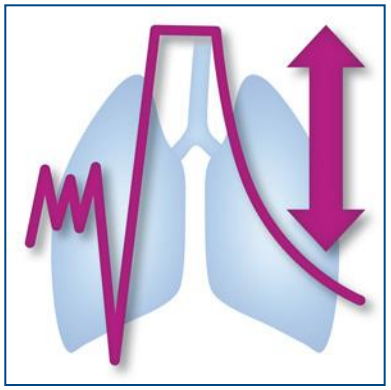
Pneumo Update Europe 2018

15 - 16 June, Budapest

Pneumonia



Mark Woodhead, UK

Contents
>1600 peer-reviewed publications between PneumoUpdate 2017 and May 2018

- ERS/ESICM/ESCMID/ALAT HAP AND VAP Guidelines
- Diagnosis of VAP
- CT visualised CAP
- Cardiac effects of CAP
- Cognitive impairment after CAP
- Steroids and CAP

Hospital-acquired and Ventilator-associated Pneumonia

Hospital-acquired and Ventilator-associated Pneumonia

State of the Art

- Nosocomial pneumonia develops in patients admitted to the hospital for >48 h
- ventilator-associated pneumonia (VAP) develops in intensive care unit (ICU) patients who have been mechanically ventilated for at least 48 h
- HAP is the second most common nosocomial infection and the leading cause of death from nosocomial infections in critically ill patients
- HAP and, most prominently, VAP increase duration of hospitalisation and healthcare costs

Hospital-acquired and Ventilator-associated Pneumonia

TASK FORCE REPORT
ERS/ESICM/ESCMID/ALAT GUIDELINES

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT)

Antoni Torres[1,16], Michael S. Niederman[2,16], 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], Robert C. Read[11], David Rigau[12], Jean François Timsit[13], Tobias Welte[14] and Richard Wunderink[15]

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Hospital-acquired and Ventilator-associated Pneumonia

Although the IDSA/ATS were also developing new guidelines, the panel thought that a European perspective was needed in view of the differences between the US and European approaches in several areas

Evidence levels and recommendation grades used in these guidelines follows the GRADE methodology

7 PICO (population–intervention–comparison–outcome) questions

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Hospital-acquired and Ventilator-associated Pneumonia

Question 1: In intubated patients suspected of having VAP, should distal quantitative samples be obtained instead of proximal quantitative samples?

Question 3: When using initial broad-spectrum empiric therapy for HAP/VAP, should it always be with two drugs or can it be with one drug and, if starting with two drugs, do both need to be continued after cultures are available?

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Hospital-acquired and Ventilator-associated Pneumonia

Question 3: When using initial broad-spectrum empiric therapy for HAP/VAP, should it always be with two drugs or can it be with one drug and, if starting with two drugs, do both need to be continued after cultures are available?

We recommend initial empiric combination therapy for high-risk HAP/VAP patients to cover Gram-negative bacteria and include antibiotic coverage for MRSA in those patients at risk. (Strong recommendation, moderate quality of evidence.)

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Hospital-acquired and Ventilator-associated Pneumonia

Question 4: In patients with HAP/VAP, can duration of antimicrobial therapy be shortened to 7–10 days for certain populations, compared with 14 days, without increasing rates of relapsing infections or decreasing clinical cure?

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. (Weak recommendation, moderate quality of evidence.)

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Hospital-acquired and Ventilator-associated Pneumonia

Question 6: In patients with HAP with severe sepsis or VAP, can serum PCT be used to reduce the duration of antibiotic therapy, compared with care that is not guided by serial biomarker measurements?

We do not recommend the routine measurement of serial serum PCT levels to reduce duration of the antibiotic course in patients with HAP or VAP when the anticipated duration is 7–8 days. (Strong recommendation, moderate quality of evidence.)

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Hospital-acquired and Ventilator-associated Pneumonia

Question 6: In patients with HAP with severe sepsis or VAP, can serum PCT be used to reduce the duration of antibiotic therapy, compared with care that is not guided by serial biomarker measurements?

The panel believes that the measurement of serial serum PCT levels together with clinical assessment in specific clinical circumstances (see table 3) with the aim of reducing antibiotic treatment duration represents good practice. (Good practice statement.)

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Hospital-acquired and Ventilator-associated Pneumonia

Take-Home Message

- Useful general recommendations

- 3 authors from USA
- How PICO questions formulated unclear
- No distinction between HAP and VAP evidence
- Most recommendations weak due to low quality evidence
- *Strong recommendation, moderate quality of evidence*

Torres A, Niederman MS, Chastre J, et al. *Eur Respir J* 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017

Diagnosis of VAP

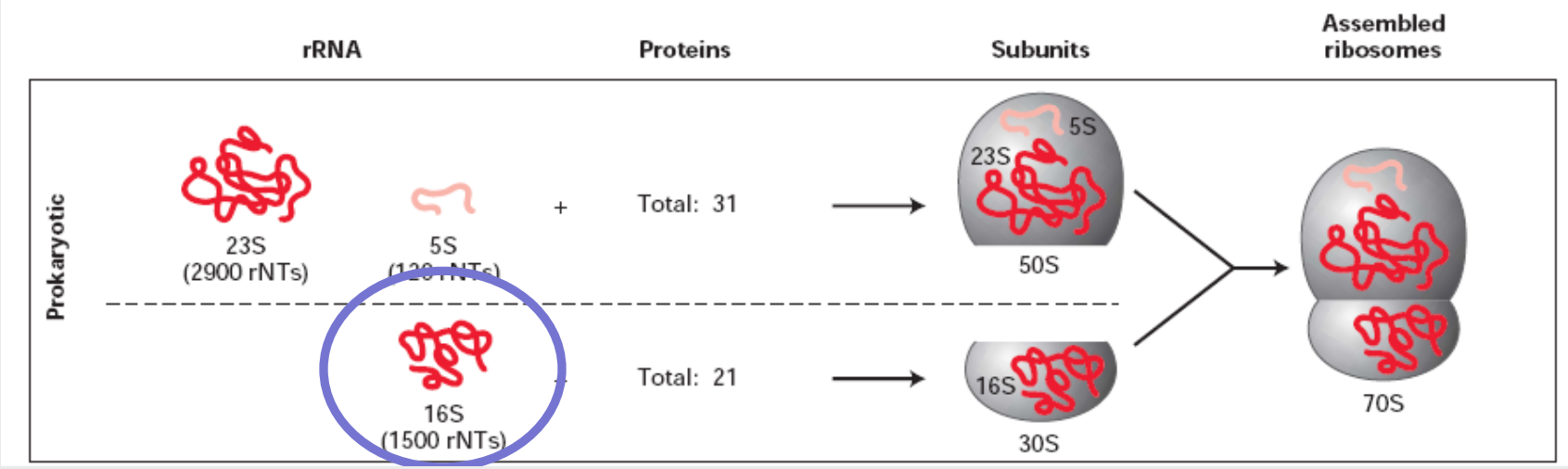
Diagnosis of VAP

State of the Art

- VAP common, prolongs LoS and expensive
- No unique features / many mimics
- Diagnosis difficult
- Only 30% suspected VAP have confirmed VAP
- Antibiotic overuse and resistance

Ribosomal Structure

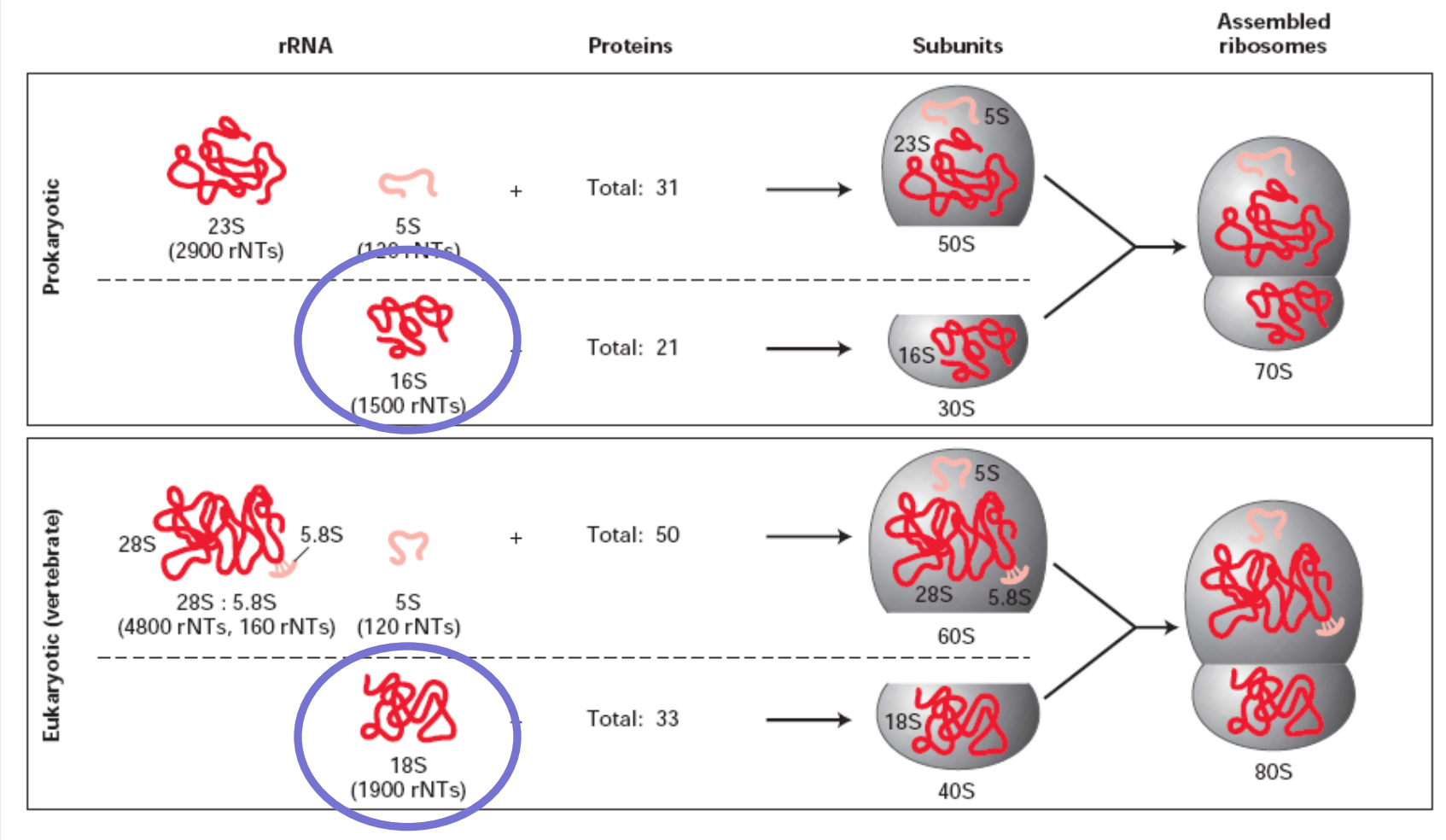
State of the Art



http://www.biologyexams4u.com/2013/02/difference-between-70s-and-80s-ribosomes.html#.WoWl8ry6_cs

Ribosomal Structure

State of the Art



http://www.biologyexams4u.com/2013/02/difference-between-70s-and-80s-ribosomes.html#.WoWl8ry6_cs

Diagnosis of VAP

Suspected VAP

- new or worsening chest X-ray changes following at least 48 hours of ventilation

accompanied by two or more of:

- temperature >38°C;
- white cell count >11×109/L;
- mucopurulent sputum.

Confirmed VAP

- growth at >10^4 colony forming units/mL (CFU/mL) of BAL fluid

Conway Morris A, et al. *Thorax* 2017;**72**:1046–1048.

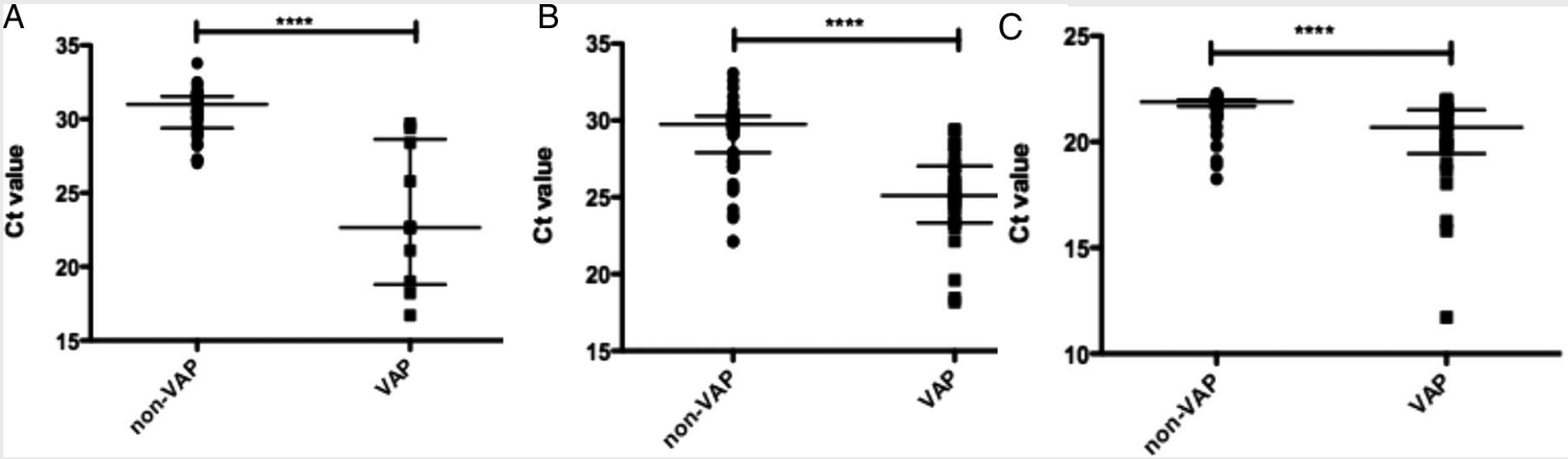
Diagnosis of VAP

derivation cohort
67 patients, 10 (15%) microbiologically confirmed VAP
confirmation cohort
92 patients, 26(28%) microbiologically confirmed VAP

2 x Realtime 16S PCR assays in 2 separate labs
Turn around time 4-6 hours

Conway Morris A, et al. *Thorax* 2017;**72**:1046–1048.

Diagnosis of VAP



A derivation
B confirmation Assay 1
C confirmation Assay 2
Assay 1
AUROC of 0.94 (95% CI 0.86 to 1.00), sensitivity of 100% and specificity 72% at the most optimal cut-off

Conway Morris A, et al. *Thorax* 2017;72:1046–1048.

Diagnosis of VAP
Take-Home Message

- New method to diagnose VAP
- Potential for better antibiotic stewardship

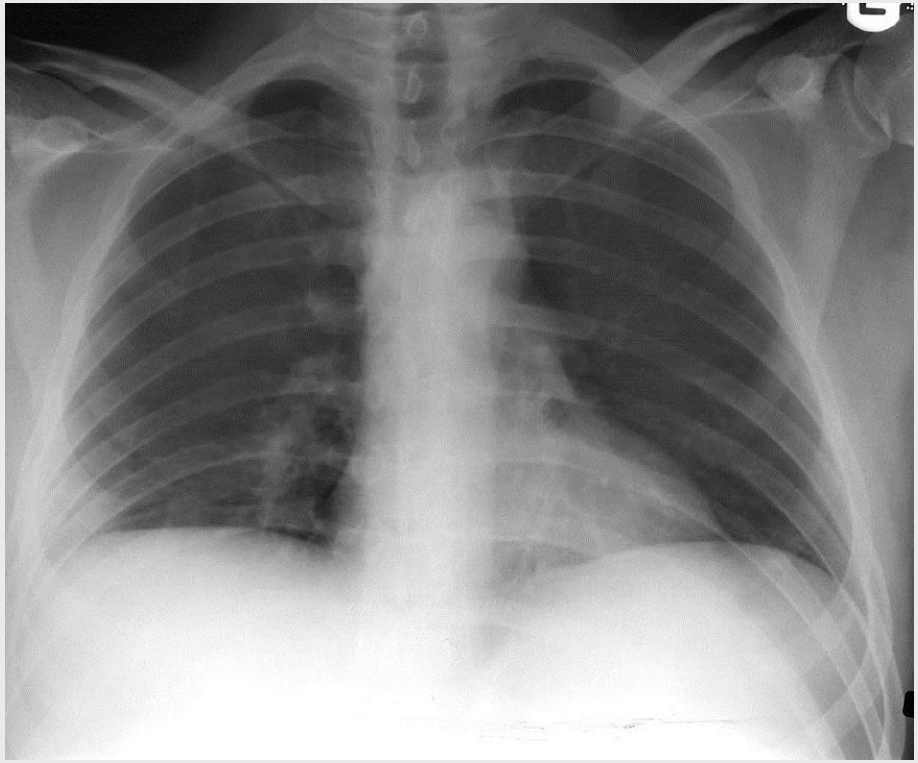
- Requires bronchoscopic samples
- Has not been compared with other methods
- Does not identify causative bacterium

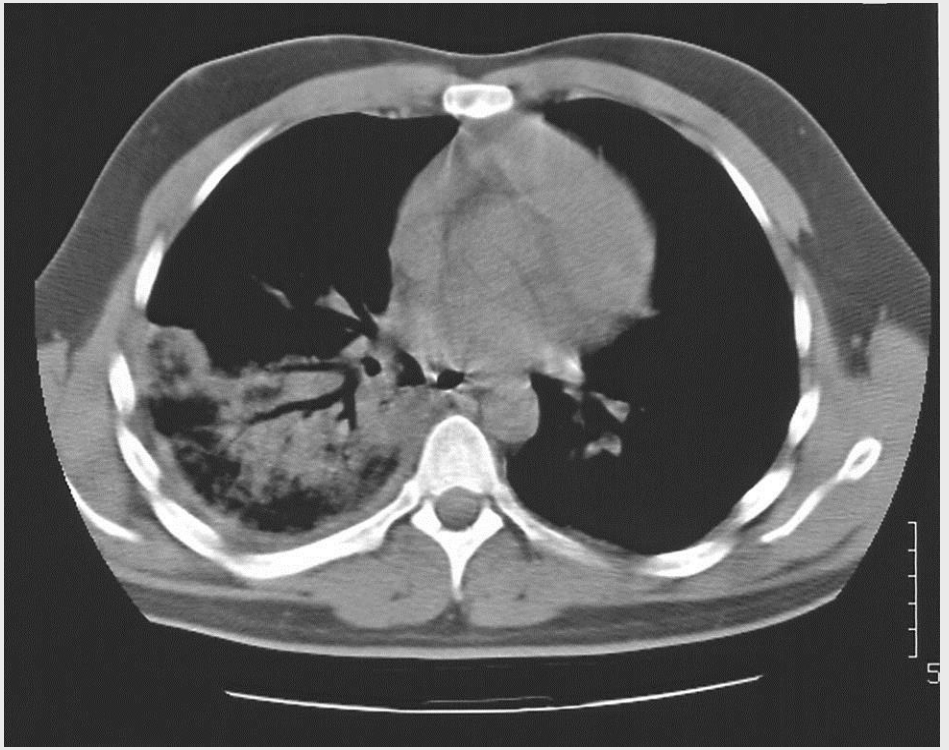
Conway Morris A, et al. *Thorax* 2017;72:1046–1048.

Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs

CAP on CT but not CXR

State of the Art





CAP on CT but not CXR

[Original Research]

Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs

Pathogens, Severity, and Clinical Outcomes

Cameron P. Upchurch, MD; Carlos G. Grijalva, MD, MPH; Richard G. Wunderink, MD; Derek J. Williams, MD, MPH; Grant W. Waterer, MBBS, PhD; Evan J. Anderson, MD; Yuwei Zhu, MD; Eric M. Hart, MD; Frank Carroll, MD; Anna M. Bramley, MPH; Seema Jain, MD; Kathryn M. Edwards, MD; and Wesley H. Self, MD, MPH

Upchurch et al *Chest* 2017
Aug 9. pii: S0012-3692(17)31392-2. doi: 10.1016/j.chest.2017.07.035

CAP on CT but not CXR

- Adults, Jan 1, 2010 - Jun 30, 2012
- 5 hospitals, three in Chicago, Illinois;and two in Nashville, Tennessee
- acute respiratory infection + radiological signs of pneumonia

- 2,251 CXR, 748 (33%) had concurrent CT imaging
- 66 / 2,251 (3%) included patients CT-only pneumonia
- 43 (65%) CT imaging and CXR on the same day
- 2,185 (97%) had pneumonia on CXR

Upchurch et al *Chest* 2017
Aug 9. pii: S0012-3692(17)31392-2. doi: 10.1016/j.chest.2017.07.035

CAP on CT but not CXR

CT-only pneumonia were

More likely to:

Be younger, have higher BMI

to present with chest pain, wheezing, and PSI I -II.

Lower Procalcitonin concentrations

Have rhinovirus identified

Less likely to

Receive antibiotic in 6 hours

Specific antibiotic regimens received were quite similar

Upchurch et al *Chest* 2017
Aug 9. pii: S0012-3692(17)31392-2. doi: 10.1016/j.chest.2017.07.035

CAP on CT but not CXR

- hospital length of stay,
- ICU admission,
- mechanical ventilation, and
- shock,

were similar between groups

- In-hospital death was rare in both the CT-only and
- pneumonia on CXR groups (0% vs 2%).

Upchurch et al *Chest* 2017
Aug 9. pii: S0012-3692(17)31392-2. doi: 10.1016/j.chest.2017.07.035

CAP on CT but not CXR
Take-Home Message

Manage patients in the same way as CXR CAP

Low mortality population

Other populations?

Upchurch et al *Chest* 2017
Aug 9. pii: S0012-3692(17)31392-2. doi: 10.1016/j.chest.2017.07.035

Cardiac effects of CAP

Cardiac effects of CAP

State of the Art

- In hospital mortality
- Survival disadvantage after discharge
- Excess vascular events

Cardiac effects of CAP

Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia. Violi F, Cangemi R, Falcone M, Taliani G, Pieralli F, Vannucchi V, Nozzoli C, Venditti M, Chirinos JA, Corrales-Medina VF; SIXTUS (Thrombosis-Related Extrapulmonary Outcomes in Pneumonia) Study Group. *Clin Infect Dis*. 2017 Jun 1;64(11):1486-1493. doi: 10.1093/cid/cix164

Severe Pneumococcal Pneumonia Causes Acute Cardiac Toxicity and Subsequent Cardiac Remodeling. Reyes LF, Restrepo MI, Hinojosa CA, Soni NJ, Anzueto A, Babu BL, Gonzalez-Juarbe N, Rodriguez AH, Jimenez A, Chalmers JD, Aliberti S, Sibila O, Winter VT, Coalson JJ, Giavedoni LD, Dela Cruz CS, Waterer GW, Witzenrath M, Suttorp N, Dube PH, Orihuela CJ. *Am J Respir Crit Care Med*. 2017 Sep 1;196(5):609-620. doi: 10.1164/rccm.201701-0104OC. PMID:28614669

Pneumonia and the Risk of Cardiovascular Death - Time to Change Our Strategy. Welte T, Pletz M. *Am J Respir Crit Care Med*. 2017 Jul 19. doi: 10.1164/rccm.201707-1421ED. [Epub ahead of print] No abstract available. PMID:28723315

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

Jeffrey C. Kwong, M.D., Kevin L. Schwartz, M.D., Michael A. Campitelli, M.P.H., Hannah Chung, M.P.H., Natasha S. Crowcroft, M.D., Timothy Karnauchow, Ph.D., Kevin Katz, M.D., Dennis T. Ko, M.D., Allison J. McGeer, M.D., Dayre McNally, M.D., Ph.D., David C. Richardson, M.D., Laura C. Rosella, Ph.D., M.H.Sc., Andrew Simor, M.D., Marek Smieja, M.D., Ph.D., George Zahariadis, M.D., and Jonathan B. Gubbay, M.B., B.S., M.Med.Sc.

Kwong et al *N Engl J Med* 2018;378:345-53.

Cardiac effects of CAP

Table 2. Incidence Ratios for Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection.*

Variable	Incidence Ratio (95% CI)
Primary analysis: risk interval, days 1–7	6.05 (3.86–9.50)
Days 1–3	6.30 (3.25–12.22)
Days 4–7	5.78 (3.17–10.53)
Days 8–14	0.60 (0.15–2.41)
Days 15–28	0.75 (0.31–1.81)
Alternative exposure	
RSV	3.51 (1.11–11.12)
Respiratory virus other than influenza or RSV	2.77 (1.23–6.24)
Illness with no respiratory virus identified‡	3.30 (1.90–5.73)
Hospitalization for diabetes and associated complications§	1.35 (0.50–3.62)

Kwong et al *N Engl J Med* 2018;378:345-53.

Cardiac effects of CAP

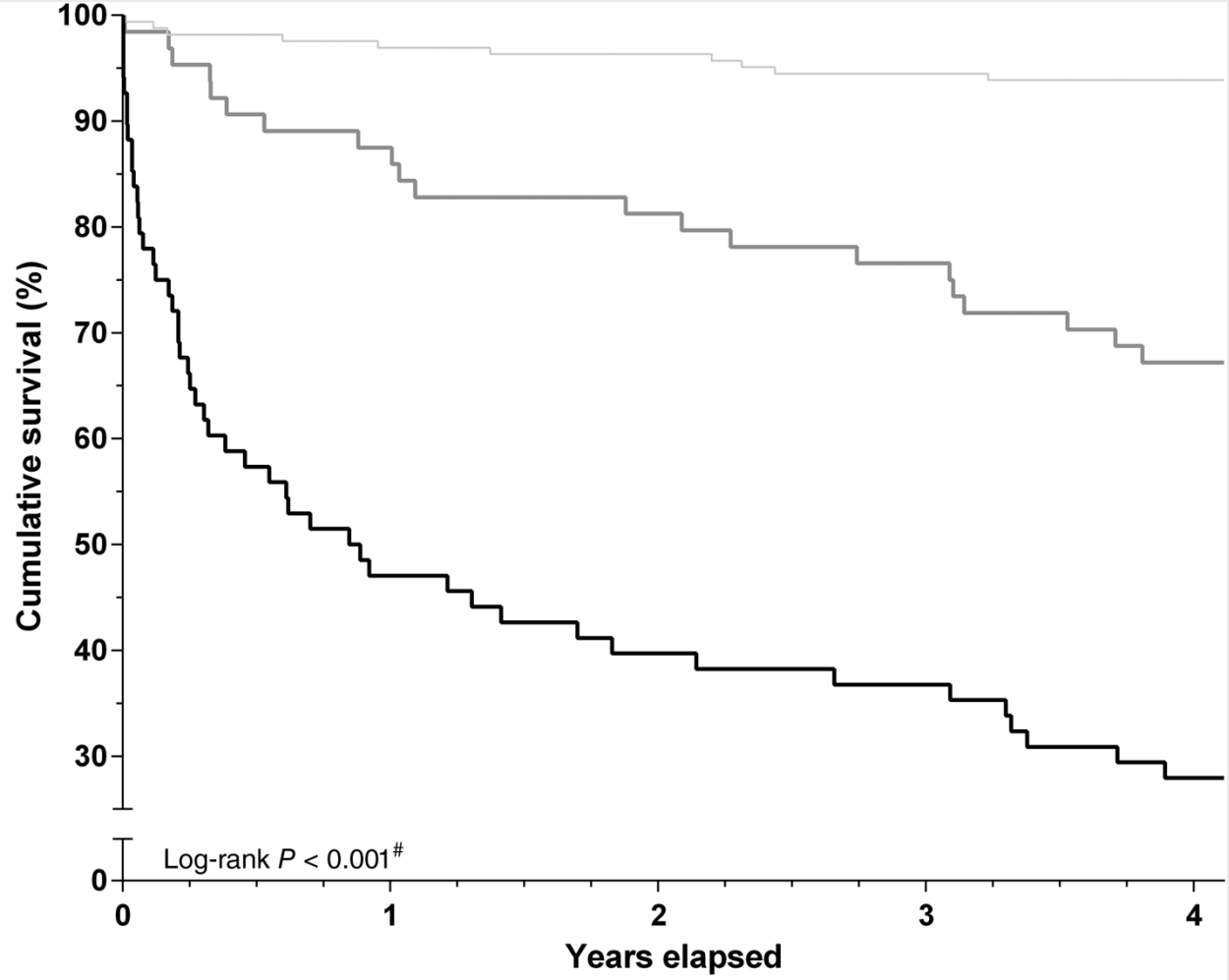
ORIGINAL ARTICLE

High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia

STEFAN M.T. VESTJENS,[1] SIMONE M.C. SPOORENBERG,[1] GER T. RIJKERS,[2,3] JAN C. GRUTTERS,[4,5] JURRIËN M. TEN BERG,[6] PETER G. NOORDZIJ,[7] EWOUDT M.W. VAN DE GARDE,[8,9] WILLEM JAN W. BOS[1] AND the Ovidius Study Group

Vestjens et al *Respirology* 2017Jul;22(5):1000-1006. doi: 10.1111/resp.12996

Cardiac effects of CAP



Vestjens et al *Respirology* 2017Jul;22(5):1000-1006. doi: 10.1111/resp.12996

Cardiac effects of CAP

Take-Home Message

- CAP has significant cardiac effects
- Important during and years after CAP
- Mechanism unclear
- Prevention strategy – trials required

Cognitive Impairment after CAP

Cognitive Impairment after CAP

State of the Art

- Outcomes mainly mortality and LoS
- Interest in long-term cardiac morbidity after CAP
- Cognitive impairment after critical illness

Cognitive Impairment after CAP

Long-Term Cognitive Impairment after Hospitalization for Community-Acquired Pneumonia: a Prospective Cohort Study

Timothy D. Girard, MD, MSCI[1], Wesley H. Self, MD, MPH[2], Kathryn M. Edwards, MD[3,4], Carlos G. Grijalva, MD, MPH[5,6], Yuwei Zhu, MD, MS[7], Derek J. Williams, MD, MPH[3,8], Seema Jain, MD[9], and James C. Jackson, PsyD[10,11,12,13]

Girard et al *J Gen Intern Med* 2018 DOI: 10.1007/s11606-017-4301-x

Cognitive Impairment after CAP

- Nested study
- Centers for Disease Control and Prevention
- (CDC) Etiology of Pneumonia in the Community (EPIC) Study
- multicenter investigation to determine the incidence and etiologies of CAP resulting in hospitalization in the US. From January 2010 to
- June 2012,

Girard et al *J Gen Intern Med* 2018 DOI: 10.1007/s11606-017-4301-x

Cognitive Impairment after CAP

survived to hospital discharge and

had none of the following exclusion criteria:

- severe cognitive or neurodegenerative disease that prevented independent living prior to CAP
- active substance abuse, psychotic disorder, homelessness, or plans to move out of the catchment area within 12 months of enrollment,
- blindness or deafness, which would prevent outcomes assessment;
- Lack of commitment to aggressive treatment (e.g., discharge to hospice); or lack of informed consent

Girard et al *J Gen Intern Med* 2018 DOI: 10.1007/s11606-017-4301-x

Cognitive Impairment after CAP

At enrollment, a trained psychology professional evaluated participants' baseline (i.e., pre-CAP hospitalization) cognitive and functional status

- Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE),
- baseline activities of daily living (ADLs) with the Katz ADL questionnaire,
- Baseline instrumental ADLs with the Functional Activities Questionnaire (FAQ)

Girard et al *J Gen Intern Med* 2018 DOI: 10.1007/s11606-017-4301-x

Cognitive Impairment after CAP

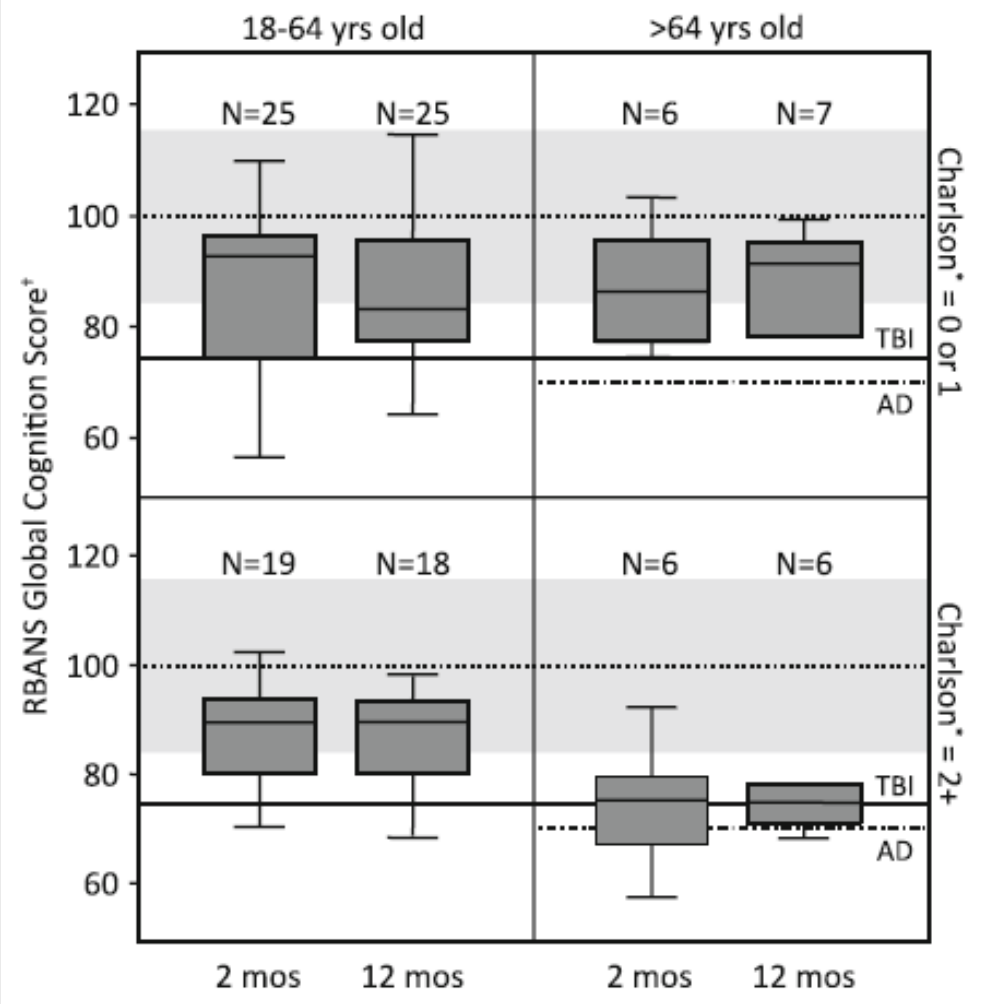
Two and 12 months after hospital discharge,

psychology professionals assessed participants' cognition Repeatable

- Battery for the Assessment of Neuropsychological Status
- (RBANS),
- Mini-Mental State Examination (MMSE)
- Trail Making Test A23, Trail Making Test B23
- Tower Test to assess executive function
- Katz Activities of Daily Living
- Functional Activities Questionnaire
- Short IQCODE18

Girard et al *J Gen Intern Med* 2018 DOI: 10.1007/s11606-017-4301-x

Cognitive Impairment after CAP



Girard et al *J Gen Intern Med* 2018 DOI: 10.1007/s11606-017-4301-x

Take-Home Message

- CAP is a multi-system disease

A year after hospitalization for CAP

- moderate-to-severe impairment in multiple cognitive domains affected one third of patients ≥ 65 years old and 20% of younger patients,
- another third of survivors had mild cognitive impairment.
- ?effect of CAP

Steroids in CAP

Steroids in CAP

State of the Art

- Not a current standard of care
- Widely used ? as rescue when Rx failing
- Meningitis and Pneumocystis
- ? benefit in severe CAP, but trials small and biased
- 15 RCTs

Steroids in CAP

Original Studies

Wagner	1955
Bennett	1963
Klastersky	1971
McHardy	1972
Marik	1993
Confalonieri	2005
El Ghamrawy	2006
Mikami	2007
Snijders	2010
Fernandez-Serano	2011
Meijvis	2011
Sabry	2011
Nafae	2013
Blum	2015
Torres	2015

Steroids in CAP

Meta-analyses	
Salluh	2010
Nie	2012
Siemieniuk	2015
Horita	2015
Chen	2015
Marti	2015
Wan	2016
Bi	2016
Wu	2018
Briel	2018

Original Studies	
Wagner	1955
Bennett	1963
Klastersky	1971
McHardy	1972
Marik	1993
Confalonieri	2005
El Ghamrawy	2006
Mikami	2007
Snijders	2010
Fernandez-Serano	2011
Meijvis	2011
Sabry	2011
Nafae	2013
Blum	2015
Torres	2015

Steroids in CAP

Meta-analyses		Studies	n	Los	Mortality
Salluh	2010	4	415	+/-	+/-
Nie	2012	9	1001		-
Siemieniuk	2015	13	2005	+	?+
Horita	2015	10	1780	-	-
Chen	2015	7	944	+	-
Marti	2015	14	2077	+	-
Wan	2016	9	1667	+	-
Bi	2016	8	528	+	+
Wu	2018	10	729	+	+
Briel	2018	6	1506	+	-

Other variables: Definitions (eg severity, 30-day mortality), steroid type, dose

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

35% of 3698 cases had pulmonary infection

Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo

Venkatesh et al *N Engl J Med* 2018;378:797-808

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

59% of 1240 cases had pulmonary infection

….90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo

Annane et al *N Engl J Med* 2018;378:378:809-818

Steroids in CAP
Take-Home Message

- Evidence does not support use of corticosteroids in CAP
- Effect of fludrocortisone?

List of References

1. Torres A, Niederman MS, Chastre J, et al. Eur Respir J
2. 2017; 50 (3): pii: 1700582. doi: 10.1183/13993003.00582-2017
3. http://www.biologyexams4u.com/2013/02/
4. difference-between-70s-and-80s-ribosomes.html#.WoWl8ry6_cs
5. Conway Morris A, et al. Thorax 2017;**72**:1046–1048
6. Upchurch et al Chest 2017Aug 9. pii: S0012-3692(17)
7. 31392-2. doi: 10.1016/j.chest.2017.07.035
8. Violi F et al SIXTUS (Thrombosis-Related Extrapulmonary Outcomes in
9. Pneumonia) Study Group. Clin Infect Dis. 2017 Jun 1;64(11):
10. 1486-1493. doi: 10.1093/cid/cix164
11. Reyes LF et al. Am J Respir Crit Care Med. 2017 Sep 1;196(5):609-620.
12. doi: 10.1164/rccm.201701-0104OC. PMID:28614669
13. Welte T, Pletz M. Am J Respir Crit Care Med. 2017 Jul 19.
14. doi: 10.1164/rccm.201707-1421ED. [Epub ahead of print] PMID:28723315
15. Kwong et al N Engl J Med 2018;378:345-53
16. Vestjens et al Respirology 2017Jul;22(5):1000-1006. doi: 10.1111/resp.12996
17. Girard et al J Gen Intern Med 2018 DOI: 10.1007/s11606-017-4301-x
18. Venkatesh et al N Engl J Med 2018;378:797-808
19. Annane et al N Engl J Med 2018;378:378:809-818

List of Abbreviations (i)

- ERS — European respiratory Society
- ESICM — European Society for Intensive Care Medicine
- ESCMID — European Society for Clinical Microbiology and Infectious Diseases
- ALAT — Asociacion Latinoamericana de Torax
- IDSA — Infectious Diseases Society of America
- HAP — Hospital-acquired Pneumonia
- VAP — Ventilator-associated Pneumonia
- CAP — Community-acquired Pneumonia
- CT — Computed Tomography
- ICU — Intensive Care Unit
- GRADE — Grading of Recommendations, Assessment, Development and Evaluations
- PICO — population–intervention–comparison–outcome
- MRSA — meticillin-resistant *Staphylococcus aureus*
- PCT — procalcitonin
- LoS — length of stay

List of Abbreviations (ii)

- CFU — Colony-forming Units
- BAL — Broncho-alveolar Lavage
- PCR — polymerase chain reaction
- AUROC — area under receiver-operator curve
- CXR — chest radiograph
- BMI — body mass index
- PSI — pneumonia severity index
- CDC — Centers for Disease Control and Prevention
- EPIC — Etiology of pneumonia in the community
- IQCODE — Informant Questionnaire on Cognitive Decline in the Elderly
- ADL — activities of daily living
- FAQ — Functional Activities Questionnaire
- RBANS — Battery for the Assessment of Neuropsychological Status
- MMSE — Mini-Mental State Examination
- RCT — randomised controlled clinical trial