Antibiotics De-escalation Therapy in HAP/VAP

Con

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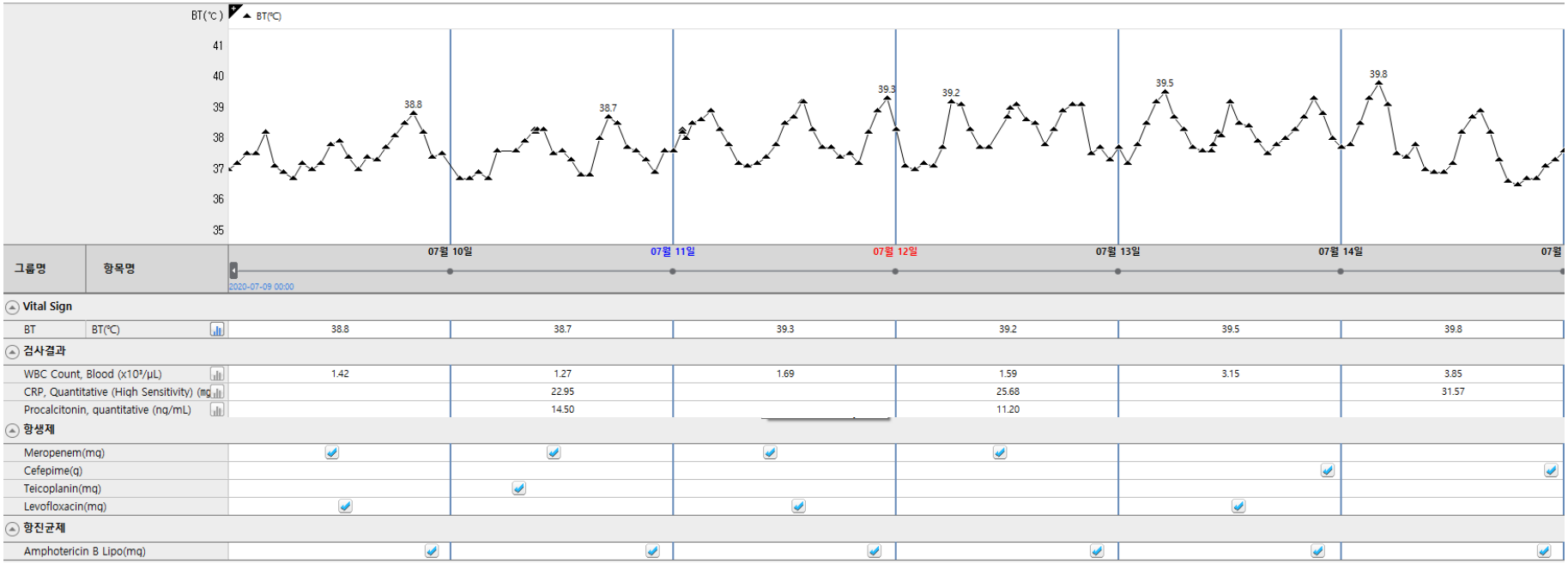
62 YO Female with Fever

Prolonged Fever, but De-escalation



그룹명	항목명	07월 10일	07월 11일	07월 12일	07월 13일	07월 14일	07월
Vital Sign							
BT	BT(℃)	38.8	38.7	39.3	39.2	39.5	39.8
검사결과							
WBC Count, Blood (x10³/μL)		1.42	1.27	1.69	1.59	3.15	3.85
CRP, Quantitative (High Sensitivity) (mg			22.95		25.68		31.57
Procalcitonin, quantitative (ng/mL)			14.50		11.20		
항생제							
Meropenem(mg)		✓	✓	✓	✓		
Cefepime(g)						✓	✓
Teicoplanin(mg)			✓				
Levofloxacin(mg)		✓		✓		✓	
항진균제							
Amphotericin B Lipo(mg)		✓	✓	✓	✓	✓	✓

【검사명】 Gram Stain and Culture, Bacteria [BL4020] 【구분】 입원
【처방일】 2020-07-08 【접수일】 2020-07-08 10:37 【검사일】 2020-07-08 10:37 【보고일】 2020-07-09 10:00

**** 【최종보고】 ****
【판독의1】 이남용 【판독의2】 이남용 【판독의3】 조덕
【검체】 Sputum
▣ 결론 및 진단

Gram positive cocci : 1 ~ 5 /HPF
Gram positive bacilli : >30 /HPF
Yeast like cell : 6 ~ 30 /HPF
WBC : <1 /LPF
Epithelial cell : >25 /LPF

2020-07-08 15:14:50

[참고] "Quality of sputum unsatisfactory"

Throat normal flora.

【검사명】 Gram Stain and Culture, Bacteria [BL4020] 【구분】 입원
【처방일】 2020-07-14 【접수일】 2020-07-14 11:09 【검사일】 2020-07-14 11:09 【보고일】 2020-07-15 08:49

**** 【최종보고】 ****
【판독의1】 이남용 【판독의2】 이남용 【판독의3】 이남용
【검체】 Sputum
▣ 결론 및 진단

Gram positive cocci : <1 /HPF
Gram negative bacilli : 1 ~ 5 /HPF
Gram positive bacilli : 1 ~ 5 /HPF
WBC : <1 /LPF
Epithelial cell : >25 /LPF

2020-07-14 14:23:41

[참고] "Quality of sputum unsatisfactory"

Throat normal flora.

Opinion>>
#. 처음부터 가래가 거의 없었고 바로 meropenem, teicoplanin으로 치료 시작하였으므로 계획하신 대로 cefepime으로 변경하여 보는 것이 좋겠습니다. LAmB는 그대로 유지하시기 바랍니다.

Pro and Con Between Pulmonary Intensivists

What is De-escalation?

- Strategy to minimize the overall exposure to broad-spectrum agents as empiric treatment for infection
  - Reducing the duration of exposure to broad-spectrum agents
  - Reducing the ecological impact of that treatment

- Various definitions of de-escalation
  - Reduction of the spectrum of antimicrobials by replacing an agent with one of a smaller spectrum
  - Decreasing the number of antimicrobials in combination therapy

  …
  - Discontinuation of all antibiotics (early discontinuation)

Clin Infect Dis 2016;62:1009

Various Definition of De-escalation

From a Systematic Review

Year	Initial Broad-Spectrum Therapy (If Specific Antimicrobials Described)	Definition of ADE			Negative Cultures Included in ADE	Ranking of Agents	ADE to Occur on or Before Specified Day of Therapy
		Decrease No. of Antimicrobials	Narrow Spectrum	Shorten (or Cease) Therapy			
2006	Imipenem ± aminoglycoside ± glycopeptide	Yes	Yes	No	No	Not ranked	Between 3rd and 5th d
2007	No specific antimicrobials described	Yes	Yes	No	No	Carbapenem > extended-spectrum penicillin > fluoroquinolone + aminoglycoside > nonantipseudomonal β-lactam	3rd d
2009	Monthly rotation of empiric therapy (cefepime, levofloxacin, imipenem or meropenem, piperacillin-tazobactam)	Yes	Yes	No	No	Not ranked	Between 2nd and 3rd d
2010	Meropenem	No	Yes	No	No	Not ranked	3rd d
2010	No specific antimicrobials described	Yes	Yes	Yes	No	Not ranked	Before 5th d for reducing number of antibiotics, before 3rd d for early cessation
2011	No specific antimicrobials described	Yes	Yes	Yes	Yes	Carbapenem > piperacillin-tazobactam > cefepime or 3rd generation cephalosporin	Specified for negative cultures: discontinuation before 5th d if >48 h of defervescence
2012	No specific antimicrobials described	Yes (including antifungal)	Yes	No	No	Not ranked	5th d after diagnosis
2012	ADE group: imipenem + vancomycin; non-ADE group: empiric antimicrobials according to national guidelines for nosocomial pneumonia	Yes	Yes	No	Yes	Not ranked	3rd to 5th d
2013	No specific antimicrobials described	Yes	Yes	Yes	Yes	Not ranked	Specified when no obvious infectious site: discontinuation before 4th d if favorable clinical evolution/ alternative diagnosis
2013	Piperacillin-tazobactam + levofloxacin + vancomycin	Yes	Yes	No	No	Gram negative: carbapenem > piperacillin-tazobactam > cefepime > fluoroquinolone; gram-positive: vancomycin > nafcillin or cefazolin	Within 24 h of culture results
2014	No specific antimicrobials described	Yes (including antifungal or antiviral)	Yes	No	No	Not ranked	Not specified
2014	No specific antimicrobials described	Yes	Yes	No	Yes	Not ranked	Once culture results were available
2014	No specific antimicrobials described (antimicrobials termed either "pivotal" or "companion")	Yes	Yes	No	No	Carbapenem > piperacillin-tazobactam or ceftazidime or cefepime or ertapenem > ticaricllin > 3rd-generation cephalosporin > aminopenicillin + clavulanate > aminopenicillin or methicillin	When antibiogram available; for "companion" antimicrobial: ceased on 3rd d
2015	No specific antimicrobials described	Yes	Yes	Yes	Yes	Not ranked	By d 5

Clin Infect Dis 2016;62:1009

Various Definition of De-escalation

Studies for Pneumonia in ICU

Primary author	Types of observational study	Number of ICU sites	Number of patients	Type of nosocomial pneumonia	De-escalation definition	Types of empirical antibiotic used	Duration of follow-up
Alvarez-Lerma et al[10]	Prospective	24	244	Nosocomial Pneumonia	Decreased number of antibiotics Narrowing the spectrum	Imipenem-based regimen: Imipenem only Imipenem + aminoglycosides Imipenem+ glycopeptides Imipenem+ aminoglycosides + glycopeptides	7 to 9 days after completion of therapy
Joung et al[25]	Retrospective	1	137	Nosocomial pneumonia (medical and surgical)	Decreased number of antibiotics Narrowing the spectrum Shortening the duration or ceased therapy	Nonspecific antibiotics	14 and 30 days post therapy
Knaak et al[12]	Retrospective	1	113 (117 cases)	HAP, VAP, HCAP	Decreased number of antibiotics Narrowing the spectrum	Piperacillin/tazobactam, levofloxacin, and vancomycin	Hospital admission
Rello et al[31]	Prospective	1	115 (121 VAP cases)	VAP	Decreased number of antibiotics Narrowing the spectrum Shortening the duration or ceased therapy	Nonspecific antibiotics	ICU stay
Kollef et al[28]	Prospective	20	394	VAP	Decreased number of antibiotics Narrowing the spectrum	Nonspecific antibiotics	30 days posttherapy
Giantsou et al[26]	Prospective	1	143	VAP	Decreased number of antibiotics Narrowing the spectrum	Nonspecific antibiotics	15 and 28 days post therapy
Joffe et al[27]	Prospective	28	739	VAP	Decreased number of antibiotics Narrowing the spectrum Shortening the duration or ceased therapy	Meropenem-based regimen: Meropenem only Meropenem + Ciprofloxacin	28 days posttherapy
Eachempati et al[29]	Retrospective	1	135	VAP (surgical)	Decreased number of antibiotics Narrowing the spectrum	Cefepime, Levofloxacin, imipenem-cilastatin/ meropenem, piperacillin/ tazobactam	ICU stay
Khan and Aziz[30]	Retrospective	1	108	VAP	Decreased number of antibiotics Narrowing the spectrum	Nonspecific antibiotics	28 days posttherapy

Int J Clin Pract 2018;72:e13245

Consensus Definition of De-escalation
ESICM and ESCMID, 2020

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.

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

    2b. 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.

▶ 93% of experts agreed with the consensus definition even after the second Delphi round

Intensive Care Med 2020;46:245

Outcomes of De-escalation

Meta-analysis with Studies for Pneumonia in ICU

Patient or population: Critically ill patients with ICU-acquired pneumonia
Setting: Intensive Care Unit
Intervention: De-escalation therapy
Comparison: Non-de-escalation therapy

Outcomes	Estimated risks (95% CI)		Relative effect (95% CI)	No. of partici-pants (Studies)	Quality of the evidence (GRADE)
	Control risk (Non-de-escalation)	Intervention risk (De-escalation)			
28-30 d mortality	274 per 1000	200 per 1000 (115-348)	RR 0.73 (0.42 to 1.27)	1384 (4)	⨁◯◯◯ VERY LOW[a,b]
ICU mortality	341 per 1000	253 per 1000 (181-355)	RR 0.74 (0.53 to 1.04)	358 (3)	⨁⨁◯◯ LOW[a]
Hospital mortality	232 per 1000	223 per 1000 (172-288)	RR 0.96 (0.74 to 1.24)	983 (2)	⨁⨁◯◯ LOW[a]
ICU stay	Mean length of stay of 21.2 d	Mean length of stay of 18.1 d	MD -3.04 (-7.57 to 1.49)	495 (3)	⨁⨁◯◯ LOW[a]
Hospital stay	Mean length of stay of 25.4 d	Mean length of stay of 21.8 d	MD -5.96 (-8.39 to -3.52)	387 (2)	⨁⨁◯◯ LOW[a]

Int J Clin Pract 2018;72:e13245

De-escalation for ICU-acquired Pneumonia

SMC Data

RESEARCH Open Access

Impact of de-escalation therapy on clinical outcomes for intensive care unit-acquired pneumonia

Mi Kyong Joung[1], Jeong-a Lee[2], Soo-youn Moon[3], Hae Suk Cheong[4], Eun-Jeong Joo[1], Young-Eun Ha[1], Kyung Mok Sohn[5], Seung Min Chung[1], Gee Young Suh[6], Doo Ryeon Chung[1], Jae-Hoon Song[1,7] and Kyong Ran Peck[1*]

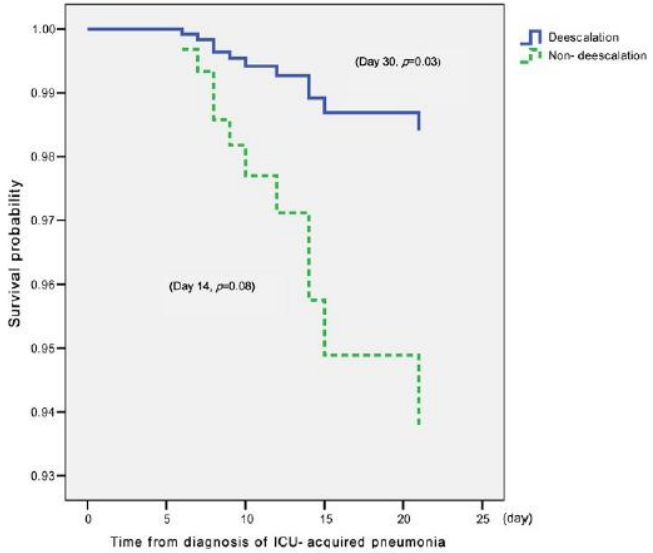


Table 3 Factors associated with 30-day pneumonia-related mortality in patients with ICU-acquired pneumonia determined by multivariable analysis[a]

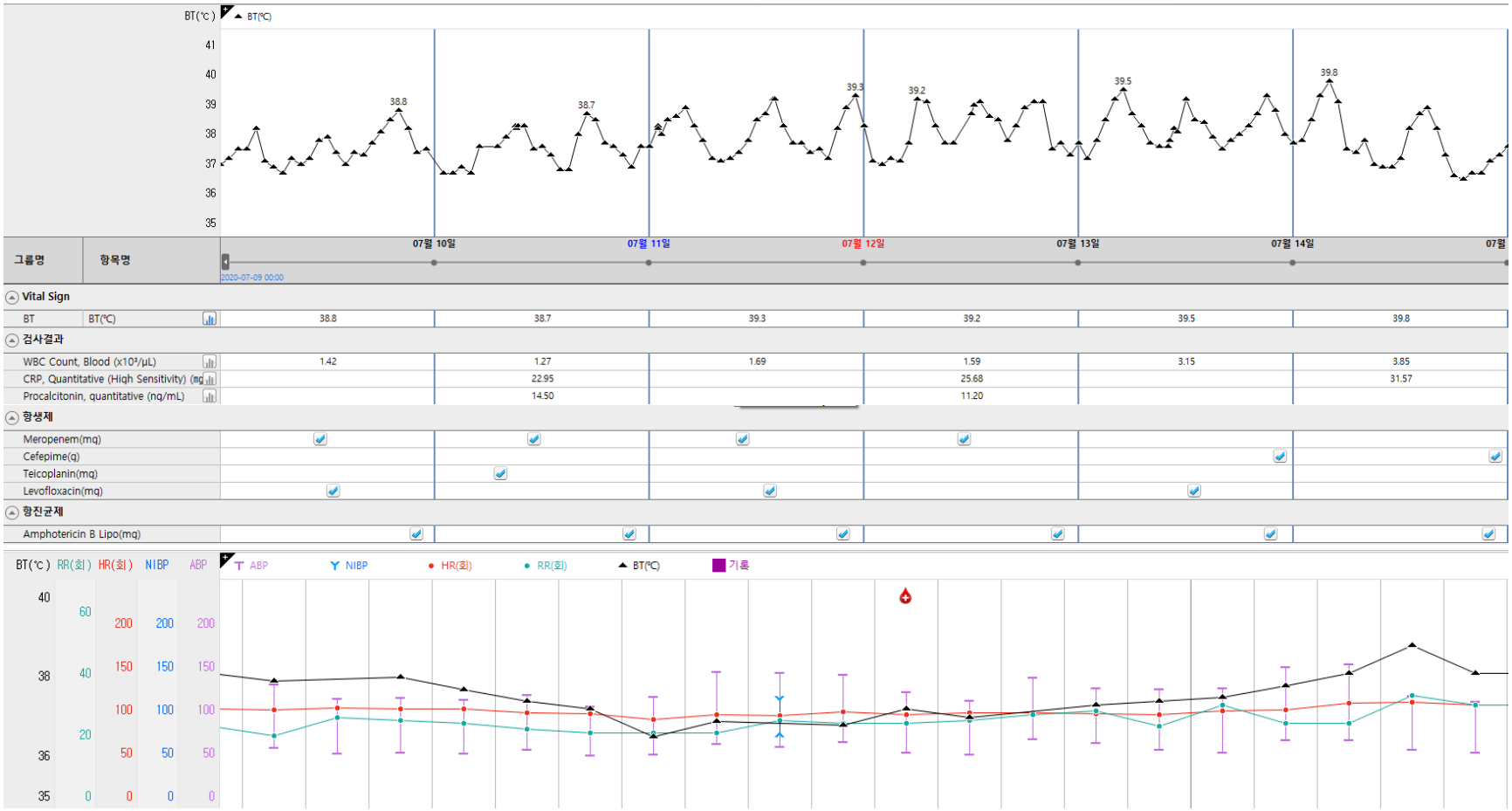
Variable	Adjusted hazard ratio[b]	95% CI	*P* value
Inadequacy of antibiotics	2.145	0.483 to 9.536	0.316
Non-de-escalation of antibiotics	3.988	0.047 to 6.985	0.245
Baseline APACHE II score (reference score <19)			0.198
20 to 23	2.528	0.609 to 10.493	0.201
≥24	7.611	0.615 to 94.179	0.114
5-day APACHE II score (reference score <19)			0.011
20 to 23	4.934	0.974 to 25.003	0.054
≥24	12.839	2.359 to 69.883	0.003
5-day CPIS (reference score 4 to 6)			0.017
7 to 9	2.154	0.361 to 12.861	0.400
≥10	26.782	2.180 to 329.011	0.010

[a]ICU, intensive care unit; 95% CI, 95% confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; CPIS, Clinical Pulmonary Infection Score; [b]Cox proportional hazard regression analysis was used to determine the relationship between mortality and independent baseline variables identified in univariable analysis, including inadequacy of initial antibiotics, de-escalation of antibiotics, baseline APACHE II score, 5-day APACHE II score and 5-day CPIS.

The 5-day APACHE II score and the 5-day CPIS were significantly lower in the de-escalation group compared to the non-de-escalation group. The cause of high mortality in the non-de-escalation group was probably related to the high APACHE II score and modified CPIS on day 5, as well as the timing of de-escalation.

Crit Care 2011;11:R79

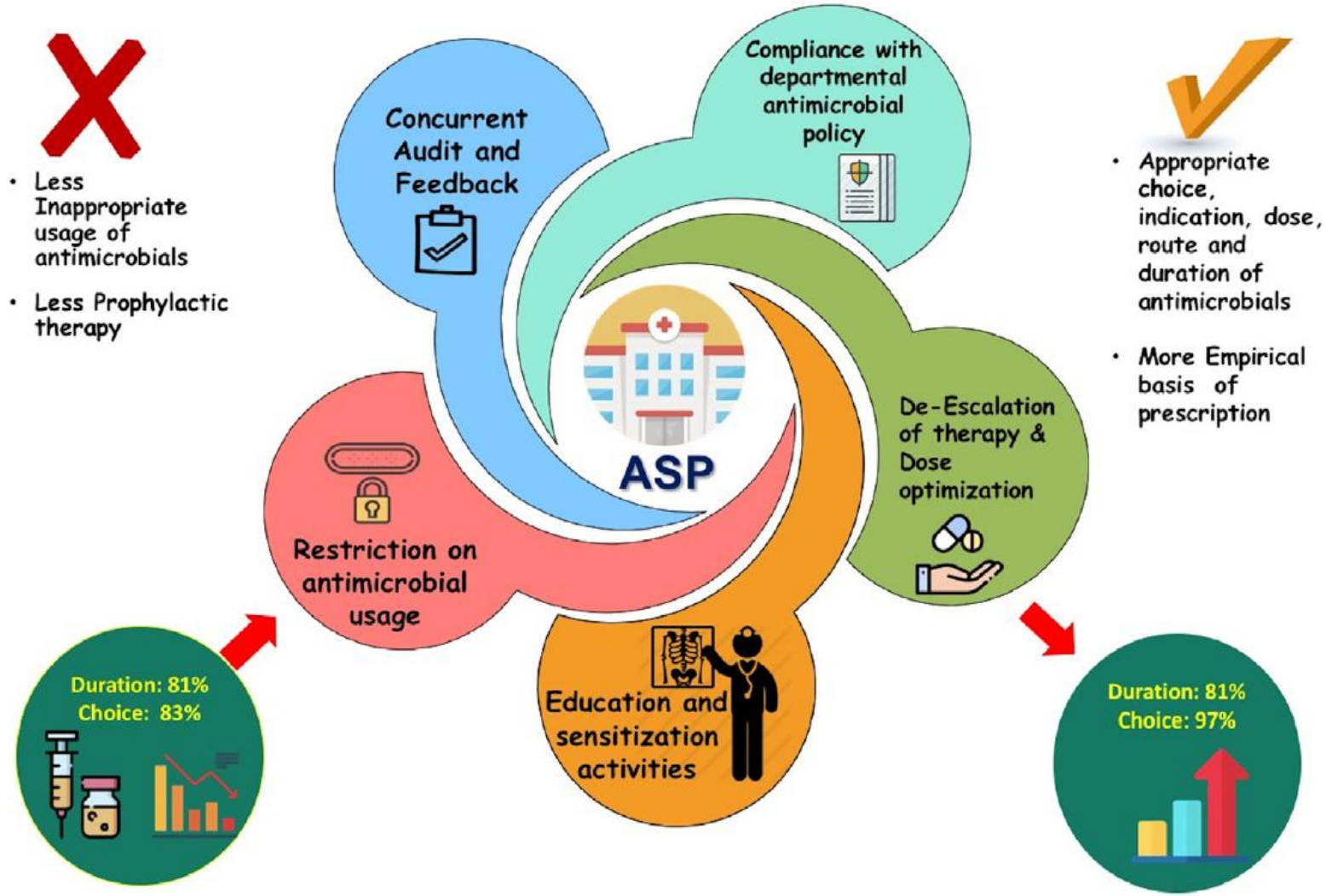
Real Practice of De-escalation



▶ De-escalation is more commonly performed in patients with improving severity scores: clinical marker of the patient improving rather than a treatment decision leading to better patient outcomes

Clin Infect Dis 2016;62:1009
Intensive Care Med 2020;46:245

Antimicrobial Stewardship Program



J Glob Antimicrob Resist 2019;17:283

Goal of De-escalation

Reducing Emergence of Resistance

Study	Setting	Infection	Emergence of resistance		
			De-escalation	Non de-escalation	
Morel 2010	ICU	All	10.0%	19.1%	0.10
Gonzalez 2013	ICU	Nosocomial pneumonia	15.3%	10.7%	0.10
Weiss 2016	ICU	VAP	14.3%	21.3%	0.32
De Bus 2016	ICU	All	28.2%	27.6%	0.91
Trupka 2017	ICU	VAP	6.3%	4.3%	0.47
Li 2018	ICU	VAP	31.0%	40.5%	0.36

▶ At this time, the evidence does not show the presence of an association between antibiotics de-escalation and decreased emergence of resistance in human subjects.

Adv Ther 2020;37:3083

Intensive Care Med 2020;46:245

Goal of De-escalation
Reducing Duration of Antibiotics

Study	Setting	Infection	Duration of antibiotics		
			De-escalation	Non de-escalation	
Leone 2014	ICU, RCT	Severe sepsis	14.1 ± 13.4 days	9.9 ± 6.6 days	0.04
Mokart 2013	ICU	Severe sepsis	9 (4–12) days	5 (3–8) days	0.005
Alvarez-Lerma 2006	ICU	Nosocomial pneumonia	18 (4–55) days	16 (3–65) days	>0.05
Weiss 2016	ICU	VAP	19 days	20 days	0.75
De Bus 2016	ICU	All	8 (6–10) days	5 (4–7) days	<0.001
Trupka 2017	ICU	VAP	7.0 (4.0–8.8) days	7.0 (4.0–9.0) days	0.62
Li 2018	ICU	VAP	11 (8–3) days	14 (8–9) days	0.045

▶ Increased duration of antibiotics observed in de-escalation group from 1 RCT and 2 observational studies

Other Interventions Reducing Antibiotic Use

Antimicrobial Stewardship Program

- Rapid and adequate diagnosis of HAP/VAP

- Reduction of treatment of duration (short course of antibiotic therapy)
  - ERS/ESICM/ESCMID/ALAT, 2017
    - We suggest using a 7~8 day course of antibiotic therapy in patients with VAP without immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation or necrotising pneumonia and with a good clinical response to therapy.
    - We suggest against routine treatment with antibiotics for >3 days in patients with low probability of HAP and no clinical deterioration within 72 h of symptom onset.
  - ATS/IDSA, 2016
    - For patients with VAP, we recommend a 7-day course of antimicrobial therapy rather than a longer duration.
    - For patients with HAP, we recommend a 7-day course of antimicrobial therapy.

- Discontinuation of antibiotics that do not cover the causative pathogen

De-escalation for C (-) Severe Pneumonia
AMC Data

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

ICU, intensive care unit; MV, mechanical ventilation; SOFA, Sepsis-related Organ Failure Assessment.

J Crit Care 2019;54:14

Antibiotics De-escalation Therapy in HAP VAP: Con

Summary

- **No universal definition of de- escalation**
  - Various definitions used in studies: impact of different approaches may be different
  -
- **Outcome of de-escalation: not different from conventional care**
  - De-escalation is more commonly performed in patients with improving severity
  - May be a clinical marker of improvement, but not decision leading to better patient outcomes
- **Goal of de-escalation**
  - Reducing emergence of resistance: not associated with decreased emergence of resistance
  - Reducing duration of antibiotics: increased duration of antibiotics observed in de-escalation group
  - Early antibiotic discontinuation and avoidance of empirical antibiotics that are not needed

▶ Don't agree that antibiotic therapy should be de-escalated in non-selected patients with HAP/VAP