

A year in review in community-acquired respiratory tract infections



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<http://www.facm.ucl.ac.be>

* this presentation is largely inspired from a lecture and documents of Prof. A. Torres

INSPIRATION: Global Perspectives and Local Insights in Infection Management
12th October 2013
6th April 2013, Moscow, Russia



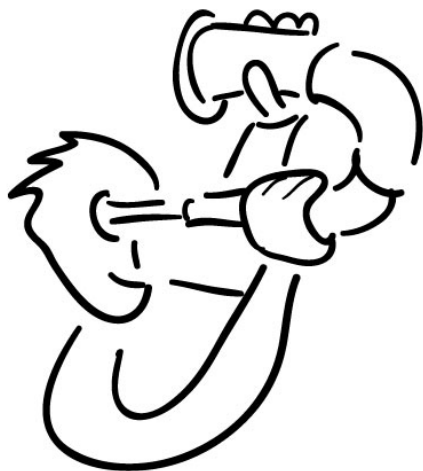
With approval of the Belgian Ethical Healthplatform – visa no. 13/V1/4123/054843

Disclosures

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- *Université catholique de Louvain* for personal support
- Commercial Relationships:
 - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics...
- Other relationships in relation to this talk
 - Belgian Antibiotic Policy Coordination Committee,
 - Belgian Transparency and Reimbursement Committees
 - Participation in EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones

Looking back ?

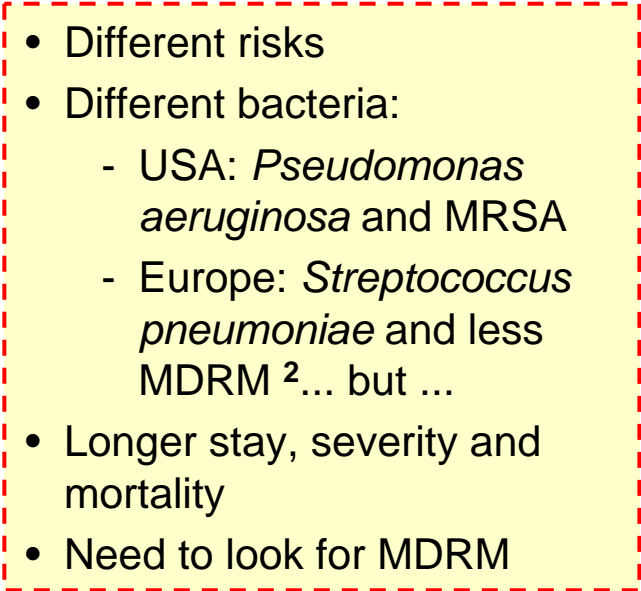


- Definitions (CAP, HCAP, HAP...) ?
- Risk factors...
- Predictive factors...
- Improvements in diagnosis...
- Antibiotic combinations ...
- New antibiotics ?
- And what about guidelines ?
- Other questions...

CAP: community acquired pneumonia
HAP: hospital acquired pneumonia
HCAP: health care associated pneumonia

Definitions ¹

- Community-acquired pneumonia (**CAP**)
 - Patient has not been in hospital (true community)
 - No risk of HCAP
- Health-care associated pneumonia (**HCAP**)
 - Previous hospitalization (>48hrs) in the last 3 months
 - Long term care facilities
 - Domiciliary endovenous therapy
 - Chronic haemodialysis in the last 30 days
 - Domiciliary wound care
 - Close contact with a family member affected by a multidrug resistant infection
- Hospital-acquired pneumonia (**HAP**)
 - Patient hospitalized for at least 48-72h

- 
- Different risks
 - Different bacteria:
 - USA: *Pseudomonas aeruginosa* and MRSA
 - Europe: *Streptococcus pneumoniae* and less MDRM ²... but ...
 - Longer stay, severity and mortality
 - Need to look for MDRM

MRSA: methicillin-resistant *Staphylococcus aureus*
MDRM: multidrug-resistant microorganism

¹ Proposed by the American Thoracic Society [ATS] /Infectious Diseases Society of America [IDSA] Statement: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416.

² Woodhead M. *Thorax*. 2013 Sep 3 [Epub ahead of print]

But are those correct and useful ?

Downloaded from thorax.bmj.com on October 1, 2013 - Published by group.bmj.com
Thorax Online First, published on September 3, 2013 as 10.1136/thoraxjnl-2013-204060

Editorial

Pneumonia classification and healthcare-associated pneumonia: a new avenue or just a cul-de-sac?

Mark Woodhead

Woodhead M. *Thorax*. 2013 Sep 3 [Epub ahead of print]

- Initial US studies supported this classification. ¹
- However, several European studies did not find major differences in the spectrum of microbial causes between CAP and HCAP. ²
- But the HCAP concept may be useful to identify patients with a worse prognosis.
- The concept may also be applicable where resistance levels are high (USA, Asian countries...) but not in Europe.

1. Kollef MH *et al*. Epidemiology and outcomes of healthcare-associated pneumonia: results from a large US database of culture positive pneumonia. *Chest* 2005;128:3854–62.
2. See e.g. Polverino E *et al*. Nursing home-acquired pneumonia: a 10-year single-centre experience. *Thorax* 2010;65:354–9

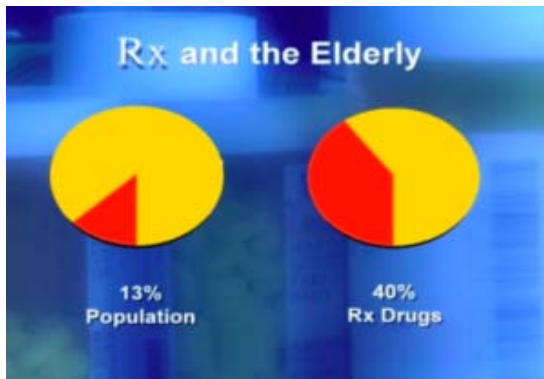
New (or well known) risk factors ?

- Multi-resistant organisms
- Co-medications ...
- Serotypes and resistance
- Aspiration pneumonia

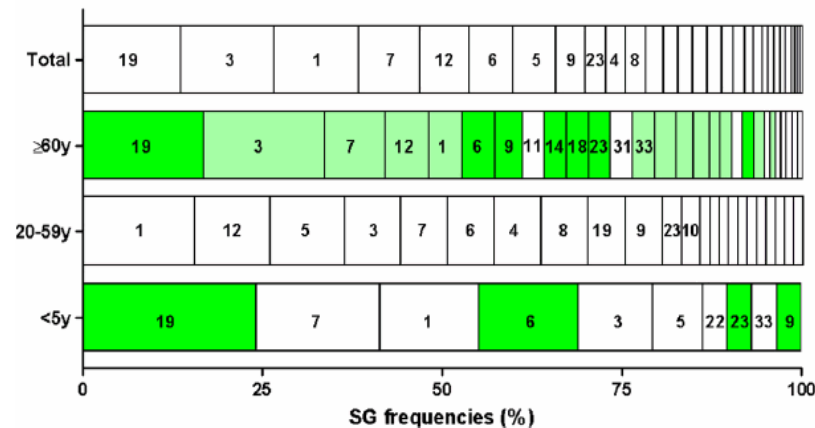


"Relax - MRSA will get you before the Asian Flu"

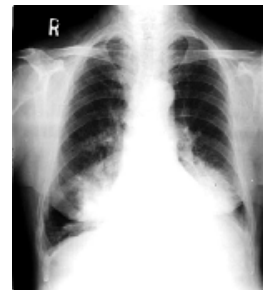
http://cooper.imb.uq.edu.au/community_background.html



Drug consumption by elderly patients in USA
<https://nccnews.expressions.syr.edu/?p=40169>



S. pneumoniae serogroups in Belgium (2007-2009)
 Lismond A et al. *Int J Antimicrob Agents* 2012;39:208-16



Aspiration Pneumonia
 Mineral Oil
<http://www.meddean.luc.edu/>

Multi-resistant organisms (in Europe) ...

Stratifying Risk Factors for Multidrug-Resistant Pathogens in Hospitalized Patients Coming From the Community With Pneumonia

Stefano Aliberti,^{1,2} Marta Di Pasquale,² Anna Maria Zanaboni,³ Roberto Cosentini,⁴ Anna Maria Brambilla,⁴ Sonia Seghezzi,⁴ Paolo Tarsia,² Marco Mantero,¹ and Francesco Blasi²

¹Dipartimento di Medicina Clinica e Prevenzione, University of Milan-Bicocca, Clinica Pneumologica, AO San Gerardo, Monza; ²Dipartimento Toraco-polmonare e Cardio-circolatorio, University of Milan, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan; ³Computer Science Department, University of Milan, and ⁴Emergency Medicine Department, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Aliberti S *et al. Clin Infect Dis.* 2012; 15;54:470-8.

- Observational, prospective study with 935 consecutive patients coming from the community and hospitalized with pneumonia.
- Data on admission and during hospitalization were collected.
- Logistic regression models to evaluate risk factors for acquiring MDR bacteria independently associated with the actual presence of a resistant pathogen and in-hospital mortality.

Multi-resistant organisms (in Europe) ...

Stratifying Risk Factors for Multidrug-Resistant Pathogens in Hospitalized Patients Coming From the Community With Pneumonia

Table 4. Scoring System to Evaluate the Presence of Multidrug-Resistant Pathogens in Patients With Pneumonia From the Community Who are Hospitalized

Variable	Score
No risk factors for MDR pathogen (including comorbidities)	0
≥1 of the following: cerebrovascular disease, diabetes, COPD, antimicrobial therapy in preceding 90 days, immunosuppression, home wound care, home infusion therapy (including antibiotics)	0.5
Residence in a nursing home or extended-care facility	3
Hospitalization for ≥2 days in the preceding 90 days	4
Chronic renal failure	5

Abbreviations: COPD, chronic obstructive pulmonary disease; MDR, multidrug-resistant.

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nza; ²Dipartimento
Milan; ³Computer
Maggiore Policlinico,

Scoring system used (as per ATS/IDSA)

Multi-resistant organisms (in Europe) ...

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Residence in a nursing home or extended-care facility	
Hospitalization for ≥2 days in the preceding 90 days	
Chronic renal failure	

Abbreviations: COPD, chronic obstructive pulmonary disease; MDR, multidrug-resistant.

Scoring system used

Brambilla,⁴

Monza; ²Dipartimento di Pneumologia, Milan; ³Computer Center, Ospedale Maggiore Policlinico,

Table 5. Independent Predictors for In-Hospital Mortality in the Study Population

Variable	OR (95% CI)	P Value
Hospitalization for ≥2 days in the preceding 90 days	1.63 (1.04–2.54)	.034
Residency in a nursing home or extended-care facility	2.83 (1.54–5.21)	.001
Pneumonia severity index	2.19 (1.58–3.03)	<.001
Severe CAP	2.52 (1.61–3.93)	<.001

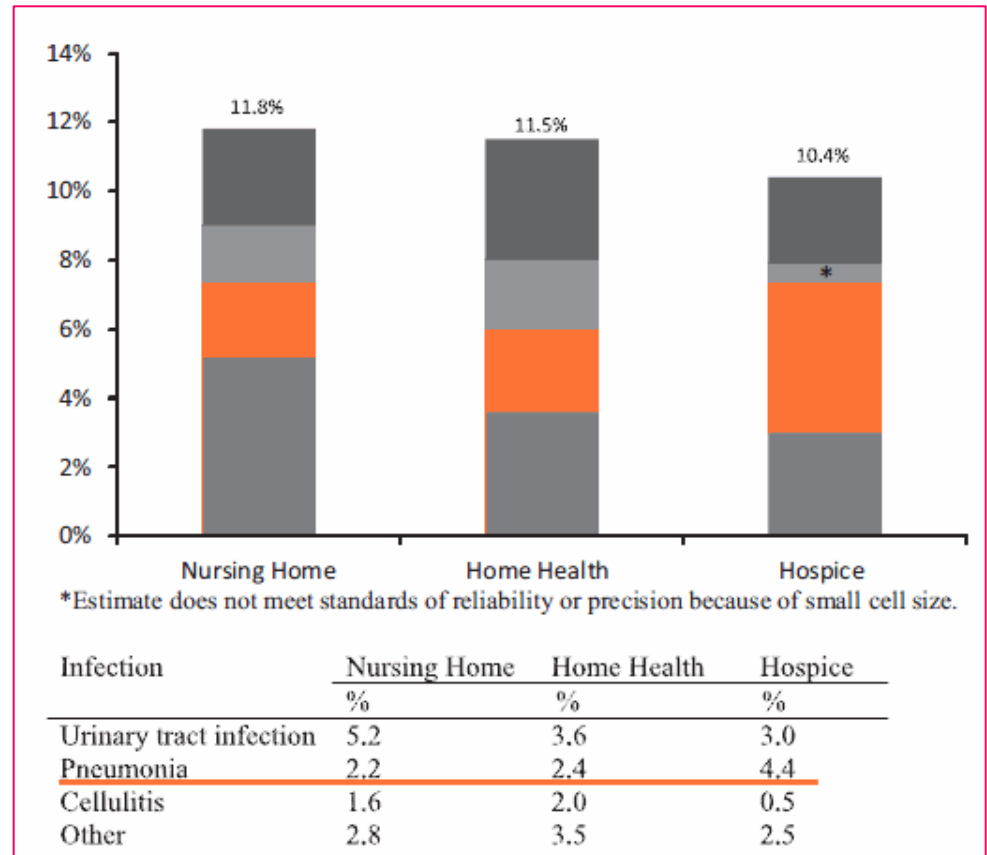
Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; OR, odds ratio.

The risk of health care and polymedication for the elderly

Infections in Long-Term Care Populations in the United States

Lisa L. Dwyer, MPH,* Lauren D. Harris-Kojetin, PhD,* Roberto H. Valverde, MPH,*
Joyce M. Frazier, MDiv,* Alan E. Simon, MD,* Nimalie D. Stone, MD, MS,[†] and
Nicola D. Thompson, PhD[†]

J Am Geriatr Soc 61:341–349, 2013.



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J Am Geriatr Soc 61:341–349, 2013.

Table 3. Prevalence of Infections in Nursing Home (NH) Residents, Individuals Receiving Home Health Care (HHC), and Individuals Receiving Hospice Care

	NH Residents	Individuals Receiving HHC	Individuals Receiving Hospice Care
Characteristic	Point Prevalence (95% Confidence Interval)		
Location before admission or at time of care ^b			
Private residence	9.5 (8.4–10.8) ^a	N/A	6.5 (5.0–8.4)
Assisted living, board and care, group home, residential care ^c	9.7 (7.6–12.3) ^a	N/A	—
NH, hospital skilled nursing facility, rehabilitation facility	11.3 (9.8–12.8) ^a	N/A	14.5 (11.0–18.9)
Number of medications received at time of survey interview			
<10 (reference)	11.0 (10.0–12.0)	8.9 (6.9–11.3)	11.0 (8.7–13.9)
≥ 10	13.0 (11.8–14.3) ^a	13.9 (11.3–17.0) ^f	9.8 (7.6–12.5)

Is serotype a main risk factor in CAP ?

ORIGINAL ARTICLE

Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia

Pontus Naucner,^{1,2} Jessica Darenberg,³ Eva Morfeldt,³ Åke Örtqvist,^{4,5}
Birgitta Henriques Normark^{1,3,6}

Thorax 2013;68:571–579. doi:10.1136/thoraxjnl-2012-203106

Is serotype and resistance a main risk factor in CAP ?

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Key messages

What is the key question?

- To what extent do host and bacterial factors contribute to mortality in bacteraemic pneumococcal pneumonia?

What is the bottom line?

- This study shows that host factors such as age, alcohol abuse, liver disease, renal disease and solid tumour contribute to mortality in patients with bacteraemic pneumococcal pneumonia, while the association between pneumococcal serotype and mortality is mitigated by adjustment for host factors.

Why read on?

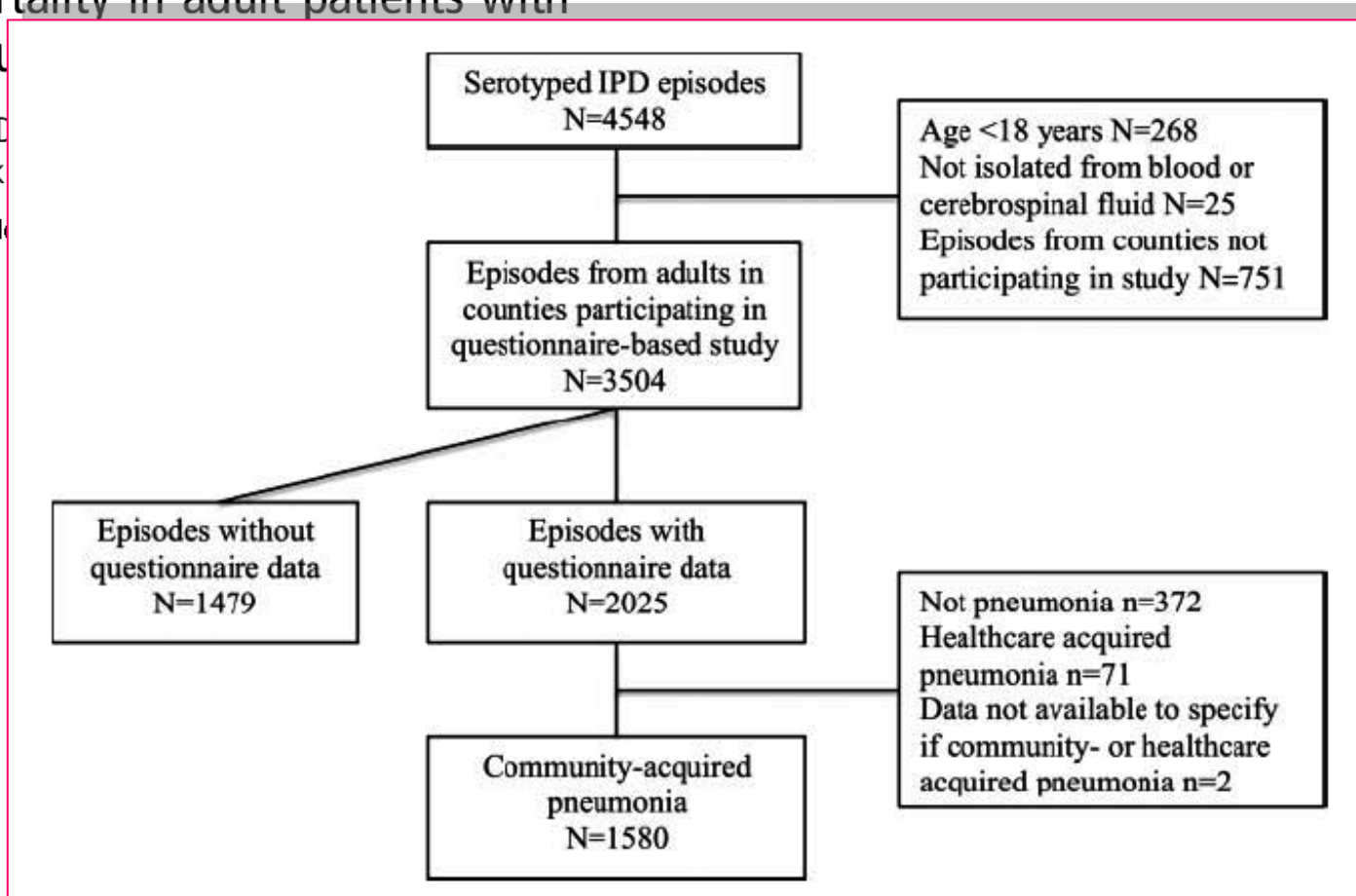
- These findings suggest that host factors appear to be more important than specific serotype as determinants of mortality in patients with bacteraemic pneumococcal pneumonia, which supports targeted intervention strategies.

Is serotype and resistance a main risk factor in CAP ?

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Birgitta

Thorax 2

Not too much of a surprise

Table 1 Host factors associated with 30-day mortality in patients with bacteraemic pneumococcal pneumonia

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Age				
≥85	203 (12.9)	52 (26.1)	26.74 (8.20 to 87.12)	29.43 (9.00 to 96.27)
75–84	323 (20.4)	40 (12.4)	10.69 (3.27 to 35.02)	11.30 (3.45 to 37.06)
65–74	301 (19.1)	25 (8.3)	6.85 (2.04 to 22.99)	7.10 (2.12 to 23.85)
55–64	341 (21.6)	20 (5.9)	4.71 (1.38 to 16.05)	4.84 (1.42 to 16.49)
45–54	182 (11.5)	6 (3.3)	2.58 (0.64 to 10.46)	2.59 (0.64 to 10.50)
<45	230 (14.6)	3 (1.3)	1.00 (ref)	1.00 (ref)
≥65	827 (52.3)	118 (14.3)	4.16 (2.73 to 6.32)	4.29 (2.82 to 6.54)
<65	753 (47.7)	29 (3.9)	1.00 (ref)	1.00 (ref)
Alcohol abuse				
Yes	113 (7.2)	18 (15.9)	2.39 (1.40 to 4.08)	3.82 (1.85 to 7.85)
No	1214 (76.8)	93 (7.7)	1.00 (ref)	1.00 (ref)
N/S	253 (16.0)	36 (14.2)		

Is se

AP ?

ORIGINAL ARTICLE

Contribution
treatment
bacteraemia

Pontus Naucle
Birgitta Henriq
Thorax 2013;68

Table 2 Thirty-day mortality risk according to serotype and antibiotic resistance in patients

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Individual serotype				
9V	191 (12.1)	10 (5.2)	0.62 (0.28 to 1.40)	0.83 (0.36 to 1.93)
7F	177 (11.2)	4 (2.3)	0.26 (0.09 to 0.79)	0.51 (0.16 to 1.59)
4	158 (10.0)	8 (5.1)	0.60 (0.25 to 1.43)	0.88 (0.36 to 2.16)
3	142 (9.0)	17 (12.9)	1.54 (0.76 to 3.12)	1.85 (0.87 to 3.93)
23F	97 (6.1)	11 (11.3)	1.44 (0.65 to 3.21)	1.23 (0.54 to 2.81)
22F	79 (5.0)	7 (8.9)	1.10 (0.44 to 2.76)	1.25 (0.48 to 3.23)
6B	78 (4.9)	15 (19.2)	2.69 (1.27 to 5.69)	2.09 (0.96 to 4.57)
6A	76 (4.8)	10 (13.1)	1.71 (0.75 to 3.92)	1.17 (0.49 to 2.75)
19A	55 (3.5)	4 (7.3)	0.89 (0.29 to 2.75)	0.69 (0.21 to 2.22)
14	209 (13.2)	17 (8.3)	1.00 (ref)	1.00 (ref)
Other	318 (20.1)	44 (13.8)	—	—
Serotype category according to CFR‡				
High	509 (32.2)	63 (12.4)	3.28 (1.89 to 5.70)	1.63 (0.89 to 2.98)
Medium	484 (30.6)	35 (7.2)	1.81 (1.00 to 3.28)	1.27 (0.67 to 2.42)
Low	412 (26.1)	17 (4.1)	1.00 (ref)*	1.00 (ref)**
Serotype category according to invasiveness§				
Low	461 (29.2)	58 (12.6)	4.21 (1.89 to 9.40)	1.67 (0.70 to 4.00)
Medium	591 (37.4)	40 (6.8)	2.13 (0.94 to 4.82)	1.19 (0.49 to 2.87)
High	212 (13.4)	7 (3.3)	1.00 (ref)*	1.00 (ref)***
PCV 13 serotypes ¶				
Yes	1277 (80.8)	107 (8.4)	0.60 (0.41 to 0.89)	0.78 (0.51 to 1.19)
No	303 (19.2)	40 (13.2)	1.00 (ref)	1.00 (ref)
Penicillin non-susceptible††				
Yes	45 (2.9)	6 (13.3)	1.52 (0.63 to 3.65)	1.07 (0.42 to 2.74)
No	1535 (97.2)	141 (9.2)	1.00 (ref)	1.00 (ref)
Erythromycin non-susceptible††				
Yes	69 (4.4)	5 (7.4)	0.75 (0.30 to 1.90)	0.83 (0.32 to 2.16)
No	1511 (95.6)	141 (9.4)	1.00 (ref)	1.00 (ref)

Whow
!

CAP: community
acquired
pneumonia

See notes in
back-up slides

Aspiration pneumonia as a specific risk...

Official Journal of the Asian Pacific Society of Respiratory

Respirology



ORIGINAL ARTICLE

Impact of aspiration pneumonia in patients with community-acquired pneumonia and healthcare-associated pneumonia: A multicenter retrospective cohort study

KOSAKU KOMIYA,^{1,3} HIROSHI ISHII,¹ KENJI UMEKI,¹ SHUNJI MIZUNOE,⁴ FUMITO OKADA,²
TAKESHI JOHKOH⁵ AND JUN-ICHI KADOTA¹

¹Internal Medicine 2 and ²Radiology, Faculty of Medicine, Oita University, ³Clinical Research Center of Respiratory Medicine, Tenshindo Hetsugi Hospital, ⁴Respiratory Medicine, Oita Prefectural Hospital, Oita, and ⁵Radiology, Kinki Central Hospital of Mutual Aid Association of Public School Teachers, Hyogo, Japan

Komiya K *et al.* *Respirology*. 2013 Apr;18(3):514-21.

SUMMARY AT A GLANCE

Aspiration pneumonia, which is defined as having risk factors for aspiration and evidence of gravity-dependent opacities on CT, was strongly associated with mortality after adjusting for the category of pneumonia, performance status and treatment failure due to resistant pathogens.

Aspiration pneumonia as a specific risk...

Official Journal of the Asian Pacific Society of Respiriology

Respirology



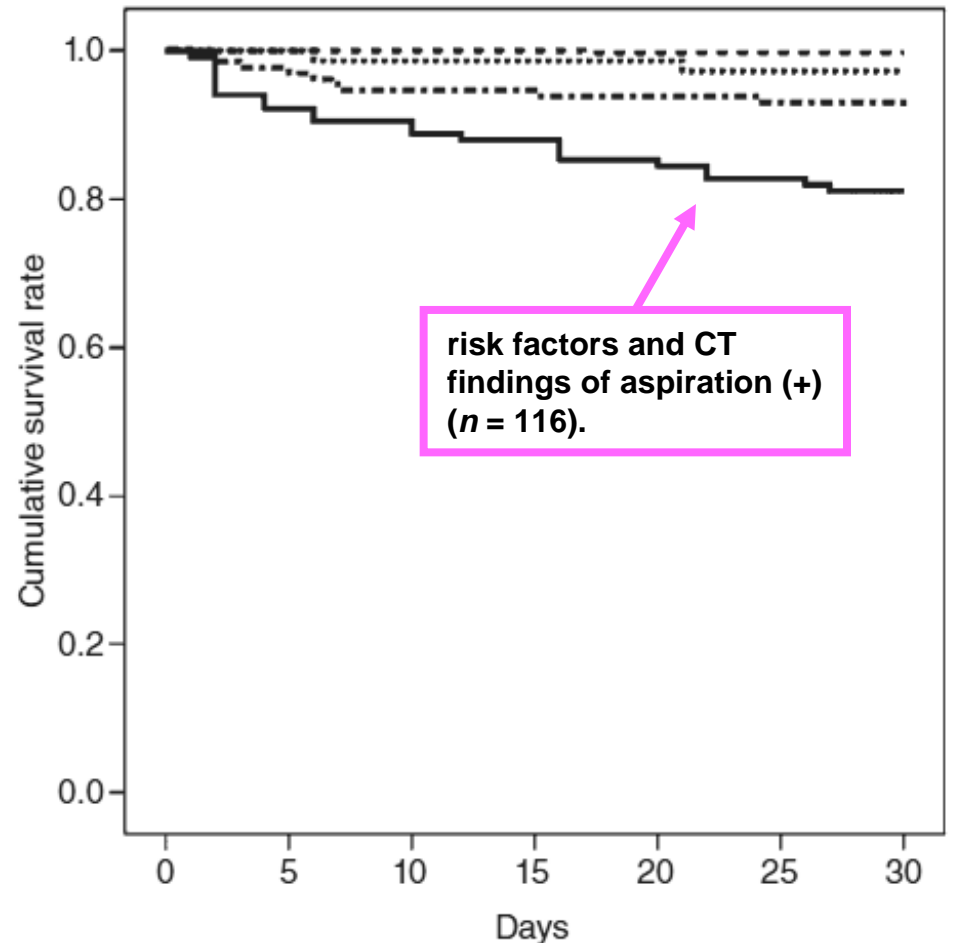
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¹Internal Medicine 2 and ²Radiology, Faculty of Medicine, Oita University, ³Clinical Research Center, Tenshindo Hetsugi Hospital, ⁴Respiratory Medicine, Oita Prefectural Hospital, Oita, and ⁵Radiology, Mutual Aid Association of Public School Teachers, Hyogo, Japan

Komiya K *et al.* *Respirology*. 2013 Apr;18(3):514-21.



CT: computed tomography

New Prognostic factors

Background:

- PSI and CURB65/CRB65 are not 100% sensitive or specific
- There is a definite percentage of patients with poor evolution that do not show initial severity, which leads to a delay in ICU admission
- These patients have two-fold mortality and it is therefore important to detect them very early

- Thrombocytosis
- Hyperglycaemia
- Vitamin D

Thrombocytosis as prognostic factor



CHEST

Original Research

CHEST INFECTIONS

Thrombocytosis Is a Marker of Poor Outcome in Community-Acquired Pneumonia

Elena Prina, MD; Miquel Ferrer, MD, PhD; Otavio T. Ranzani, MD; Eva Polverino, MD, PhD; Catia Cillóniz, PhD; Encarnación Moreno, RN; Josep Mensa, MD; Beatriz Montull, MD; Rosario Menéndez, MD, PhD; Roberto Cosentini, MD; and Antoni Torres, MD, PhD

Prina E *et al. Chest.* 2013 Mar;143(3):767-75

- 2423 hospitalized CAP patients
- 53 thrombocytopenia ($< 100,000/ \text{mm}^3$), 204 thrombocytosis ($> 400,000/ \text{mm}^3$)
- More respiratory complications with thrombocytosis, more septic shock with thrombocytopenia
- Thrombocytosis added to mortality (OR 2.7), but there was a biphasic relationship

Thrombocytosis as prognostic factor



CHEST

Original Research

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Prina E et al. *Chest*. 2013 Mar;143(3):7

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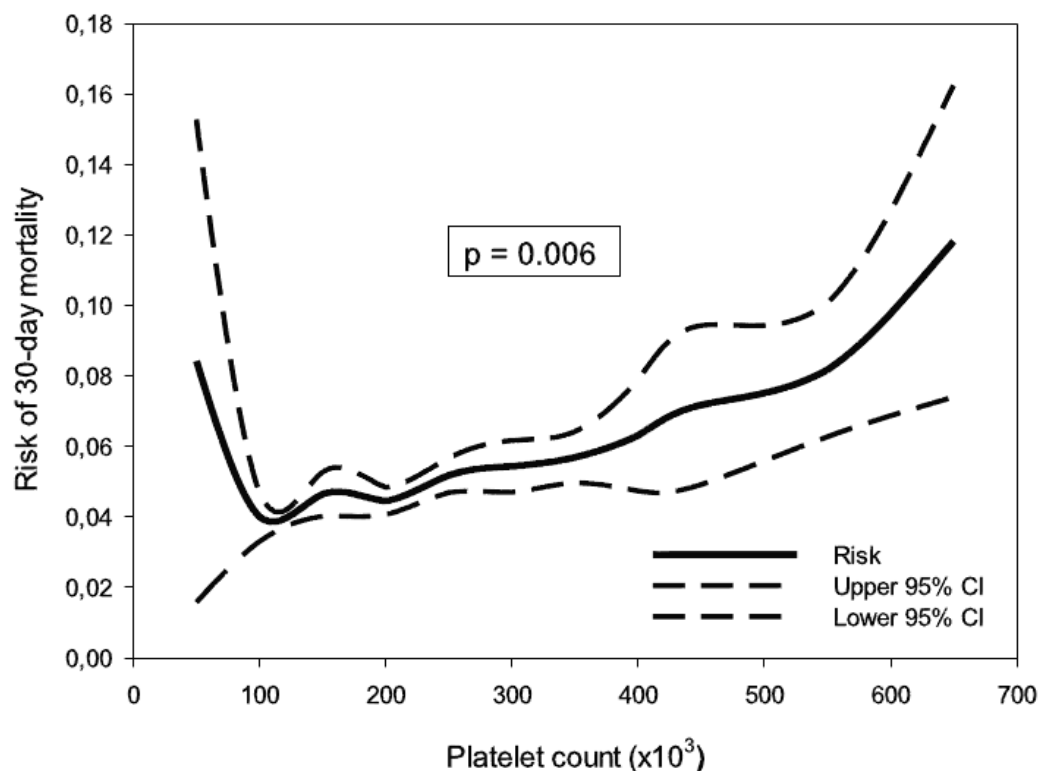


FIGURE 2. Multivariate logistic regression model to evaluate the association between platelet count as a continuous variable and mortality.

Glucose as a predictive factor...

Lepper PM *et al. BMJ.* 2012;344:e3397.

Serum glucose levels for predicting death in patients admitted to hospital for community acquired pneumonia: prospective cohort study



OPEN ACCESS

Philipp M Lepper *consultant physician*¹, Sebastian Ott *consultant physician*², Eveline Nüesch *statistician*^{3,4}, Maximilian von Eynatten *consultant physician*⁵, Christian Schumann *consultant physician*⁶, Mathias W Pletz *professor*⁷, Nicole M Mealing *statistician*^{3,4}, Tobias Welte *professor*⁸, Torsten T Bauer *professor*⁹, Norbert Suttrop *professor*¹⁰, Peter Jüni *professor*^{3,4}, Robert Bals *professor*¹, Gernot Rohde *professor*¹¹, on behalf of the German Community Acquired Pneumonia Competence Network (CAPNETZ)

Increased serum glucose level at admission without pre-existing diabetes was a predictor of death at 28 and 90 days:

- 6-10.99 mmol/L → OR 90 days mortality: 1.56 [1.22 to 2.01]
- >14 mmol/L → OR 90 days mortality: 2.37 (1.62 to 3.46)

Higher serum glucose levels were associated with increased mortality in all patients

Adding vitamin D levels to other scores

Addition of Vitamin D Status to Prognostic Scores Improves the Prediction of Outcome in Community-Acquired Pneumonia

Hilde H. F. Remmelts,^{1,2,3} Ewoudt M. W. van de Garde,^{4,5} Sabine C. A. Meijvis,¹ Evelyn L. G. C. A. Peelen,^{6,7,8} Jan G. M. C. Damoiseaux,⁹ Jan C. Grutters,^{10,11} Douwe H. Biesma,^{1,2} Willem Jan W. Bos,¹ and Ger T. Rijkers^{12,13}

¹Department of Internal Medicine, St Antonius Hospital, Nieuwegein; ²Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht; ³Department of Internal Medicine, Gelderse Vallei Hospital, Ede; ⁴Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein; ⁵Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University; ⁶School for Mental Health and Neuroscience; ⁷Department of Internal Medicine, Division of Clinical and Experimental Immunology, Maastricht University Medical Centre; ⁸Academic MS Centre Limburg, Orbis Medical Centre, Sittard; ⁹Laboratory for Clinical Immunology, Maastricht University Medical Centre; ¹⁰Department of Pulmonology, St Antonius Hospital, Nieuwegein; ¹¹Division of Heart and Lungs, University Medical Centre Utrecht; ¹²Department of Sciences, Roosevelt Academy, Middelburg, and ¹³Department of Medical Microbiology and Immunology, St Antonius Hospital, Nieuwegein, The Netherlands

Remmelts HHF *et al. Clin Infect Dis.* 2012; 55:1488-94.

- 272 hospitalized patients with CAP.
- At admission:
 - Levels of 25-hydroxyvitamin D, leukocytes, C-reactive protein, and total cortisol
 - Pneumonia Severity Index (PSI) and CURB-65 measured on admission.
- Outcomes:
 - intensive care unit (ICU) admission
 - 30-day mortality.

CAP: community acquired pneumonia

Adding vitamin D levels to other scores

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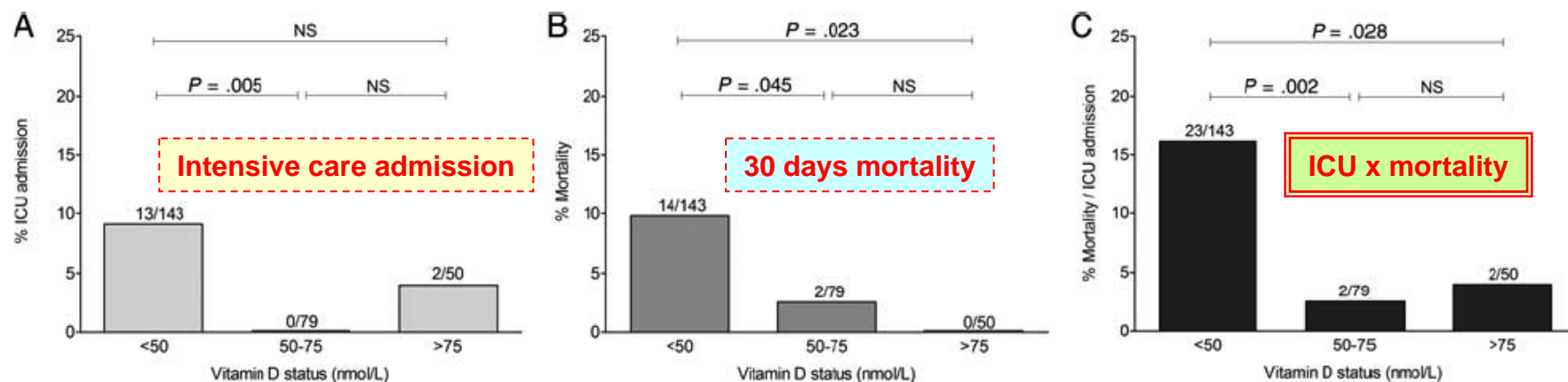


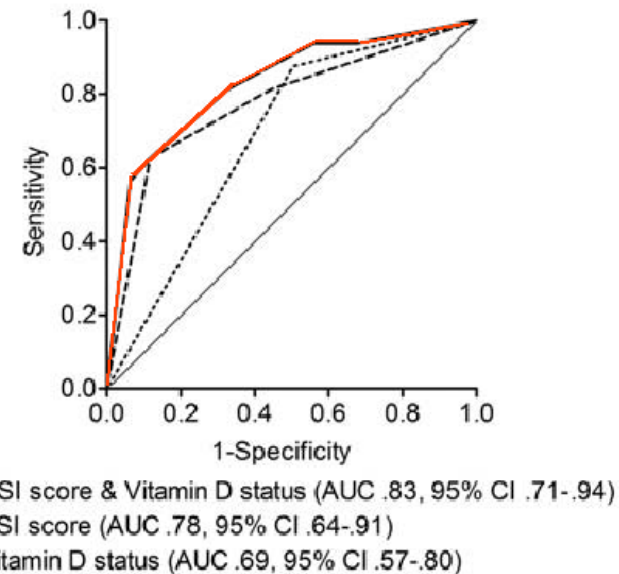
Figure 2. The rate of intensive care unit admission (A), 30-day mortality (B), and the composite endpoint mortality/ICU admission (C) stratified by serum 25-hydroxyvitamin D levels measured on presentation in patients with community-acquired pneumonia. Numbers above the bars indicate the number of patients with an adverse outcome. Abbreviations: ICU, intensive care unit; NS, not significant.

Adding vitamin D levels to other scores

Addition of Vitamin D Status to Prognostic Scores Improves the Prediction of Outcome in Community-Acquired Pneumonia

Hilde H. F. Remmelts,^{1,2,3} Ewoudt M. W. van de Garde,^{4,5} Sabine C. A. Meijvis,¹ Ev Jan G. M. C. Damoiseaux,⁹ Jan C. Grutters,^{10,11} Douwe H. Biesma,^{1,2} Willem Jan

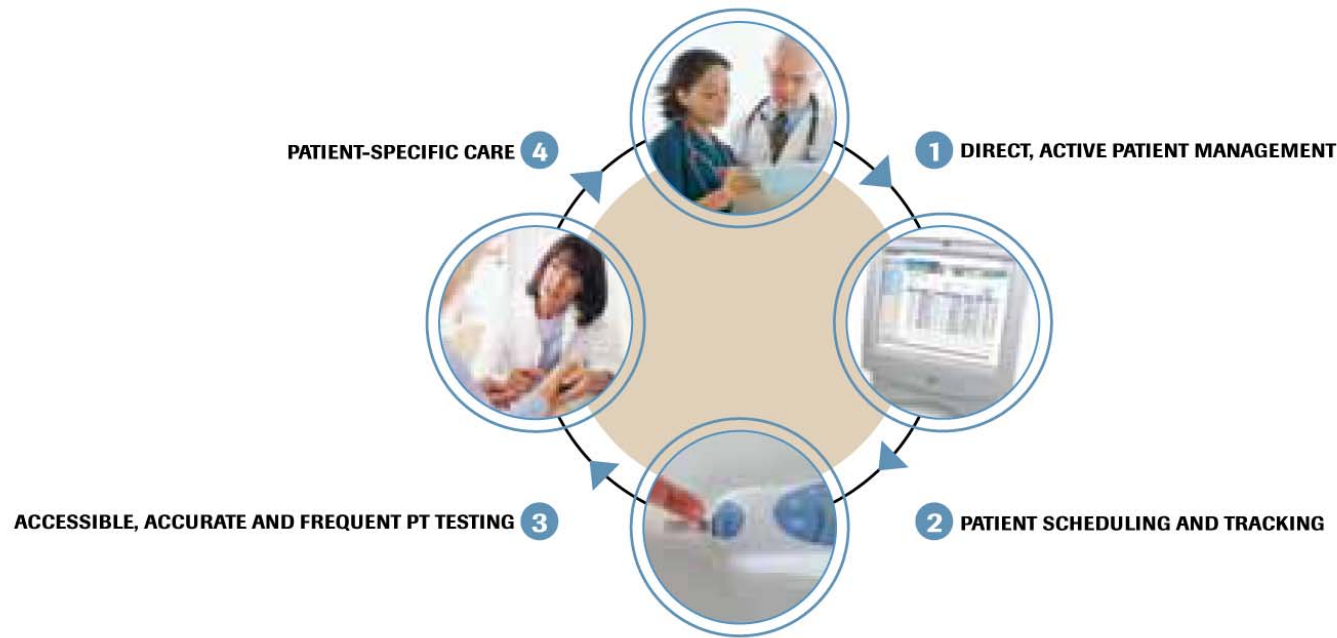
¹Department of Internal Medicine, St Antonius Hospital, Nieuwegein; ²Department of Internal Medicine, Centre Utrecht; ³Department of Internal Medicine, Gelderse Vallei Hospital, Ede; ⁴Department of Clinical Pharmacology, Utrecht University; ⁵Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University; ⁶School for Mental Internal Medicine, Division of Clinical and Experimental Immunology, Maastricht University Medical Centre, Sittard; ⁷Laboratory for Clinical Immunology, Maastricht University Medical Centre; ⁸Hospital, Nieuwegein; ⁹Division of Heart and Lungs, University Medical Centre Utrecht; ¹⁰Department of Medical Microbiology and Immunology, St Antonius Hospital, Nieuwegein, The



- Vitamin D deficiency is associated with adverse outcome in CAP.
- Vitamin D status on presentation is a significant predictor for 30-day mortality, and more specific when combined with other biomarkers or prognostic scores.
- Vitamin D supplementation might be a promising candidate for adjuvant treatment in CAP.

Figure 3. Receiver operating characteristic curve analysis of the prediction of 30-day mortality by Pneumonia Severity Index (PSI) score, vitamin D status, and the combined model "PSI score & vitamin D status." Data from day of admission are shown. Abbreviations: AUC, area under the curve; CI, confidence interval; PSI, Pneumonia Severity Index.

Improvements in diagnostics ...



<http://www.roche-diagnostics.us/PublishingImages/coagImage1.png>
accessed on 6/10/13

➤ Point of care Ultrasonography

Ultrasonographic diagnosis in children and adults

ARTICLE

JOURNAL CLUB

Prospective Evaluation of Point-of-Care Ultrasonography for the Diagnosis of Pneumonia in Children and Young Adults

Vaishali P. Shah, MD; Michael G. Tunik, MD; James W. Tsung, MD, MPH

JAMA Pediatr. 2013;167(2):119-125.

Published online December 10, 2012.

doi:10.1001/2013.jamapediatrics.107

Shah VP *et al.* *JAMA Pediatr.* 2013 Feb;167(2):119-25.

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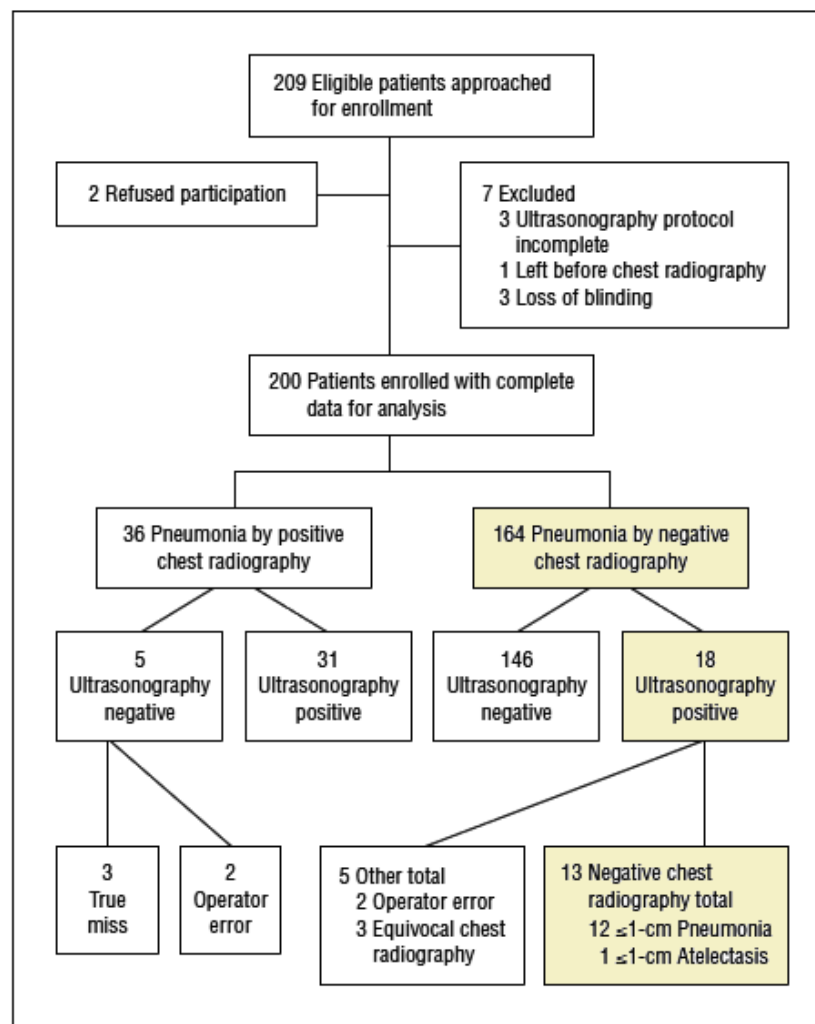


Figure 3. Standards for Reporting of Diagnostic Accuracy¹⁷ flowchart.

Ultrasonographic diagnostic in children and adults

ARTICLE

JOURNAL CLUB

Prospective Evaluation of Ultrasonography in Children and Adults

Vaishali P. Shah, MD; Michael C. ...

JAMA Pediatr. 2013;167(2):119-125.
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Shah VP et al.
JAMA Pediatr.
2013
Feb;167(2):119-125.

Video (explaining how to perform the investigation) available at
<http://archpedi.jamanetwork.com/multimediaPlayer.aspx?mediaid=4888767>
accessed on 6/10/13

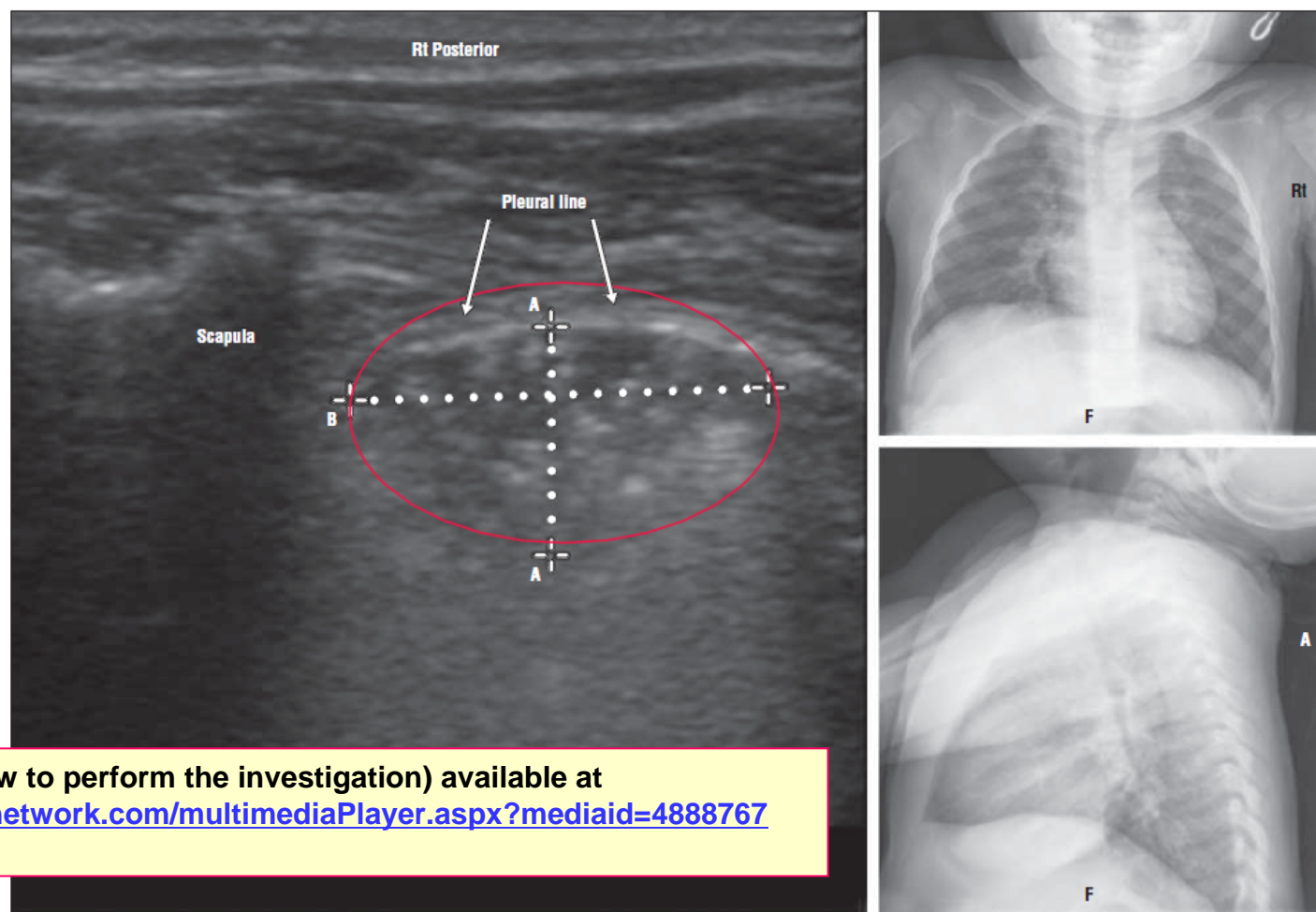


Figure 2. Lung consolidation of 1 cm or less with sonographic air bronchograms on ultrasonography not detected by chest radiography. F indicates frontal view; RT, right; and red oval, lung consolidation. A is caliper A measurement, and B is caliper B measurement.

Antibiotic combinations...

- The controversy about the necessity to add a macrolide to a β -lactam continues...



Medical controversies by Honoré Daumier (1837)

From '*Histoire de la médecine et des médecins*' by J.C. Sournia (Ed. Larousse, Paris, 1991)

Adding a macrolide in adults ?



AUDIT, RESEARCH AND GUIDELINE UPDATE

Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia

Chamira Rodrigo,¹ Tricia M McKeever,² Mark Woodhead,³ Wei Shen Lim,¹
on behalf of the British Thoracic Society

Rodrigo C *et al.* *Thorax*. 2013; 68:493-5.

- 5240 adults hospitalised with CAP from 72 secondary care trusts across England and Wales.
- The overall 30-day inpatient (IP) death rate was 24.4%.
- Combination therapy was prescribed in 3239 (61.8%) patients.

Adding a macrolide in adults ?



AUDIT, RESEARCH AND GUIDELINE UPDATE

Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia

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on behalf of the British Thoracic Society

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Table 1 Multivariate analyses of the association between antibiotic therapy and clinical outcomes

Outcome measures	Total (n=5240)	β -lactam therapy (n=2001)	β -lactam/ macrolide therapy (n=3239)	Adjusted OR (95% CI)	p Value
30 day IP death rate	1281 (24.4)	536 (26.8)	745 (23.0)	0.72 (0.60 to 0.85)*	<0.001
ICU admission	419 (8)	136 (6.8)	282 (8.7)	0.94 (0.72 to 1.22)†	0.635
Need for MV	151 (2.9)	58 (2.9)	93 (2.9)	0.99 (0.71 to 1.38)†	0.508
Need for INS	130 (2.5)	42 (2.1)	88 (2.7)	0.87 (0.55 to 1.38)†	0.544
30-day IP death rate stratified by pneumonia severity					
Low severity (CURB65=0–1)	201/2247 (8.9)	95/908 (10.5)	106/1339 (7.9)	0.80 (0.56 to 1.16)‡	0.238
Moderate severity (CURB65=2)	370/1480 (25)	171/561 (30.5)	199/919 (21.7)	0.54 (0.41 to 0.72)‡	<0.001
High severity (CURB65≥3)	710/1513 (46.9)	270/532 (50.8)	440/981 (44.9)	0.76 (0.60 to 0.96)‡	0.025

IP: in-patient - MV: mechanic ventilation – INS: intropic support – CURB65: see asbtract and Lim *et al.* *Thorax* 2003; 58:377–82

See notes in
back-up slides

Adding a macrolide in children ?

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL
ARTICLES

Comparative Effectiveness of Empiric β -Lactam Monotherapy and β -Lactam–Macrolide Combination Therapy in Children Hospitalized with Community-Acquired Pneumonia

Lilliam Ambroggio, PhD, MPH^{1,4}, Jennifer A. Taylor, PhD, MPH², Loni Philip Tabb, PhD¹, Craig J. Newschaffer, PhD¹, Alison A. Evans, ScD¹, and Samir S. Shah, MD, MSCE^{3,4,5}

Ambroggio L *et al.* *J Pediatr.* 2012;161:1097-103.

- 20743 patients hospitalized with CAP.
- 24% received b-lactam and macrolide combination therapy on admission.

Adding a macrolide in children ?

THE JOURNAL OF PEDIATRICS • WWW.

Comparative Effectiveness and β -Lactam–Macrolide Hospitalized with

Lilliam Ambroggio, PhD, MPH^{1,4}, Jennifer A.
Alison A. Evans

Ambroggio L *et al.* *J*
Pediatr. 2012;161:1097-
103.

- 20743 patients
- 24% received combination therapy

Table IV. LOS according to empiric antibiotic therapy

Antibiotic category	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI) ^{*,†,‡}
Main analysis		
Monotherapy	Reference	Reference
Combination therapy	0.91 (0.87-0.96)	0.80 (0.75-0.86)
Age category, y		
1-5	N/A	0.96 (0.86-1.06)
6-11	N/A	0.85 (0.79-0.91)
12-18	N/A	0.69 (0.49-0.98)
Monotherapy		
Aminopenicillin	Reference	Reference
Second-generation cephalosporin	1.06 (0.96-1.17)	1.01 (0.91-1.12)
Third-generation cephalosporin	1.16 (1.05-1.28)	1.03 (0.94-1.14)
Combination therapy		
Aminopenicillin + macrolide	Reference	Reference
Second-generation cephalosporin + macrolide	1.03 (0.93-1.15)	1.01 (0.90-1.13)
Third-generation cephalosporin + macrolide	0.88 (0.77-1.01)	0.91 (0.79-1.04)

See notes in
back-up slides

Adding a macrolide in children ?

THE JOURNAL OF PEDIATRICS • WWW.

Comparative Effectiveness and β -Lactam–Macrolide Hospitalized with

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Monotherapy		
Aminopenicillin	Reference	Reference

Authors' final words:

These findings suggest the need for a randomized clinical trial comparing β -lactam and macrolide therapies in treating children hospitalized with CAP to identify populations or subpopulations that may benefit from combination antibiotic therapy.

See notes in
back-up slides



New antibiotics ?



**THEME: COMBATTING ANTIBIOTIC RESISTANCE:
NEWDRUGS4BADBUGS (ND4BB)**

But for
today ...

- Ceftaroline

Is ceftaroline a useful new antibiotic for CAP ?

Diagnostic Microbiology and Infectious Disease 75 (2013) 298–303



Clinical Study

Assessment of ceftaroline fosamil in the treatment of community-acquired bacterial pneumonia due to *Streptococcus pneumoniae*: insights from two randomized trials ☆☆☆☆☆☆☆☆☆

Andrew F. Shorr^{a,*}, Marin Kollef^b, Paul B. Eckburg^c, Lily Llorens^d, H. David Friedland^d

^a Pulmonary and Critical Care Medicine, Washington Hospital Center, Rm 2A-68, 110 Irving St NW, Washington, DC 20010, USA

^b Washington University School of Medicine, St Louis, MO, USA

^c Stanford University School of Medicine, Stanford, CA, USA

^d Cerexa, Inc. (a wholly owned subsidiary of Forest Laboratories, Inc., New York, NY), Oakland, CA, USA

Shorr AF *et al.* *Diagn Microbiol Infect Dis.* 2013 Mar;75(3):298-303.

Is ceftaroline a useful new antibiotic for CAP ?



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^d Cerexa, Inc. (a wholly owned subsidiary of Forest Laboratories, Inc., New York, NY, USA)

Shorr AF *et al.* *Diagn Microbiol Infect Dis.* 2013 Mar;75(3):298-303.

Table 2

Clinical and microbiological response rates in patients with *Streptococcus pneumoniae* as a baseline pathogen in the integrated FOCUS studies (mMITTE population).

Response rates by pathogen	Ceftaroline fosamil, n/N (%)	Ceftriaxone, n/N (%)	Weighted difference, % (95% CI)
Clinical cure			
All <i>S. pneumoniae</i> (baseline isolates)	59/69 (85.5)	48/70 (68.6)	$P = 0.009$ 17.0 (2.9 to 30.7)
MDRSP	4/4 (100)	2/9 (22.2)	77.8 (N/A)
Positive by urinary antigen only	25/28 (89.3)	23/31 (74.2)	15.1 (−5.7 to 34.9)
Positive by culture ^a	34/41 (82.9)	25/39 (64.1)	18.9 (−0.7 to 37.7)
Plus atypical pathogens	8/10 (80.0)	6/9 (66.7)	13.3 (−27.3 to 51.3)
Favorable^b microbiological response			
All <i>S. pneumoniae</i> (baseline isolates)	60/69 (87.0)	51/70 (72.9)	$P = 0.0003$ 14.1 (0.6 to 27.4)
MDRSP	4/4 (100)	4/9 (44.4)	55.6 (N/A)
Positive by urinary antigen only	25/28 (89.3)	23/31 (74.2)	15.1 (−5.7 to 34.9)
Positive by culture ^a	35/41 (85.4)	28/39 (71.8)	13.5 (−4.8 to 31.8)

CI = confidence interval; MDRSP = multidrug-resistant *S. pneumoniae*, defined as *S. pneumoniae* strains resistant to ≥ 2 antimicrobial classes; mMITTE = modified microbiological intent-to-treat efficacy; N/A = not available.

^a Includes *S. pneumoniae* isolates that were identified from a respiratory or blood specimen.

^b Eradicated or presumed eradicated.

Is ceftaroline a useful new antibiotic for CAP ?

Diagnostic Microbiology and Infectious Disease 75 (2013) 298–303



Contents lists available at SciVerse ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio



The S/R EUCAST
breakpoint for
ceftriaxone is
 $\leq 0.5 / > 2$ mg/L

Clinical Study

Assessment of ceftaroline for
pneumonia due to *Streptococcus*
trials☆☆☆☆☆☆☆☆

Andrew F. Shorr^{a,*}, Marin Kollef^b

^a Pulmonary and Critical Care Medicine, Washington Hospital Center

^b Washington University School of Medicine, St Louis, MO, USA

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Shorr AF *et al.*
Diagn Microbiol
Infect Dis. 2013
Mar;75(3):298-303.

Table 3

Clinical response rates by baseline ceftaroline fosamil and ceftriaxone MIC for CABP isolates of *Streptococcus pneumoniae* in the integrated FOCUS studies (mMITTE population).

Baseline ceftriaxone MIC ($\mu\text{g/mL}$)	Total	
	Ceftaroline fosamil, n/N (%)	Ceftriaxone, n/N (%)
≤ 0.015	6/7 (85.7)	4/4 (100)
0.03	20/25 (80.0)	13/19 (68.4)
0.06	3/4 (75.0)	1/1 (100)
0.12	1/1 (100)	0/1 (0)
0.25	0	4/6 (66.7)
1	1/1 (100)	0/4 (0)
2	1/1 (100)	1/1 (100)

CABP = Community-acquired bacterial pneumonia.

What are the indications for ceftaroline * ?

1.2 Community-Acquired Bacterial Pneumonia

Teflaro is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.



4.1 Therapeutic indications

Zinforo is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- Community-acquired pneumonia (CAP)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.



Teflaro prescribing information (USA) available at:
http://www.frx.com/pi/teflaro_pi.pdf accessed on 6/10/13

* in relation to respiratory tract infections

Zinforo Summary of Product Characteristics available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002252/WC500132586.pdf accessed on 6/10/13

What are the indications for ceftaroline * ?

1.2 Community-Acquired Bacterial Pneumonia

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4.1 Therapeutic indications

Zinf ФАРМАКОЛОГИЧЕСКИЕ СВОЙСТВА

• Фармакодинамика

Cons После внутривенного введения пролекарство цефтаролина фосамил быстро превращается в активный цефтаролин.

Механизм действия

Цефтаролин – антибиотик класса цефалоспоринов с *in vitro* активностью в отношении грамположительных и грамотрицательных микроорганизмов. Бактерицидное действие цефтаролина приводит к ингибированию биосинтеза клеточной стенки бактерий, за счет связывания с пенициллинсвязывающими белками (ПСБ). Цефтаролин проявляет бактерицидную активность в отношении *Staphylococcus aureus* за счет высокой аффинности к ПСБ2а и в отношении *Streptococcus pneumoniae* из-за своего высокого сродства к ПСБ2х.



* in relation to respiratory tract infections

What are the indications for ceftaroline * ?

1.2 Community-Acquired Bacterial Pneumonia

Teflaro is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.

4.1 Therapeutic indications

ПОКАЗАНИЯ

Препарат Зинforo™ показан для лечения у взрослых следующих инфекций:

- внебольничная пневмония, вызванная чувствительными штаммами следующих грамположительных и грамотрицательных микроорганизмов: *Streptococcus pneumoniae* (включая случаи, сопровождающиеся бактериемией), *Staphylococcus aureus* (только метициллин-чувствительные штаммы), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* и *Escherichia coli*.



* in relation to respiratory tract infections

What is new about guidelines?



<http://pharmamktng.blogspot.com/2010/10/call-for-pharma-social-media.html> accessed on 6/10/13

- Do they change something in your practice?

Guidelines in paediatrics

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Influence of Hospital Guidelines on Management of Children Hospitalized With Pneumonia

Mark I. Neuman, Matt Hall, Adam L. Hersh, Thomas V. Brogan, Kavita Parikh, Jason G. Newland, Anne J. Blaschke, Derek J. Williams, Carlos G. Grijalva, Amy Tyler and Samir S. Shah

Pediatrics 2012;130:e823; originally published online October 22, 2012;
DOI: 10.1542/peds.2012-1285

Neuman MI *et al. Pediatrics.* 2012 Nov;130(5):e823-30.

43 freestanding tertiary care children's hospitals with emergency departments located in noncompeting markets of 27 states plus the District of Columbia and accounting for 15% of all pediatric hospitalizations in the United States in 2009 (677 291 of 4 508 323 admissions)



WHAT'S KNOWN ON THIS SUBJECT: There are limited data on current testing and treatment patterns for children hospitalized with pneumonia, and on whether institutional guidelines affect care.



WHAT THIS STUDY ADDS: The use of institutional clinical practice guidelines was not associated with changes in diagnostic testing, hospital length of stay, or costs for children hospitalized with pneumonia, but was associated with increased use of narrow-spectrum antibiotics.

Guidelines in paediatrics

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Pediatrics 2012;130:e823-30. originally published online October 22, 2012; DOI: 10.1542/peds.2012-0823

DOI

Neuman MI *et al.*
Pediatrics. 2012
Nov;130(5):e823-30.

Guidelines
seem not
very useful...

TABLE 3 Outcomes of Patients Based on Presence of a Pneumonia CPG

Group	Median [IQR]	P	Mean Difference (95% CI)	P ^a
Length of hospitalization, d				
No guideline	2 [1–3]	.269	Ref	
Guideline	2 [1–3]		–0.05 (–0.29 to 0.20)	.745
Total cost, index hospitalization, \$				
No guideline	10 015 [6304–15 931]	.773	Ref	
Guideline	9361 [6274–14 989]		1667 (–1747 to 5081)	.339
Total cost, episode of illness, \$				
No guideline	13 265 [6477–16 281]	.553	Ref	
Guideline	9478 [6332–15 292]		1843 (–1861 to 5547)	.329
Group	Percent (95% CI)	P	OR (95% CI)	P ^b
Readmission rate, %				
No guideline	2.3 (2.0–2.6)	.367	Ref	
Guideline	2.1 (1.7–2.5)		0.89 (0.69 to 1.14)	.396

^a P values comparing medians are unadjusted and aggregate (combining across hospitals).

^b P values are adjusted for hospital clustering.

Guidelines in paediatrics

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Influence of Hospital Guidelines on Management of Children Hospitalized With Pneumonia

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Pediatrics 2012;130:e823; originally published online October 22, 2012;

DOI: 10.1542/peds.2012-1285

But OK for penicillins...
in a few hospitals

Neuman MI
et al.
Pediatrics.
2012
Nov;130(5):e
823-30.

TABLE 5 Antimicrobial Use Based on CPG Specific Recommendations

Group	Hospitals, <i>n</i> (%)	Patients, <i>n</i>	% Received	<i>P</i> ^a	OR (95% CI)	<i>P</i> ^b
Penicillin/Aminopenicillins						
No CPG	28 (68.3)	13 265	23.9	<.0001	Ref	
CPG: recommend as first-line agent	7 (17.1)	3710	46.3		2.7 (1.4–5.5)	.005
CPG: not addressed	6 (14.6)	2735	19.8		0.8 (0.5–1.3)	.37
Macrolide (>5 y old)						
No CPG	28 (68.3)	4013	55.2	<.0001	Ref	
CPG: recommends macrolide use for children ≥5 y	10 (24.4)	1633	58.2		1.1 (0.7–1.9)	.64
CPG: no recommendation for macrolide use	3 (7.3)	286	41.3		0.6 (0.3–0.9)	.026

^a *P* values comparing differences in proportion of patients receiving antibiotics based on specific mention in the CPG are unadjusted and aggregate (combining across hospitals).

^b *P* values are adjusted for hospital clustering.

Other questions (no time to address them but ask questions ...)

- Does the new conjugated vaccine effectively cover important serotypes such as those associated with pleural effusion and non-invasive pneumococcal pneumonia
 - Yes, but bacteria "adapt" to the new situation...
- Is the administration of corticosteroids in CAP useful and safe
 - This remains disputable (and disputed...)
- Are fluoroquinolones better than macrolides in the empirical treatment of CAP
 - They probably are but with a low margin...

Back-up slides

	No of patients (column %)	No of deaths (row %)	Crude OR (95% CI)	Adjusted OR† (95% CI)
Individual serotype				
9V	191 (12.1)	10 (5.2)	0.62 (0.28 to 1.40)	0.83 (0.36 to 1.93)
7F	177 (11.2)	4 (2.3)	0.26 (0.09 to 0.79)	0.51 (0.16 to 1.59)
4	158 (10.0)	8 (5.1)	0.60 (0.25 to 1.43)	0.88 (0.36 to 2.16)
3	142 (9.0)	17 (12.9)	1.54 (0.76 to 3.12)	1.85 (0.87 to 3.93)
23F	97 (6.1)	11 (11.3)	1.44 (0.65 to 3.21)	1.23 (0.54 to 2.81)
22F	79 (5.0)	7 (8.9)	1.10 (0.44 to 2.76)	1.25 (0.48 to 3.23)
6B	78 (4.9)	15 (19.2)	2.69 (1.27 to 5.69)	2.09 (0.96 to 4.57)
6A	76 (4.8)	10 (13.1)	1.71 (0.75 to 3.92)	1.17 (0.49 to 2.75)
19A	55 (3.5)	4 (7.3)	0.89 (0.29 to 2.75)	0.69 (0.21 to 2.22)
14	209 (13.2)	17 (8.3)	1.00 (ref)	1.00 (ref)
Other	318 (20.1)	44 (13.8)	—	—
Serotype category according to CFR‡				
High	509 (32.2)	63 (12.4)	3.28 (1.89 to 5.70)	1.63 (0.89 to 2.98)
Medium	484 (30.6)	35 (7.2)	1.81 (1.00 to 3.28)	1.27 (0.67 to 2.42)
Low	412 (26.1)	17 (4.1)	1.00 (ref)*	1.00 (ref)**
Serotype category according to invasiveness§				
Low	461 (29.2)	58 (12.6)	4.21 (1.89 to 9.40)	1.67 (0.70 to 4.00)
Medium	591 (37.4)	40 (6.8)	2.13 (0.94 to 4.82)	1.19 (0.49 to 2.87)
High	212 (13.4)	7 (3.3)	1.00 (ref)*	1.00 (ref)***
PCV 13 serotypes ¶				
Yes	1277 (80.8)	107 (8.4)	0.60 (0.41 to 0.89)	0.78 (0.51 to 1.19)
No	303 (19.2)	40 (13.2)	1.00 (ref)	1.00 (ref)
Penicillin non-susceptible††				
Yes	45 (2.9)	6 (13.3)	1.52 (0.63 to 3.65)	1.07 (0.42 to 2.74)
No	1535 (97.2)	141 (9.2)	1.00 (ref)	1.00 (ref)
Erythromycin non-susceptible††				
Yes	69 (4.4)	5 (7.4)	0.75 (0.30 to 1.90)	0.83 (0.32 to 2.16)
No	1511 (95.6)	141 (9.4)	1.00 (ref)	

Significant results in bold.

p Value trend: * <0.001 , **0.09, ***0.11.

†Adjusted ORs: individual serotypes and antibiotic resistance adjusted for age, sex and Charlson Index score; grouped serotypes adjusted for age, sex, smoking, alcohol and comorbidities associated with mortality at a p value of <0.1 in univariate analyses (ie, heart disease, pulmonary disease, liver disease, renal disease and solid tumour).

‡Serotypes classified as associated with low (serotype 1, 4, 5, 7F, 8), medium (serotypes 9V, 12F, 14, 22F) and high (serotypes 3, 6A, 6B, 9N, 19A, 19F, 23F) case fatality rate in a recent meta-analysis.⁹ There were 175 patients infected with serotypes not included in this classification.

§Serotypes classified as associated with high (serotype 1, 5 and 7F), medium (serotype 4, 9V, 14 and 18C) and low (serotype 3, 6A, 6B, 8, 19F and 23F) invasiveness.^{8, 15} There were 316 patients infected with serotypes not included in this classification.

¶Serotypes included in 13-valent pneumococcal conjugate vaccine: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

††Non-susceptibility for penicillin was defined as minimal inhibitory concentration ≥ 0.12 mg/l and for erythromycin a zone diameter of ≤ 21 mm.²²

CFR, case-fatality rates; PCV, pneumococcal vaccine.

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Table 1 Multivariate analyses of the association between antibiotic therapy and clinical outcomes

Outcome measures	Total (n=5240)	β -lactam therapy (n=2001)	β -lactam/ macrolide therapy (n=3239)	Adjusted OR (95% CI)	p Value
30 day IP death rate	1281 (24.4)	536 (26.8)	745 (23.0)	0.72 (0.60 to 0.85)*	<0.001
ICU admission	419 (8)	136 (6.8)	282 (8.7)	0.94 (0.72 to 1.22)†	0.635
Need for MV	151 (2.9)	58 (2.9)	93 (2.9)	0.99 (0.71 to 1.38)†	0.508
Need for INS	130 (2.5)	42 (2.1)	88 (2.7)	0.87 (0.55 to 1.38)†	0.544
30-day IP death rate stratified by pneumonia severity					
Low severity (CURB65=0–1)	201/2247 (8.9)	95/908 (10.5)	106/1339 (7.9)	0.80 (0.56 to 1.16)‡	0.238
Moderate severity (CURB65=2)	370/1480 (25)	171/561 (30.5)	199/919 (21.7)	0.54 (0.41 to 0.72)‡	<0.001
High severity (CURB65≥3)	710/1513 (46.9)	270/532 (50.8)	440/981 (44.9)	0.76 (0.60 to 0.96)‡	0.025

Values given as n (%).

*OR adjusted for age, sex, binary variables within CURB65 excluding age (confusion, urea>7 mmol/l, respiratory rate ≥30/min, systolic blood pressure<90 mmHg or diastolic blood pressure ≤60 mmHg), individual comorbidities, intravenous antibiotic use, nursing home residency and ICU admission.

†OR adjusted for age, sex, binary variables within CURB65 excluding age (confusion, urea>7 mmol/l, respiratory rate ≥30/min, systolic blood pressure<90 mmHg or diastolic blood pressure ≤60 mmHg), individual comorbidities, intravenous antibiotic use and nursing home residency.

‡OR adjusted for sex, individual comorbidities, intravenous antibiotic use, nursing home residency and ICU admission.

ICU, intensive care unit; IP, inpatient; MV, mechanical ventilation; INS, inotropic support.

Table IV. LOS according to empiric antibiotic therapy

Antibiotic category	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI) ^{*,†,‡}
Main analysis		
Monotherapy	Reference	Reference
Combination therapy	0.91 (0.87-0.96)	0.80 (0.75-0.86)
Age category, y		
1-5	N/A	0.96 (0.86-1.06)
6-11	N/A	0.85 (0.79-0.91)
12-18	N/A	0.69 (0.49-0.98)
Monotherapy		
Aminopenicillin	Reference	Reference
Second-generation cephalosporin	1.06 (0.96-1.17)	1.01 (0.91-1.12)
Third-generation cephalosporin	1.16 (1.05-1.28)	1.03 (0.94-1.14)
Combination therapy		
Aminopenicillin + macrolide	Reference	Reference
Second-generation cephalosporin + macrolide	1.03 (0.93-1.15)	1.01 (0.90-1.13)
Third-generation cephalosporin + macrolide	0.88 (0.77-1.01)	0.91 (0.79-1.04)

*Results for main analysis were adjusted for age category, principal payer, prior hospitalization for asthma, receipt of chronic asthma therapy, systemic corticosteroid medication, β -agonist therapy, testing for arterial blood gases, intensive imaging testing, and interaction of therapy and age. The results are also stratified by age as the interaction of therapy and age was statistically significant.

†Results for monotherapy subanalysis were adjusted for age, principal payer, prior hospitalization for asthma, receipt of chronic asthma therapy, systemic corticosteroid medication, β -agonist therapy, testing for arterial blood gases, and intensive imaging testing.

‡Results for combination therapy subanalysis were adjusted for age, principal payer, prior hospitalization for asthma, receipt of chronic asthma therapy, systemic corticosteroid medication, β -agonist therapy, testing for arterial blood gases, and intensive imaging testing.