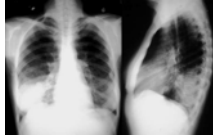


Canadian HAP/VAP Guidelines 2008: “Infiltrating” the Data and “Consolidating” the Evidence



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Conflict of Interest

- None to declare

2

Learning Objectives

- To outline an approach to evaluate the methodological quality of clinical practice guidelines
- To describe the clinical pulmonary infection score and its role in HAP/VAP diagnosis and monitoring
- To review the rationale and supporting evidence behind short-course antibiotic therapy
- To determine when empiric combination antibiotic therapy is warranted versus monotherapy

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Overview

- Definitions & Epidemiology
- Canadian HAP/VAP Guidelines Overview
- Guideline Methodology Assessment
- Algorithms
- “Infiltrating” the Data
 - Duration of Treatment
 - Empiric Combination Therapy
- “Consolidating” the Evidence

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Epidemiology of HAP

- 2nd most common nosocomial infection
- Highest mortality of nosocomial infections
 - Overall mortality 20% (range: 7-62%)
- Substantial costs
 - Prolonged hospitalization
 - Increased expenditures

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Traditional Definitions

- Hospital-acquired pneumonia (HAP)
 - Not incubating at hospital admission
 - Presentation \geq 48 hours post-admission
 - “Early-onset” within 96 hours of admission
 - “Late-onset” > 96 hours from admission
- Ventilator-associated pneumonia (VAP)
 - Subset of HAP
 - Mechanically ventilated \geq 48 hours at time of diagnosis

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Am J Respir Crit Care Med 2005; 171:388-416

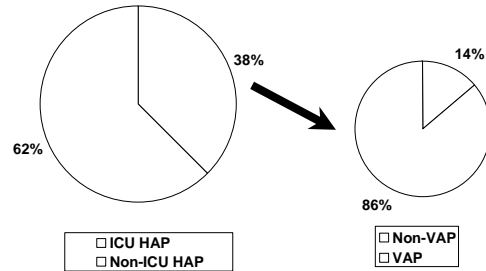
Traditional Definitions

- Healthcare-associated pneumonia (HCAP)
 - Hospitalization ≥ 2 days in preceding 90 days
 - Nursing home, long-term care resident
 - Home infusion therapy, chemotherapy or wound care within past 30 days
 - Attended a hospital or hemodialysis clinic
 - Family member with multi-drug resistant organism

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Am J Respir Crit Care Med 2005; 171:388-416

Epidemiology



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Other HAP/VAP Guidelines

- American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) 2005
 - Am J Respir Crit Care Med* 2005; 171:388-416
 - Next update projected Fall 2009
- Canadian Critical Care Trials Group VAP Guidelines 2008
 - Journal of Critical Care* 2008; 23:138-47

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AMMI CANADA GUIDELINES

Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults

Coleman Rotstein MD FRCP FACP¹, Gerald Evans MD FRCP², Abraham Born MD FACP FCCP FRCP³, Ronald Grossman MD FACP FCCP FRCP⁴, R Bruce Light MD⁵, Sheldon Magler MD FRCP⁶, Ravneet Mehta MD PhD⁷, Karl Wassil ATC MSc FRCP⁸, George G. Zhanel PhD FCCP^{9,10}

C Rotstein, G Evans, A Born, et al. Clinical practice guidelines for hospital-acquired pneumonia and ventilator-associated pneumonia in adults. *Can J Infect Dis Med Microbiol* 2008;19(1):19-53.

Des lignes directrices cliniques pour la pneumonie nosocomiale et la pneumonie sous ventilation assistée chez les adultes

Joint document

- Association of Medical Microbiology and Infectious Disease (AMMI) Canada
- Canadian Thoracic Society (CTS)

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Canadian Guidelines 2008

“The ultimate goal of the present guideline is to provide a framework to make informed decisions regarding the diagnosis and management of HAP and VAP”

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Canadian Guidelines 2008

- Highlights
 - Rapid diagnosis
 - Immediate empiric antibiotics
 - Streamlining and de-escalation of unnecessary antibiotics
 - Patient risk stratification based on initial clinical presentation

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Guideline Methodology

- Interdisciplinary working group – infectious disease, respirology, critical care, pharmacy
- Search Strategy:
 - Peer-reviewed English language papers and abstracts until December 2006
 - “relevant key words pertinent to that subject”
- Information sorted, tabulated, documents merged
- Grading of evidence according to IDSA guidelines
- Working draft reviewed by all members, approved by AMMI and CTS

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AGREE Appraisal Instrument

- Appraisal of Guidelines for Research & Evaluation
- To help guideline users assess the methodological quality of clinical practice guidelines before adopting them
- Validated checklist
- 23 items organized in six domains
 - Scope and purpose
 - Stakeholder involvement
 - Rigor of development
 - Clarity and presentation
 - Applicability
 - Editorial independence

Qual Saf Health Care 2003; 12:18-23
www.agreecollaboration.org

AGREE Appraisal Instrument

EDITORIAL INDEPENDENCE

22. The guideline is editorially independent from the funding body.

Strongly Agree 4 3 2 1 Strongly Disagree

Comments

23. Conflicts of interest of guideline development members have been recorded.

Strongly Agree 4 3 2 1 Strongly Disagree

Comments

15

www.agreecollaboration.org

AGREE Appraisal Instrument

EDITORIAL INDEPENDENCE

22. The guideline is editorially independent from the funding body.

Strongly Agree 4 3 2 1 Strongly Disagree

Comments

23. Conflicts of interest of guideline development members have been recorded.

Strongly Agree 4 3 2 1 Strongly Disagree

Comments

Total score = 5, Standardized score = 50%

16

www.agreecollaboration.org

AGREE Appraisal Instrument

AGREE Domain	Total Score 1	Total Score 2	Standardized Score
Scope and purpose	7	9	56%
Stakeholder involvement	7	7	25%
Rigor of development	14	15	36%
Clarity and presentation	13	14	79%
Applicability	6	3	17%
Editorial independence	5	5	50%

Overall assessment: Recommend with provisions

Qual Saf Health Care 2003; 12:18-23
www.agreecollaboration.org

How do the 2008 Canadian AMMI guidelines differ from the 2005 ATS/IDSA guidelines?

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Canadian HAP/VAP Definitions

Core pathogens	<i>S. pneumoniae</i> and <i>Streptococcus</i> sp., <i>H. influenzae</i> , <i>Enterobacter</i> sp., <i>E. coli</i> , <i>Klebsiella</i> sp., <i>Proteus</i> sp., <i>S. marcescens</i> , methicillin-sensitive <i>S. aureus</i>
Risk factors for resistance	Antimicrobial therapy in past 90 days, late onset during hospitalization
Severe presentation	Hypotension, intubation, sepsis syndrome, rapid progression of infiltrates, end-organ dysfunction
Resistant pathogens	<i>P. aeruginosa</i> , <i>Acinetobacter</i> sp., <i>S. maltophilia</i> , methicillin-resistant <i>S. aureus</i> (MRSA)

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HAP

Group 1
Mild-mod illness, no risk factors
Core pathogens

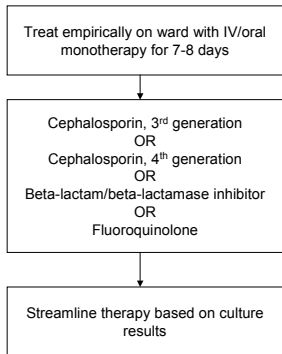
Group 2
Mild-mod illness + risk factors resistance
Core pathogens, MRSA, *P. aeruginosa*

Group 3
Severe illness ± risk factors resistance
Core pathogens, MRSA, Legionella, *P. aeruginosa*

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HAP Group 1

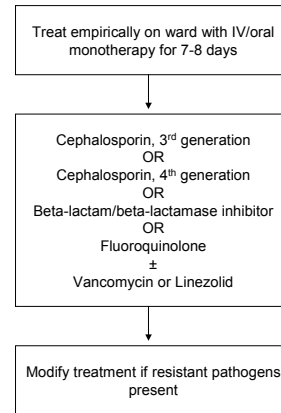
Mild-mod illness, no risk factors



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HAP Group 2

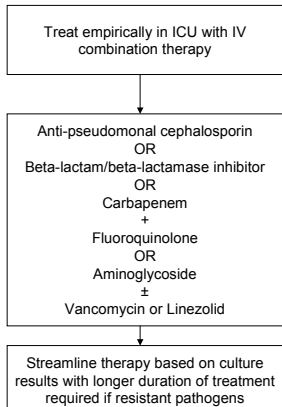
Mild-mod illness + risk factors resistance



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HAP Group 3

Severe illness ± risk factors resistance



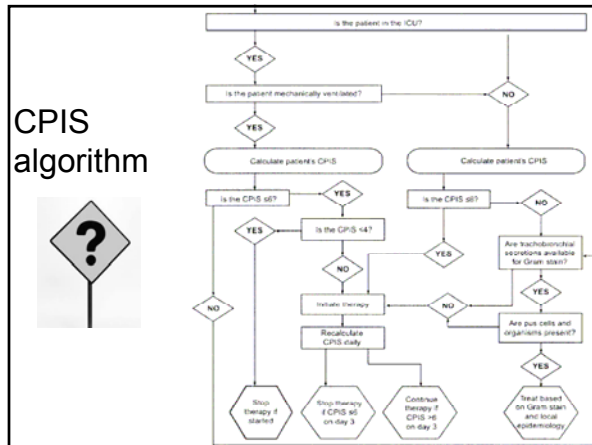
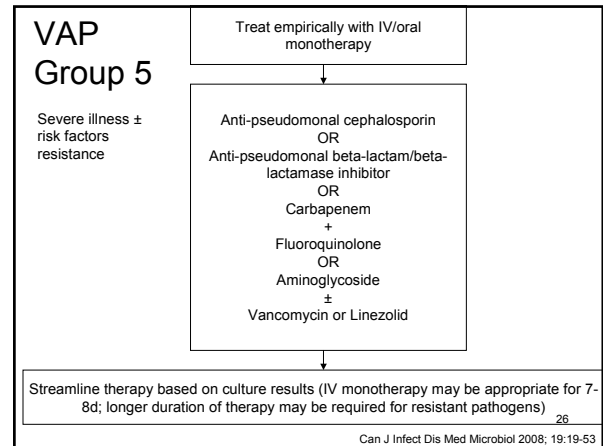
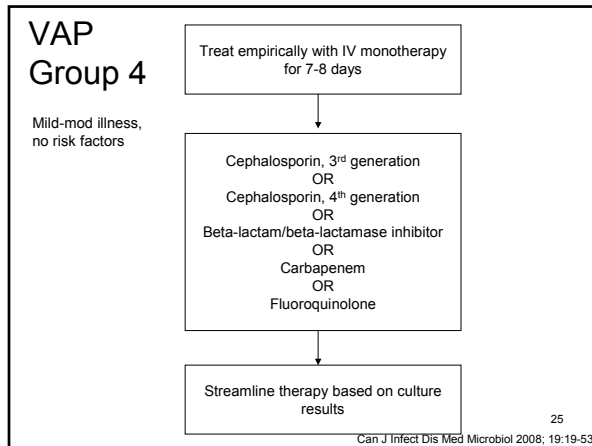
Can J Infect Dis Med Microbiol 2008; 19:19-53

VAP

Group 4
Mild-mod illness, no risk factors
Core pathogens

Group 5
Severe illness ± risk factors resistance
Core, MRSA, *P. aeruginosa*, Legionella, *Acinetobacter*, *Stenotrophomonas*

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Clinical Pulmonary Infection Score

Prediction model using quantitative criteria, CPIS >6 predictive of pneumonia

Parameter	0 points	1 point	2 points
Temperature (°C)	> 36.5-38.4	38.5-38.9	>39 or <36
WBC (x10 ⁹ /L)	4-11	<4 or >11	-
Tracheal secretions	Absent	Non-purulent	Purulent
Oxygenation PaO ₂ /FiO ₂ ratio (mmHg)	> 240 or acute resp. distress syndrome	-	<240, not acute resp. distress syndrome
Chest X-ray infiltrate	No infiltrate	Diffuse or patchy	Localized infiltrate
Microbiology	Negative	Positive	Gram stain (+), reflects culture

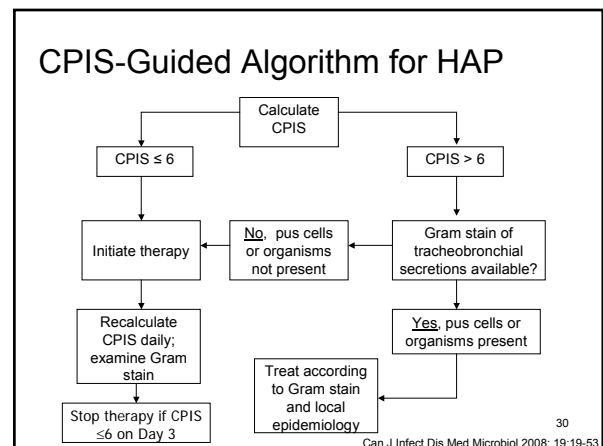
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Am Rev Respir Dis 1991; 143:1221-9
Crit Care Med 2004; 8 (Suppl.1): 209

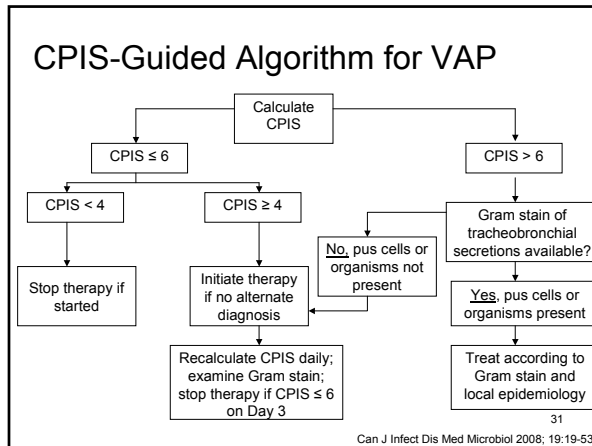
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30
Am Rev Respir Dis 1991; 143:1221-9
Crit Care Med 2004; 8 (Suppl.1): 209





- ### CPIS Limitations
- Clinical parameters easier to obtain in ICU than general ward
 - Clinical parameters often not available initially or during course of treatment
 - Oxygenation values
 - Presence of tracheal secretions
 - Serial Chest X-rays
 - Unreliable in certain populations
 - Trauma (sensitivity 61%, specificity 43%)
 - Thermal injury (sensitivity 30%, specificity 80%)
 - Immunocompromised patients
- J Trauma 2006; 60: 523-8
J Burn Care Res 2007; 28: 76-9

- ### “Infiltrating” the Data
- #### Selected Controversies
- “Streamlining and de-escalation of unnecessary antibiotics”
 - Duration of treatment
 - “Patient risk stratification based on initial clinical presentation”
 - Monotherapy vs. combination empiric antibiotics
- 33

- ### Duration of Treatment
- Short-course antibiotic therapies may:
 - ↓ development of multi-resistant organisms
 - ↓ super-infections (e.g. C difficile, fungus)
 - ↓ antibiotic side effects
 - ↓ antibiotic costs
- 34

Author	N	Intervention	Findings
Singh et al. 2000 HAP patients <i>Am J Resp Crit Care Med</i> 2000; 162:505-11	81	CPIS ≤6 Standard care vs. CPIS-guided therapy (ciprofloxacin 400 mg IV q8h x3 days)	CPIS group had decreased length of stay, total antibiotic days and cost but no mortality difference
Chastre et al. 2003 VAP patients (bronch diagnosis) <i>JAMA</i> 2003; 290:2588-98	401	Onset > 5 days Broad-spectrum beta-lactam plus aminoglycoside or fluoroquinolone 8-days vs. 15-days if initial regimen appropriate	8-days group had more antibiotic-free days but no difference in mortality or in infection recurrence (except resistant organisms)
Micek et al. 2004 VAP patients <i>Chest</i> 2004; 125:1791-7	290	Formal discontinuation policy by pharmacist (if criteria met) or standard care	Discontinuation policy decreased antibiotic days, no effect on hospital stay or mortality
Meropenem Short-Course <i>ClinicalTrials.gov</i> NCT00410527		ICU ≥3 days, CPIS ≤6, new infiltrate Meropenem x3 days vs. Standard antibiotics x 8 days	Unpublished

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- ### Duration of Treatment
- Patients with low likelihood of HAP or VAP (CPIS ≤6) can be assessed for antibiotic discontinuation after 3 days
 - VAP patients with few risk factors, not infected with resistant pathogens, and on appropriate initial antibiotics can safely stop therapy after 7-8 days
 - VAP patients infected with resistant pathogens should receive antibiotic treatment >8 days (optimal duration unclear)
- 36

Empiric Combination Therapy

- Empiric combination antibiotic therapy for Gram negative bacilli may:
 - ↑ likelihood of adequate antibiotic coverage
 - ↓ complications from inadequate coverage
 - ↓ length of hospitalization
 - ↓ mortality
 - prevent resistance?

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Empiric Combination Therapy

Heyland et al. (Canadian Critical Care Trials Group)

- MC, P, R, open-label
- N= 740, suspected VAP > 96 hours ICU admission
- Meropenem 1000mg IV q8h + Ciprofloxacin 400mg IV q12h vs. Meropenem alone
- Endpoints: All-cause mortality, mechanical ventilation duration, rate of ICU/hospital discharge, clinical response, microbiological response

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Crit Care Med 2008; 36:737-44

Empiric Combination Therapy

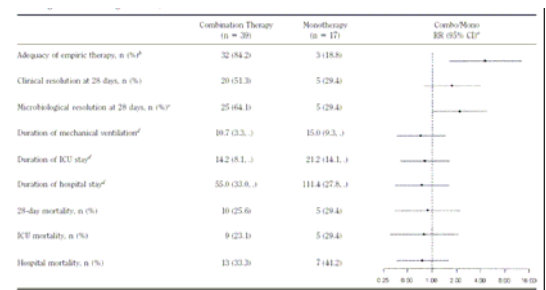
Endpoint	Combo (%) (N=369)	Mono (%) (N=370)	p
Mortality	Overall mortality: 18.7 RR 1.05 (0.78-1.42)		0.74
Mechanical Ventilation	8.7	9.3	0.79
Discharged from ICU	12.1	12.8	0.84
Discharged from hospital	45.8	39.1	0.49

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Crit Care Med 2008; 36:737-44

Empiric Combination Therapy

Subgroup of patients with difficult-to-treat Gram (-) bacilli on enrollment



Combination therapy may provide better microbiological and clinical outcomes in this subgroup (hypothesis-generating)

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Crit Care Med 2008; 36:737-44

Empiric Combination Therapy

Aarts et al.

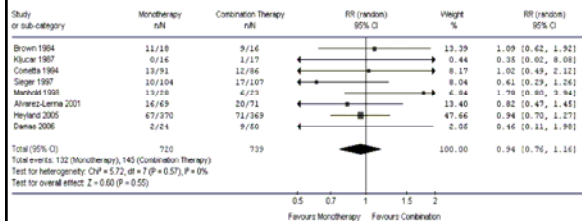
- Design: Meta-analysis
- N=41 RCTs (7,015 patients) of empiric parenteral antibiotics in adults with clinical VAP included
- Endpoints: all-cause mortality, treatment failure
- Appropriate methodology
- Quality of included studies low (double-blind design, allocation concealment, complete follow-up)

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Crit Care Med 2008; 36:108-17

Empiric Combination Therapy

Mortality



There is no evidence that combination therapy improves survival when compared with monotherapy

42

Crit Care Med 2008; 36:108-17

Empiric Combination Therapy

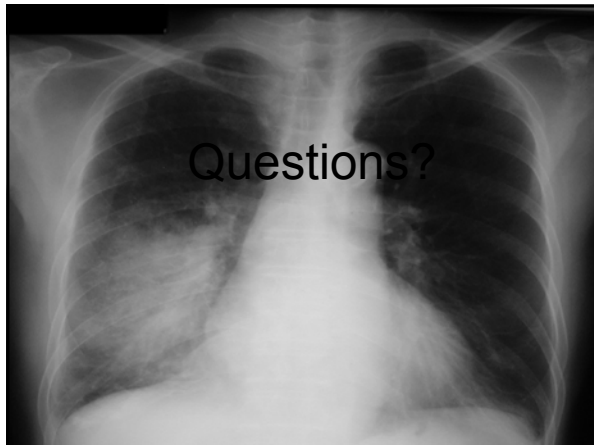
- Consider local resistance patterns in your institution and your ICU first!
- Patients with VAP and at low risk for resistance can safely receive monotherapy
- Empiric combo therapy may be preferred for patients at high risk of resistant Gram-negative bacteria

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“Consolidating” the Evidence

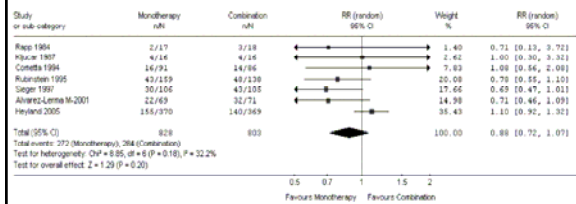
- Canadian Guideline Strengths
 - Multi-disciplinary, Canadian perspective
 - Emphasizes antibiotic streamlining, de-escalation
 - Tables, algorithms provided
- Canadian Guideline Limitations
 - Methodological quality (as per AGREE)
 - High-risk groups (HCAP) not fully addressed
 - Tables and algorithms difficult to follow
 - Patient risk stratification not strongly supported in literature
 - Do not apply to immunocompromised patients!

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Empiric Combination Therapy

Treatment Failure



There is no evidence that combination therapy results in lower rates of treatment failure

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Crit Care Med 2008; 36:108-17