Severe Community-Acquired Pneumonia:

We don't know what we don't know

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Conflicts of Interest

- Achaogen
- Arsanis
- Bayer
- Glaxo/Smith/Kline
- KBP Biosciences
- Meiji-Seiko
- Melinta
- Merck
- Microbiotix
- Nabriva
- Pfizer
- Polyphor
- Roche/Genentech
- Shionogi
- The Medicines Co
- **IDBYDNA**
- **Accelerate Diagnostics**
- **bioMerieux**
- **Curetis**
- **GenMark**

Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide

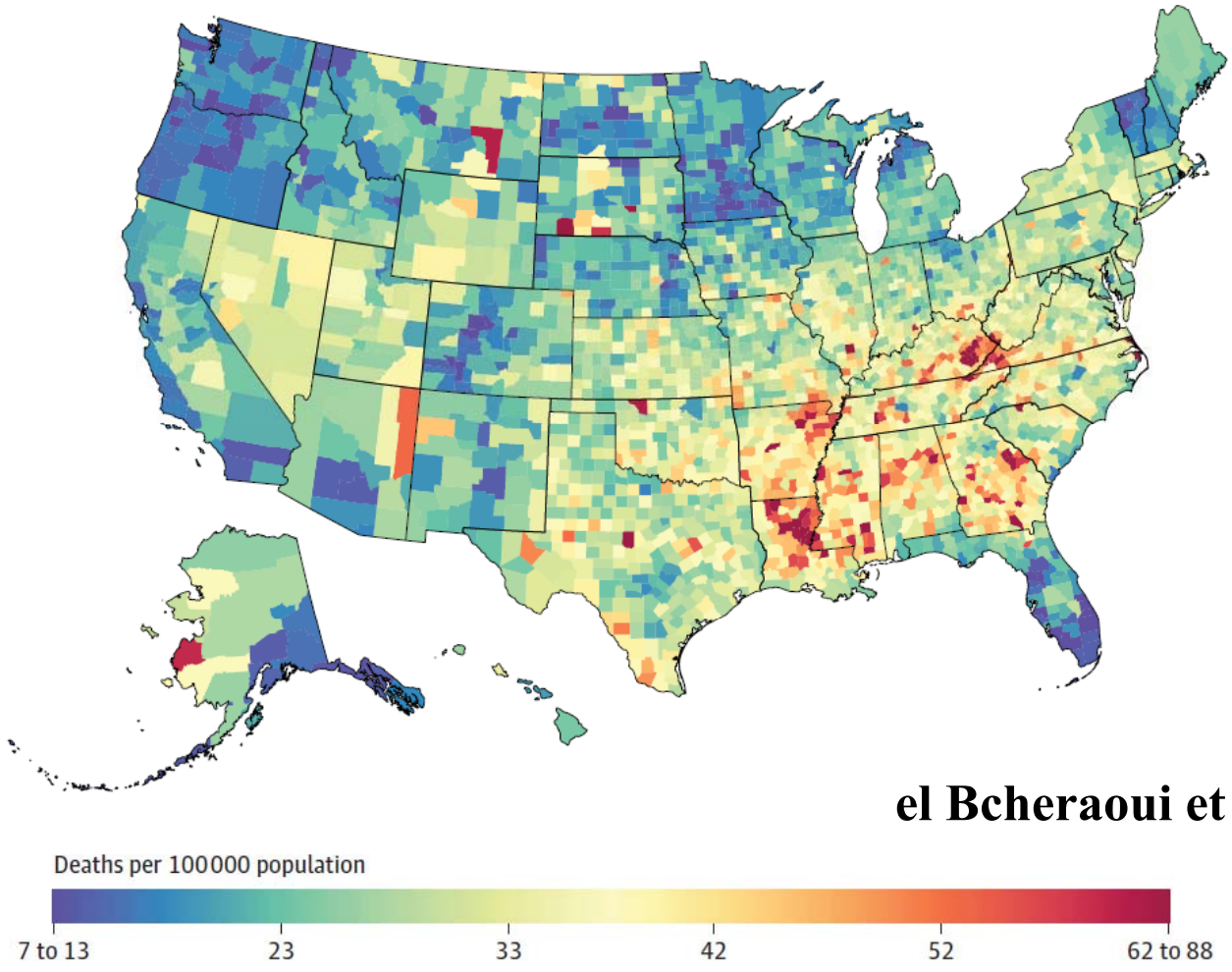
Pneumonia is the leading Cause of Infectious Deaths in US

	No. in Thousands (95% Uncertainty Interval)	
Cause of Death	Deaths	Years of Life Lost
All infectious diseases	113.65 (108.76-117.94)	1865.53 (1820.40-1932.73)
Lower respiratory infections[c]	89.88 (86.25-93.82) 79%	1221.41 (1178.72-1272.52) 65%
Diarrheal diseases[c]	8.03 (2.77-8.88)	118.31 (60.32-128.40)
HIV/AIDS[c]	7.75 (7.66-7.84)	299.13 (296.03-302.53)
Meningitis[c]	1.34 (1.28-1.41)	50.89 (48.72-53.66)
Hepatitis[c]	0.97 (0.89-1.07)	27.99 (25.53-30.69)
Tuberculosis[c]	0.85 (0.81-0.89)	17.71 (16.93-18.49)

el Bcheraoui et al, JAMA, 2018

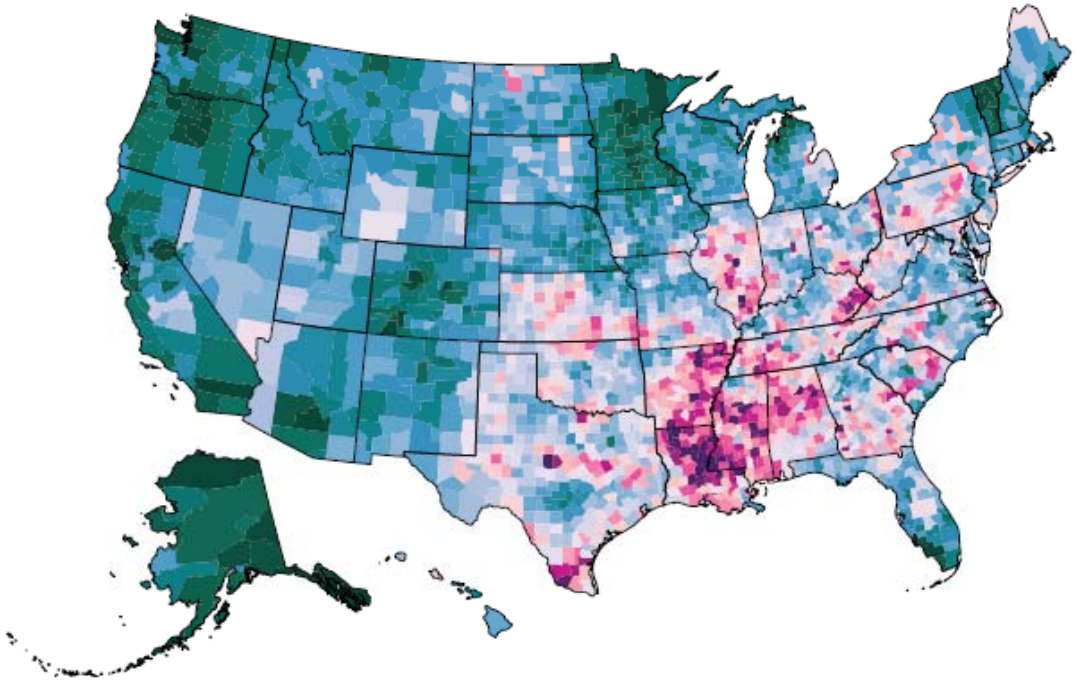
Figure 2. County-Level Mortality From Lower Respiratory Infections

A Age-standardized mortality rate from lower respiratory infections, both sexes, 2014

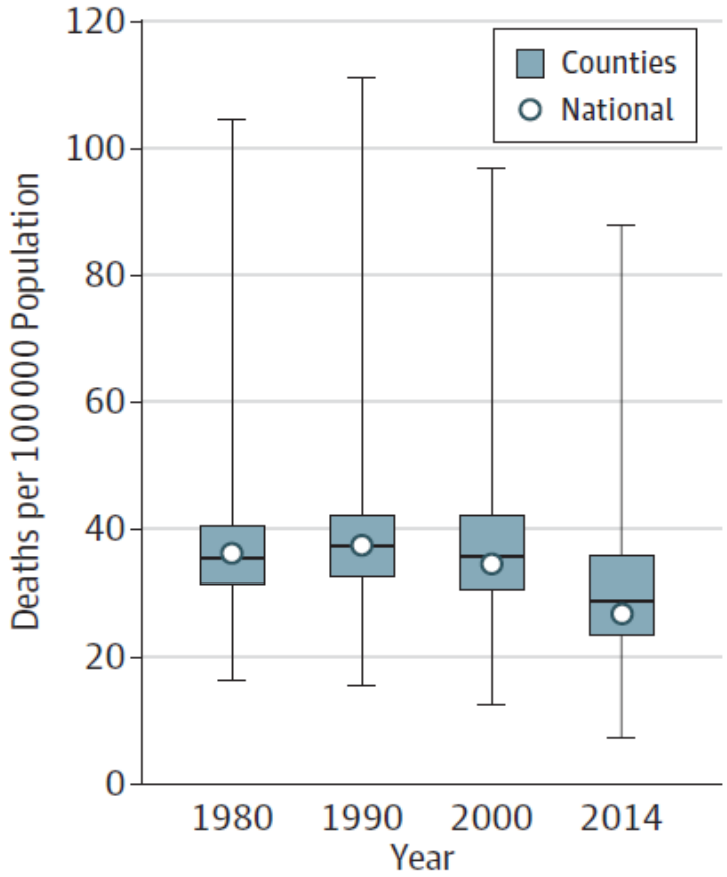


el Bcheraoui et al, JAMA, 2018

B Percent change in age-standardized mortality rate from lower respiratory infections between 1980 and 2014, both sexes



C Age-standardized mortality rate from lower respiratory infections over time, both sexes



el Bcheraoui et al, JAMA, 2018

Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
  - Probably underestimated by CDC
- CAP is a disease of health disparities and underlying co-morbidities

Clinical Infectious Diseases

MAJOR ARTICLE

Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality

Julio A. Ramirez,[1] Timothy L. Wiemken,[1] Paula Peyrani,[1] Forest W. Arnold,[1] Robert Kelley,[1] William A. Mattingly,[1] Raul Nakamatsu,[1] Senen Pena,[1] Brian E. Guinn,[1] Stephen P. Furmanek,[1] Annuradha K. Persaud,[1] Anupama Raghuram,[1] Francisco Fernandez,[1] Leslie Beavin,[1] Rahel Bosson,[1] Rafael Fernandez-Botran,[2] Rodrigo Cavallazzi,[3] Jose Bordon,[4] Claudia Valdivieso,[5] Joann Schulte,[6] and Ruth M. Carrico[1]; for the University of Louisville Pneumonia Study Group

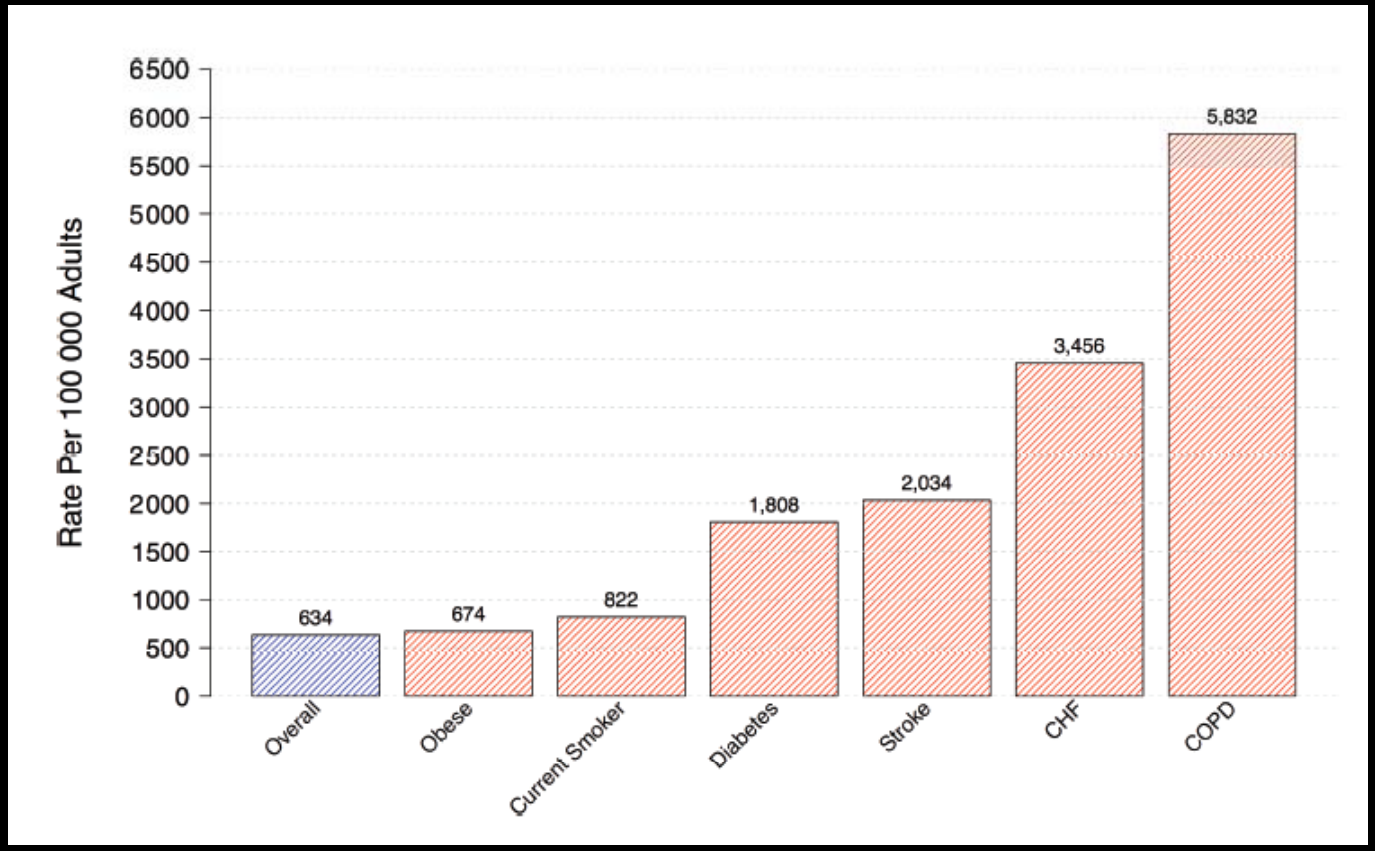
Incidence: 634/100,000 population

- **NO exclusions**
- **Recent hospitalization and immunocompromised included**

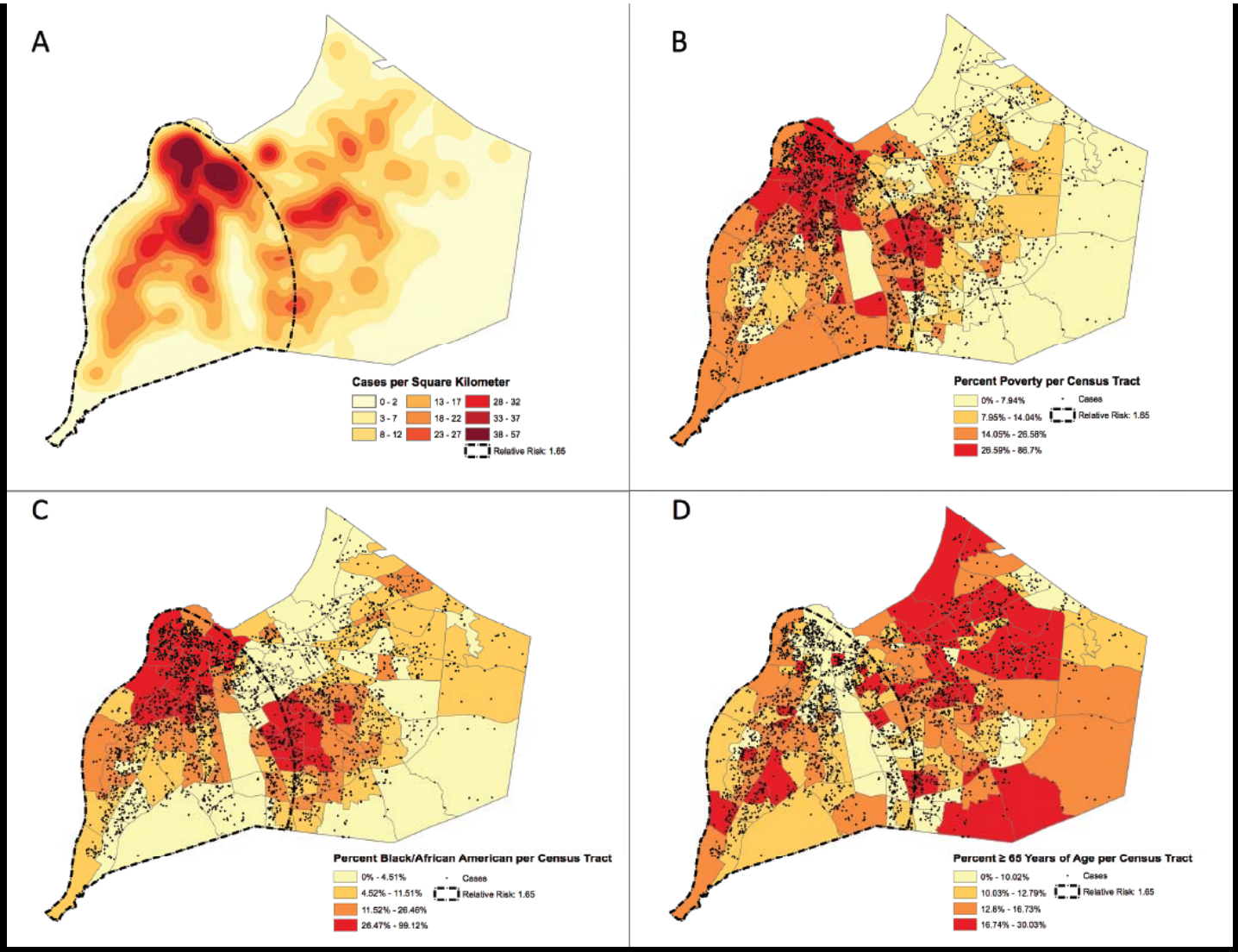
Translates into 1.5 million admissions/year in US

Second most common admission diagnosis in both adults and children – HCUP database

Impact of Comorbid Conditions



Ramirez et al, CID, 2017



Ramirez et al, CID, 2017

Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
- CAP is a disease of health disparities and underlying co-morbidities
- **Outcome of many critical illnesses, including CAP, is determined by the timely provision of appropriate antibiotic(s)**

Gattarello *et al. Critical Care* (2015) 19:335
DOI 10.1186/s13054-015-1051-1

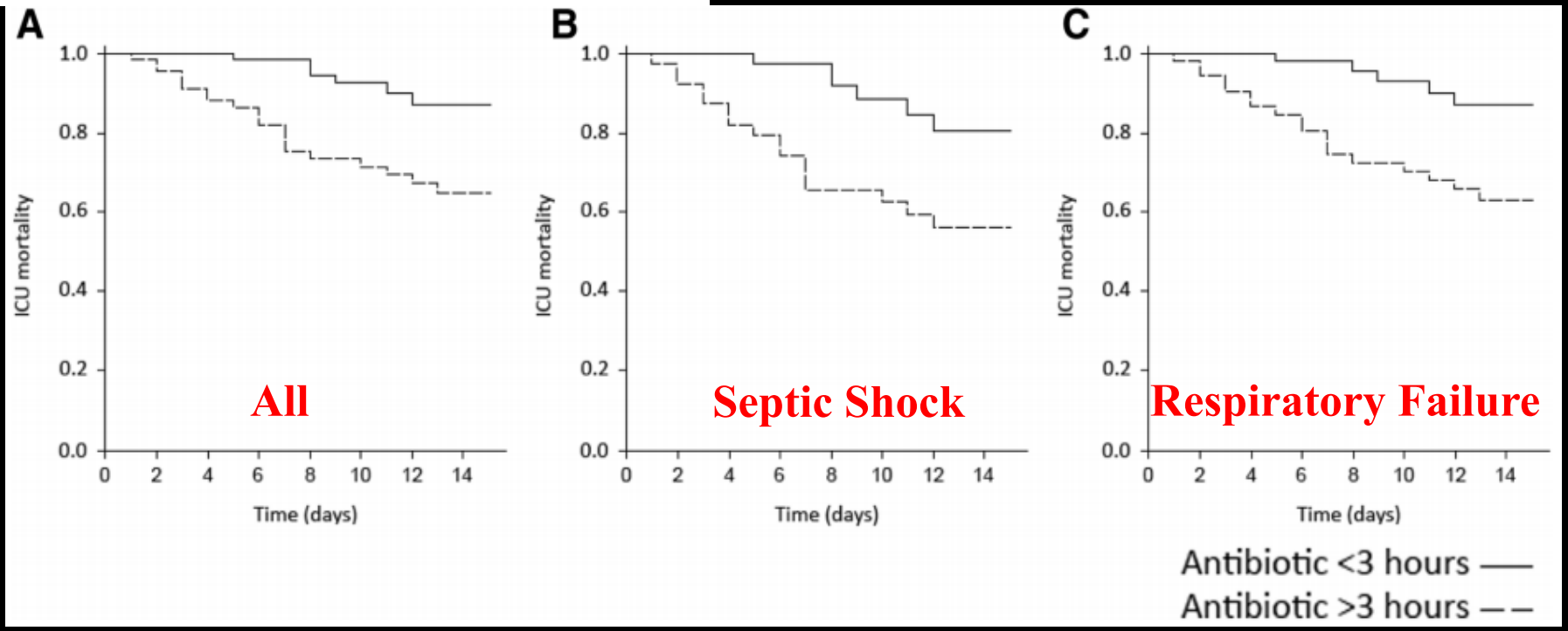
CRITICAL CARE

RESEARCH Open Access

Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case–control study

Simone Gattarello[1,2*], Leonel Lagunes[1,2], Loreto Vidaur[3,4], Jordi Solé-Violán[3,5], Rafael Zaragoza[6], Jordi Vallés[3,7], Antoni Torres[3,8], Rafael Sierra[9], Rosa Sebastian[4] and Jordi Rello[1,2,3]

***p* < 0.01 for all**



ARDS Preventive Strategies: Appropriate Antibiotics

Septic Shock

Table 2. Risk factors for development of ALI in patients with septic shock: multiple logistic regression analysis

	Odds Ratio	95% CI	*p* Value
Delayed goal-directed resuscitation	3.55	1.52–8.63	.004
Delayed antibiotics	2.39	1.06–5.59	.039
Respiratory rate (per SD)	2.03	1.38–3.08	<.001
Chemotherapy	6.47	1.99–24.9	.003
Chronic alcohol use	2.09	.88–5.10	.098
Transfusion	2.75	1.22–6.37	.016
Aspiration	3.48	1.22–10.78	.024
Diabetes mellitus	.44	.17–1.07	.076

Iscimen et al, Crit Care Med 2008;36:1518-1522

Pneumonia

Table 4 Conditional regression analysis of ALI risk factors

	OR	95% CI
PSI	1.01	1.00-1.03
Inappropriate initial antimicrobial treatment	3.1	1.5-7.0
Any transfusion	3.2	1.3-8.8
HAP	1.8	0.9-3.8

HAP, hospital-acquired pneumonia; PSI, pneumonia severity index.

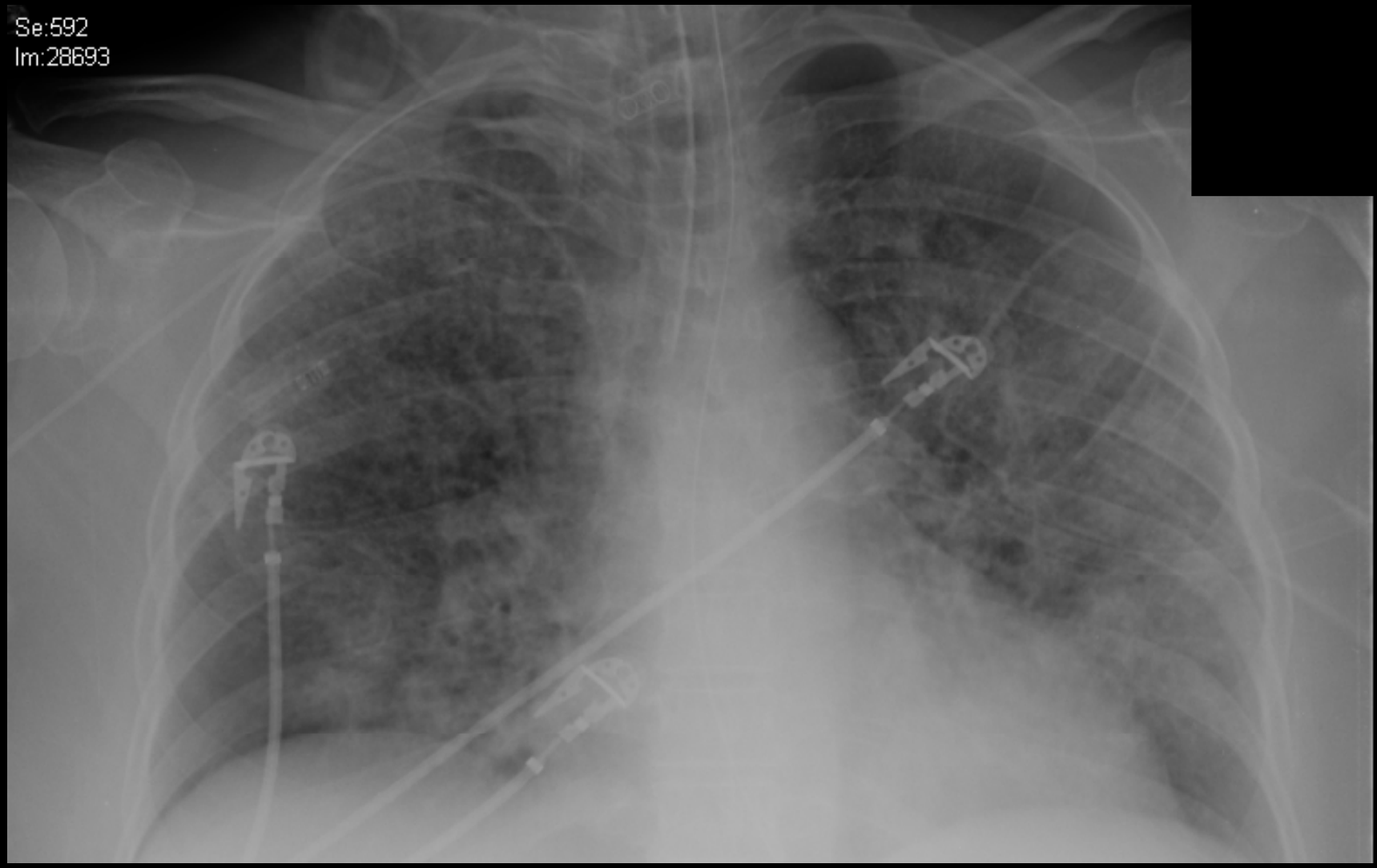
Kojicic et al Crit Care 2012;16:R46

Levitt JE and Matthay MA. Critical Care 2012;1:223

What is (are) the correct antibiotic(s), specifically for Severe CAP?

A 44 yo without prior medical history presents with cough, hemoptysis, shortness of breath and fever. He has marked increase work of breathing and is intubated. CXR demonstrates bilateral infiltrates. Preliminary laboratories demonstrate a neutrophil count of 550/uL. Your initial antibiotic therapy would be:

1. **Vancomycin and piperacillin/tazobactam**
2. **Ceftriaxone and azithromycin**
3. **Vancomycin, cefipime, and doxycycline**
4. **Moxifloxacin**
5. **Ceftriaxone, azithromycin, and linezolid**


Se:592
Im:28693
C511
W1024

SUPPLEMENT ARTICLE

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

Lionel A. Mandell,[1,a] Richard G. Wunderink,[2,a] Antonio Anzueto,[3,4] John G. Bartlett,[7] G. Douglas Campbell,[8] Nathan C. Dean,[9,10] Scott F. Dowell,[11] Thomas M. File, Jr.[12,13] Daniel M. Musher,[5,6] Michael S. Niederman,[14,15] Antonio Torres,[16] and Cynthia G. Whitney[11]

Inpatient, ICU treatment

20. A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) or a fluoroquinolone (level I evidence) (strong recommendation) (For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)
21. For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750-mg dose)

    or

    the above β-lactam plus an aminoglycoside and azithromycin

    or

    the above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam).

    (Moderate recommendation; level III evidence.)
22. For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid. (Moderate recommendation; level III evidence.)

What is the most likely reason for treatment "failure" in severe CAP?

1. Antibiotic resistance
2. Unusual pathogen
3. Exaggerated host response
4. Bacterial virulence factors
5. Genetic immunodeficiency

Journal of Critical Care 43 (2018) 183–189

Contents lists available at ScienceDirect

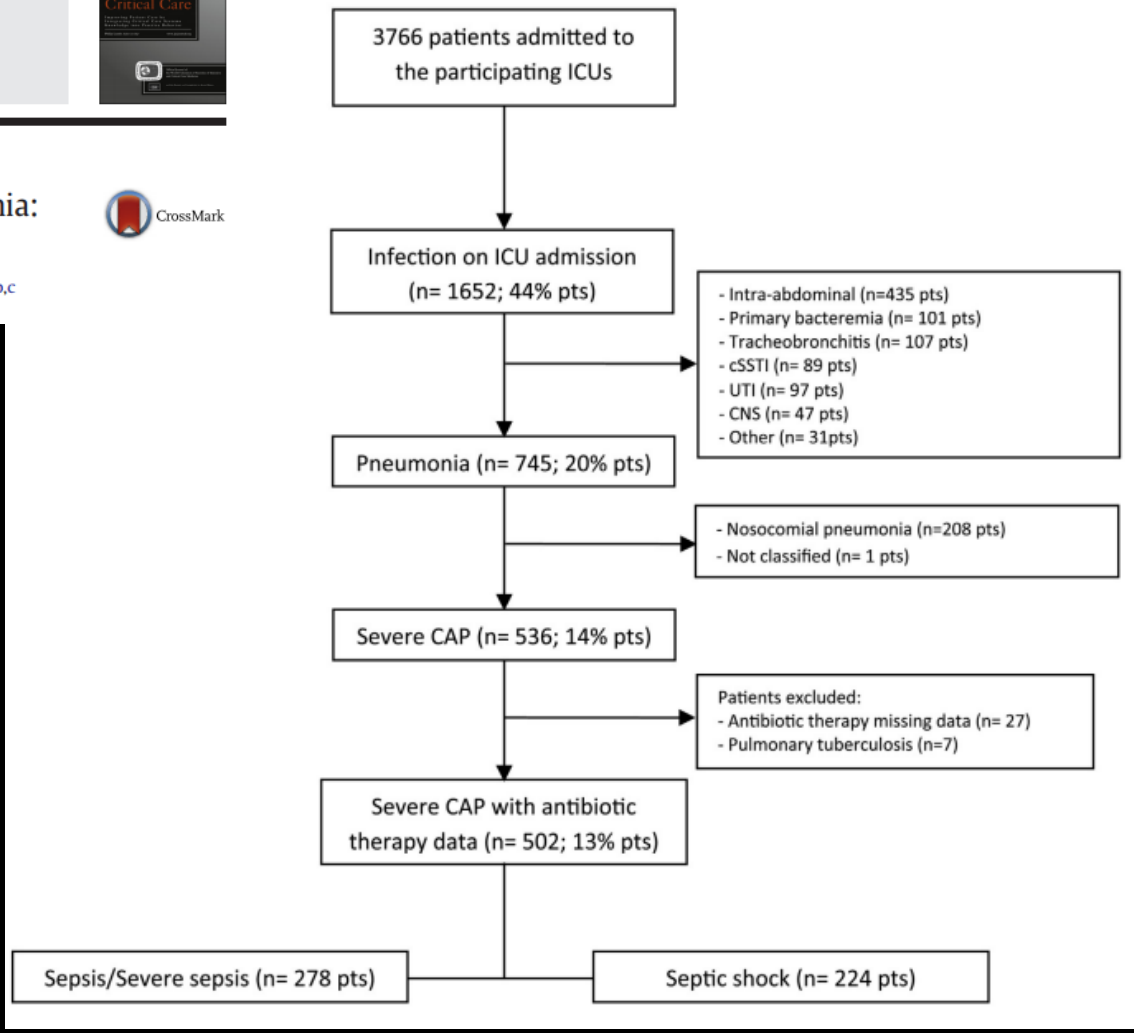
Journal of Critical Care

journal homepage: www.jccjournal.org

Impact of antibiotic therapy in severe community-acquired pneumonia: Data from the Infauci study

J.M. Pereira [a,b,c,*], J. Gonçalves-Pereira [d,h], O. Ribeiro [e], J.P. Baptista [f], F. Froes [g], J.A. Paiva [a,b,c]

- **Prospective observational cohort from 14 Portuguese ICUs over 1 year**
- **All infections at admission to the ICU**



Etiology in SCAP

Pereira et al, J Crit Care, 2018

- **Etiology in 35%**
- **Secondary bacteremia in 11%**
- **40% "immunosuppressed"**

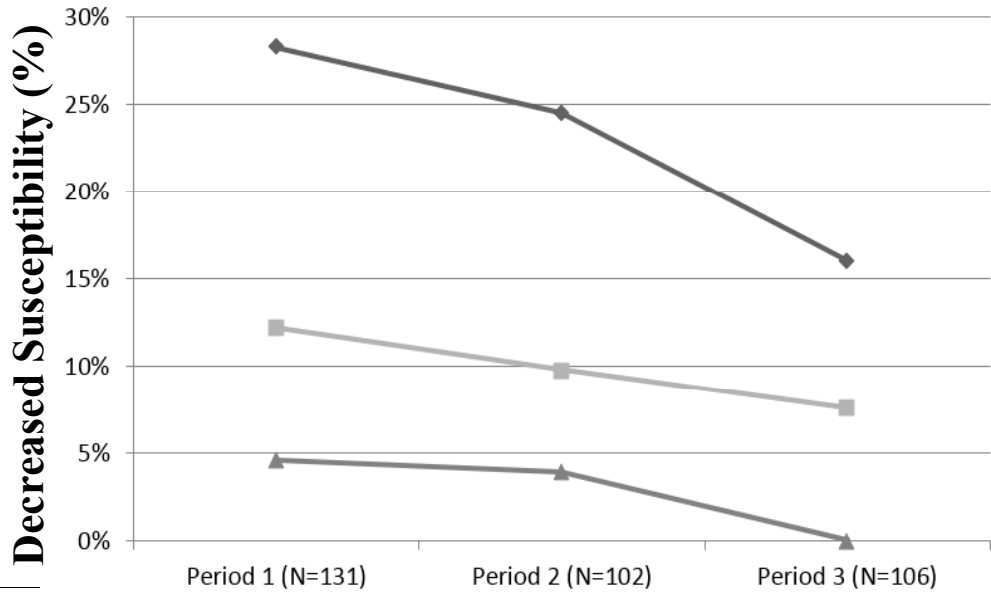
Etiology of SCAP (n = 502 episodes).

Microrganisms		n = (%)
Gram positive		79 (15.7)
	Streptococcus pneumoniae	50 (10)
	Staphylococcus aureus	28 (5.6)
	Other Streptococcus spp.	1 (0.2)
Gram negative		78 (15.5)
	Pseudomonas spp.	16 (3.2)
	E. coli	15 (3.2)
	Klebsiella spp.	12 (2.4)
	Haemophilus influenza	12 (2.4)
	Enterobacter spp.	7 (1.4)
	Proteus spp.	4 (0.8)
	Legionella pneumophila	3 (0.6)
	Acinetobacter spp.	3 (0.6)
	Serratia spp.	2 (0.4)
	Moraxella catarrhalis	2 (0.4)
	Other Gram negative	2 (0.4)
Virus		37 (7.4)
	H1N1	36 (7.2)
	Other virus	1 (0.2)
Other microrganisms		8 (1.6)

ORIGINAL

Host–pathogen interactions and prognosis of critically ill immunocompetent patients with pneumococcal pneumonia: the nationwide prospective observational STREPTOGENE study

614 Caucasian patients from 51 French ICUs
18.9% hospital mortality
NO strain was resistant to β-lactam



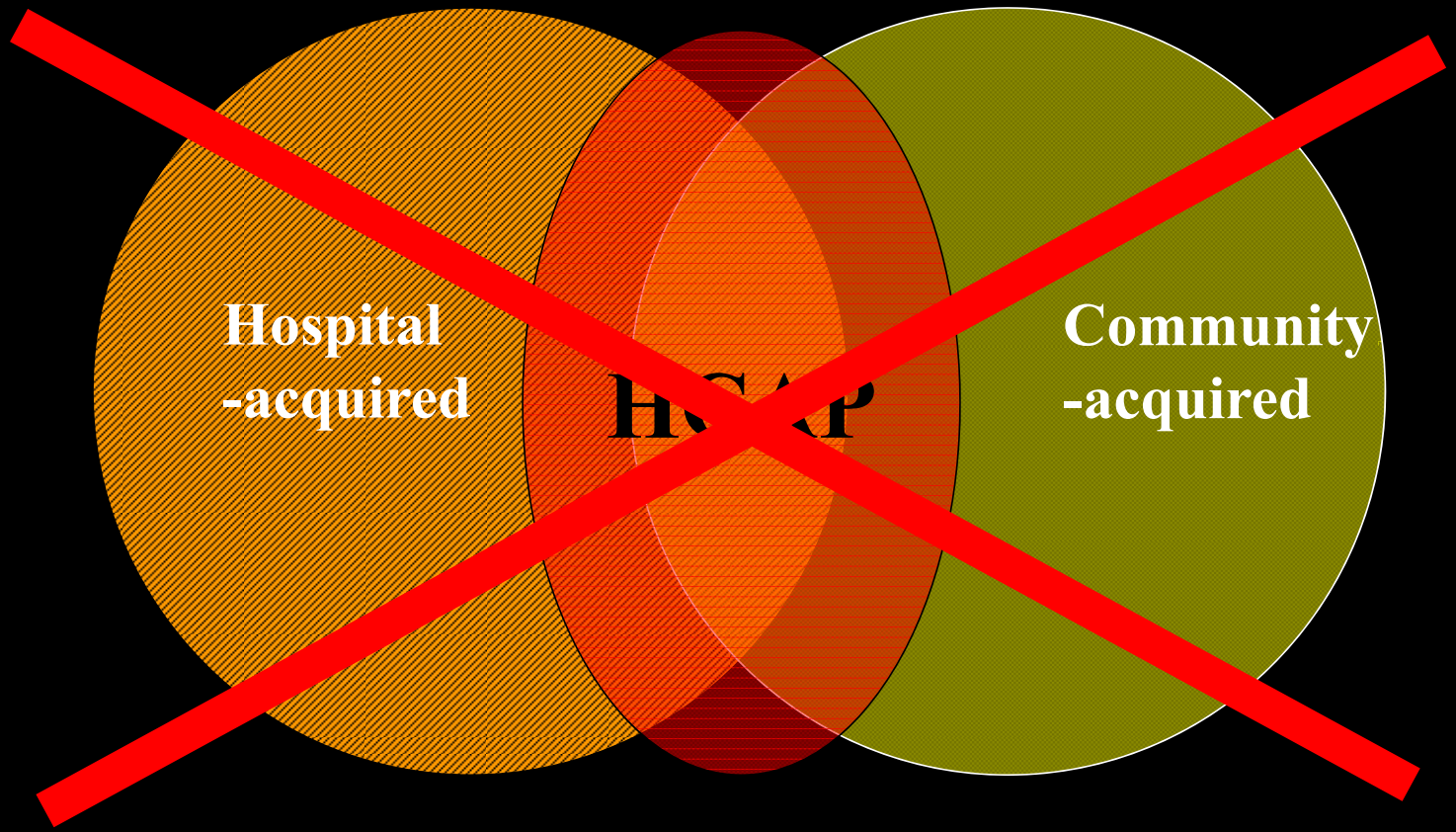
ESM 5. Hospital mortality according to antibiotic regimen

Antibiotic regimen	N patients (column %)	N deaths (row %)	Crude OR (95%CI)	Adjusted OR[a] (95%CI)
β-lactam+macrolide	223 (36.3)	45 (20.2)	1	1
β-lactam+quinolone	210 (34.2)	32 (15.2)	0.71 (0.43 to 1.17)	0.73 (0.41 to 1.31)
β-lactam only	139 (22.6)	26 (18.7)	0.91 (0.55 to 1.56)	1.25 (0.65 to 2.40)
Other	42 (6.8)	13 (31.0)	1.77 (0.85 to 3.68)	1.60 (0.62 to 4.12)

[a]Adjusted for the multivariable score predicting hospital death

Bedos et al, Intens Care Med, 2018

Healthcare-Associated Pneumonia (HCAP)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

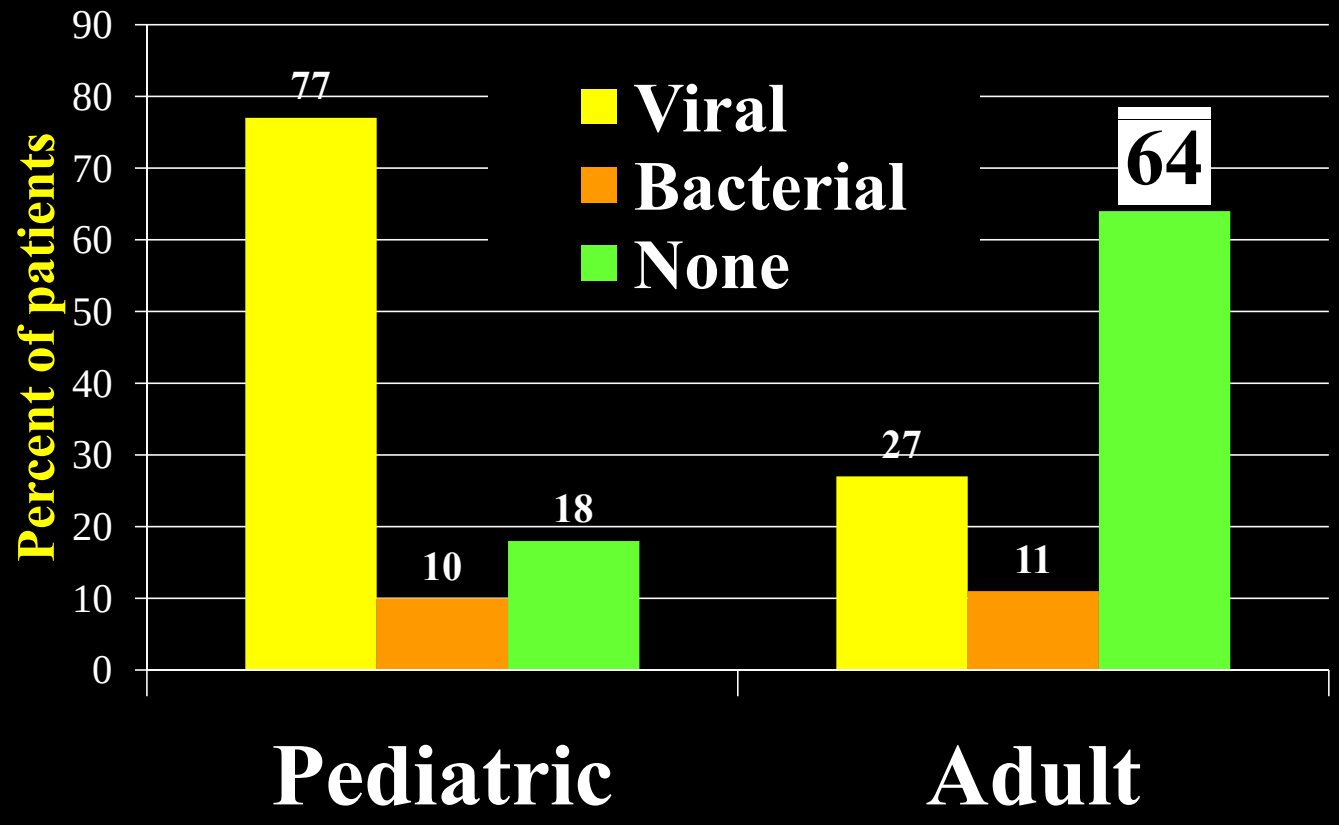
Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

S. Jain, W.H. Self, R.G. Wunderink, S. Fakhran, R. Balk, A.M. Bramley, C. Reed, C.G. Grijalva, E.J. Anderson, D.M. Courtney, J.D. Chappell, C. Qi, E.M. Hart, F. Carroll, C. Trabue, H.K. Donnelly, D.J. Williams, Y. Zhu, S.R. Arnold, K. Ampofo, G.W. Waterer, M. Levine, S. Lindstrom, J.M. Winchell, J.M. Katz, D. Erdman, E. Schneider, L.A. Hicks, J.A. McCullers, A.T. Pavia, K.M. Edwards, and L. Finelli, for the CDC EPIC Study Team*

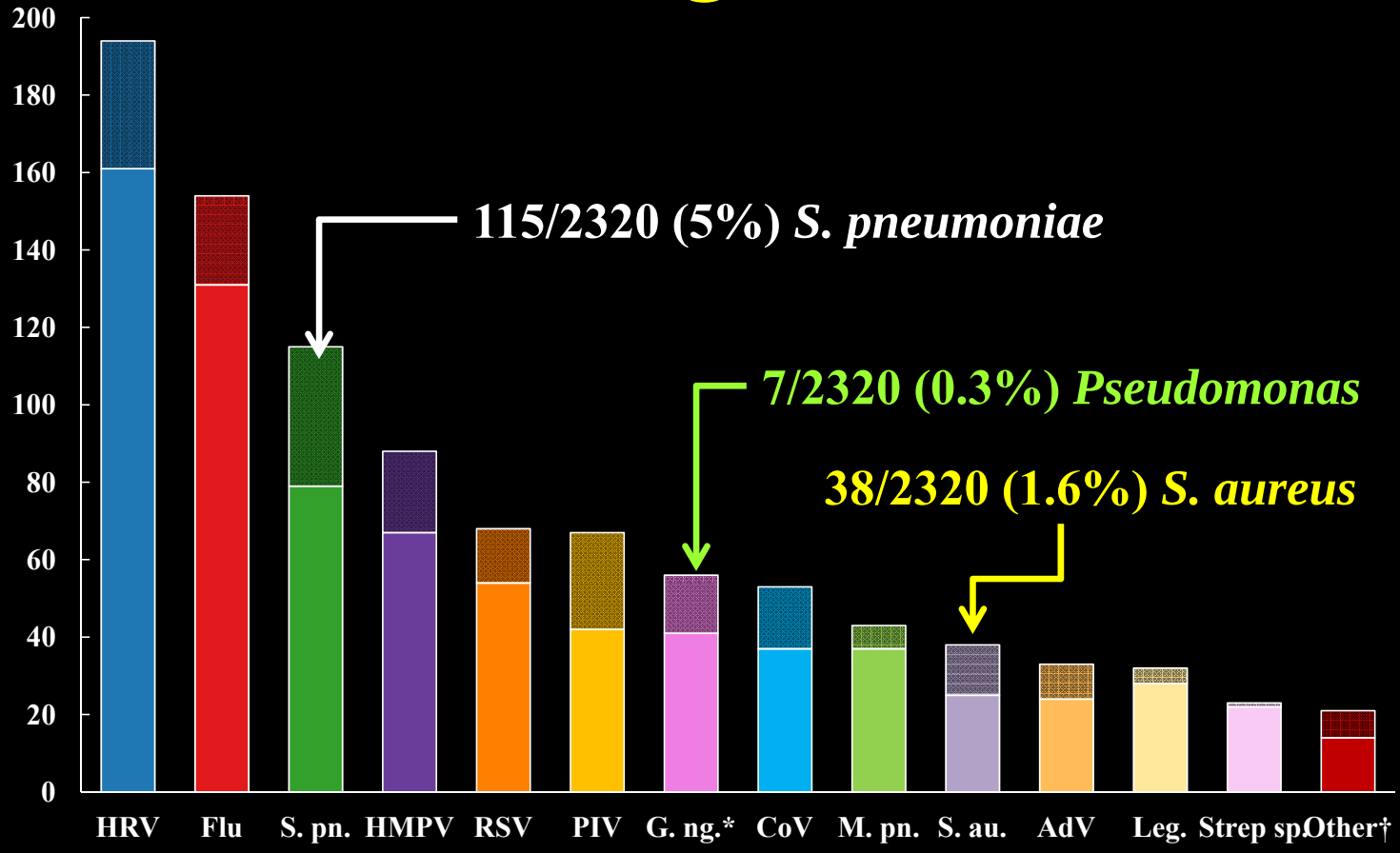
July 14, 2015

CDC-EPIC Etiology of CAP:

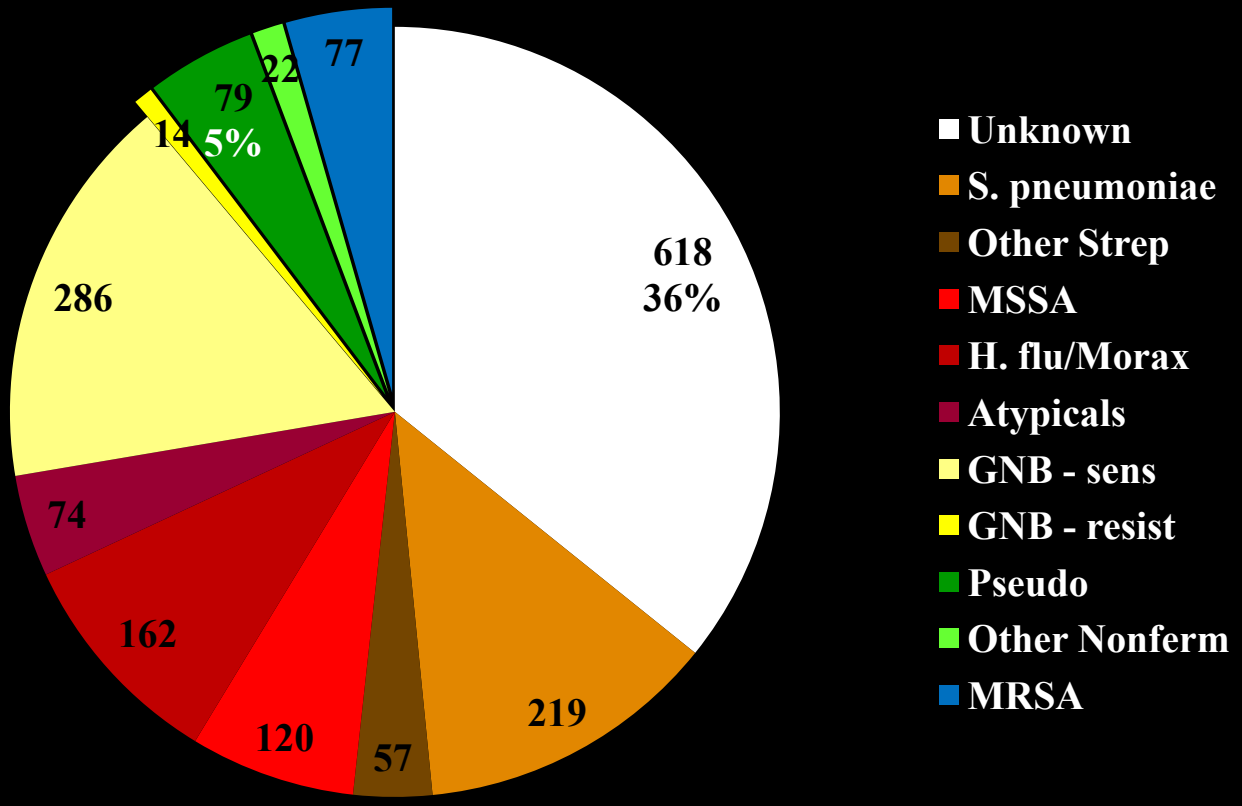
Etiology Results



EPIC – Pathogen Detections



CAP-Drug Resistant Pathogens



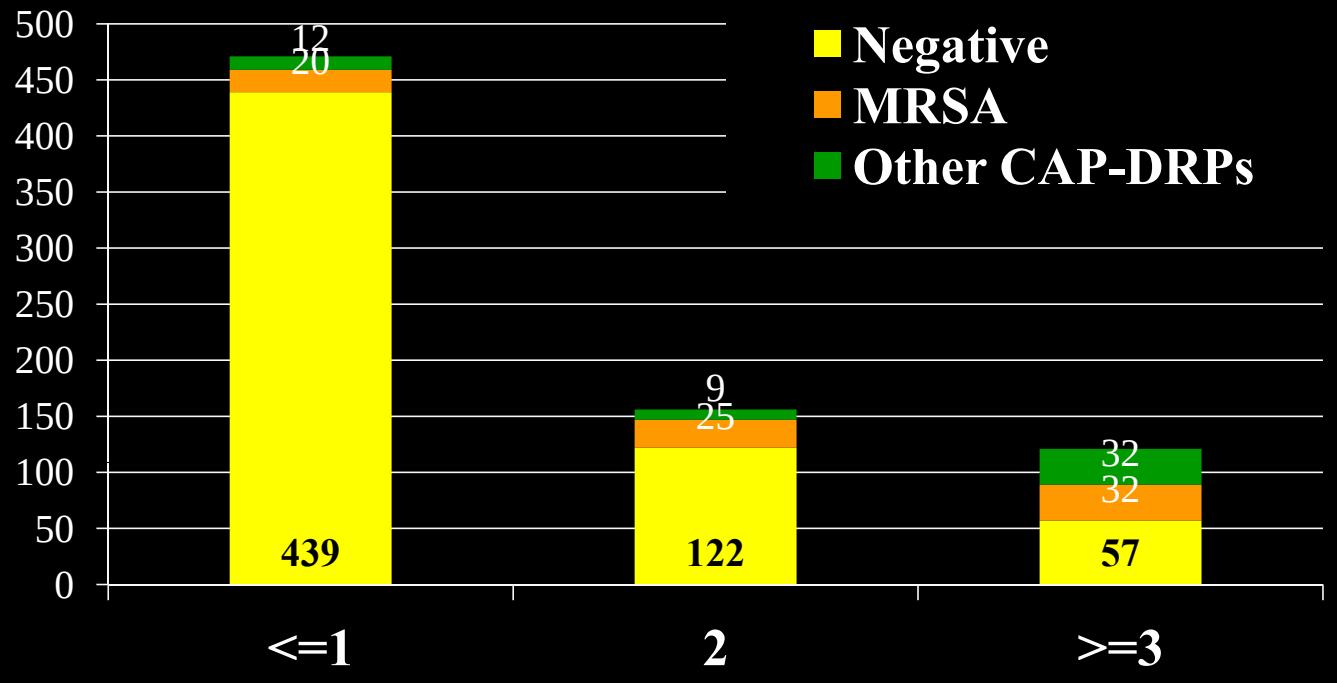
Shindo, Am J Respir Crit Care Med, 2013

Independent Risk Factors for Pneumonia Secondary to:	
CAP-DRP	**MRSA**
Hospitalization ≥ 2 days in previous 90 days	Hospitalization ≥ 2 days in previous 90 days
Use of antibiotics in previous 90 days	Use of antibiotics in previous 90 days
Immunosuppression	Chronic hemodialysis in previous 30 days*
Non-ambulatory status	Prior MRSA colonization*
Tube feedings	Congestive heart failure*
Gastric acid suppression	Gastric acid suppression

* MRSA- specific risk factors

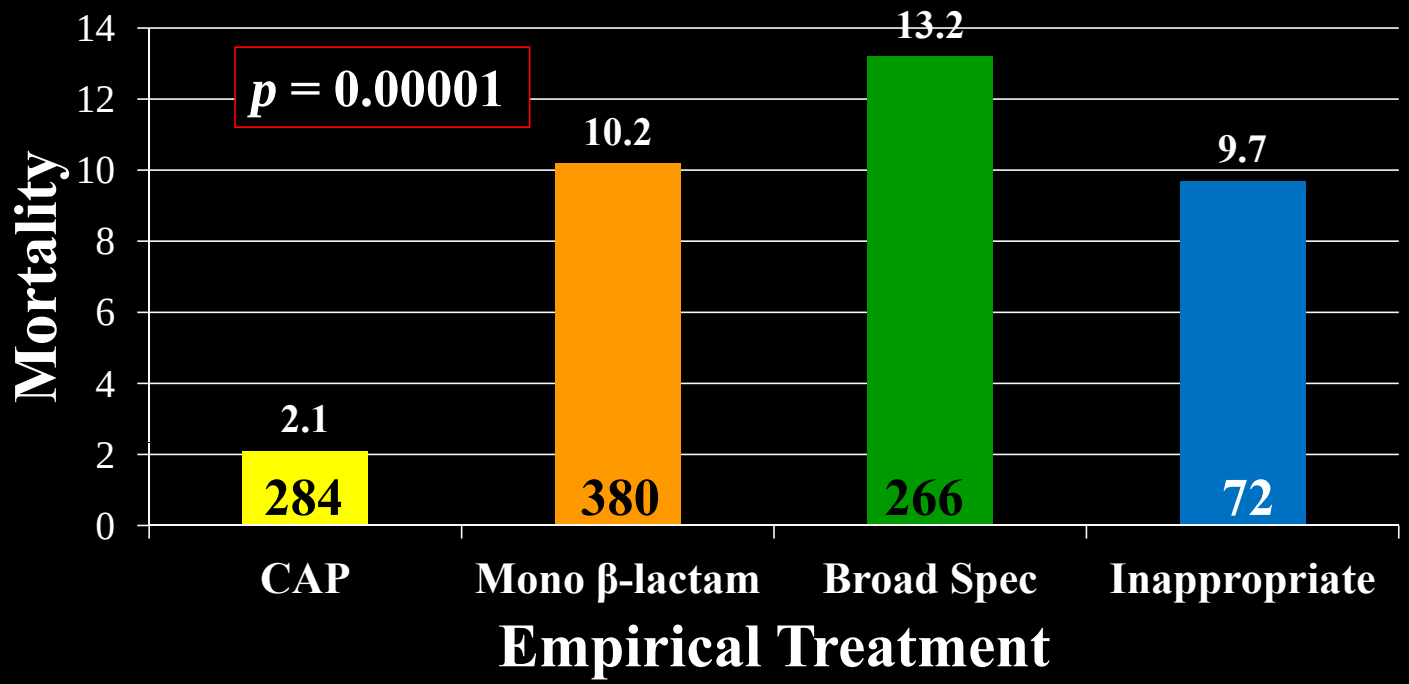
Shindo, Am J Respir Crit Care Med, 2013

Risk for CAP-Drug Resistant Pathogens



Shindo, Am J Respir Crit Care Med, 2013

Treatment Response for Patients with ≤ 1 Risk for CAP-DRPs



Shindo, Am J Respir Crit Care Med, 2013

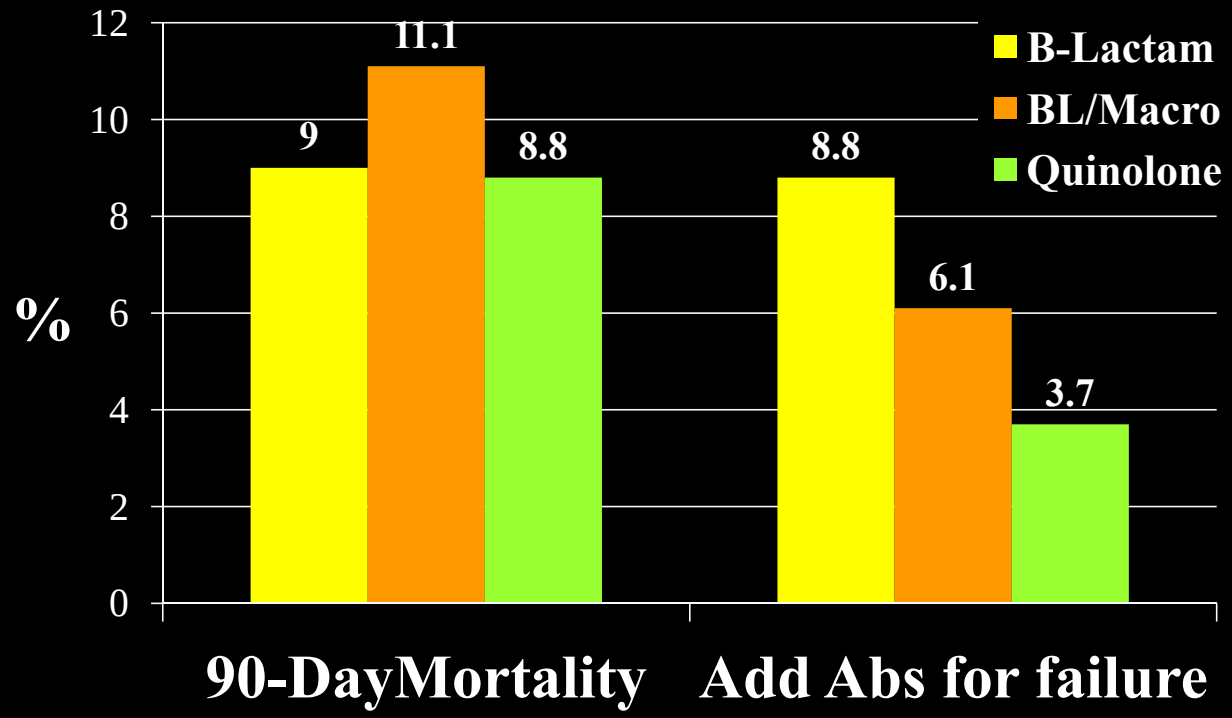
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

Douwe F. Postma, M.D., Cornelis H. van Werkhoven, M.D., Leontine J.R. van Elden, M.D., Ph.D., Steven F.T. Thijsen, M.D., Ph.D., Andy I.M. Hoepelman, M.D., Ph.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Wim G. Boersma, M.D., Ph.D., Clara J. Compaijen, M.D., Eva van der Wall, M.D., Jan M. Prins, M.D., Ph.D., Jan J. Oosterheert, M.D., Ph.D., and Marc J.M. Bonten, M.D., Ph.D., for the CAP-START Study Group*

CAP-START Endpoints



Postma et al, NEJM, 2015

Research

Original Investigation

β-Lactam Monotherapy vs β-Lactam–Macrolide Combination Treatment in Moderately Severe Community-Acquired Pneumonia

A Randomized Noninferiority Trial

Nicolas Garin, MD; Daniel Genné, MD; Sebastian Carballo, MD, DPhil; Christian Chuard, MD; Gerhardt Eich, MD; Olivier Hugli, MD, MPH; Olivier Lamy, MD; Mathieu Nendaz, MD, MHPE; Pierre-Auguste Petignat, MD; Thomas Perneger, MD, PhD; Olivier Rutschmann, MD, MPH; Laurent Seravalli, MD; Stephan Harbarth, MD, MS; Arnaud Perrier, MD

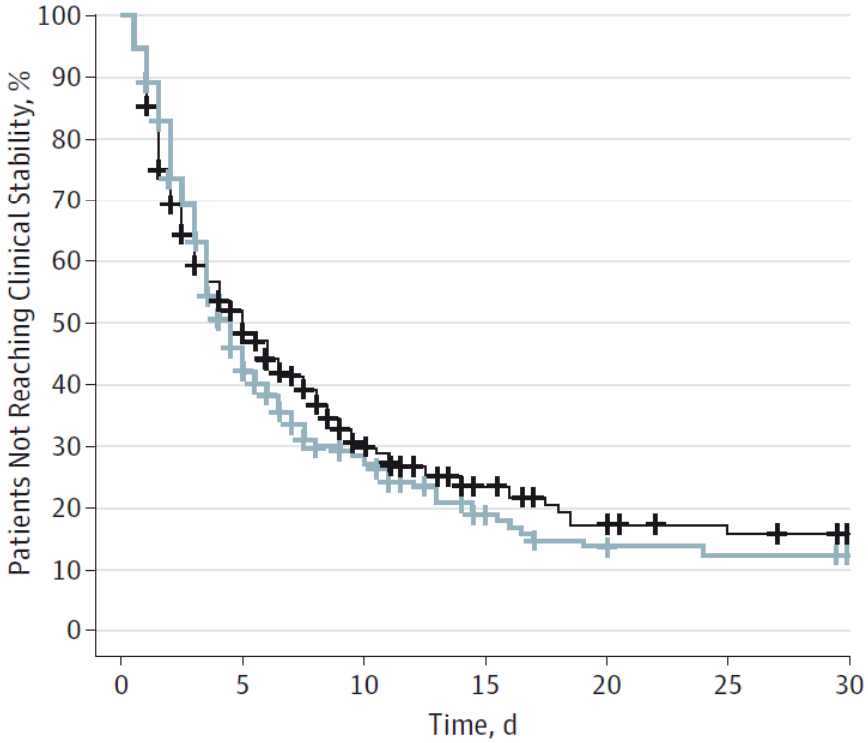
JAMA Intern Med 2014

TCS difference at 7 days – 7.6% (95%CI:-0.8 to 16, *p* = .07)

HR PSI IV = 0.81 (0.59-1.10)
HR CURB65 >2 = 0.80 (0.61-1.06)

ICU transfer: 3 (Legionella) vs. 0
Death 2 (Mycoplasma) vs. 0
Significantly more readmissions

Figure 2. Proportions of Patients Not Reaching Clinical Stability



Black line indicates monotherapy arm; blue line, combination arm. *P* = .44 (log-rank test).

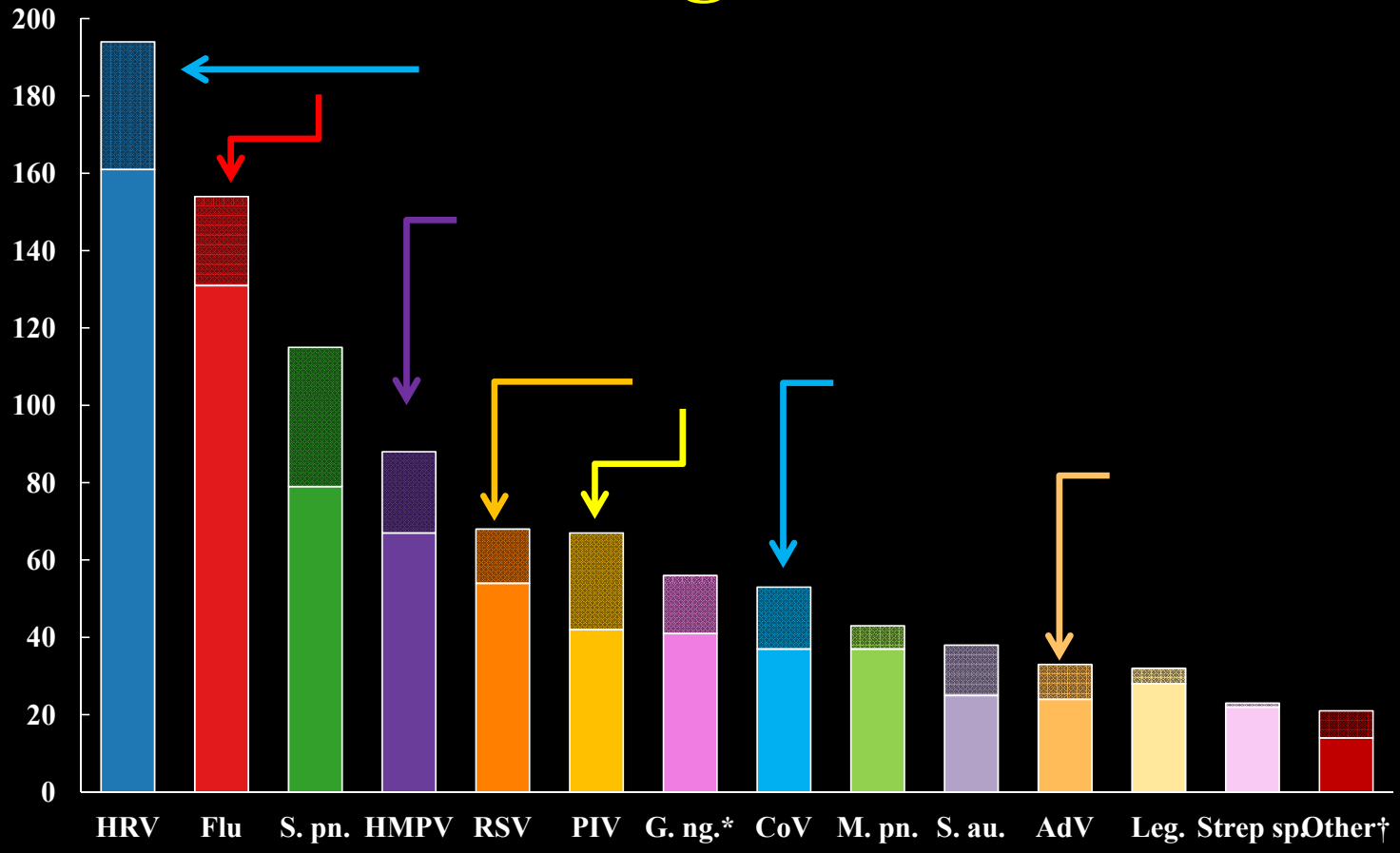
Paradigm Change:
Should have good reasons to not treat with traditional CAP drugs, even for SCAP

Paradigm Change

Viruses are a common cause of adult CAP - up to 50% in SCAP

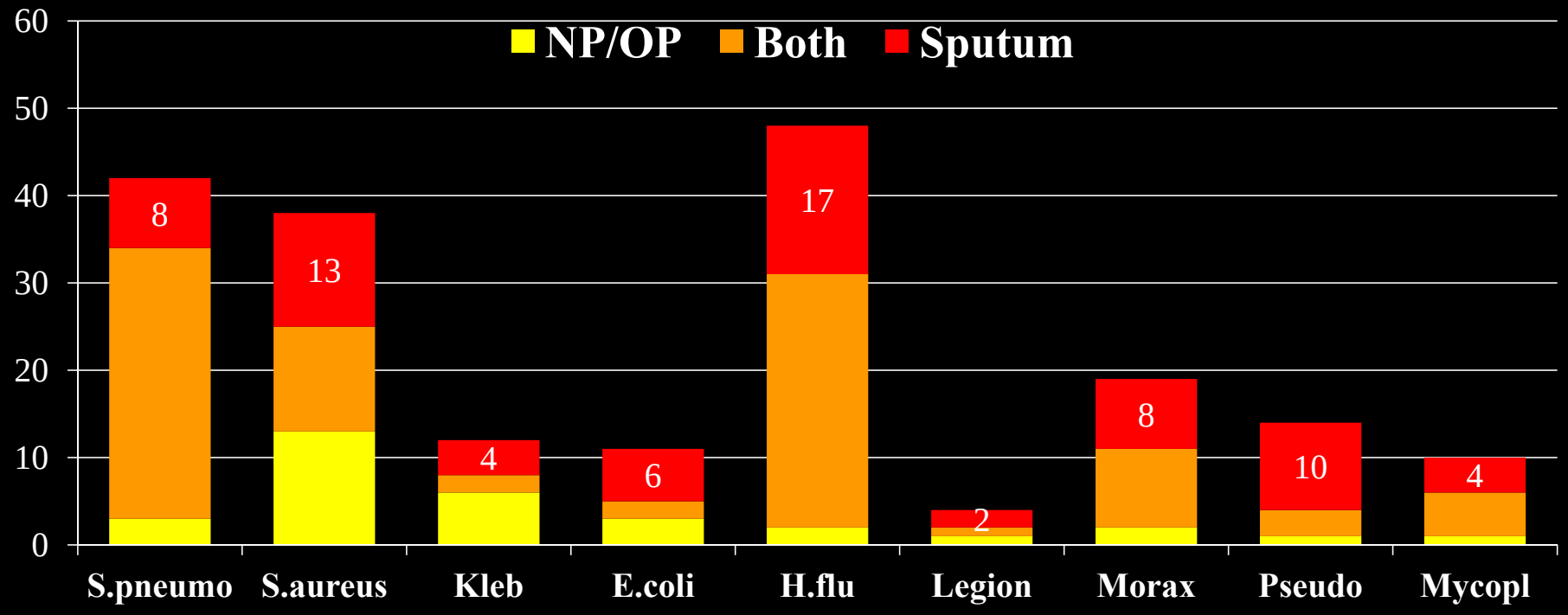
Karhu et al, CID, 2014

EPIC – Pathogen Detections



NP/OP vs. Sputum PCR

Bacteria detected by TaqMan Array PCR in otherwise negative samples



Wolff B, et al, J Clin Microbiol, 2016

What is the most likely reason for treatment "failure" in severe CAP?

~~1. Antibiotic resistance~~

2. Unusual pathogen - ?

3. Exaggerated host response

4. Bacterial virulence factors

5. Genetic immunodeficiency

FilmArray® Pneumonia Panel (Investigational Use Only)

Bacteria

Semi - Quantitative

Acinetobacter calcoaceticus-baumannii complex
Serratia marcescens
Proteus spp.
Klebsiella pneumoniae group
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Moraxella catarrhalis
Pseudomonas aeruginosa
Staphylococcus aureus
Streptococcus pneumoniae
Klebsiella oxytoca
Streptococcus pyogenes
Streptococcus agalactiae

Atypical Bacteria

Qualitative

Legionella pneumophila
Mycoplasma pneumoniae
Chlamydia pneumoniae

Viruses

Influenza A
Influenza B
Adenovirus
Coronavirus
Parainfluenza virus
Respiratory Syncytial virus
Human Rhinovirus/Enterovirus
Human Metapneumovirus
Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

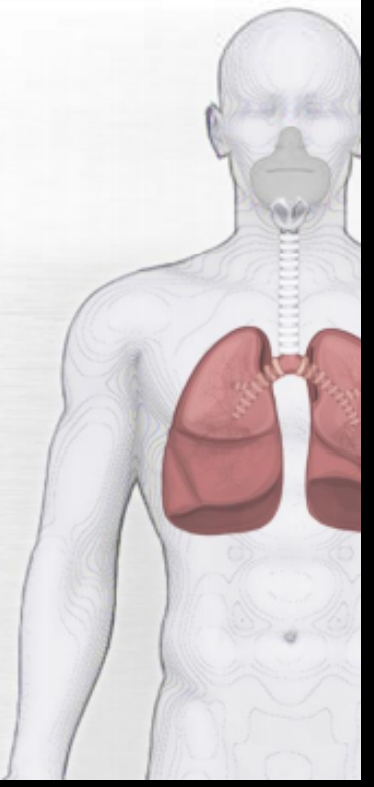
Resistance Markers

mecA/mecC and MREJ
KPC
NDM
Oxa48-like
CTX-M
VIM
IMP

Sample Types:

Sputum
- Induced
- Aspirated
- Expectorated

Bronchoalveolar Lavage
- BAL
- Mini - BAL



If not HCAP pathogens, what are resistance issues in CABP?

- **Methicillin-resistant *S. aureus* (MRSA)**
- **Macrolide-resistant *Mycoplasma pneumoniae***
- **Cephalosporin-resistant Streptococci or other "normal flora"**
  - ***S. pneumoniae* - ? Macrolide>beta-lactam>quinolone**
  - **ESBL Enterobacteriaceae**

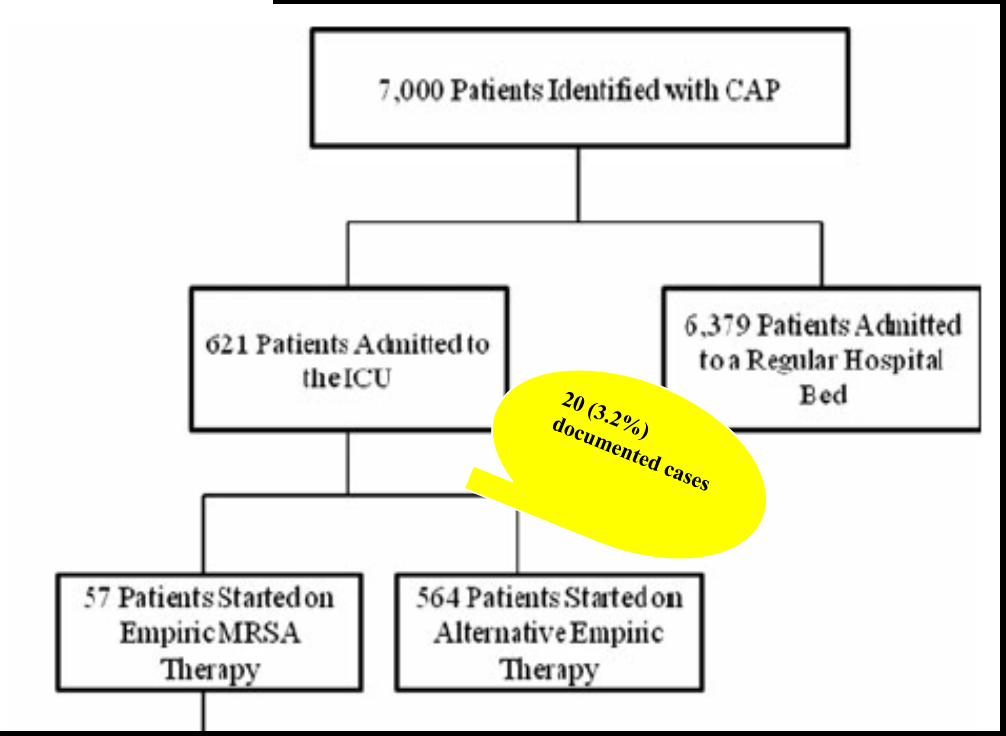
Infection (2013) 41:517–523
DOI 10.1007/s15010-012-0363-1

CLINICAL AND EPIDEMIOLOGICAL STUDY

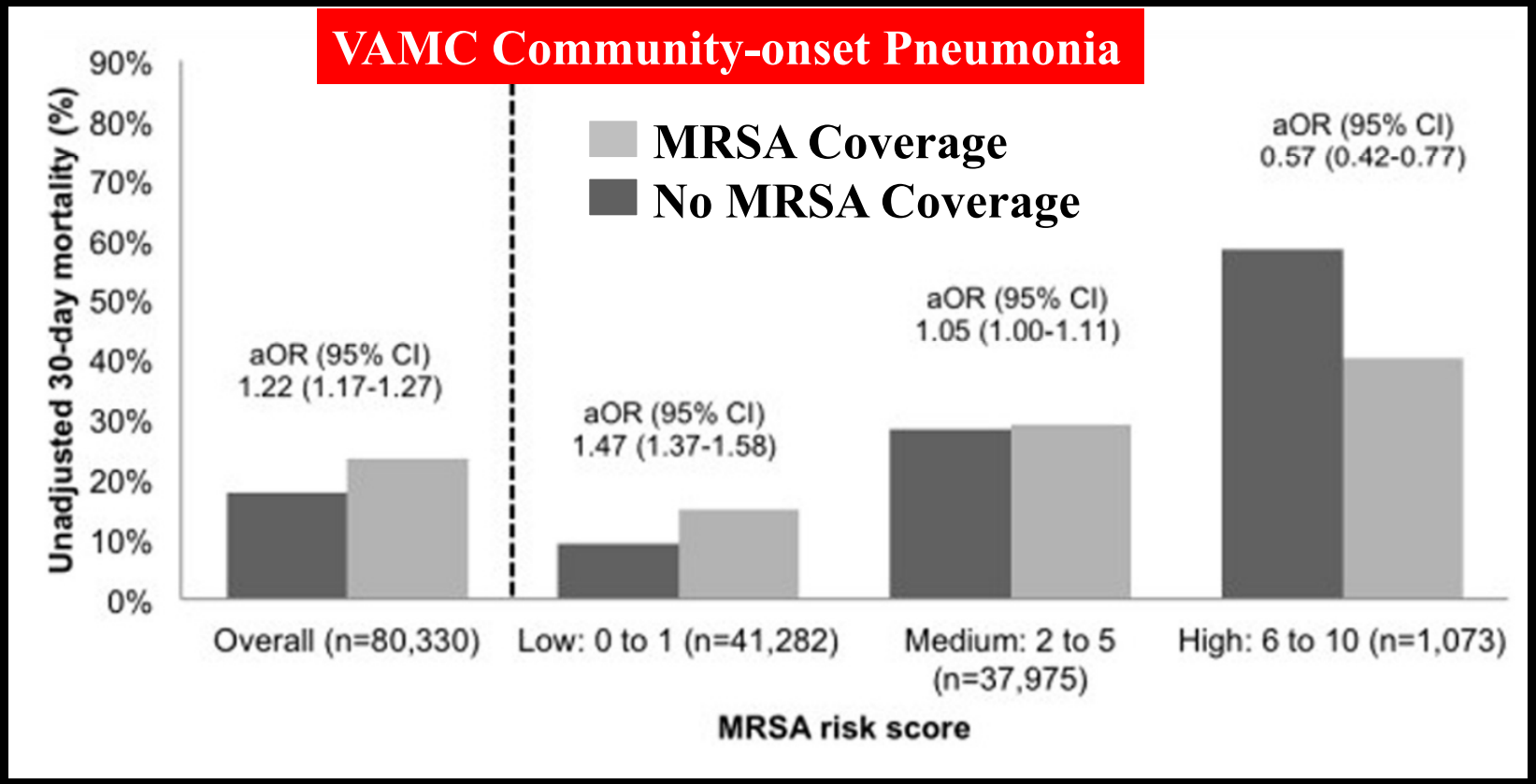
Empiric therapy directed against MRSA in patients admitted to the intensive care unit does not improve outcomes in community-acquired pneumonia

A. T. Griffin · P. Peyrani · T. L. Wiemken · J. A. Ramirez · F. W. Arnold

- No difference in hospital (25% vs. 24%) or 28-day mortality (38% vs. 43%)
- No difference in LOS
- No difference in TCS



MRSA Treatment based on Risk Factor



Teshome et al, BMC Infect Dis, 2015

Table 4. Prevalence of Previously Reported Potential Risk Factors for Methicillin-Resistant *Staphylococcus aureus* Community-Acquired Pneumonia, by Etiology Group

Characteristic	MRSA CAP, n (%) (n = 15)	Methicillin-Susceptible *Staphylococcus aureus* CAP, n (%) (n = 22)	Pneumococcal CAP, n (%) (n = 115)	*P* Value[a] (MRSA vs Pneumococcal)	All-Cause non-*Staphylococcus aureus* CAP, n (%) (n = 2222)	*P* Value[a] (MRSA vs All-Cause non-*Staphylococcus aureus*)
Hemodialysis use	3 (20.0)	2 (9.1)	3 (2.6)	0.02	82 (3.7)	0.02
Seizure disorder	1 (6.7)	1 (4.6)	4 (3.5)	0.46	85 (3.8)	0.45
Diabetes mellitus	7 (46.7)	8 (36.4)	23 (20.0)	0.04	569 (25.6)	0.08
Recurrent soft tissue infections	1 (6.7)	4 (18.2)	9 (7.8)	1.00	145 (6.5)	1.00
Hemoptysis	2 (13.3)	3 (13.6)	13 (11.3)	0.68	192 (8.6)	0.38
Daily alcohol use	1 (6.7)	3 (13.6)	11 (9.6)	1.00	156 (7.0)	1.00
Multilobar or cavitary infiltrates	5 (33.3)	7 (31.8)	39 (33.9)	1.00	667 (30.0)	0.78
Pleural effusion	4 (26.7)	5 (22.7)	41 (35.7)	0.58	687 (30.9)	1.00
Concurrent influenza infection	1 (6.7)	2 (9.1)	4 (3.5)	0.46	129 (5.8)	0.59
Current proton pump inhibitor use prior to admission	5 (33.3)	5 (22.7)	18 (15.6)	0.14	505 (22.7)	0.35
Outpatient antibiotic use prior to admission	2 (13.3)	0	15 (13.0)	1.00	440 (19.8)	0.75

Self W, et al, Clin Infect Dis, 2016

Table 3. Clinical Features Suggesting Community-Acquired MRSA Pneumonia.*

Cavitary infiltrate or necrosis
Rapidly increasing pleural effusion
Gross hemoptysis (not just blood-streaked)
Concurrent influenza
Neutropenia
Erythematous rash
Skin pustules
Young, previously healthy patient
Severe pneumonia during summer months

Wunderink RG, Waterer GW. N Engl J Med 2014;370:543-551.

The NEW ENGLAND JOURNAL of MEDICINE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Lung 1.5 B60s
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Gross Findings: The Lung

Validation of BAL MRSA Rapid Diagnostic Test

MRSA/SA SSTI Assay for Cepheid Xpert® platform

MRSA		Growth in Culture		
		Yes	No	Total
A-PCR Positive	Yes	22	4	26
	No	1*	220	221
	Total	23	224	247

MSSA		Growth in Culture		
		Yes	No	Total
A-PCR Positive	Yes	24	20	44
	No	1	173	174
	Total	25	193	218

* Growth 100 cfu/ml in culture, clinically thought negative and no treatment

MRSA Negative Predictive Value – 99.6%, Negative LR – 0.04

What is the most likely reason for treatment "failure" in severe CAP?

~~1. Antibiotic resistance~~

2. Unusual pathogen - ?

3. Exaggerated host response

4. Bacterial virulence factors

5. Genetic immunodeficiency

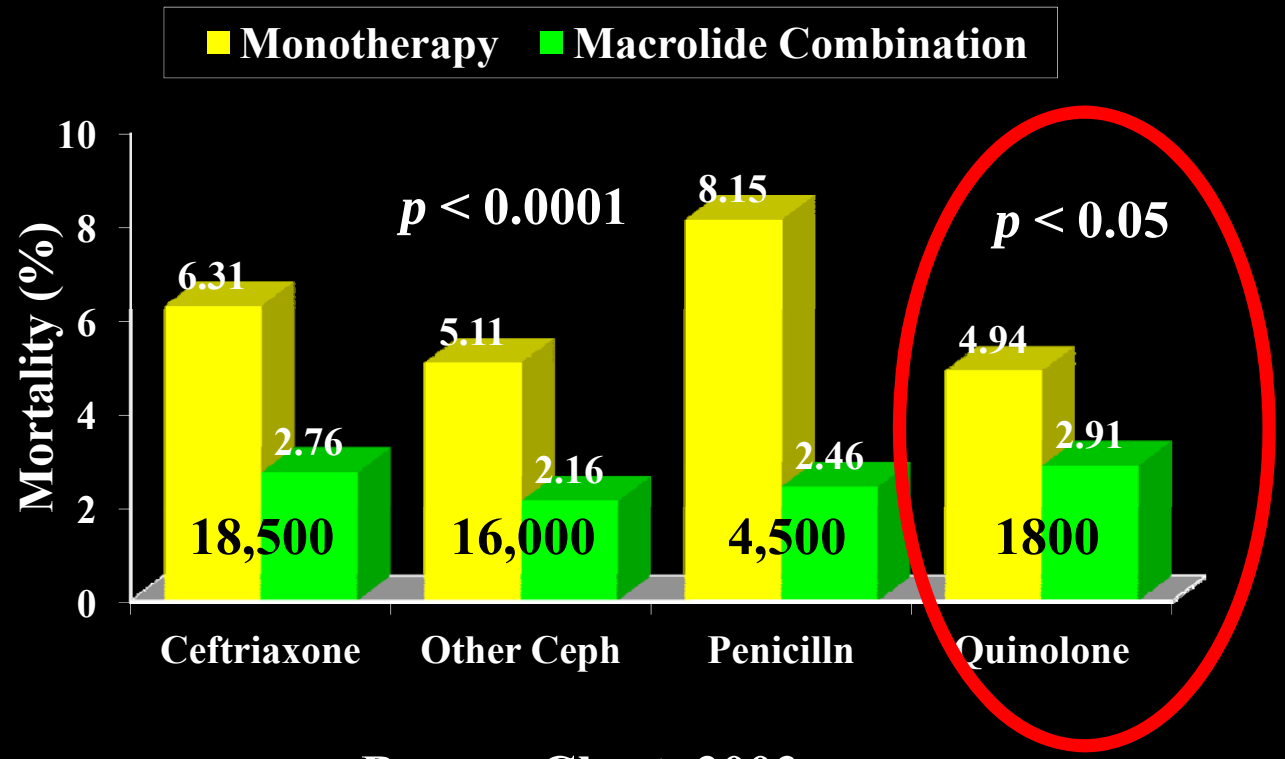
TABLE 2. Cox regression analysis of factors associated with 30 days mortality in community-acquired, Panton–Valentine leukocidin-positive *Staphylococcus aureus* necrotizing pneumonia[a]

Variable	p-value	Multivariate adjusted hazard ratio (95% CI)
Airway haemorrhage	0.004	2.96 (1.41–6.25)
Leucocyte count (10^9/L)[b]	0.001	0.32 (0.17–0.61)
Antitoxinic treatment	0.002	0.11 (0.03–0.49)

[a]The model was adjusted on severity and presence of the *mec*A gene.
[b]In this model, natural logarithms of leucocyte counts were used.

Sicot et al, Clin Microbiol Inf, 2012

Macrolide Combination Therapy



Brown, Chest, 2003

A 44 yo without prior medical history presents with cough, hemoptysis, shortness of breath and fever. He has marked increase work of breathing and is intubated. CXR demonstrates bilateral infiltrates. Preliminary laboratories demonstrate a neutrophil count of 550/uL. Your initial antibiotic therapy would be:

1. Vancomycin and piperacillin/tazobactam
2. Ceftriaxone and azithromycin
3. Vancomycin, cefipime, and doxycycline
4. Moxifloxacin
5. Ceftriaxone, azithromycin, and linezolid

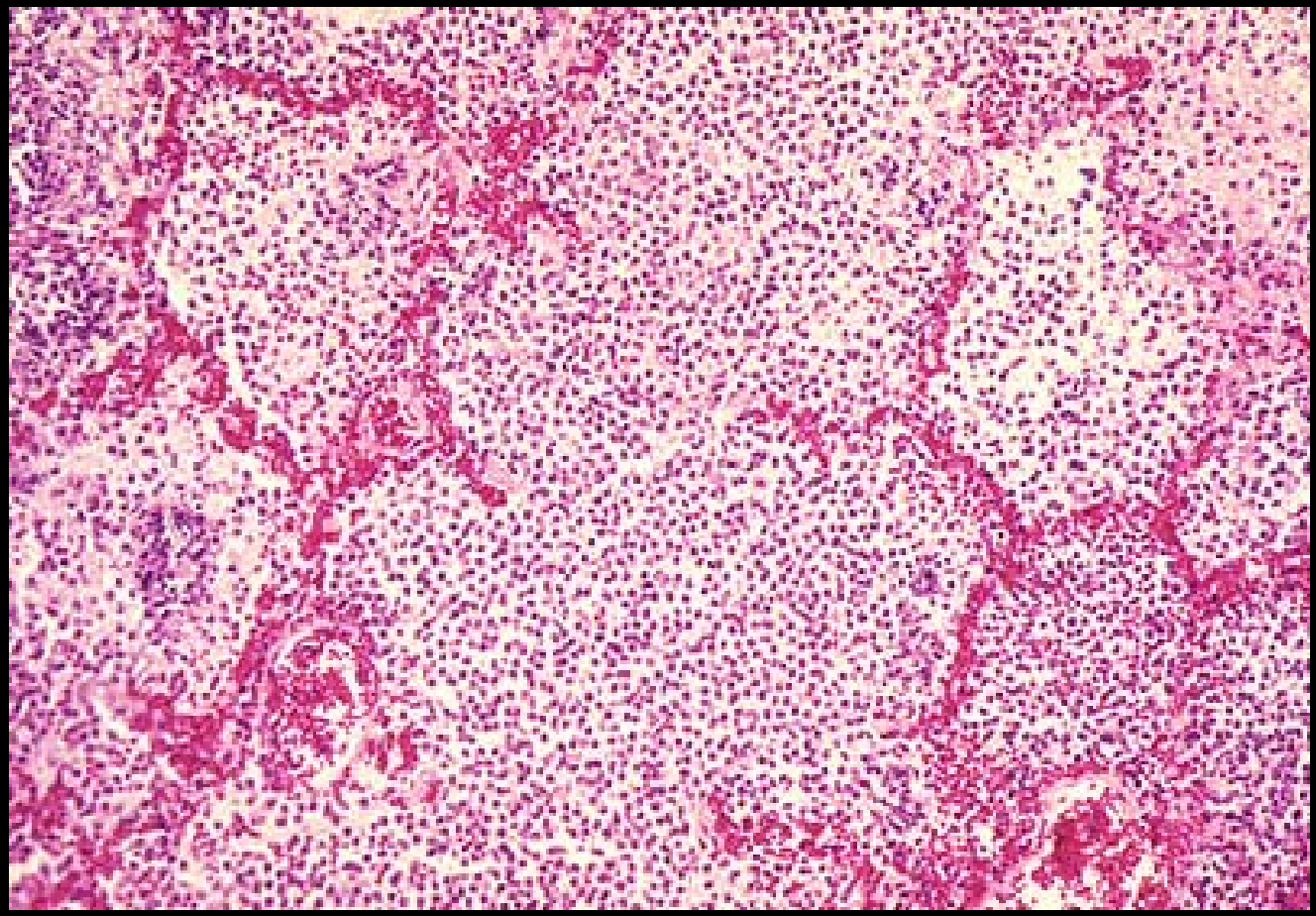
A 44 yo male presents with cough and fever. CXR demonstrates bilateral alveolar infiltrates. A urinary antigen is positive for pneumococcus and a nasal swab is positive for influenza A – he has been started on ceftriaxone and azithromycin.

After 6 hours in the ICU, he is on FiO2 .90, PEEP 20 cmH_2O, assist control mode with 6 cc/kg tidal volume, RR 35 with minimal auto-PEEP. Norepinephrine had to be added when PEEP was increased from 16 to 20 cmH_2O.

What would you do at this point?

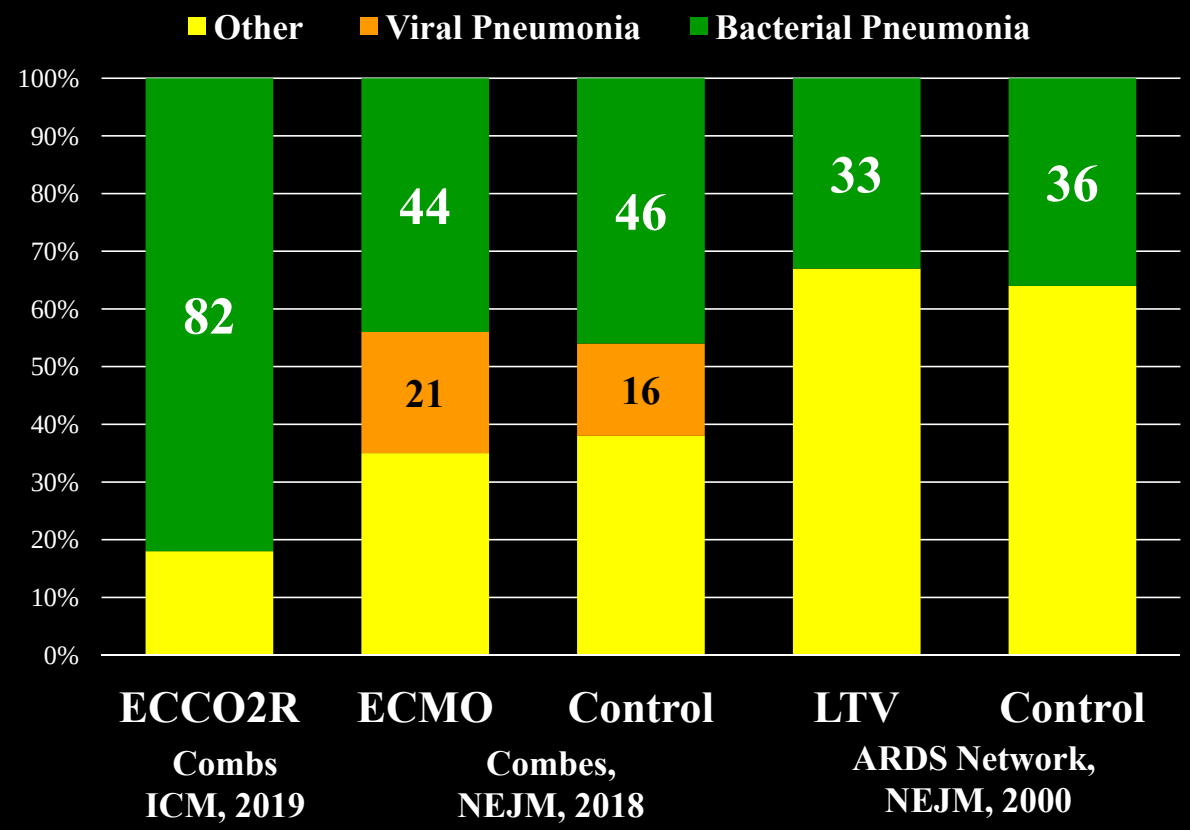
1. Start high dose steroids
2. Prone positioning
3. Switch antibiotic to vancomycin and piperacillin/tazobactam
4. VV-ECMO
5. Inhaled nitric oxide

Bacterial pneumonia (usually) doesn't respond to recruitment maneuvers



Pneumonia as Cause of ARDS

- Mortality rate second only to aspiration
- May be less likely to respond to recruitment maneuvers, inhaled pulmonary vasodilators, and/or proning



ECMO for Severe ARDS (EOLIA) – Combes et al, NEJM, 2018

Table 2. End Points.*

End Point	ECMO Group (N=124)	Control Group (N=125)	Relative Risk or Difference (95% CI)†	P Value
Primary end point: mortality at 60 days — no. (%)	44 (35)	57 (46)	0.76 (0.55 to 1.04)	0.09
Key secondary end point: treatment failure at 60 days — no. (%)‡	44 (35)	72 (58)	0.62 (0.47 to 0.82)	<0.001
Other end points				
Mortality at 90 days — no. (%)	46 (37)	59 (47)	−10 (−22 to 2)	
Median length of stay (interquartile range) — days				
In the ICU	23 (13–34)	18 (8–33)	5 (−1 to 10)	
In the hospital	36 (19–48)	18 (5–43)	18 (6 to 25)	
Median days free from mechanical ventilation (interquartile range)§	23 (0–40)	3 (0–36)	20 (−5 to 32)	
Median days free from vasopressor use (interquartile range)§	49 (0–56)	40 (0–53)	9 (0 to 51)	
Median days free from renal-replacement therapy (interquartile range)§	50 (0–60)	32 (0–57)	18 (0 to 51)	
Prone position — no. (%)¶	82 (66)	113 (90)	−24 (−34 to −14)	
Recruitment maneuvers — no. (%)¶	27 (22)	54 (43)	−21 (−32 to −10)	
Inhaled nitric oxide or prostacyclin — no. (%)¶	75 (60)	104 (83)	−23 (−33 to −12)	
Glucocorticoids — no. (%)¶	80 (65)	82 (66)	−1 (−13 to 11)	

What is the most likely reason for treatment “failure” in severe CAP?

~~1. Antibiotic resistance~~

2. Unusual pathogen - ?

3. Exaggerated host response

✓Bacterial virulence factors

5. Genetic immunodeficiency

Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
- CAP is a disease of health disparities and underlying co-morbidities
- **Outcome CAP determined by the timely provision of appropriate antibiotic(s)**
  - **Need to address toxin production for most common pathogens**
  - **Viral SCAP is underappreciated**
- **An important minority die of hypoxemic death**
- **Immune modulation is needed to improve overall outcome**

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response

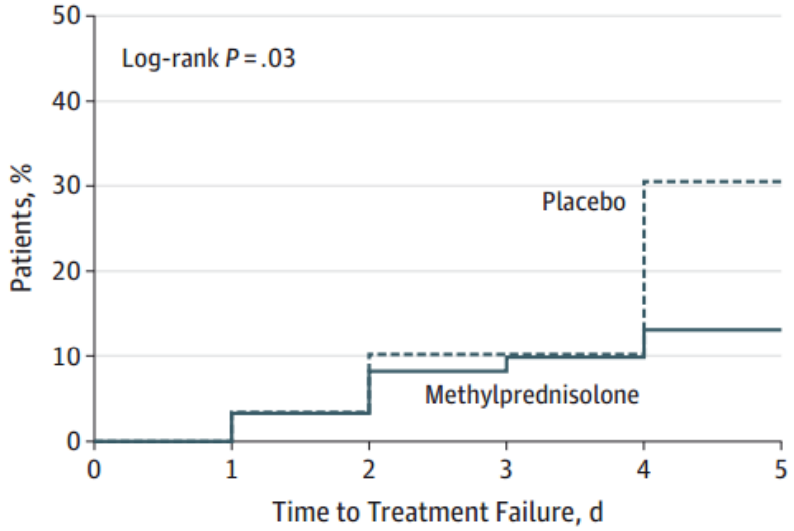
A Randomized Clinical Trial

Antoni Torres, MD, PhD; Oriol Sibila, MD, PhD; Miquel Ferrer, MD, PhD; Eva Polverino, MD, PhD; Rosario Menendez, MD, PhD; Josep Mensa, MD, PhD; Albert Gabarrús, MSc; Jacobo Sellarés, MD, PhD; Marcos I. Restrepo, MD, MSc; Antonio Anzueto, MD, PhD; Michael S. Niederman, MD; Carles Agustí, MD, PhD

JAMA, Feb 2015

- **Required CRP > 150 mg/L for enrollment**
- **7.5 years to recruit 112 patients from 3 hospitals = 5 pts/yr**
- **No mortality difference**
- **Mostly late failure (> 72 hours) by radiographic criteria**

Figure 2. Kaplan-Meier Analysis of the Effect of Methylprednisolone on Time to Treatment Failure



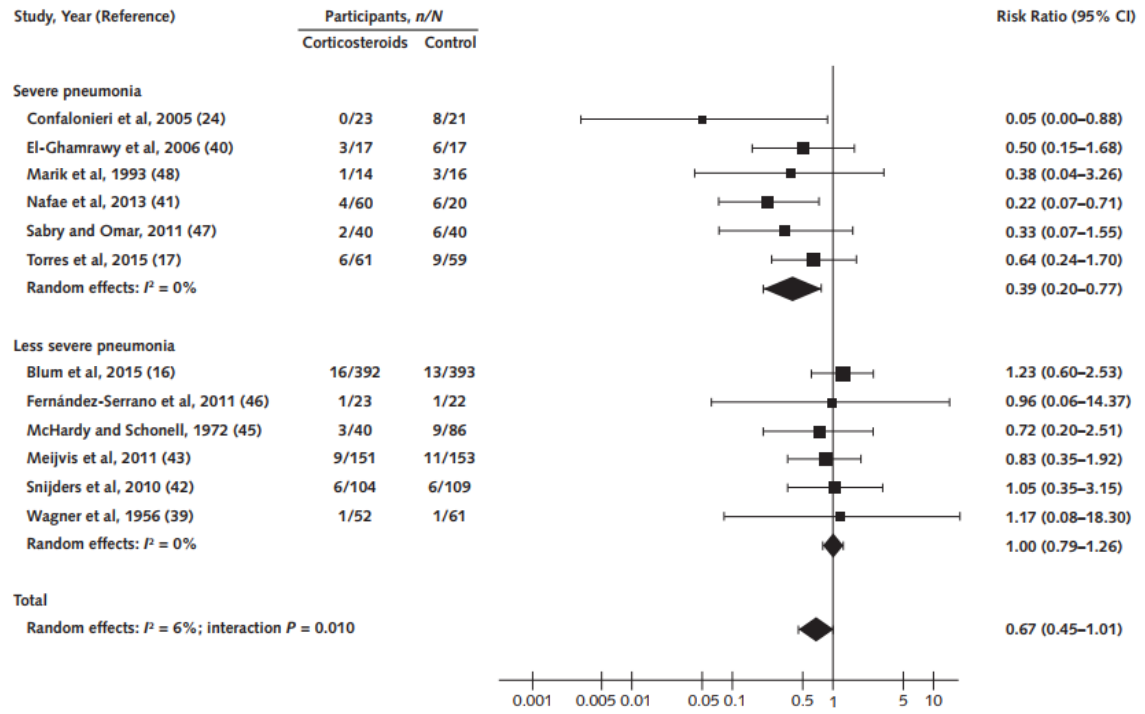
Annals of Internal Medicine REVIEW

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Reed A.C. Siemieniuk, MD; Maureen O. Meade, MD; Pablo Alonso-Coello, MD, PhD; Matthias Briel, MD, MSc; Nathan Evaniew, MD; Manya Prasad, MBBS; Paul E. Alexander, MSc, PhD; Yutong Fei, MD, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD, MSc; and Gordon H. Guyatt, MD, MSc

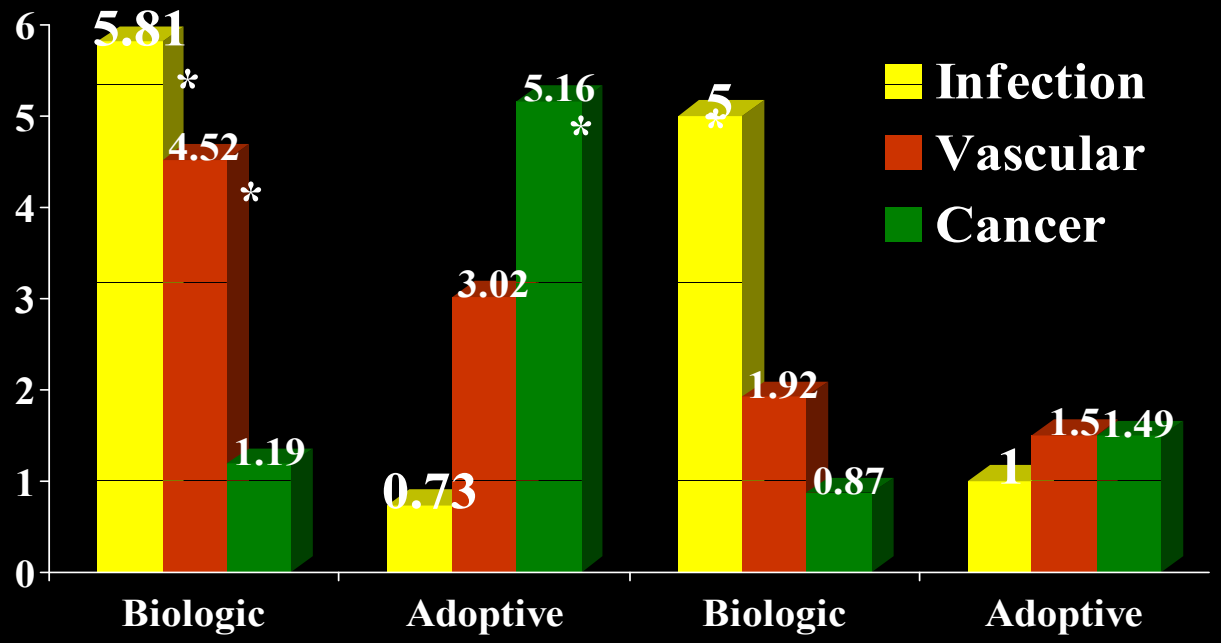
Figure 1. Effect of corticosteroids on all-cause mortality in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.



Corticosteroids for CAP

- For non-ICU patients:
  - Dutch and Swiss studies – β-lactam monotherapy is the standard, lower 95% CI of LOS in placebo is 6 days
  - Some increased risk of hyperglycemia and readmission
  - Would NOT use but give macrolide instead
- For ICU patients, works in some
  - Defining patient groups is difficult
  - Worse outcome in influenza/viral pneumonia

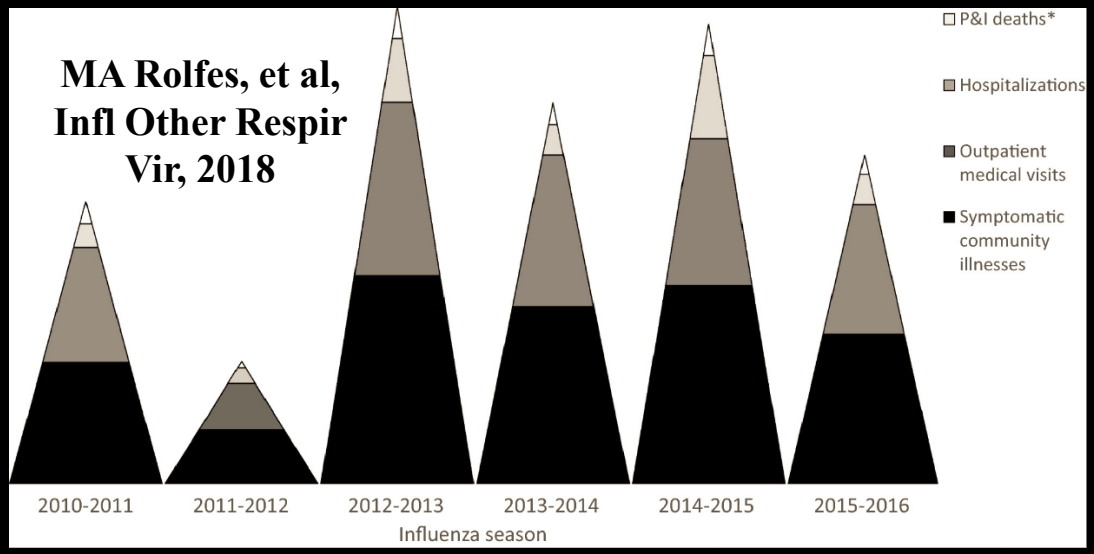
Genetic Influences on Premature Death



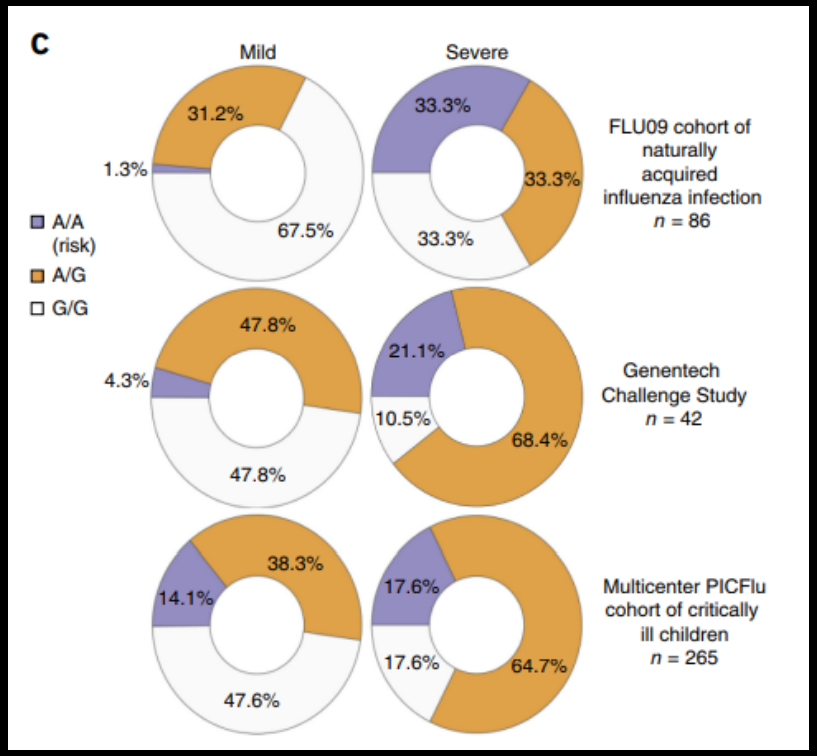
Parent Death < 50 Parent Death < 70

*$p < 0.001$

Genetic Risk of Severe Influenza



- Mechanical ventilation
- ECMO



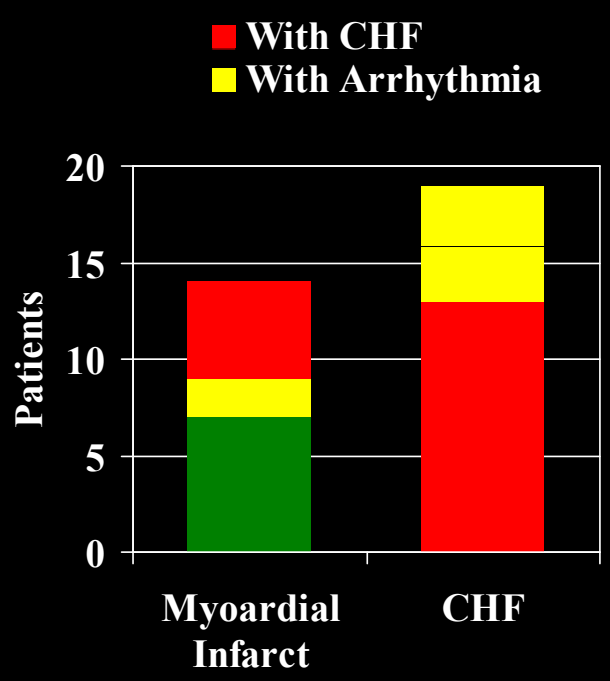
Interferon-induced transmembrane protein-3 (IFITM-3) rs34481144 SNP
EK Allen et al, Nature Medicine, 2017

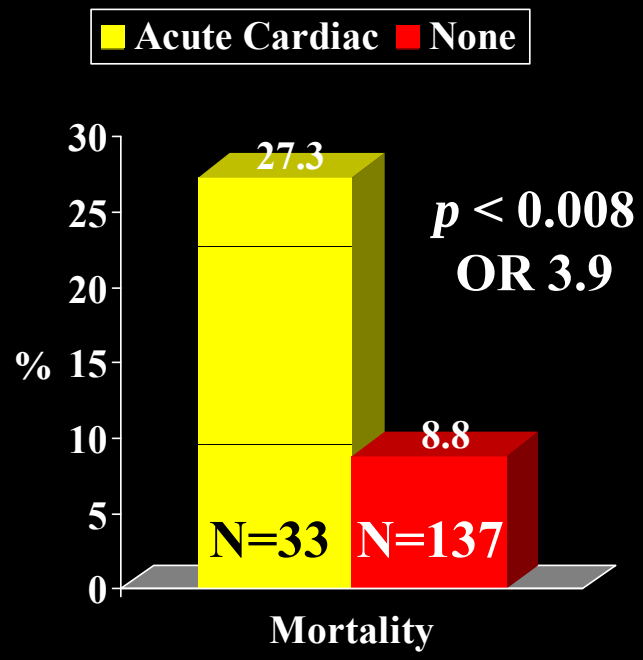
A 65 yo Type 2 diabetic male with urinary antigen-positive pneumococcal pneumonia had atrial fibrillation for approximately 12 hours and a minor troponin elevation while on noninvasive ventilation in the ICU. In anticipation of discharge 5 days later, you should:

a. Place on aspirin and initiate a statin
b. Check an echocardiogram
c. Discontinue amiodarone
d. Perform a left heart catheterization
e. Perform noninvasive coronary evaluation

Association between Pneumococcal Pneumonia and Inpatient Acute Cardiac Events

33/170 (19.4%) had at least one major cardiac event





Musher et al, Clin Infect Dis, 2007

Myocardial Infarct and CAP

Retrospective review:
500 cases at Louisville VAMC

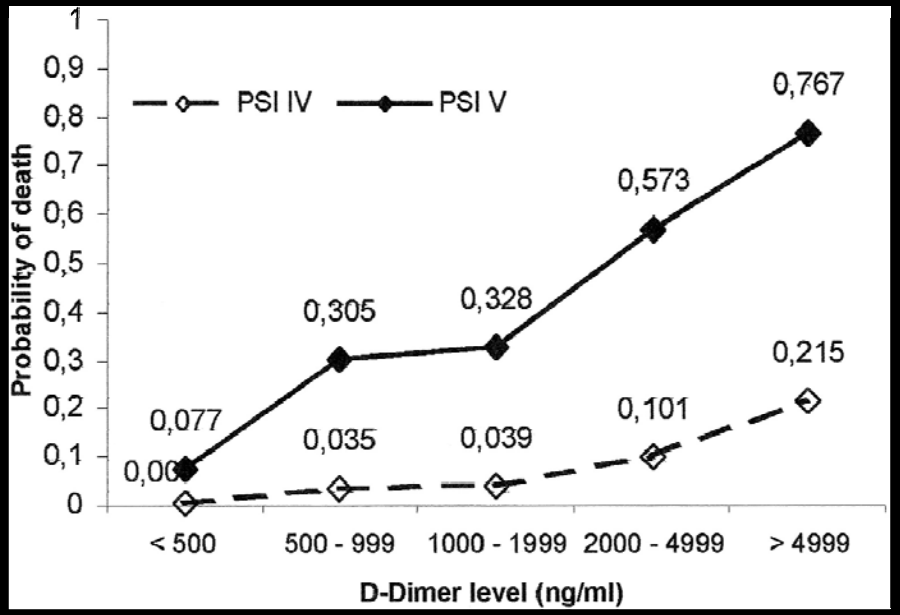
- Biomarkers of myocardial injury and either EKG changes or intervention
- Severe sepsis excluded since can elevate troponins

Ramirez, Clin Infect Dis, 2008

- AMI diagnoses in 5.8% (29/500)
  - 15% (13/86) of ICU admissions
  - ST changes in 25%, NSTEMI 75%
- 50% (10/20) of transfers to ICU in first 24 hours had MI
- More likely if have clinical failure (51.7% vs. 11%)
- Increased mortality
  - 27.6% vs. 6.8% in hospital
  - 31% vs. 9.6% at 30 days

Coagulation Abnormalities in Severe CAP

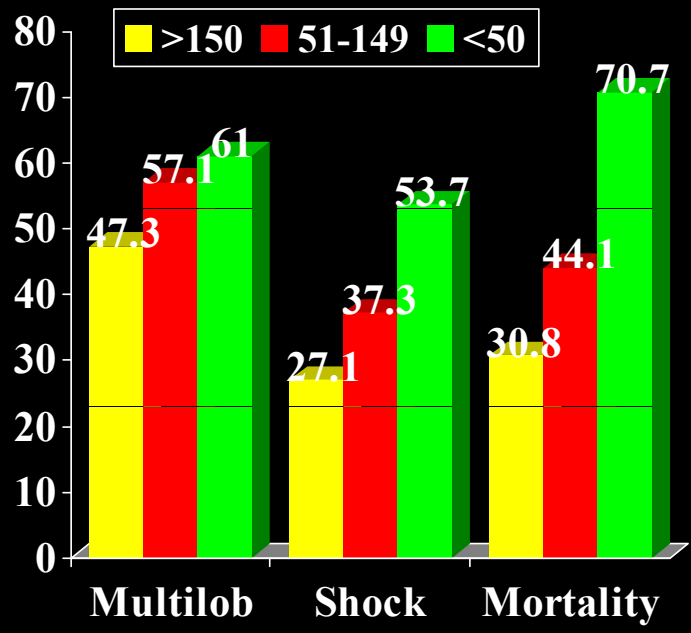
D-dimer



Querol-Ribelles, J. M. et al. Chest 2004;126:1087-1092

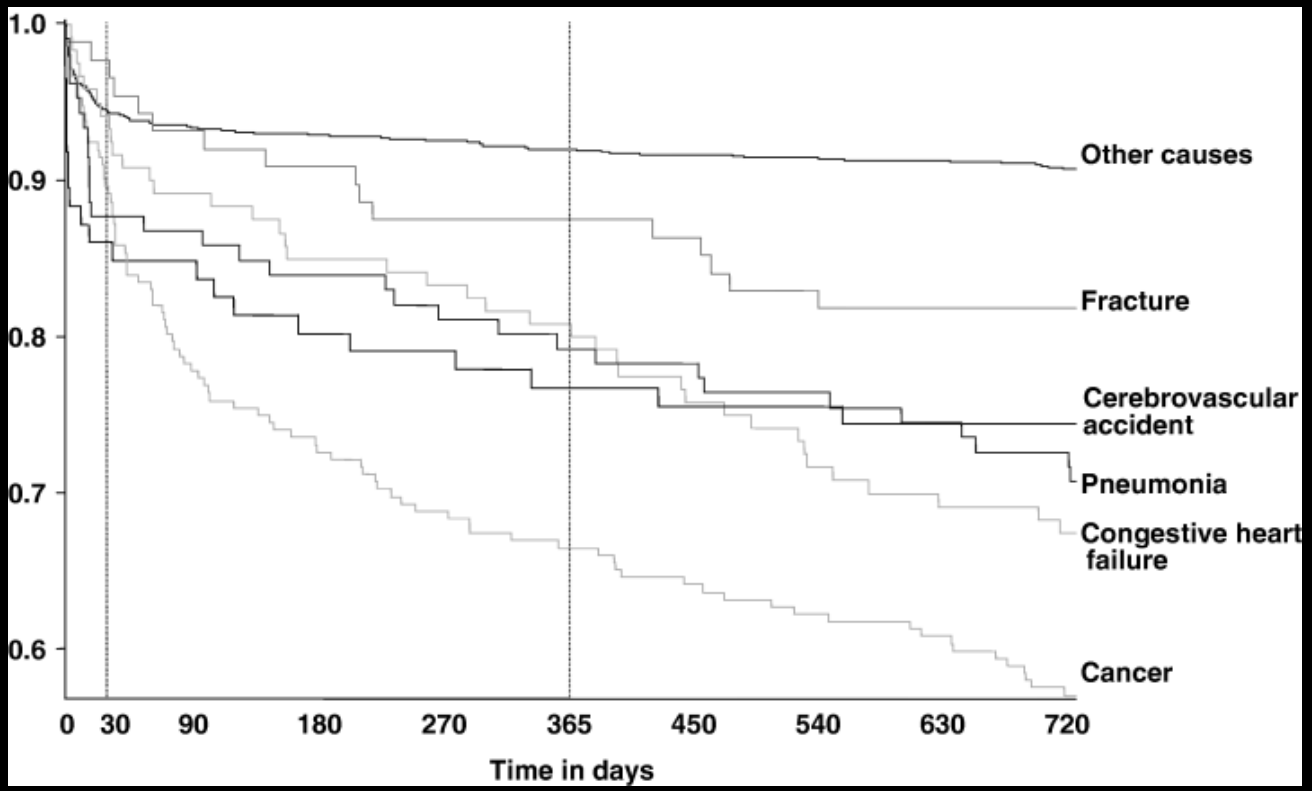
CHEST
The Cardiopulmonary and Critical Care Journal

Thrombocytopenia



Brogly et al, J Infection, 2007

Subsequent Mortality in Previously Well-functioning Elderly Admitted for CAP

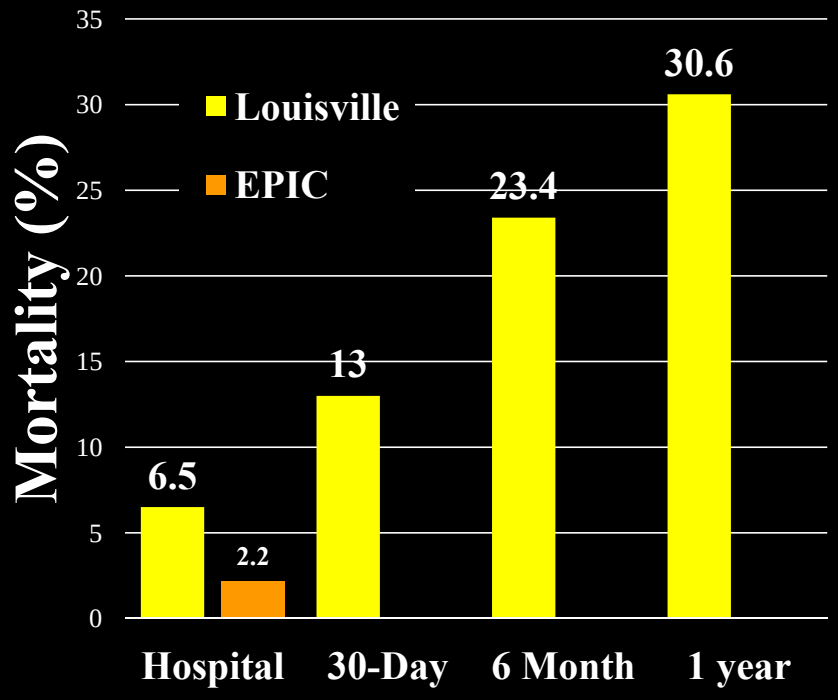


Yende et al, J Am Geriatr Soc, 2007

Mortality from CAP - Louisville

All cause mortality

- Includes recent hospitalized and immunocompromised
- Death certificates of hospitalized don't necessarily indicate pneumonia
- Emerging data of increased risk of cardiovascular deaths after CAP admission – not infectious



Estimated Annual US Pneumonia Mortality – 484,000

Changing Paradigms of SCAP

- Pneumonia remains the most common infectious cause of death in the US, and worldwide
- CAP is a disease of health disparities and underlying co-morbidities
- Outcome determined by the timely provision of appropriate antibiotic(s)
  - Need to address toxin production for common bacterial pathogens
  - Viral SCAP is underappreciated
- An important minority die of hypoxemic death
- Immune modulation is needed to improve overall outcome
- CAP is not just an acute disease