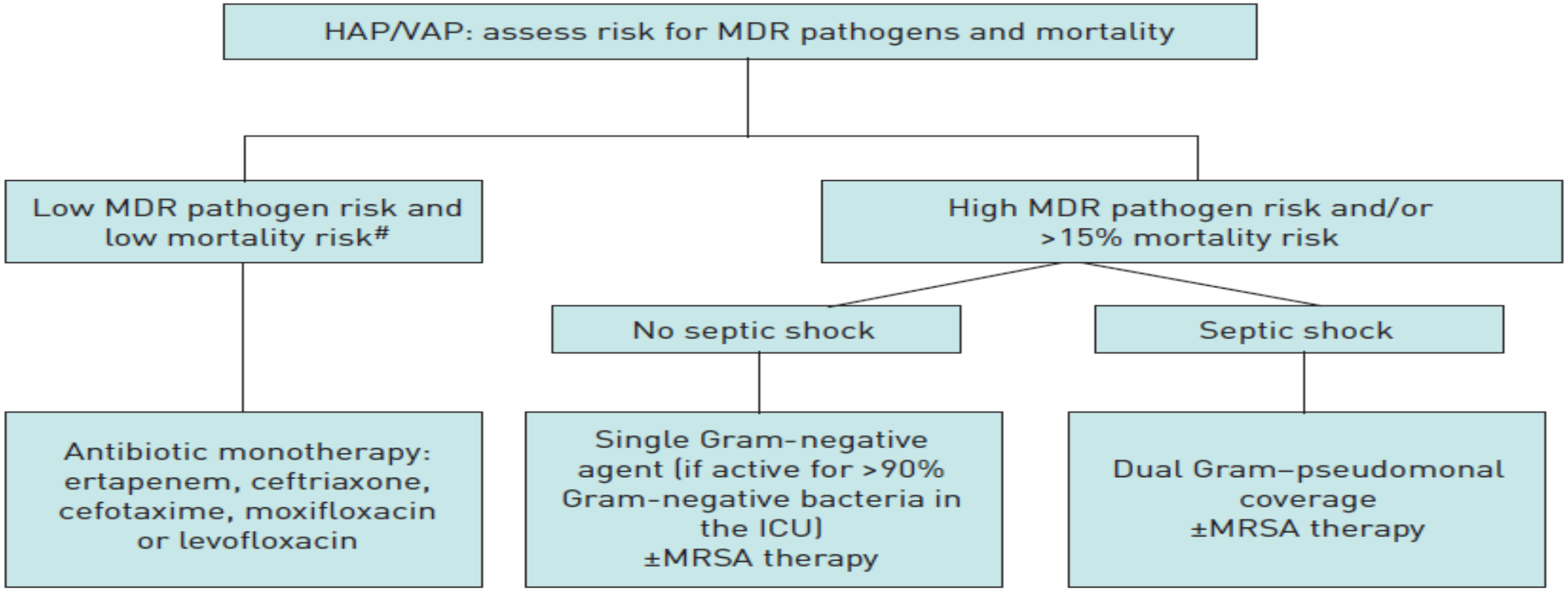


FIGURE 1 Empirical antibiotic treatment algorithm for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP). MDR: multidrug-resistant; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*. #: low risk for mortality is defined as a ⩽15% chance of dying, a mortality rate that has been associated with better outcomes using monotherapy than combination therapy when treating serious infection [18]. Reproduced from [2].

Distribution of pathogens and antimicrobial resistance patterns associated with 8,474 cases of ventilator-associated pneumonia reported to the U.S. Centers for Disease Control and Prevention, 2009-2010		
Pathogen	Frequency	Antimicrobial Resistance Rates
Staphylococcus aureus	24.1%	Methicillin / oxacillin resistant – 48%
Pseudomonas aeruginosa	16.6%	Ciprofloxacin / levofloxacin resistant – 33% Imipenem / meropenem resistant – 30% Cefepime / ceftazidime resistant – 28% Piperacillin-tazobactam resistant – 19% Aminoglycoside resistant – 11% Resistant to ≥3 of the above classes – 18%
Klebsiella species	10.1%	Cefepime / ceftazidime / cefotaxime resistant – 24% Imipenem / meropenem resistant – 11% Resistant to ≥3 classes – 13%
Enterobacter species	8.6%	Cefepime / ceftazidime / ceftriaxone resistant – 30% Imipenem / meropenem resistant – 4% Resistant to ≥3 classes – 1%
Acinetobacter baumannii	6.6%	Imipenem / meropenem resistant – 61% Resistant to ≥3 classes – 63%
Escherichia coli	5.9%	Ciprofloxacin / levofloxacin resistant – 35% Cefepime / ceftazidime / ceftriaxone resistant – 16% Imipenem / meropenem resistant – 4% Resistant to ≥3 classes – 3%

SUMMARY OF META-ANALYSES COMPARING DIFFERENT CLASSES OF GRAM-NEGATIVE AGENTS FOR EMPIRIC TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA				
Comparison	Mortality Risk Ratio (95% CI)	Clinical Response Risk Ratio (95% CI)	Acquired Resistance Risk Ratio (95% CI)	Adverse Events Risk Ratio (95% CI)
Combination versus monotherapy	1.11 (0.90, 1.38)	0.89 (0.75, 1.07)	1.13 (0.42, 3.00)	0.90 (0.69, 1.18)
Cephalosporin versus non-cephalosporin regimens	0.97 (0.74, 1.27)	0.92 (0.78, 1.09)	2.36 (0.63, 8.86)	1.01 (0.82, 1.25)
Quinolone versus non-quinolone regimens	1.13 (0.92, 1.39)	1.05 (0.91, 1.20)	0.77 (0.59, 1.01)	0.88 (0.78, 0.99)
Anti-Pseudomonal penicillin versus non-anti-Pseudomonal penicillin regimens	1.12 (0.76, 1.66)	1.10 (0.80, 1.52)	Not Reported	0.96 (0.77, 1.20)
Aminoglycoside versus non-aminoglycoside regimens	1.15 (0.88, 1.50)	0.82 (0.71, 0.95)	Not Reported	0.96 (0.70, 1.33)
Carbapenem versus non-carbapenem regimens	0.78 (0.65, 0.94)	1.02 (0.93, 1.12)	1.16 (0.53, 2.55)	1.08 (0.90, 1.28)

항생제는 한 가지 혹 두 가지 혹 세 가지

VAP-Initial Empiric Antibiotics Gram Positive

We suggest including an agent active against MRSA for the empiric treatment of suspected VAP only in patients with risk factors for antimicrobial resistance, patients being treated in units where >10-20% of *S. aureus* isolates are methicillin-resistant, and patients in units where the prevalence of MRSA is not known

VAP-Initial Empiric Antibiotics Gram Negative

We suggest prescribing TWO anti-Pseudomonal antibiotics from different classes for the empiric treatment of suspected VAP only in patients with risk factors for antimicrobial resistance, patients in units where >10% of Gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available

Kim et al. Critical Care 2012, 16:R28
http://ccforum.com/content/16/1/R28

CRITICAL CARE

RESEARCH Open Access

Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial

Jong Wook Kim[1†], Joowon Chung[2†], Sang-Ho Choi[3], Hang Jea Jang[4], Sang-Bum Hong[5], Chae-Man Lim[5] and Younsuck Koh[5*]

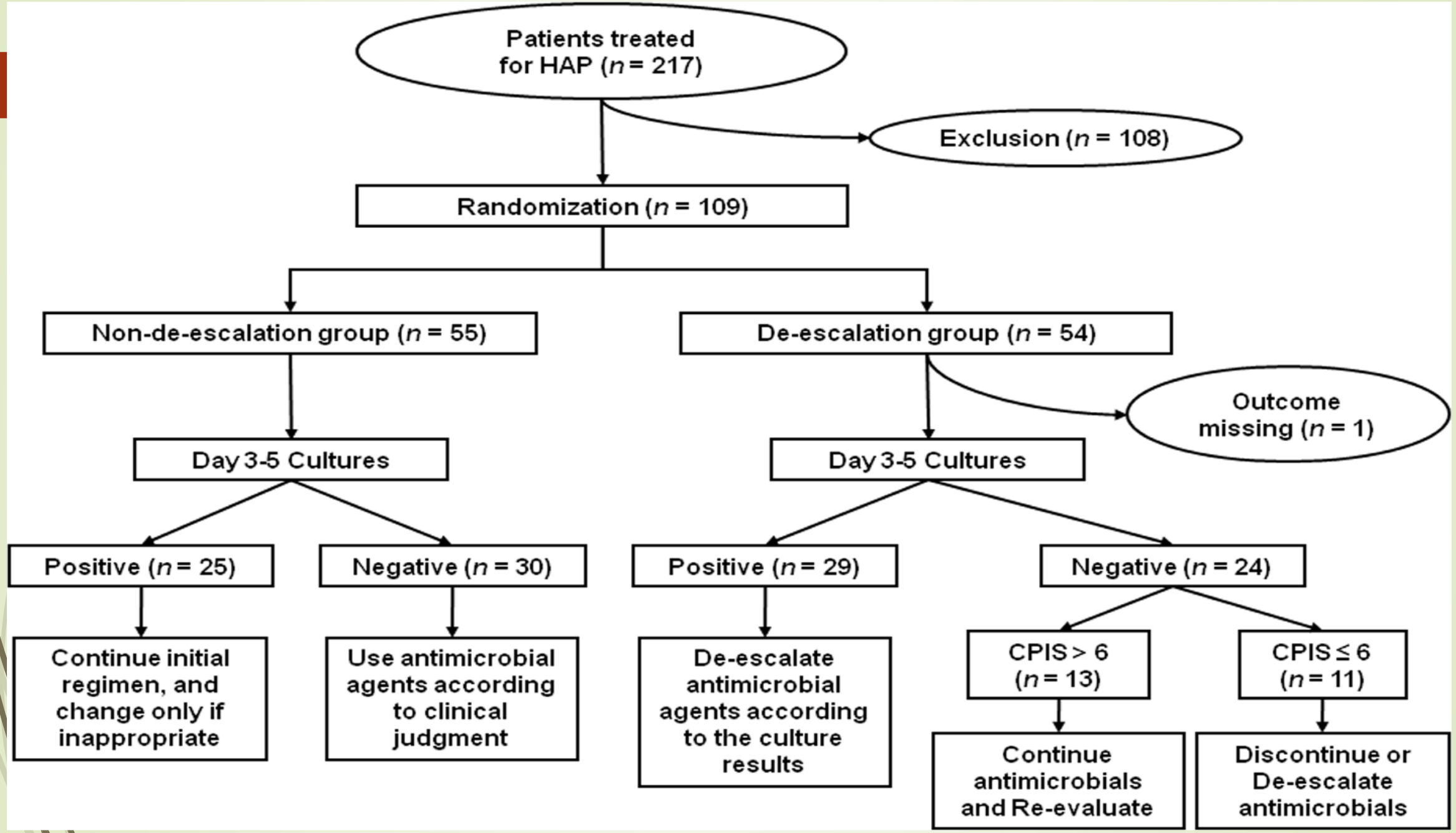

Patients treated for HAP (n = 217)
Exclusion (n = 108)
Randomization (n = 109)
Non-de-escalation group (n = 55)
De-escalation group (n = 54)
Outcome missing (n = 1)
Day 3-5 Cultures
Day 3-5 Cultures
Positive (n = 25)
Negative (n = 30)
Positive (n = 29)
Negative (n = 24)
Continue initial regimen, and change only if inappropriate
Use antimicrobial agents according to clinical judgment
De-escalate antimicrobial agents according to the culture results
CPIS > 6 (n = 13)
CPIS ≤ 6 (n = 11)
Continue antimicrobials and Re-evaluate
Discontinue or De-escalate antimicrobials

Table 3 Treatment outcomes of patients with HAP in the DE and NDE groups

	DE (n = 53)	NDE (n = 55)	Overall (n = 108)	P
Time to adequate antimicrobials, days, mean (SD)[a]	1.9 (0.5)	2.8 (0.6)	2.4 (0.4)	0.280
Mortality				
Day 14	13 (24.5%)	9 (16.7%)	22 (20.6%)	0.314
Day 28	21 (39.6%)	14 (25.9%)	35 (32.7%)	0.131
Hospital mortality	23 (44.2%)	18 (34.6%)	41 (39.4%)	0.316
ICU stay, days, mean (IQR)[b]	21.1 (6-35)	14.1 (6-19)	17.2 (6-19)	0.464[c]
Emergence of MDR organisms[d]	11 (37.9%)	7 (16.7%)	18 (25.4%)	0.043
Time to development, days, mean (IQR)	19.4 (11-30)	22.7 (9-30)	21 (11-30)	0.108[c]
Methicillin-resistant *S. aureus*	8 (27.6%)	4 (9.5%)	12 (16.9%)	0.059
Gram-negative non-Enterobacteriaceae	4 (13.8%)	5 (11.9%)	9 (12.9%)	> 0.999
S. maltophilia	3 (10.7%)	2 (4.8%)	5 (7.1%)	0.383
Imipenem-resistant *A. baumannii*	0	2 (4.8%)	2 (2.9%)	0.513
Imipenem-resistant *P. aeruginosa*	0	1 (2.4%)	1 (1.4%)	> 0.999
ESBL-producing *K. pneumonia*	1 (3.6%)	0	1 (2.9%)	0.400

Journal of Critical Care 54 (2019) 14–19

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Safety of antimicrobial de-escalation for culture-negative severe pneumonia

Byoung Soo Kwon, M.D. [a,c], Sang Ho Choi, M.D., Ph.D. [b], Younsuck Koh, M.D., Ph.D. [a], Jin-Won Huh, M.D., Ph.D. [a], Sang-Bum Hong, M.D., Ph.D. [a], Chae-Man Lim, M.D., Ph.D. [a,*]

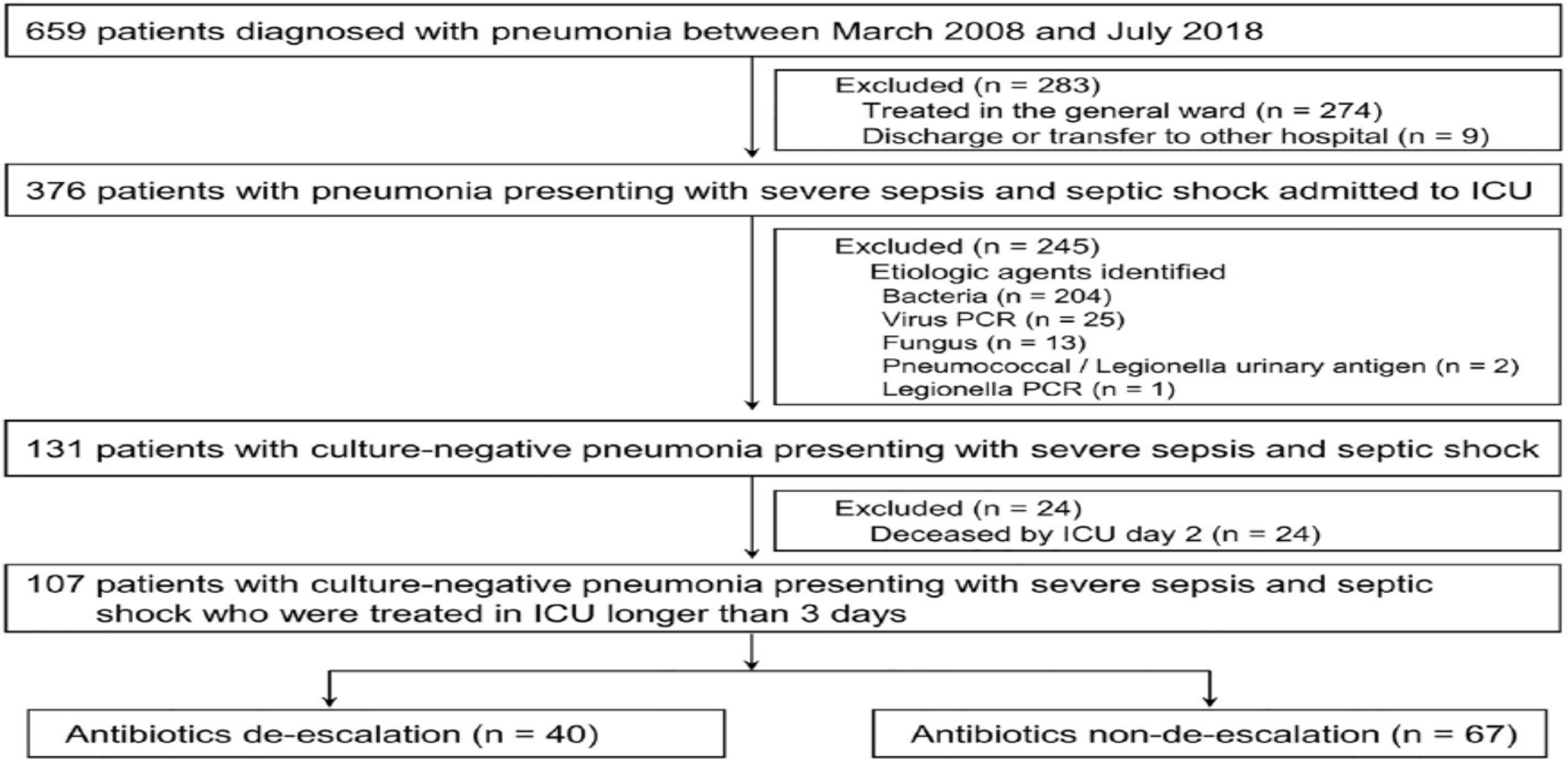

659 patients diagnosed with pneumonia between March 2008 and July 2018
Excluded (n = 283)
Treated in the general ward (n = 274)
Discharge or transfer to other hospital (n = 9)
376 patients with pneumonia presenting with severe sepsis and septic shock admitted to ICU
Excluded (n = 245)
Etiologic agents identified
Bacteria (n = 204)
Virus PCR (n = 25)
Fungus (n = 13)
Pneumococcal / Legionella urinary antigen (n = 2)
Legionella PCR (n = 1)
131 patients with culture-negative pneumonia presenting with severe sepsis and septic shock
Excluded (n = 24)
Deceased by ICU day 2 (n = 24)
107 patients with culture-negative pneumonia presenting with severe sepsis and septic shock who were treated in ICU longer than 3 days
Antibiotics de-escalation (n = 40)
Antibiotics non-de-escalation (n = 67)

Table 3
Survival outcomes of 107 patients with culture-negative pneumonia who presented with sepsis and septic shock.

	Total (n = 107)	De-escalation (n = 40)	Non-de-escalation (n = 67)	P-value
ICU mortality	39 (36.8%)	11 (27.5%)	28 (41.8%)	0.137
In-hospital mortality	52 (48.6%)	15 (37.5%)	37 (55.2%)	0.076
ICU length of stay, days	11 (6.0–19.0)	11.5 (5–18.8)	10 (6.0–21.0)	0.592
Duration of MV, days	10 (4.3–16.8)	10.5 (4.8–15.3)	9 (4.0–18.3)	0.782
Duration of antibiotic administration	22 (14.8–40.3)	21 (13.0–41.3)	24 (15.0–39.0)	0.737
Burden of antibiotics[a]	12.0 ± 4.6	11.0 ± 3.6	12.6 ± 5.0	0.050
Follow-up SOFA score	8.9 ± 3.8	9.0 ± 4.2	8.8 ± 3.6	0.805
Δ-SOFA score[b]	0.8 ± 3.7	0.4 ± 3.7	1.0 ± 3.8	0.392

어떤 항생제를 선택할 것인가?
각자 병원 균 및 내성 패턴 중요.

성인중환자실 원내폐렴의 치료실태 : 다기관 전향적 관찰연구

- **Study Period**

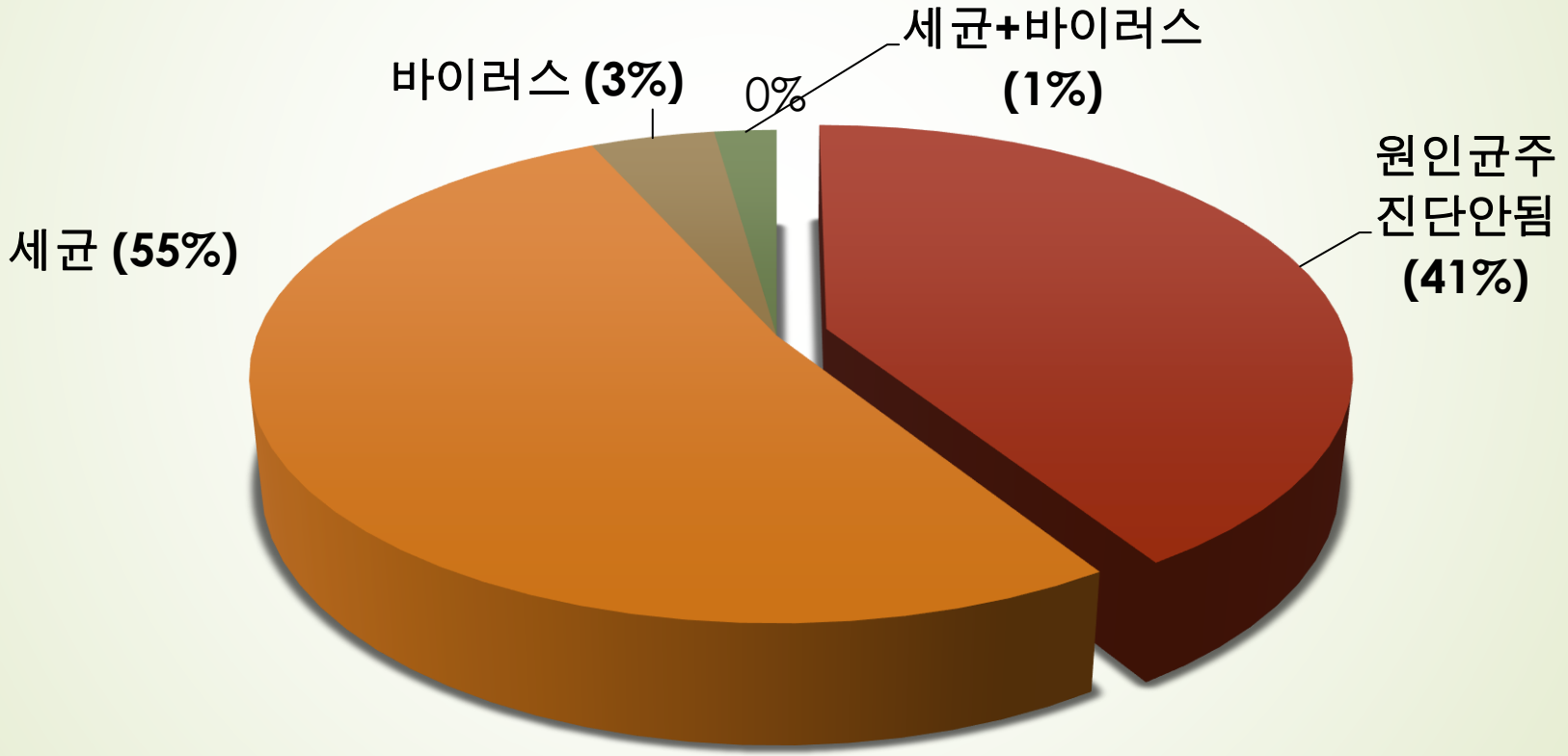
  : 2012.8.1 - 2015. 6.30

- **Study Centers**

: 서울아산병원, 삼성서울병원, 서울대병원, 세브란스병원, 분당서울대병원, 서울성모병원

원인병원체 (356명 환자 분석 자료)

원인균주 진단 59% (205명)



원인병원체 (356명 환자 분석 자료)

Pathogens	n (polymicrobial) (%)
Bacteria	**194/205 (93%)**
Acinetobacter baumannii	78 (6) (38%)
Staphylococcus aureus	50 (13) (24%)
Klebsiella pnemoniae	20 (8) (10%)
Pseudomonas aerusinosa	20 (5) (10%)
Stenotrophomonas maltophilia	14 (5) (7%)
Enterococcus faecium	6 (1) (3%)
Others (Pneumoccocus, Enterobacter..)	24 (1) (12%)

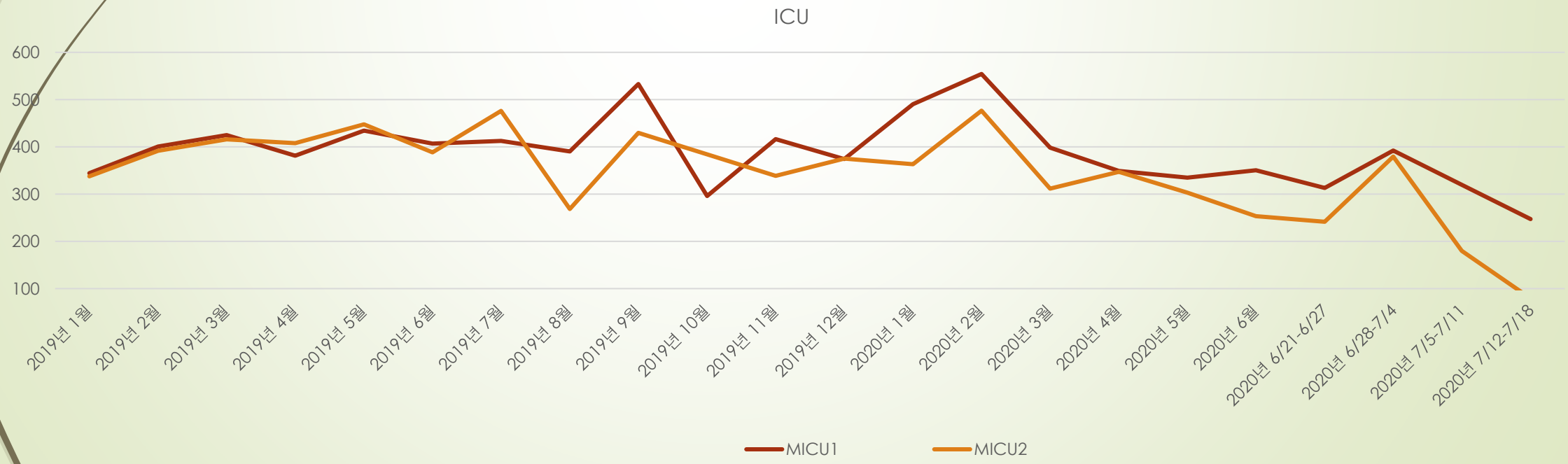
Variables	n /N (%)
초기 (첫 1-2일) 경험적 항생제 선택	N=354
Carbapenem-based	137 (39)
Extended-spectrum penicillin/β-lactamase inhibitor-based	130 (37)
3rd cephalosporin or cefepime-based	25 (7)
Colistin-based	20 (6)
Quinolone only	10 (3)
Carbapenem + Tigecycline	7 (2)
Tigecycline-based	7 (2)
Colistin + Tigecycline	3 (1)
Others	3 (1)
Glycopeptide only	12 (3)
Glycopeptide 포함 (Vancomycin or Teicoplanin)	165 (47)

AMC data : 2,221 patients with severe pneumonia in MICU (2010-9)

Identified organism	Total (N=2,221)	CAP† (N=1,482)	HAP (N=739)	P value
None	711(32.0)	483 (32.6)	228 (30.9)	0.41
Bacteria	888 (40.0)	575 (38.8)	313 (42.4)	0.11
S. pneumoniae	126 (5.7)	114 (7.7)	12 (1.6)	< 0.001
S. aureus	197 (8.9)	112 (7.6)	85 (11.5)	< 0.01
Enteric gram-negative bacilli	270 (12.2)	196 (13.2)	74 (10.0)	0.03
K. pneumonia	166 (7.5)	119 (8.0)	47 (6.4)	0.16
E. coli	64 (2.9)	50 (3.4)	14 (1.9)	0.050
Non-enteric gram-negative bacilli	284 (12.8)	135 (9.1)	149 (20.2)	< 0.001
P. aeruginosa	126 (5.7)	86 (5.8)	40 (5.4)	0.71
A. baumannii	125 (5.6)	41 (2.8)	84 (11.4)	< 0.001
S. maltophilia	29 (1.3)	5 (0.3)	24 (3.2)	< 0.001

ADE 조건 : 중환자실 감염 관리- MDR 감소

- ICU environmental control : hydrogen peroxide system, UV device
- chrolohexidine bathing
- Antibiotics rounding (2/wks)
- VAP prevention bundle, CLASI bundle etc
- Carbapenem – decreasing, CRAB, MRSA – decreasingNo need for coverage of CRAB



Take home message

- HAP/VAP : 빠른 광범위 항생제 투여, 그러나 Carbapenem 필요성 적다
- 초기 항생제 : inappropriate therapy vs. risks of antibiotics overuse
- 초기 광범위 항생제를 사용할 수 밖에 없는 상황이지만 환경 개선 등을 통하여 MDR pathogen 감소에 노력해야 된다
- MDR 감소를 위해서 de-escalation : esp carbapenem sparing 이 중요
- antibiotics stewardship 프로그램을 각 병원에서 셋팅하는 것이 중요함.

- 균주 동정시에는 narrow spectrum AB 로 즉시 전환해야 됨.
- 균주가 동정되지 않았을 경우 환자가 호전시 de-escalation 해도 안전함.

- Saving Carbapenem