


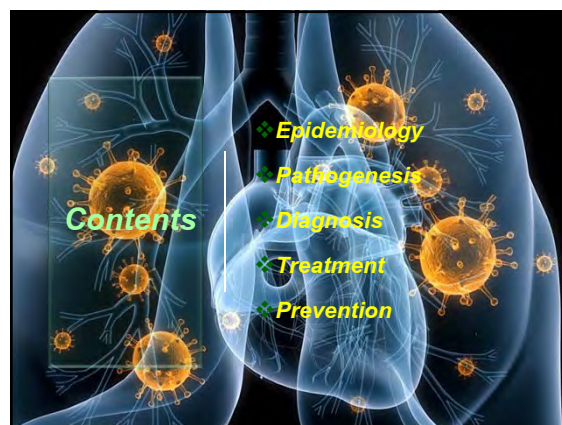
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Hospital-acquired (HAP) and ventilator-associated pneumonia (VAP)

ID WEEK 2018



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Epidemiology

- ❖ HAP/VAP - common nosocomial infection
 - incidence of VAP 2 - 16 episodes/1000 ventilator-days (US study)
- ❖ VAP is associated with long hospital stays and significant costs
 - ↑ length of ventilation (7.6 → 11.5 days) and hospital stay (11.5 → 13.1 days)
 - ↑ health care costs of \$40,000 /patient
- ❖ All-cause mortality from VAP ranges from 20-50% and attributable mortality was 13%

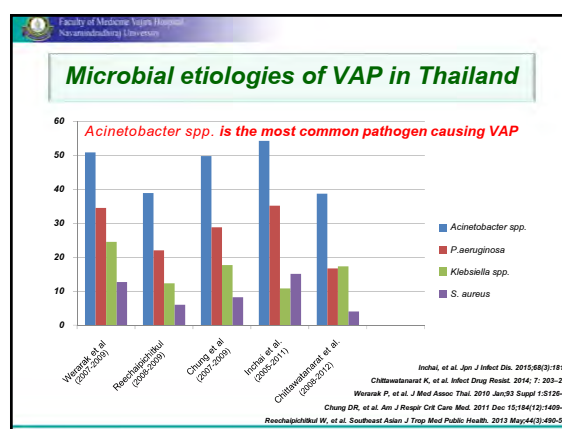
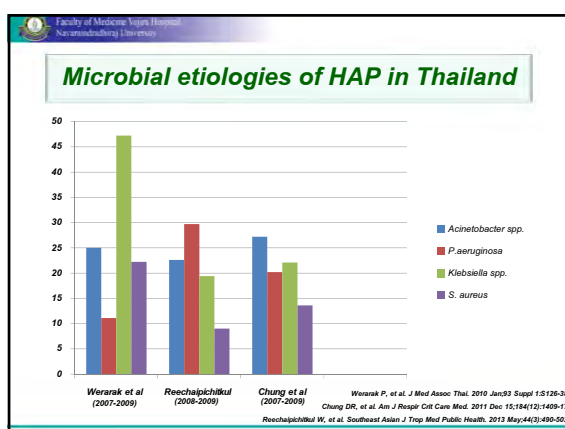
Rosenkranz VD, et al. Am J Infect Control. 2012 Jun;40(5):396-407
Mascarelli JO, et al. Clin Infect Dis. 2010 Aug 1;51 Suppl 1:S120-8
Kohler MH, et al. Infect Control Hosp Epidemiol. 2012 Mar;33(3):350-6
Melson WD, et al. Lancet Infect Dis. 2013 Aug;13(8):665-71

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Definitions

Pneumonia	New lung infiltration and clinical evidence of infection (new onset of fever, purulent sputum, leukocytosis)
HAP	Pneumonia that occurring ≥ 48 hours after admission
VAP	Pneumonia that develops > 48 hours after endotracheal intubation

Am J Respir Crit Care Med. 2005 Feb 15;171(4):388-416.



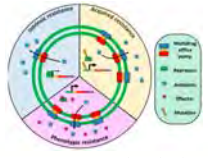
Percentage of susceptible organisms isolated from sputum, university hospital, 4 hospitals, Jan - Jun 2017

	Acinetobacter baumannii	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Pseudomonas aeruginosa</i>
Ampicillin/sulbactam	38.7	-	8.3	-
Piperacillin/tazobactam	23.4	88.9	65.5	83.8
Ceftazidime	24.7	67.7	64.7	82.4
Ceftriaxone	-	41.7	63.8	-
Cefepime	30	-	-	82.2
Imipenem	16	98.9	92.6	73
Meropenem	15.7	99.1	85.5	76.1
Ciprofloxacin	25.2	50	67.1	85.8

National Antimicrobial Resistance Surveillance, Thailand (NARST)

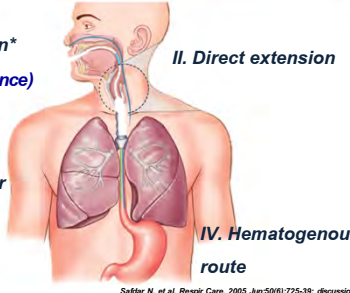
Risk factor for MDRs

VAP	HAP
MDR pathogen ❖ Septic shock at time of VAP ❖ ARDS preceding VAP ❖ ≥ 5 days of hospitalization prior to the occurrence of VAP ❖ Acute renal replacement therapy prior to VAP onset MRSA and Pseudomonas spp. MDR ❖ Prior IV antibiotic use within 90 d	MDR pathogen, MRSA and Pseudomonas spp. MDR ❖ Prior IV antibiotic use within 90 d



Kaib AC, et al. Clin Infect Dis. 2016;63:1-51.

Pathogenesis



I. Aspiration*
(most importance)

II. Direct extension

III. Inhalation of contaminated air or medical aerosols


IV. Hematogenous route

Seltzer N, et al. Respir Care. 2005 Jun;50(6):725-39; discussion 739-41
 Lacherade JC, et al. Am J Respir Crit Care Med Vol 182, pp 910-917, 2010.

Diagnosis

- ❖ Clinical diagnosis
 - signs and symptoms, ventilator setting, laboratory, imaging
- ❖ Microbiologic methods
 - conventional culture, molecular testing
- ❖ Biomarker and the Clinical Pulmonary Infection Score (CPIS)

Clinical diagnosis



New lung infiltrate

Clinical evidence of infection (2 of 3)


- New onset of fever
- Purulent sputum
- Leukocytosis

Sensitivity 69% and specificity 75% (compared with autopsy as the reference)

Fabregas N, et al. Thorax 1999;54:867-873
 Am J Respir Crit Care Med. 2005 Feb 15;171(4):388-416.

Clinical diagnosis - clinical presentation


Signs and symptoms <ul style="list-style-type: none"> ■ fever ■ dyspnea, tachypnea ■ increased or purulent secretion ■ crackles, reduced breath sounds, bronchospasm 	Ventilator setting <ul style="list-style-type: none"> ■ ↑ tidal volume ■ ↑ inspiratory pressures
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Laboratory

- ↑ hypoxemia
- leukocytosis

Clinical diagnosis - chest imaging



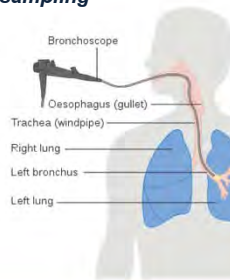
Common findings

- Alveolar infiltrates, air bronchograms, and silhouetting of adjacent solid organs
- To determine the severity of the disease (multilobar vs unilobar)
- Identify complications; pleural effusions or cavitation

Diagnosis - microbiologic methods

Respiratory tract sampling

- Noninvasive methods**
 - Spontaneous expectoration
 - Sputum induction
 - Endotracheal aspiration (EA)
- Invasive methods**
 - Nonbronchoscopic methods (eg, mini-BAL)
 - Bronchoscopic methods (eg, bronchoscopic BAL or PSB)



PSB - Protected Specimen Brush

Diagnosis - microbiologic methods

- Qualitative culture: present, absent
- Semiquantitative culture: 1+, 2+, 3+ or few, moderate, numerous
 - more rapidly
 - fewer laboratory resources
 - less expertise needed
- Quantitative culture

Diagnosis - microbiologic methods

- Quantitative culture

Diagnostic Methods	Sensitivity	Specificity
BBS / TBAS / EA (Any Growth)	75% (58-88%)	47% (29-65%)
BBS / TBAS / EA ($\geq 10^4$ CFU/ml)	57% (47-66%)	80% (71-88%)
Protected Specimen Brush ($\geq 10^3$ CFU/ml)	48% (38-57%)	72% (63-80%)

BBS - blind bronchial sampling, TBAS - tracheobronchial aspirate

Kali AC, et al. Clin Infect Dis. 2016;63:1-51

Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator associated pneumonia

Mortality

Study or Subgroup	Quantitative culture	Qualitative culture	Mean Difference	Mean Difference
OCCTO 2008	100	100	10.34	10.34
Fager 2005	100	100	10.34	10.34
Stark 2005	100	100	10.34	10.34
Total (95% CI)	100	100	10.34	10.34

Duration on mechanical ventilation (days)

Study or Subgroup	Quantitative culture	Qualitative culture	Mean Difference	Mean Difference
OCCTO 2008	100	100	10.34	10.34
Fager 2005	100	100	10.34	10.34
Stark 2005	100	100	10.34	10.34
Total (95% CI)	100	100	10.34	10.34

ICU stay (days)

Study or Subgroup	Quantitative culture	Qualitative culture	Mean Difference	Mean Difference
OCCTO 2008	100	100	10.34	10.34
Fager 2005	100	100	10.34	10.34
Stark 2005	100	100	10.34	10.34
Total (95% CI)	100	100	10.34	10.34

Burton DC, et al. Cochrane Database Syst Rev. 2014 Oct 30(10):CD006482.

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

Suggest noninvasive sampling with semiquantitative cultures to diagnose VAP, rather than invasive sampling with quantitative cultures and rather than noninvasive sampling with quantitative cultures

Kali AC, et al. Clin Infect Dis. 2016;63:1-51

Diagnosis - molecular test

Systems	No. of pathogens/markers	Technology
Abbot IRIDICA System	780 bacteria, 200 fungi, 13 virus, and 4 resistance markers	PCR/ESI-MS
Accelerate PhenoTest™ BC kit	20 bacteria and 2 yeast and AST	FISH
Amplidag CarbaR+VRE	5 carbapenemase and 2 vancomycin-resistance markers	Multiplex RT-PCR
GeneXpertMRSA/SA	MRSA and MSSA	RT-PCR
MALDI-TOF	Wide spectrum of bacteria and fungus	MS
NxTAG® Respiratory Pathogen Panel	18 viruses and 3 bacteria	Multiplex RT-PCR
R-Biopharm RIDA® GENE-kits	mea/mecC, SCCmec cassette, and S. aureus	Multiplex RT-PCR

❖ **Gene targets**

- meaA gene in *S. aureus*
- bla_{TEM} and bla_{IMP} genes in *P. aeruginosa*
- bla_{POA} genes in *Acinetobacter* spp.
- bla_{KPC} gene in *Enterobacteriaceae*.

Molecular test

- Qualitative
- Risk of contamination
- High costs
- Lack of validation
- Rapid results
- Detection of low amounts of gene sequences
- Identify the agent and/or the resistance gene markers
- Search for multiple agents and resistance markers
- Higher sensitivity

Procalcitonin (PCT)

❖ Precursor of calcitonin, secreted by C cells of the thyroid gland and K cells of the lung

❖ Stimulated by endotoxin and bacterial infection

Sensitivity of 67% and specificity of 83%

Kali AC. Clin Infect Dis. 2016;63:1-51
Stolt D. Eur Respir J. 2009;34:1364-75
Boudreau L. Lancet. 2010;375:463-74

Triggering receptor expressed on myeloid cells (sTREM-1)

❖ Member of immunoglobulin superfamily

❖ Expressed on neutrophils and monocytes infiltrating tissues invaded by bacteria and fungi

Sensitivity of 84% and specificity of 49%

Kali AC. Clin Infect Dis. 2016;63:1-51
Stolt D. Eur Respir J. 2009;34:1364-75
Boudreau L. Lancet. 2010;375:463-74

Clinical Pulmonary Infection Score (CPIS)

CPIS point	0	1	2
Temperature, °C	≥ 38.1 and < 38.4	> 38.5 and < 38.9	≤ 36.0 or ≥ 39
Blood leukocyte, per 10 ⁹ /l	≥ 4.0 - ≤ 11.0	≤ 3.9 ≥ 11.1 and in differentiation absence of band forms	≥ 11.1 and in differentiation presence of band forms
Tracheal secretions	Absence	Presence and non-purulent (color: white or light yellow)	Presence and purulent (color: yellow, green or brown)
Oxygenation (PaO ₂ /FIO ₂)	> 240		< 240 and no ARDS
CXR	No infiltrate	Diffused or patchy infiltrate	Localized infiltrate
Cultured tracheal aspirate	< 10	≥ 10 and ≤ 100	> 100

If CPIS ≤ 6 - VAP unlikely

Sensitivity (65%) and specificity (64%) for VAP

Diagnosis - biomarker and the CPIS

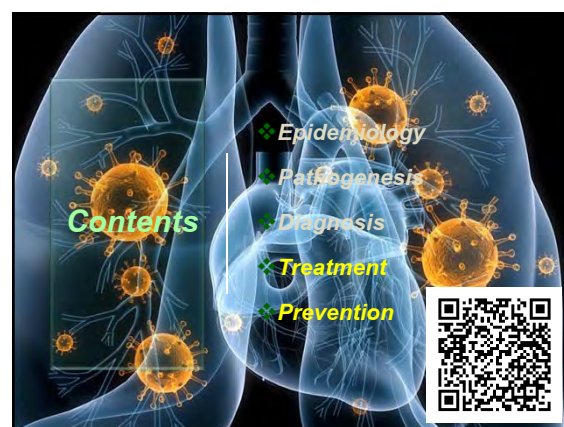
Biomarkers to diagnosis along with clinical criteria

- ❖ PCT
 - not recommended
- ❖ sTREM-1
 - not recommended
- ❖ CPIS
 - not recommended

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Diagnosis - conclusion

- ❖ **Clinical diagnosis**
 - chest imaging and clinical evidence of infection
- ❖ **Microbiologic methods**
 - noninvasive sampling with semiquantitative cultures
- ❖ **Biomarker (PCT, sTREM-1) and the Clinical Pulmonary Infection Score (CPIS)**
 - not recommend



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Treatment Guidelines

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia 2005

This official statement of the American Thoracic Society and the Infectious Diseases Society of America is published by the ATS Board of Directors, December 2005 and the IDSA Guidelines Committee, October 2006.

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

Am J Respir Crit Care Med. 2005;171(4):388-416.
Kali AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.

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Major Differences Between 2005 & 2016 Guidelines

- ❖ **Use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for the evaluation of all available evidence**
- ❖ **Remove the concept of healthcare-associated pneumonia (HCAP)**
 - Patients defined as having HCAP are not at high risk for MDR pathogens
- ❖ **The recommendation that each hospital generate antibiograms to guide to the optimal choice of antibiotics**

Am J Respir Crit Care Med. 2005;171(4):388-416.
Kali AC, et al. Clin Infect Dis. 2016;63(5):e61-e111.

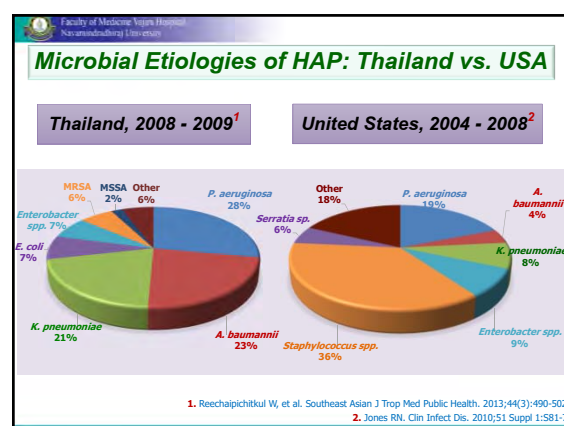
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GRADE* System

Strong Recommendations	Weak Recommendations
■ Benefits clearly outweigh the risks, or clearly do not	■ Benefits and risks are closely balanced

Quality of Evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact and may change the estimate
Low	Further research is very likely to have an important impact & likely to change the estimate
Very low	Any estimate of effect is very uncertain

* Grading of Recommendations Assessment, Development and Evaluation (GRADE) Guyatt GH, et al. Bmj. 2008;336(7650):924-6.



Empirical Treatment for HAP (1)

❖ Recommend including coverage for *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli

MRSA coverage,	One active <i>P. aeruginosa</i> coverage, use 2 ATB if.
<ul style="list-style-type: none"> Prior IV antibiotic use within 90 d Units where >20% of <i>S. aureus</i> isolates are methicillin resistant Units where the prevalence of MRSA is unknown High risk for mortality <ul style="list-style-type: none"> Need for ventilator support due to HAP Septic shock Have factors that probably increase likelihood of MRSA pneumonia <ul style="list-style-type: none"> Prior known MRSA colonization via nasal or resp. cultures/nonculture screening High-quality gram stain: numerous and predominant GP cocci in clusters 	<ul style="list-style-type: none"> Risk factors for MDR HAP <ul style="list-style-type: none"> Prior IV ATB use within 90 d High risk for mortality <ul style="list-style-type: none"> Need for ventilator support due to HAP Septic shock Have factors likely increasing the probability of GN infection <ul style="list-style-type: none"> Structural lung disease High-quality gram stain: numerous and predominant GNB Patients in units where > 10% of GN isolates are resistant to an agent being considered for monotherapy

❖ Avoiding aminoglycosides and colistin if alternative agents for GNB are available

Empirical Treatment for HAP (2)

Not at high risk of mortality ^a , & No factors increasing the likelihood of MRSA	Not at High Risk of Mortality ^a but with Factors increasing the likelihood of MRSA
One of the following:	One of the following:
Piperacillin-tazobactam ^b	Piperacillin-tazobactam ^b
or	or
Cefepime ^b	Cefepime ^b /Ceftazidime ^{b,c}
or	or
Levofloxacin	Levofloxacin/Ciprofloxacin ^c
or	or
Imipenem ^b /Meropenem ^b	Imipenem ^b /Meropenem ^b
	plus
	Vancomycin or Linezolid

^a Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock
^b Extended infusions may be appropriate
^c Less activity against gram positive organisms

Empirical Treatment for HAP (3)

High risk of mortality ^a or Receipt of IV ATB during the prior 90 d, but No factors increasing the likelihood of MRSA	High risk of mortality ^a or Receipt of IV ATB during the prior 90 d, and with Factors increasing the likelihood of MRSA
Two of the following, avoid 2 B-lactams:	Two of the following, avoid 2 B-lactams:
Piperacillin-tazobactam ^c	Piperacillin-tazobactam ^c
or	or
Cefepime ^b /Ceftazidime ^{b,d}	Cefepime ^b /Ceftazidime ^{b,d}
or	or
Levofloxacin/Ciprofloxacin ^d	Levofloxacin/Ciprofloxacin ^d
or	or
Imipenem ^b /Meropenem ^c	Imipenem ^b /Meropenem ^c
or	or
Amikacin/Gentamicin/Tobramycin	Amikacin/Gentamicin/Tobramycin
	plus
	Vancomycin or Linezolid

^a Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock
^b If patient has factors increasing the likelihood of gram-negative infection
^c Extended infusions may be appropriate
^d Less activity against gram positive organisms

Role of Inhaled Antibiotic Therapy

❖ For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), we suggest both inhaled and systemic antibiotics, rather than systemic antibiotics alone (weak recommendation, very low-quality evidence)

Inhaled colistin + Systemic antibiotic

Colistin for inhalation should be administered promptly after being mixed with sterile water

This recommendation was made by the FDA after a report that a cystic fibrosis patient died after being treated with a premixed colistin formulation

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124896.htm>

Inhaled Antibiotic Therapy: Colistin (1)

Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria

Pinyo Rattanaumpawan, Jintano Lorsuthitham, Puangpoka Ungprasert, Nasikarn Angkasekwini and Visanu Thamlikitkul*

Assessed for eligibility (n=128)
 Excluded (n=24): did not meet inclusion criteria (n=12), declined to participate (n=12)
 Randomized (n=104)
 Allocated to CMS group (n=53): received allocated intervention (n=53), did not receive allocated intervention (n=0)
 Lost to follow-up (n=6): Discontinued intervention (n=6)
 Analyzed (n=53): Excluded from analysis (n=0)
 Allocated to NSS group (n=51): received allocated intervention (n=48), did not receive allocated intervention (n=3)
 Lost to follow-up (n=6): Discontinued intervention (n=6)
 Analyzed (n=48): Excluded from analysis (n=0)

❖ RCT, 100 adults GN VAP
 ❖ Siriraj hospital, 2006 – 09
 ❖ Randomized to receive 4 mL of nebulized NSS or nebulized CMS (75 mg of colistin base) in NSS q 12 hr until systemic antibiotic therapy of VAP was ended
 ❖ Carbapenem & colistin

Rattanaumpawan P, et al. J Antimicrob Chemother. 2010;65(12):2645-9.

Inhaled Antibiotic Therapy: Colistin (2)

Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria

Pinyo Rattanaumpawan, Jintano Lorsuthitham, Puangpoka Ungprasert, Nasikarn Angkasekwini and Visanu Thamlikitkul*

Table 2. Clinical and microbiological outcomes of the study patients

	CMS group (n=51)	NSS group (n=49)	% Risk difference (95% CI)	Risk ratio (95% CI)	P value
28-day clinical outcome					
favorable outcome	51.0%	53.1%	-2.1% (-22%-18%)	0.96 (0.66-1.40)	0.84
death due to VAP	39.2%	36.7%	2.5% (-17%-22%)	1.07 (0.65-1.76)	0.80
overall mortality	43.1%	40.8%	2.3% (-17%-22%)	1.06 (0.67-1.68)	0.81
Favorable microbiological outcome	60.3%	38.2%	22% (3%-41%)	1.57 (1.03-2.37)	0.03
Incidence of complication	31.4%	24.5%	7% (-11%-24%)	1.28 (0.68-2.42)	0.44
bronchospasm	7.8%	2.0%	6% (-3%-14%)	3.84 (0.45-33.19)	0.36
renal impairment	25.5%	22.4%	3% (-10%-20%)	1.13 (0.56-2.29)	0.82

❖ Patients in the CMS group had significantly more favorable microbiological outcome when compared with patients in the control group

Rattanaumpawan P, et al. J Antimicrob Chemother. 2010;65(12):2645-9.

P. Aeruginosa: Doripenem (2)

FDA Drug Safety Communication: FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia

Doripenem

This is an update to the January 5, 2012 FDA Statement on a recently terminated clinical trial with Doribax (doripenem).

2014: Not approved to treat any type of pneumonia

Safety Announcement

[03-05-2014] The U.S. Food and Drug Administration (FDA) has concluded that Doribax (doripenem), an antibacterial drug that has been used to treat patients who develop pneumonia while on ventilators, carries an increased risk of death and lower clinical cure rates compared to use of imipenem and cefepime for infection (marketed in the U.S. under the name Primaxin). Based on our analysis of data from a three-year clinical trial that was prematurely stopped in 2011 due to these safety concerns, we have approved changes to the Doribax drug label that describe these risks.

Doribax is not approved to treat any type of pneumonia, and the revised label also includes a new warning about this unapproved use. Health care professionals should consider whether the benefits of Doribax treatment are likely to exceed its potential risks in patients who develop pneumonia while on ventilators.

Doribax is still considered safe and effective for its FDA-approved indications - treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections, including kidney infections called pyelonephritis.

<https://www.fda.gov/Drugs/DrugSafety/ucm387971>

Pathogen Specific Therapy: A. baumannii

Organism	Suggestion
A. baumannii	<ul style="list-style-type: none"> Either a carbapenem or ampicillin/sulbactam if the isolate is susceptible to these agents If isolate is sensitive only to polymyxins, recommend intravenous polymyxin (colistin or polymyxin B) and adjunctive inhaled colistin If isolate is sensitive only to colistin, we suggest NOT using adjunctive rifampicin Recommend against the use of tigecycline

A. Baumannii: Role of Rifampicin

Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

MAJOR ARTICLE

Enrique Duran-Mangoni,¹ Giuseppe Sigismondi,¹ Roberto Andini,¹ Antonino Mares,¹ Maria De Cristoforo,² Patricia Murias,³ Matteo Bassotti,⁴ Paolo Macarone,⁵ Nicola Gallo,⁶ Paola Maccioni,⁷ Antonio Concato,⁸ Claudio Viazzi,⁹ Raffaele Zariti,¹⁰ Guy Galle,¹¹ and Riccardo Iotti¹²

✦ Multicenter, parallel, randomized, open-label clinical trial

✦ Enrolled 210 patients with life-threatening infections due to XDR A. baumannii

✦ Randomly allocated (1:1) to either colistin alone, or colistin, plus RFP 600 mg every 12 hours IV

✦ The primary end point was overall 30-day mortality

Durante-Mangoni E, et al. Clin Infect Dis. 2013;57(3):349-58.

A. Baumannii: Role of Rifampicin

Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

MAJOR ARTICLE

Table 2. Efficacy Outcomes

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 106)	P Value
Primary outcome			
30-d mortality			
Yes	85 (81.3%)	85 (80.2%)	.89 ^a
No	19 (18.7%)	21 (19.7%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	26 (24.6%)	.29 ^a
No	22 (21.2%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	83 (80.6%)	87 (81.6%)	.83 ^a
No	21 (20.5%)	19 (18.4%)	
Median hospital length of stay (d)	41 (39-41)	44 (27-53)	.36 ^b
Development of colistin resistance, %	0	0	

Addition of RFP to IV colistin did not improve 30-day mortality (even though it improved microbiological eradication, P = .034)

Durante-Mangoni E, et al. Clin Infect Dis. 2013;57(3):349-58.

Pathogen Specific Therapy: ESBL-Producing GNB and Carbapenem-Resistant Pathogen

Organism	Suggestion
ESBL-producing GNB	Based upon the results of antimicrobial susceptibility testing and patient specific factors
Carbapenem-resistant pathogen	If sensitive only to polymyxins, recommend IV polymyxins (colistin or polymyxin B) and adjunctive inhaled colistin

Treatment Duration

VAP	HAP
Recommend a 7-day course of antimicrobial therapy rather than a longer duration (moderate-quality evidence) strong recommendation (very low-quality evidence)	
Depending on the rate of improvement of clinical, radiologic, and lab. parameters	

Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults (Review)

Pugh R, Grant C, Cooke RPD, Dempsey G

✦ Short courses ATB (7-8 d) compared with Long courses (10-15 d),

- Increased 28-day ATB-free days (mean diff. = 4.02 d)
- No diff. in mortality, recurrent pneumonia, Tx failure, hospital LOS, or MV duration
- Subgroup of NF-GNB VAP, short courses of ATB asso. with recurrent infection (OR, 2.18; 95% CI, 1.14-4.16)

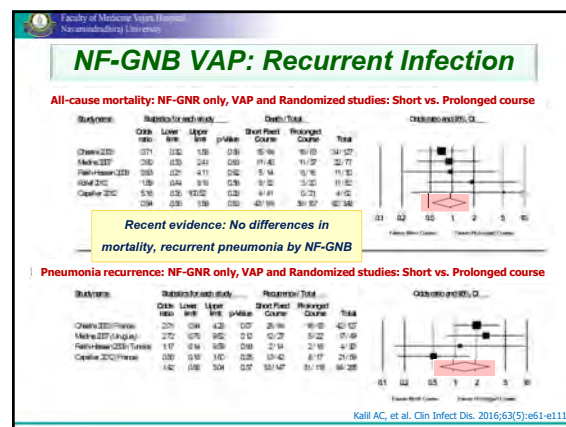
Pugh R, et al. Cochrane Database Syst Rev. 2015(8):Cd007577

Outcomes	Illustrative comparative risks* (95% CI)		Relative effects (95% CI)	No. of participants (studies)
	Assumed risk	Corresponding risk		
	Prolonged-course antibiotic therapy	Short-course antibiotic therapy		
Mortality Follow-up: 28 days	175 per 1000	291 per 1000 (141 to 277)	OR 1.18 (0.77 to 1.8)	938 (8 studies)
Mortality NF-GNB Follow-up: 28 days	355 per 1000	355 per 1000 (173 to 900)	OR 0.95 (0.39 to 2.27)	178 (2 studies)
Mortality MRSA Follow-up: 28 days	238 per 1000	285 per 1000 (91 to 614)	OR 1.25 (0.38 to 4.08)	48 (1 study)
Recurrence of pneumonia Clinical and/or microbiological criteria	180 per 1000	237 per 1000 (174 to 318)	OR 1.41 (0.94 to 2.12)	753 (19 studies)
Recurrence of pneumonia NF-GNB Clinical and/or microbiological criteria	247 per 1000	417 per 1000 (272 to 577)	OR 2.18 (1.14 to 4.16)	176 (2 studies)
Recurrence of pneumonia MRSA Clinical and/or microbiological criteria	370 per 1000	478 per 1000 (95 to 920)	OR 1.55 (0.12 to 19.61)	49 (2 studies)
28-day antibiotic-free days Follow-up: 28 days	The mean 28-day antibiotic free days in the intervention groups was 4.02 higher (2.26 to 5.76 higher)			431 (2 studies)

❖ **Short courses ATB (7-8 d) compared with Long courses (10-15 d),**

- Increased 28-day ATB-free days (mean diff. = 4.02 d)
- No diff. in mortality, recurrent pneumonia, Tx failure, hospital LOS, or MV duration
- Subgroup of NF-GNB VAP, short courses of ATB asso. with recurrent infection (OR, 2.18; 95% CI, 1.14-4.16)

Pugh R, et al. Cochrane Database Syst Rev. 2015(8):Cd007577



Antibiotic De-escalation

❖ Suggest that antibiotic therapy be de-escalated rather than fixed (weak recommendation, very low-quality evidence)

De-escalation compared to fixed regimen for VAP

Setting: Hospital (ICU) patients with VAP
Intervention: De-escalation
Comparison: Fixed regimen

Outcomes	Illustrative comparative risks* (95% CI)	Relative effects (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk		
	Fixed regimen	De-escalation		
Mortality Follow-up: mean 31 days	225 per 1000	157 per 1000 (127 to 186)	OR 0.64 (0.54 to 1.4)	1218 (8 studies) very low ¹

The basis for the assumed risk (e.g. the median control group risk across studies) is shown in the forest plot. The assumed risk in the comparison group and the relative effect of the intervention (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

OR, Odds Ratio; CI, Confidence Interval.

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Supplemental data tables and figures for the IDSA-ATS management of adults with hospital-acquired and ventilator-associated pneumonia 2016

Antibiotic Discontinuation

❖ Discontinuation of antibiotic

- Suggest using PCT levels + clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone (weak recommendation, low-quality evidence)
- Suggest not using the CPIS to guide the discontinuation of antibiotic therapy (weak recommendation, low-quality evidence)

Remarks

Unknown benefits of using PCT levels to guide the discontinuation of ATB therapy in settings where standard therapy for VAP is ≤ 7 days

Antibiotic Discontinuation: Procalcitonin Guidance

Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections (Review)

Cochrane Library

Outcomes	Illustrative comparative risks* (95% CI)	Relative effects (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Standard care	PCT algorithm			
Mortality Follow-up: 30 days	Study population 185 per 1000 (76 to 393)	86 per 1000 (76 to 93)	OR 0.53 (0.70 to 0.90)	8728 (23 studies)	Graded: High ¹
Treatment failure Clinical assessment ² Follow-up: 30 days	Study population 249 per 1000 (153 to 405)	230 per 1000 (153 to 345)	OR 0.90 (0.80 to 1.01)	8728 (23 studies)	Graded: Moderate ¹
Antibiotic-related side effects Follow-up: 30 days	Study population 163 per 1000 (57 to 245)	163 per 1000 (57 to 245)	OR 0.95 (0.57 to 0.82)	3024 (8 studies)	Graded: Moderate ¹
Antibiotic exposure Total days of antibiotic therapy in all non-dominated participants 8.1 days	The mean antibiotic exposure in the control group was 2.43 days lower (2.15 to 2.71)			8728 (23 studies)	Graded: High ¹

Schuetz P, et al. Cochrane Database Syst Rev. 2017;10:Cd007498.

Antibiotics for HAP/VAP

Medication	Study
Tigecycline¹	<ul style="list-style-type: none"> Randomized phase 3 double-blind trial, 945 patients Tigecycline ± ceftazidime vs. imipenem/cilastatin ± vancomycin Significantly lower cure rates in VAP patients compared to imipenem In non-VAP patients, non-inferior to imipenem FDA: Only approved the drug for CAP treatment (+ cSSSI & cIAI)
Ceftobiprole²	<ul style="list-style-type: none"> Randomized phase 3 double-blind trial, 781 patients Vs. ceftazidime + linezolid in HAP/VAP Safe and effective for the empiric treatment of HAP (excluding VAP)
Ceftazidime-avibactam³	<ul style="list-style-type: none"> Randomized phase 3 double-blind, non-inferiority trial Vs. meropenem in HAP/VAP Non-inferior to meropenem in nosocomial pneumonia (including VAP) Jan 2018: FDA approves for treatment of HAP/VAP

1. Freire AT, et al. Diagn Microbiol Infect Dis. 2010;68(2):140-51. 3. Torres A, et al. Lancet Infect Dis. 2018;18(3):285-95.
2. Awad SS, et al. Clin Infect Dis. 2014;59(1):51-61.

Tigecycline in HAP/VAP (1)

Available online at www.sciencedirect.com
ScienceDirect
ELSEVIER
BLAGNESTIC MICROBIOLOGY AND INFECTIOUS DISEASE

Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia

Antônio T. Freire^a, Vasei Melnyk^b, Min Ja Kim^c, Oleksiy Datsenko^d, Oleksandr Dzyubak^e, Felix Glunicher^f, Yin-Ching Chuang^g, Robert T. Maroko^h, Gary Dukartⁱ, C. Angel Cooper^j, Jean M. Korth-Bradley^k, Nathalie Dartois^l, Hassan Gandini^m for the 311 Study Group

- ❖ Phase 3, multicenter, randomized, double-blind study, 945 patients
- ❖ Compare the efficacy and safety of a tigecycline ± ceftazidime vs. imipenem/cilastatin ± vancomycin regimen
- ❖ Primary end points were clinical response in clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) populations at test-of-cure

Freire AT, et al. Diagn Microbiol Infect Dis. 2010;68(2):140-51

Tigecycline in HAP/VAP (2)

	n/N	Tigecycline (95% CI) (%)	n/N	Imipenem/cilastatin (95% CI) (%)	Difference (95% CI)
CE population					
VAP					
Cure	35/73	47.9 (36.1–60.0)	47/67	70.1 (57.7–80.7)	-22.2 (-37.8 to -4.9)
Failure	38/73	52.1	20/67	29.9	
Non-VAP					
Cure	147/195	75.4 (68.7–81.3)	143/176	81.3 (74.7–86.7)	-5.9 (-14.5 to 3.0)
Failure	48/195	24.6	33/176	18.8	
c-mITT population					
VAP					
Cure	59/127	46.5 (37.6–55.5)	67/116	57.8 (48.2–66.9)	-11.3 (-24.6 to 2.0)
Failure	57/127	44.9	32/116	27.6	
Indeterminate	11/127	8.6	17/116	14.6	
Non-VAP					
Cure	217/313	69.3 (63.9–74.4)	223/313	71.2 (65.9–76.2)	-1.9 (-9.4 to 5.6)
Failure	65/313	20.8	59/313	18.9	
Indeterminate	31/313	9.9	31/313	9.9	

FDA Safety Announcement: Tigecycline is not indicated for treatment of HAP/VAP

- ❖ Significantly lower cure rates in tigecycline VAP patients compared to imipenem
- ❖ In non-VAP patients, tigecycline was noninferior to imipenem

Freire AT, et al. Diagn Microbiol Infect Dis. 2010;68(2):140-51

Ceftobiprole in HAP/VAP (1)

A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

Samir S. Awad,^a Alejandro H. Rodriguez,^b Yin-Ching Chuang,^c Zorana Marjanovic,^d Alex J. Paragica,^e Gilmar Reis,^f Thomas W. L. Scheenen,^g Alejandro S. Sanchez,^h Xin Zhou,ⁱ Mikael Sautay,^j and Marc Engelhardt^k

- ❖ Study of 781 patients with HAP (210/781= VAP)
- ❖ Ceftobiprole vs. ceftazidime + linezolid, 7-14 d
- ❖ Overall cure rates were comparable, cure rates in VAP patients were 23.1% vs. 36.8% (ITT, 95% CI, -26.0 to -1.5) and 37.7% vs 55.9% (CE, 95% CI, -36.4 to 0)

Awad SS, et al. Clin Infect Dis. 2014;59(1):51-61.

Ceftobiprole in HAP/VAP (2)

Analysis Set Group	Ceftobiprole		Ceftazid		Difference (95% CI)
	No.	No. (%)	No.	No. (%)	
Intention-to-treat					
All patients	391	195 (49.9)	390	195 (50.1)	
HAP (including VAP)	287	171 (59.6)	284	165 (58.1)	
VAP	104	24 (23.1)	106	39 (36.8)	-13.7 (-26.0 to -1.5)
HAP, mechanically ventilated	69	21 (30.4)	70	19 (27.1)	3.3 (-11.8 to 18.3)
Clinically evaluable					
All patients	251	174 (69.3)	244	174 (71.3)	-2.0 (-10.0 to 6.1)
HAP (including VAP)	189	154 (81.5)	185	141 (76.2)	4.8 (-8.9 to 18.6)
VAP	53	20 (37.7)	59	33 (55.9)	-18.2 (-36.4 to 0)
HAP (excluding VAP), mechanically ventilated	38	21 (55.3)	37	19 (40.5)	14.7 (-7.8 to 37.1)

Ceftobiprole is a safe and effective for the empiric treatment of HAP (excluding VAP)

- ❖ Study of 781 patients with HAP (210/781= VAP)
- ❖ Ceftobiprole vs. ceftazidime + linezolid, 7-14 d
- ❖ Overall cure rates were comparable, cure rates in VAP patients were 23.1% vs. 36.8% (ITT, 95% CI, -26.0 to -1.5) and 37.7% vs 55.9% (CE, 95% CI, -36.4 to 0)

Awad SS, et al. Clin Infect Dis. 2014;59(1):51-61.

Ceftazidime-avibactam in HAP/VAP (1)

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Combines ceftazidime, and the novel non-BLBI avibactam
Covers most carbapenem-non-susceptible Enterobacteriaceae and MDR P. aeruginosa
Randomised phase 3 trial to assess the non-inferiority of ceftazidime-avibactam to meropenem
Efficacy and safety in the treatment of nosocomial pneumonia

Figure 2: Clinical cure rates at test-of-cure visit (Data are number of patients with clinical cure (%)). Dashed line indicates non-inferiority margin of -12.5%.

Torres A, et al. Lancet Infect Dis. 2018;18(3):285-95.

Ceftazidime-avibactam in HAP/VAP (2)

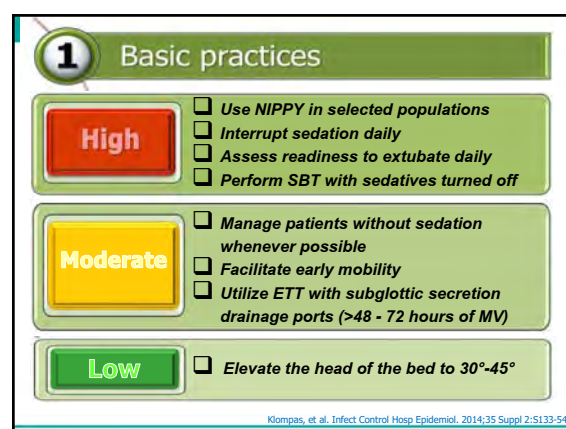
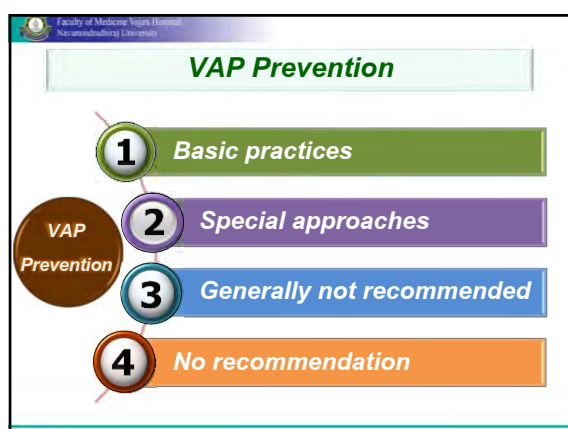
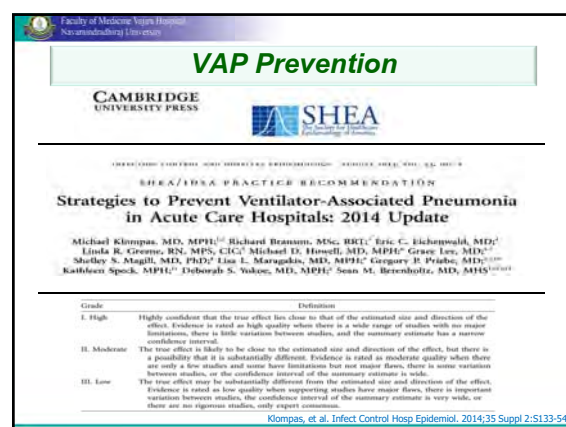
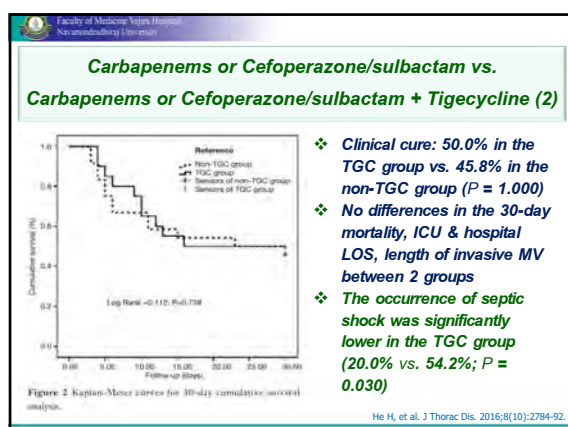
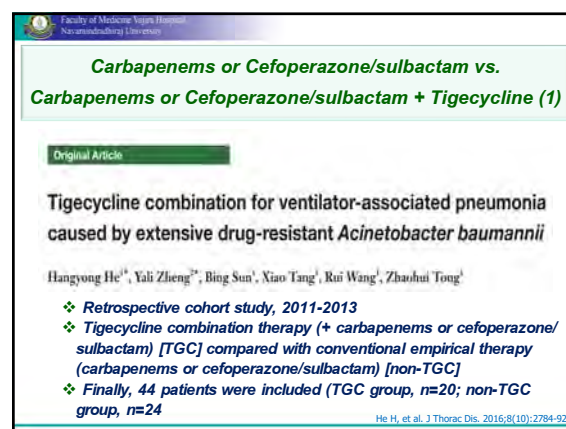
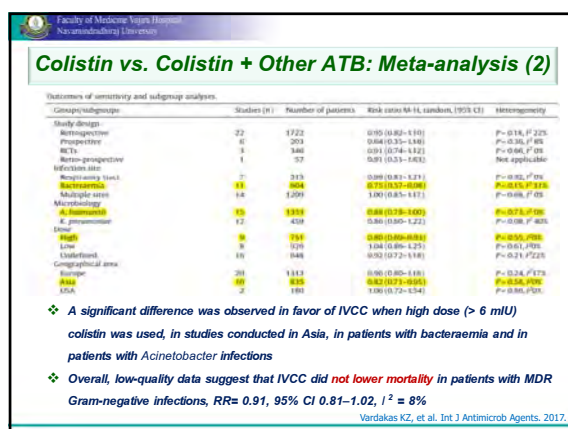
Ceftazidime-avibactam was non-inferior to meropenem in the Tx of nosocomial pneumonia (including VAP) caused by GN pathogens

FDA Approves AVYCAZ® (ceftazidime and avibactam) for the Treatment of Patients with Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

AVYCAZ (ceftazidime and avibactam) for injection, for intravenous use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES
Indications and Usage, Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (1,3) 01/2018
Dosage and Administration (2) 01/2018

Torres A, et al. Lancet Infect Dis. 2018;18(3):285-95.



2 Special approaches

High	<input type="checkbox"/> <i>Selective oral or digestive decontamination</i>
Moderate	<input type="checkbox"/> <i>Regular oral care with chlorhexidine</i> <input type="checkbox"/> <i>Prophylactic probiotics</i>
Low	<input type="checkbox"/> <i>Ultrathin polyurethane ET tube cuffs</i> <input type="checkbox"/> <i>Automated control of ET tube cuff pressure</i> <input type="checkbox"/> <i>Saline instillation before tracheal suctioning</i> <input type="checkbox"/> <i>Mechanical tooth brushing</i>

Klompas, et al. Infect Control Hosp Epidemiol. 2014;35 Suppl 2:S133-54.

3 Generally not recommended

High	<input type="checkbox"/> <i>Early tracheotomy</i>
Moderate	<input type="checkbox"/> <i>Silver-coated endotracheal tubes</i> <input type="checkbox"/> <i>Kinetic beds</i> <input type="checkbox"/> <i>Prone positioning</i> <input type="checkbox"/> <i>Stress ulcer prophylaxis</i> <input type="checkbox"/> <i>Monitoring residual gastric volumes</i> <input type="checkbox"/> <i>Early parenteral nutrition</i>

Klompas, et al. Infect Control Hosp Epidemiol. 2014;35 Suppl 2:S133-54.

4 No recommendation

Moderate	<input type="checkbox"/> <i>Closed/in-line endotracheal suctioning</i>
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Klompas, et al. Infect Control Hosp Epidemiol. 2014;35 Suppl 2:S133-54.

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Thank You