

Management of pneumonia – more than just antibiotics?

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Pneumonia



Pathogen



Treat

Clinical case

46 year old man

Unwell a few days only.

Fever, cough, green sputum.

Very tired. Loss of appetite.

Hypertension. Fit and well.

Work: fibre glass factory

Hb 120

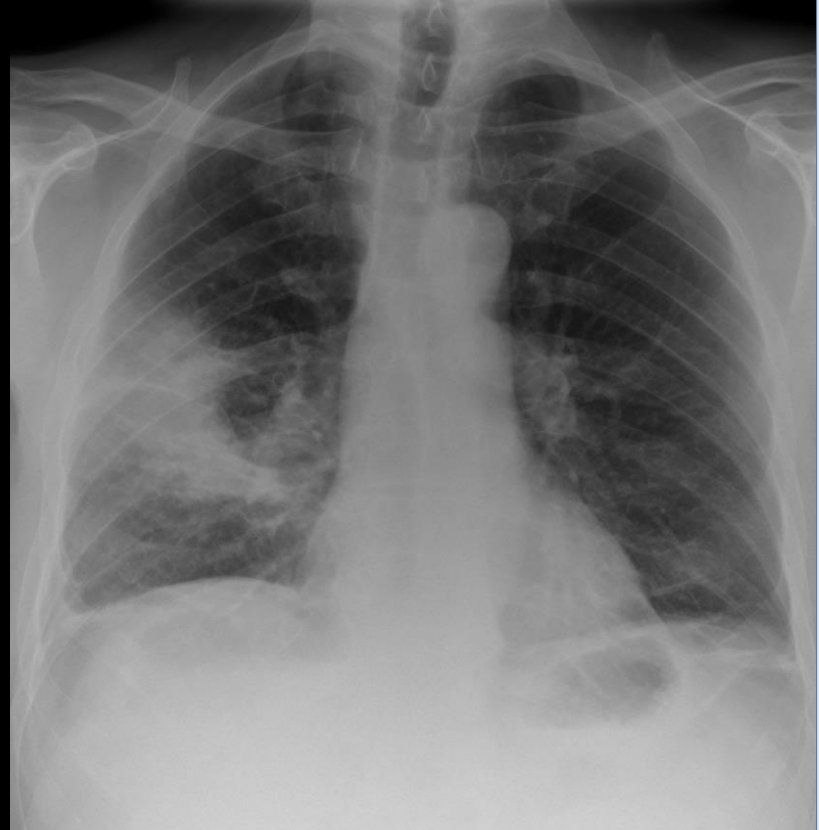
Urea 4.0

WCC 12

Creat 63

Platelets 628

CRP 95



Question 1

Which other diagnostic test would you do?

- A. ANCA
- B. CT thorax
- C. D-dimer
- D. HIV test
- E. Ultrasound of the chest

Question 2

What treatment would you offer?

- A. Antibiotics
- B. Antibiotics + corticosteroid
- C. Antibiotics + antiviral

Question 3

What would you do at discharge from hospital?

- A. Advise GP follow up (FU) within 2 weeks
- B. Organise CXR in 4 weeks
- C. Organise chest physiotherapy weekly x 4 wks
- D. Provide rescue antibiotics to take if cough persists > 4 weeks
- E. Organise hospital clinic FU in 4 - 6 weeks

Pneumonia ?



Pathogen ?



Treat ?

ED diagnosis of CAP

3-centre US study

800 adults with ED diagnosis of CAP

219 (27%) non-pneumonia diagnosis at discharge

- non-CAP lung disease (asthma, COPD etc.)
- renal disease
- other infections
- cardiovascular disorders

18% of 581 with final diagnosis of CAP → normal CXR

4 hour target in CAP: Speed vs Misdiagnosis

Before-after observational study: US (n=518)

↑ antibiotics <4 h (65.8% v 53.8%; p = 0.007)

↑ diagnosis CAP without CXR abn (29% v 21%; p = 0.04)

↓ in final diagnosis of CAP (58.9% v 75.9%; p < 0.001)

No significant differences in mortality.

CT in suspected CAP: elderly

- Cohort study, n=200 aged >65 yrs.
- Admitted and treated for CAP. CT within 72 hr.
- Clinicians graded their diagnostic certainty for each patient.

	Before	After CT
High prob of CAP	56.5%	57%
Intermediate	35%	14.5%
Low	8.5%	28.5%

Antibiotic therapy withdrawn in 8.5%

Infection? Pathogen?

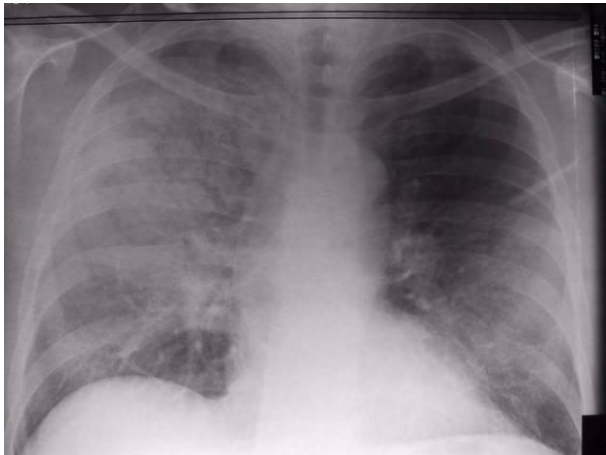
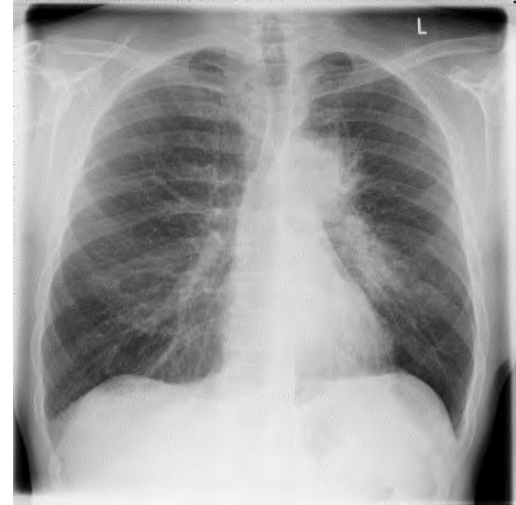
A



B



C



D



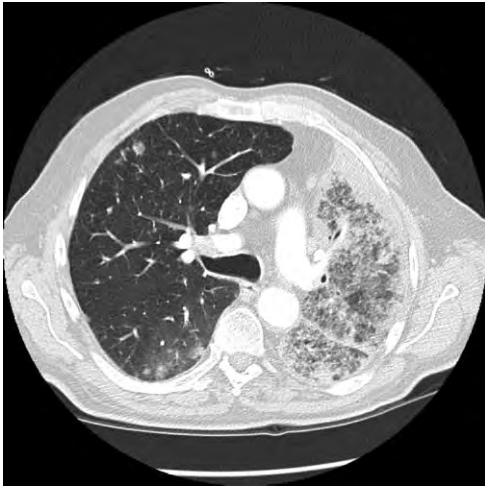
E



F

Making a diagnosis

lung adenocarcinoma



pneumococcal



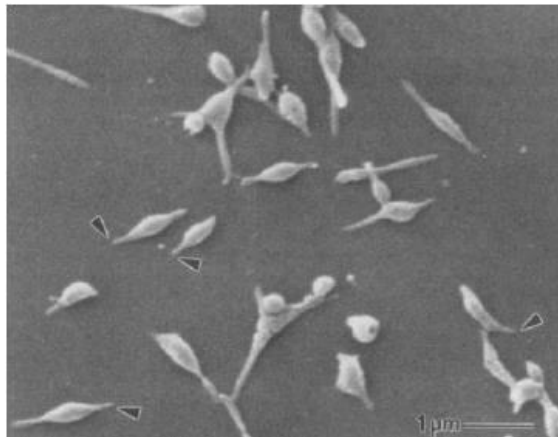
cryptogenic organising pneumonia



legionella



mycoplasma



pneumococcal in myeloma



Pneumonia 'lookalikes'

Fluid	-	Pulmonary oedema
Blood	-	Pulmonary haemorrhage
Cancer	-	Bronchoalveolar cell carcinoma
Eosinophils	-	Eosinophilic pneumonia

Cryptogenic organising pneumonia (COP)

Pneumonia - Review. Consider mimics.



Pathogen ?



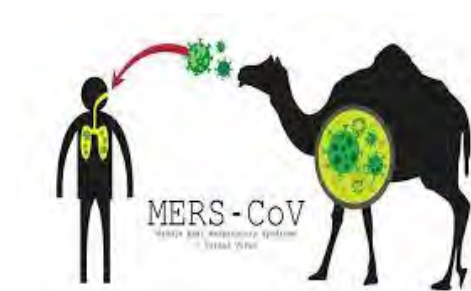
Treat ?

Middle East Respiratory Syndrome (MERS) in the UK

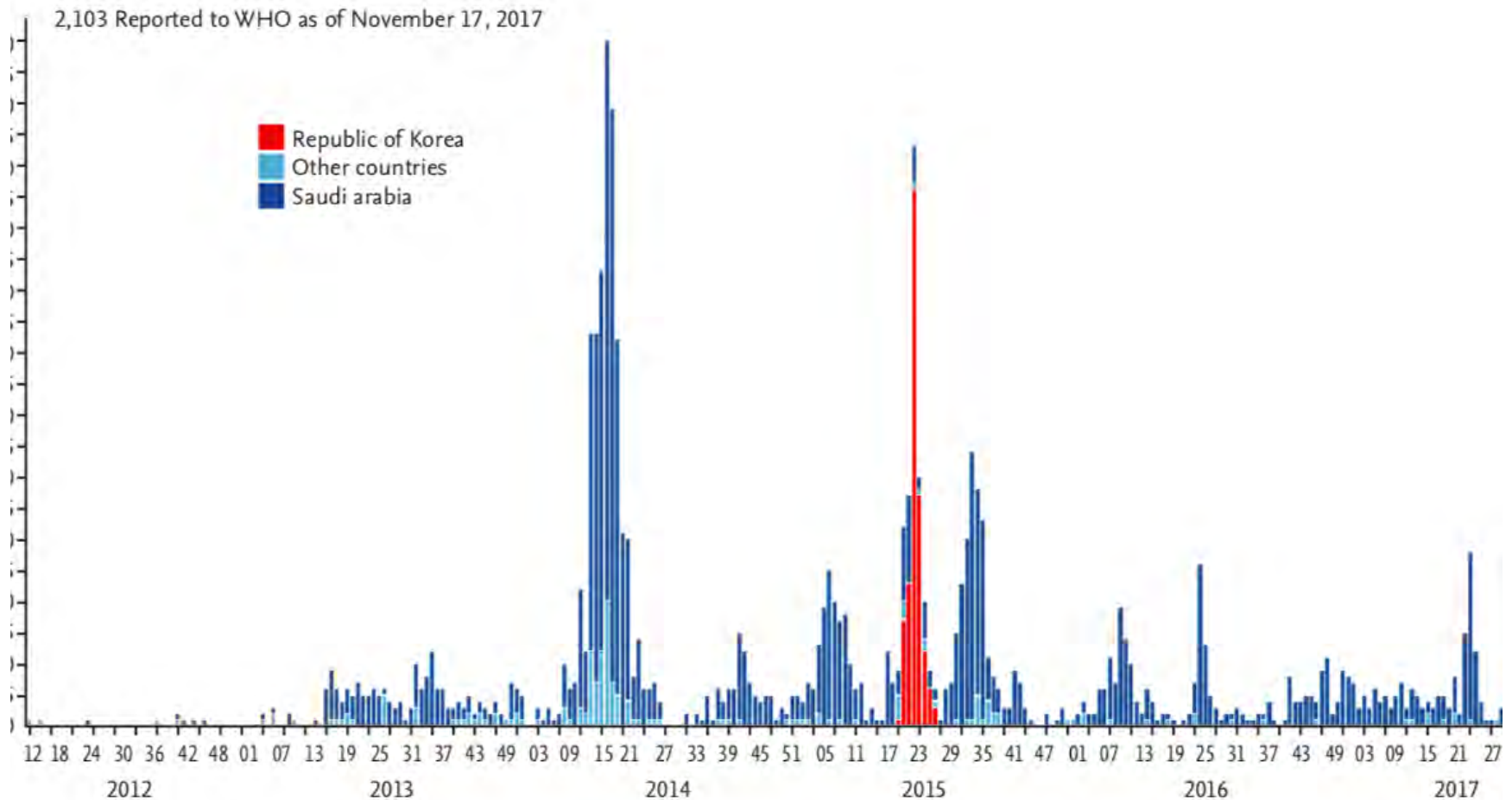
- 80+ year old man with underlying chronic medical conditions.
- 16 August 2018, while symptomatic: Kingdom of Saudi Arabia → Manchester → Leeds.
- Hospitalised in Leeds - received treatment while in isolation.
- Transferred to specialist ID facility in Liverpool.
- No history of contact with sick patients in the KSA
- Had history of direct contact with camels

5th case detected in the UK.

Previous cases 2012- 13.

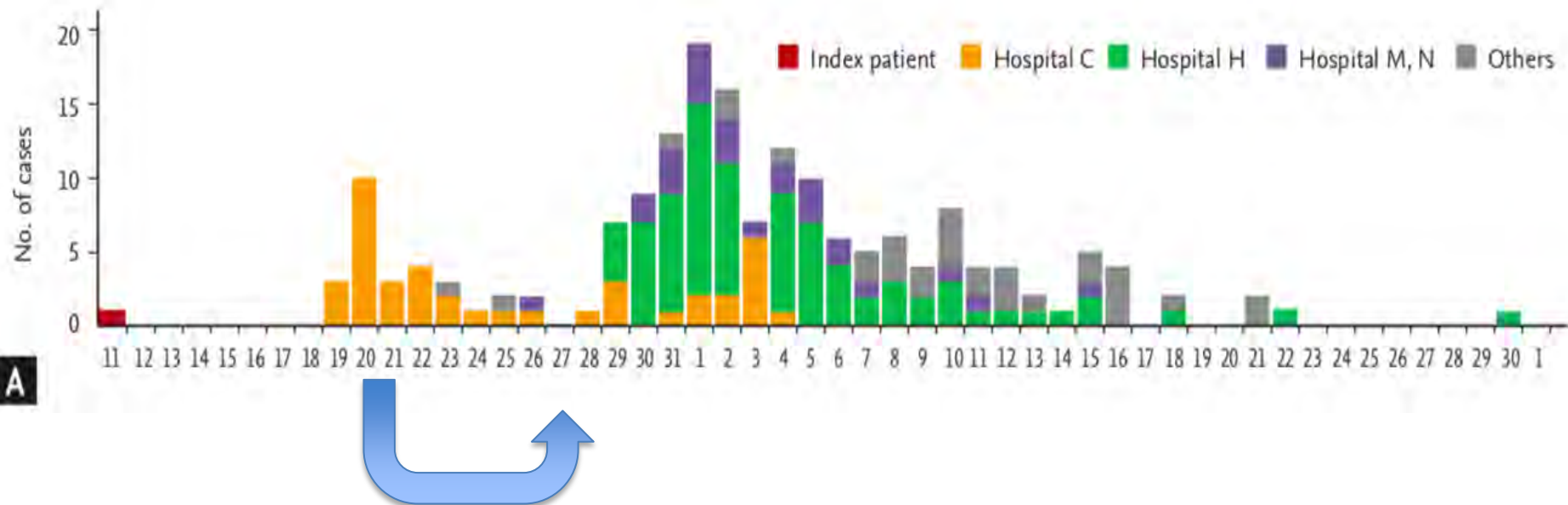


MERS-CoV cases since 2012



South Korean MERS outbreak 2015

- 1 imported case → 186 cases, 38 deaths
- 44% of cases: nosocomial infection



Patient from Hospital C attends Hospital H → superspreading event

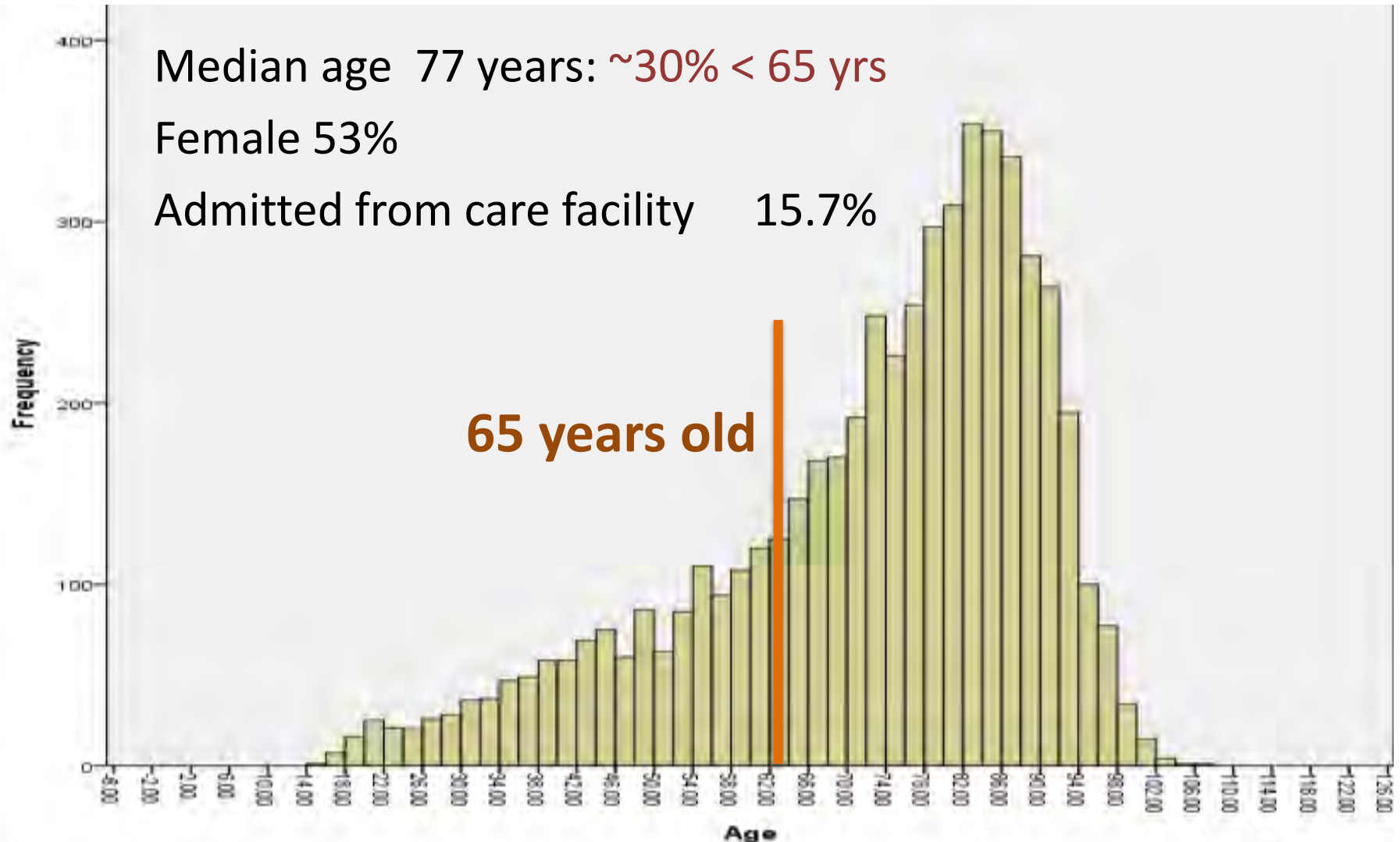
British Thoracic Society National CAP audit (n=24,180)



Median age 77 years: ~30% < 65 yrs

Female 53%

Admitted from care facility 15.7%



HIV and bacterial pneumonia

- most frequent infection in HIV-infected patients
- most common admission diagnosis
- 10-fold increase bacterial pneumonia

Additional risks

- Intravenous drugs
- Smoking: 2 to 5-fold increase risk
- Previous pneumonia
- 80% of cases: CD4 < 400 cells/mm³

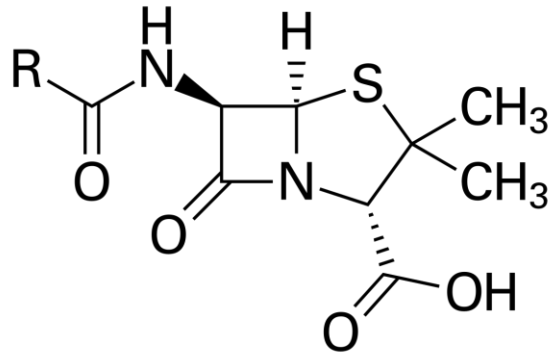
Pneumonia - Review. Consider mimics.



Pathogen - Vigilance: outbreaks/host.



Treat ?



Penicillin

Discovery

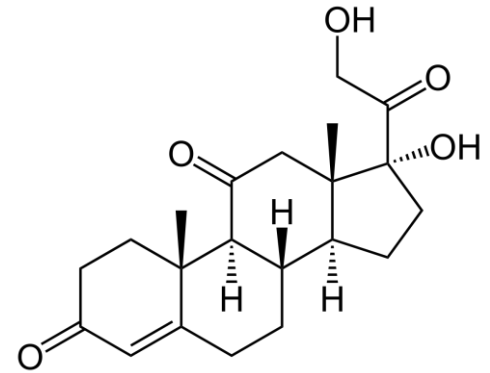
1928

First patient

1941

Oxford

Mould
fermentation (1939)



Cortisone

1930

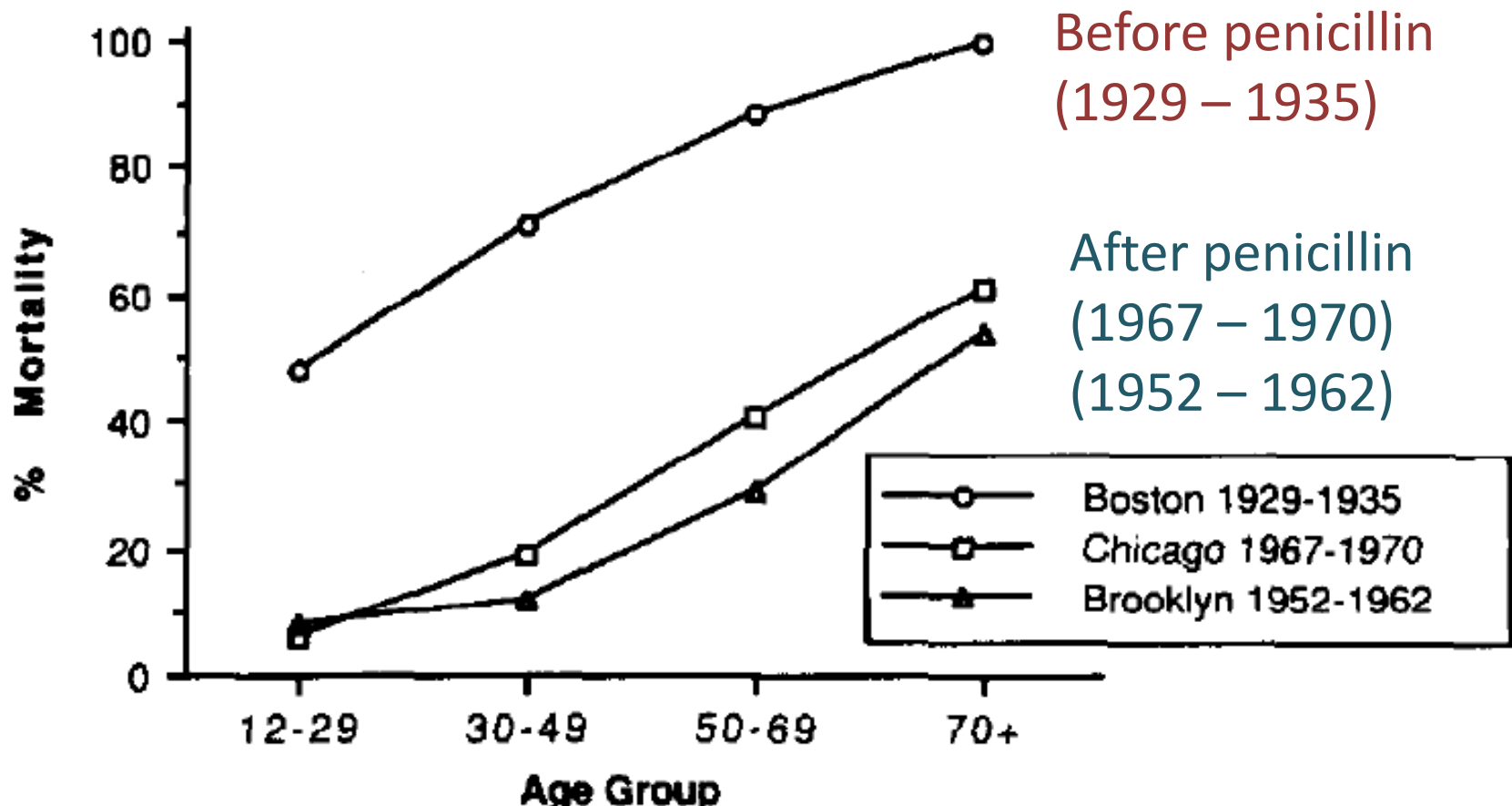
1948

Mayo

cattle adrenals
(1942)

Treatment of pneumococcal infection

Pneumococcal bacteraemia – all age-groups (US)

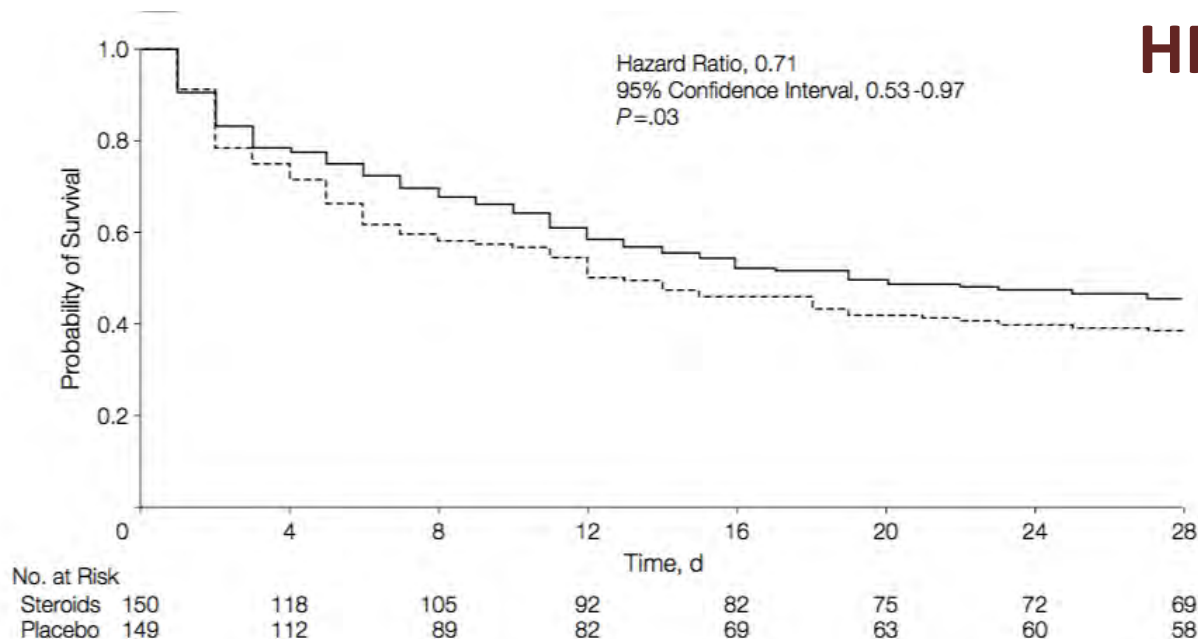


Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

French ICUs

Hydrocortisone 50 mg 6H x 7 days

Fludrocortisone 50 ug od x 7 days



HR 0.7 (0.53 – 0.97)

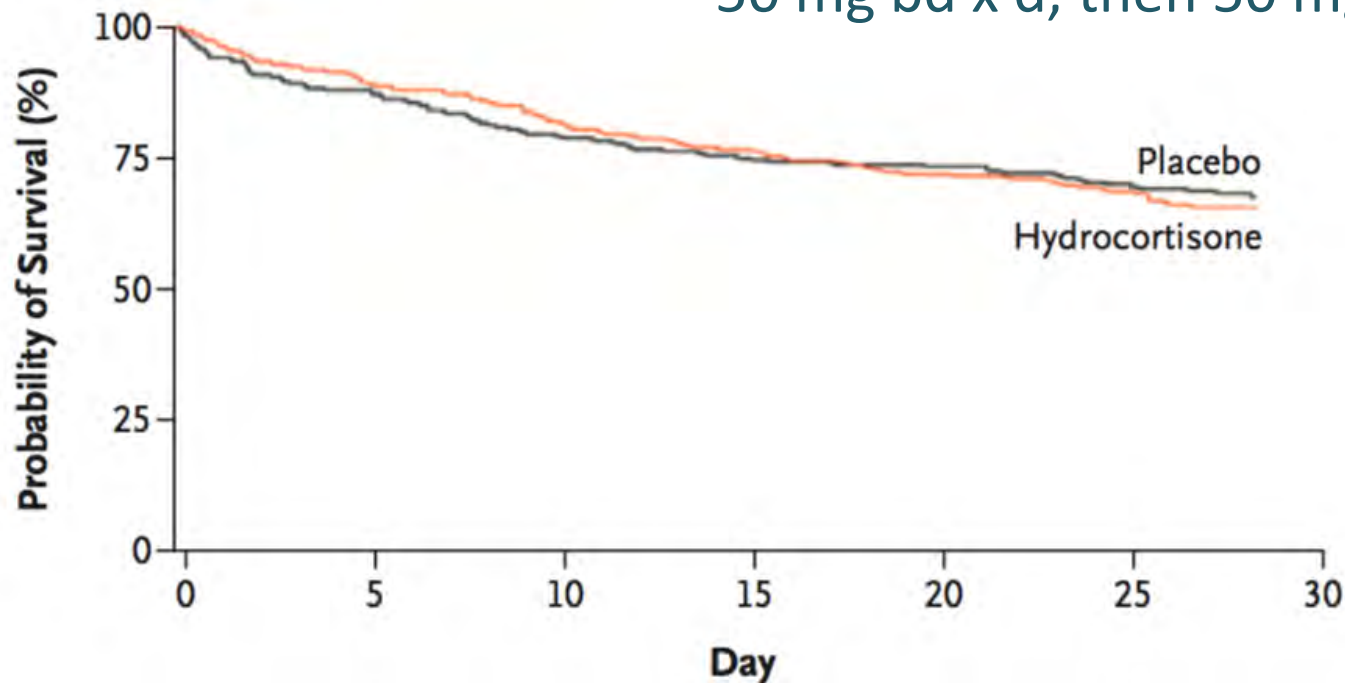
Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rufi Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., *et al.*, for the CORTICUS Study Group*

CORTICUS Trial. Multicentre
(n=499)

Hydrocortisone 50 mg 6H x 5d, then
50 mg bd x d, then 50 mg od x 3 d

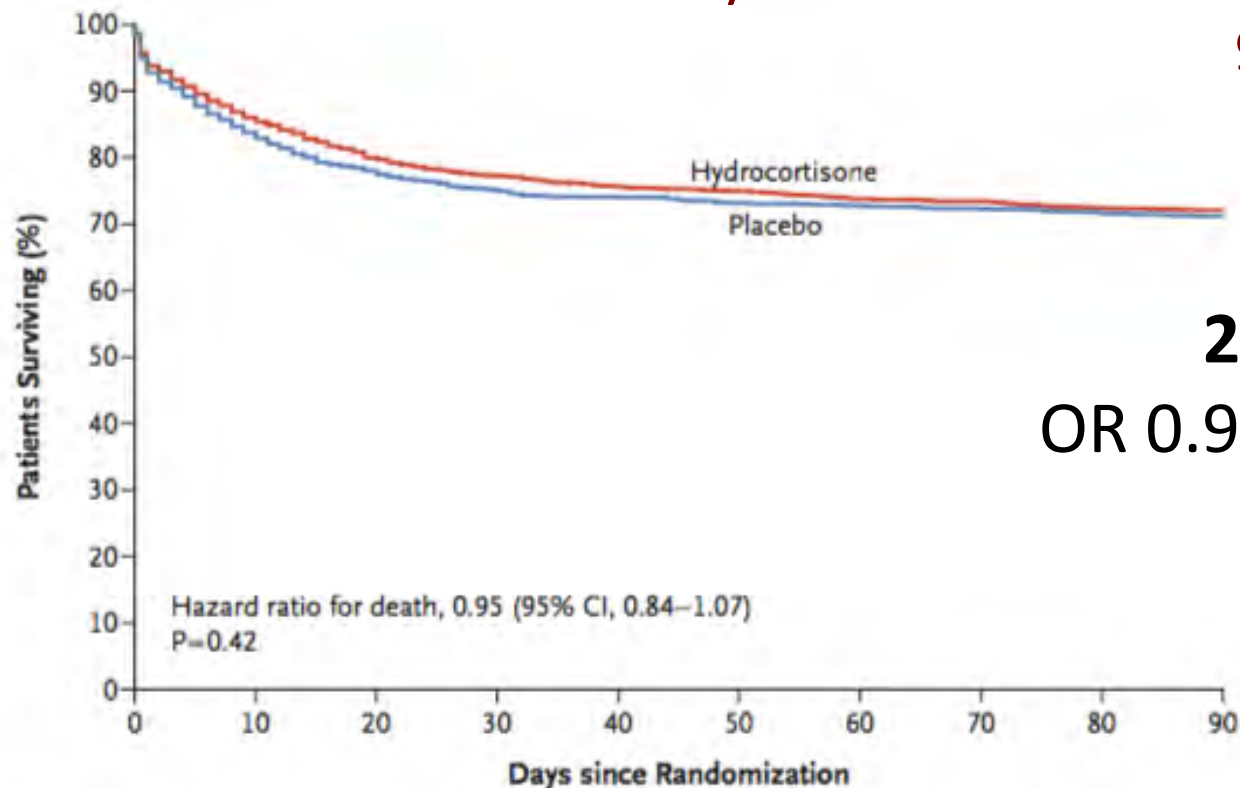
C All Patients



Adjunctive Glucocorticoids in Septic Shock

ADRENAL Trial: Australian - NZ ICU network
2013 – 2017, n= 3800

IV hydrocortisone infusion 200mg/d x 7d
90-day mortality



29.7% vs 28.8%
OR 0.95, 0.82 to 1.10

No. at Risk

Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

NEJM, Mar 2018

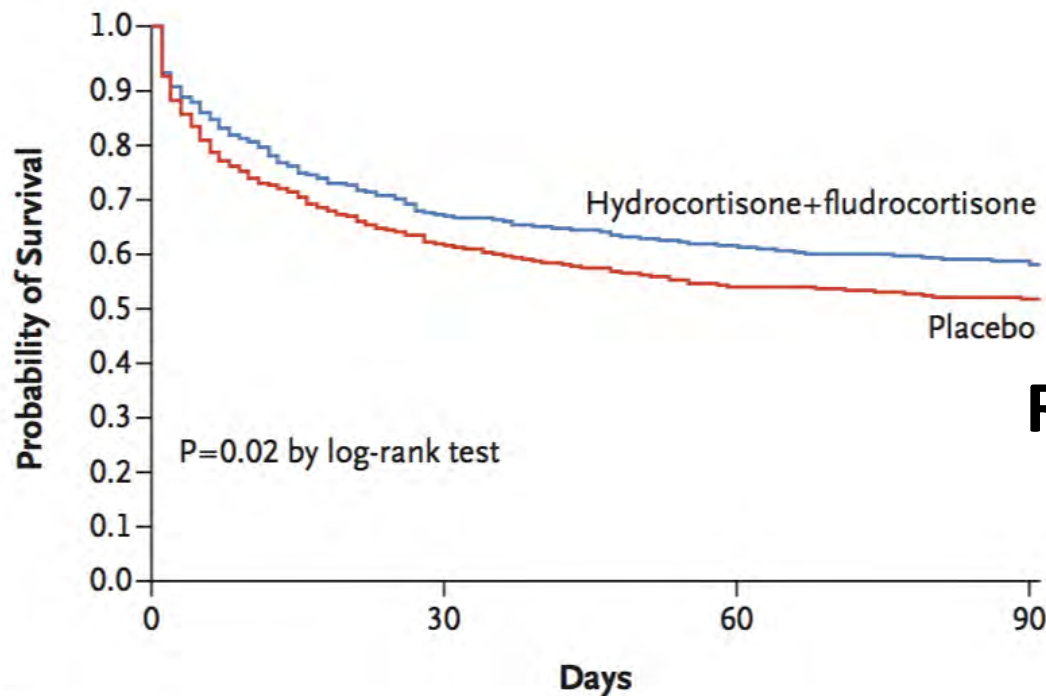
Hydrocortisone plus Fludrocortisone in Septic Shock (APROCCHSS)

French ICUs, n=1241

2008 – 2015 (APC arms discontinued)

Hydrocortisone 50mg IV 6 hourly, plus
fludrocortisone 50µg NG x 7 days

Lung infection: 61% vs 58%



43% vs 49.1%

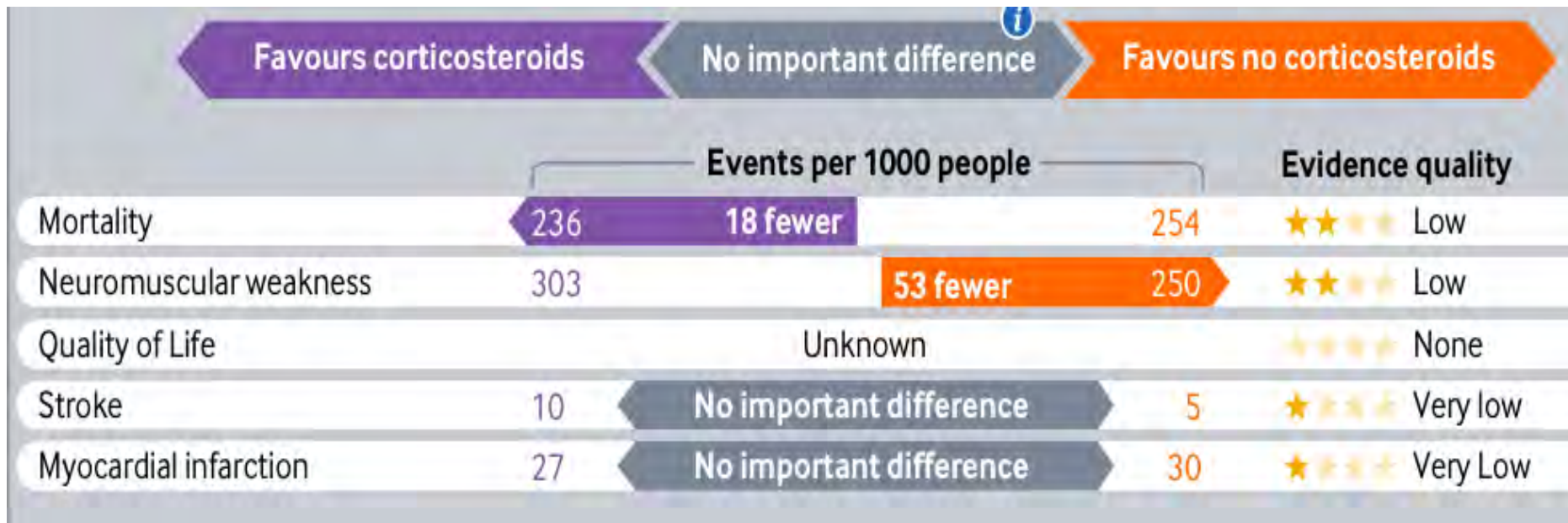
RR 0.88 (0.78 to 0.99)

No. at Risk

Hydrocortisone+ fludrocortisone	614	405	372	353
Placebo	627	381	333	319

Corticosteroids for sepsis

Meta-analysis: 42 trials, n=10 194 participants

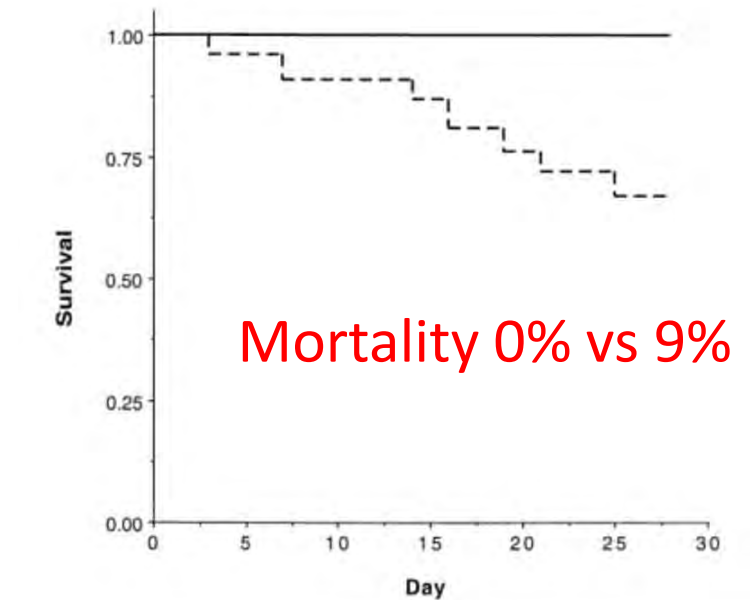
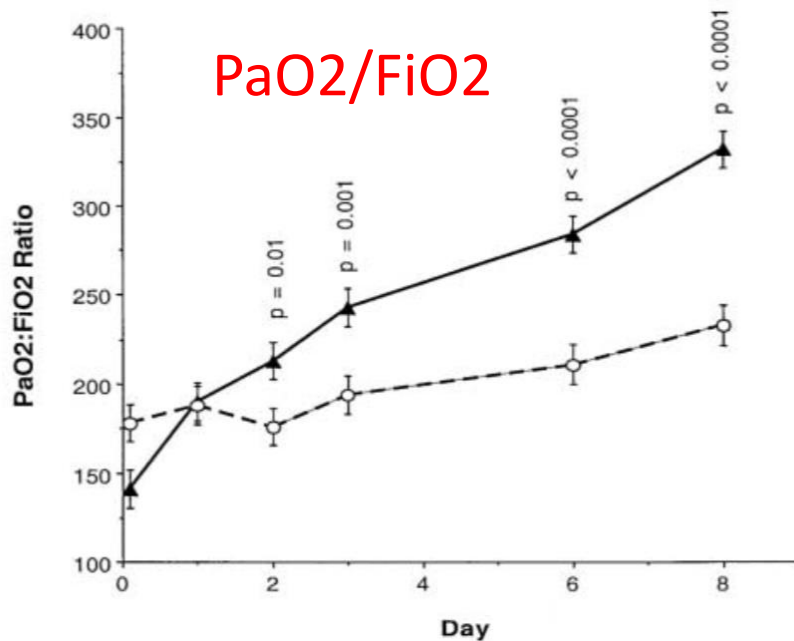


Corticosteroids in CAP

Hydrocortisone 200 mg bolus, then infusion over 7 d

Primary outcome: Improvement in $\text{FiO}_2/\text{PaO}_2$

Trial stopped after n=46

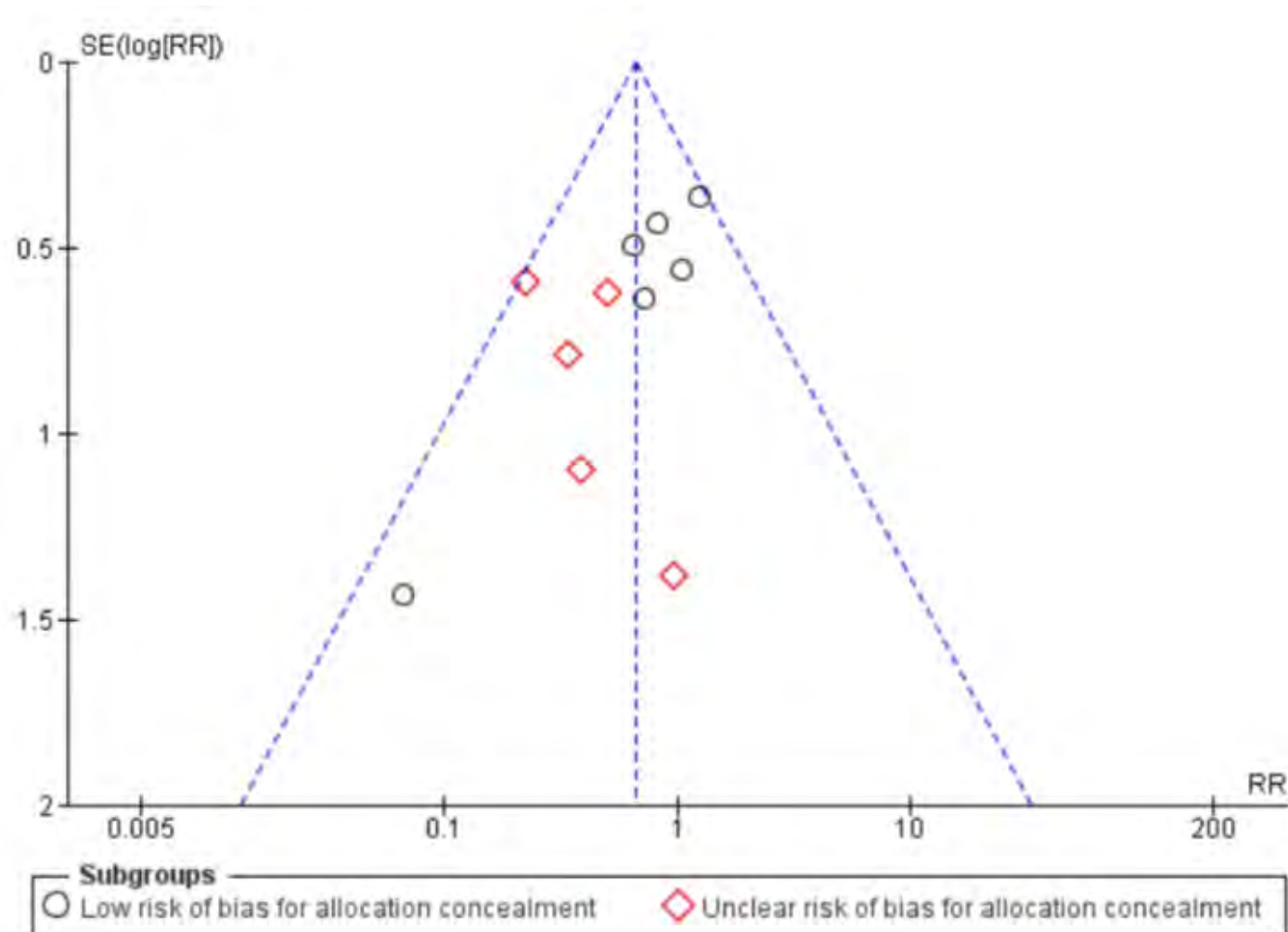


Cochrane Review: Steroids in CAP (Dec 2017)

Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)
Risk with control	Risk with corticosteroids		
Study population	All adults	RR 0.66 (0.47 to 0.92)	1863 (11 RCTs)
82 per 1000	53 per 1000 (38 to 74)		
Study population	Severe CAP	RR 0.58 (0.40 to 0.84)	995 (9 RCTs)
131 per 1000	76 per 1000 (52 to 110)		
Study population	Non-severe CAP	RR 0.95 (0.45 to 2.00)	868 (4 RCTs)
29 per 1000	28 per 1000 (13 to 58)		

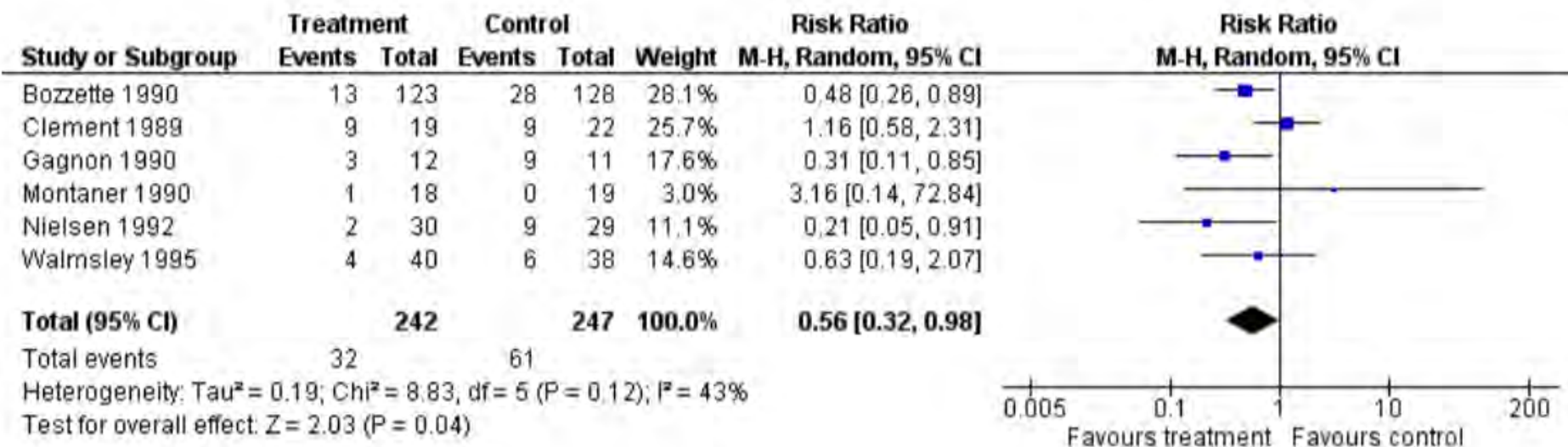
Cochrane Review: Steroids in CAP (Dec 2017)

Effect of allocation concealment



Cochrane review (2015): Steroids in PCP

n=489 (6 studies). 1-month mortality 13% vs 24%
RR 0.56 (0.32 to 0.98)



Bozzette:

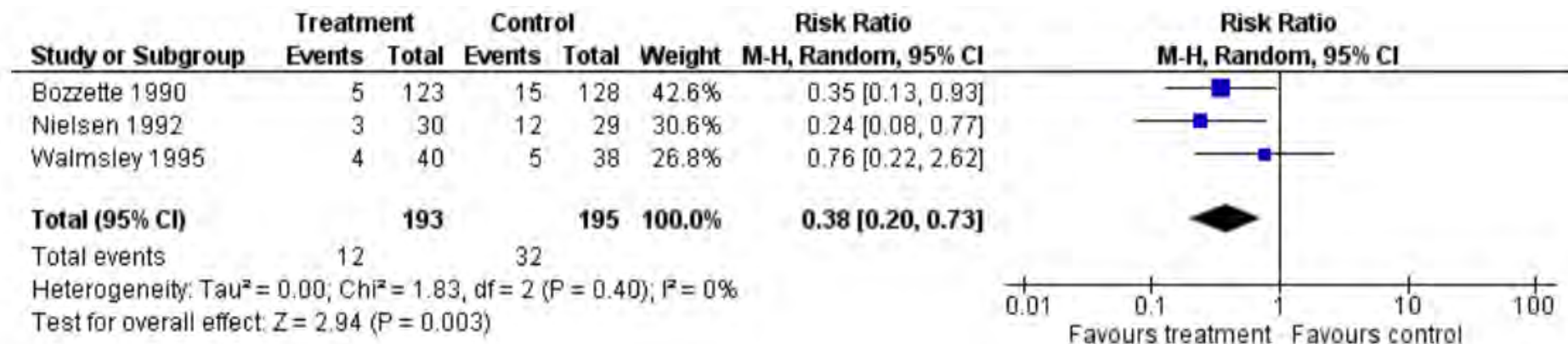
Prednisone 40 mg PO bd Days 1 – 5,

Prednisone 40 mg PO od Days 6 – 10

Prednisone 20 mg PO od Days 11 - 21

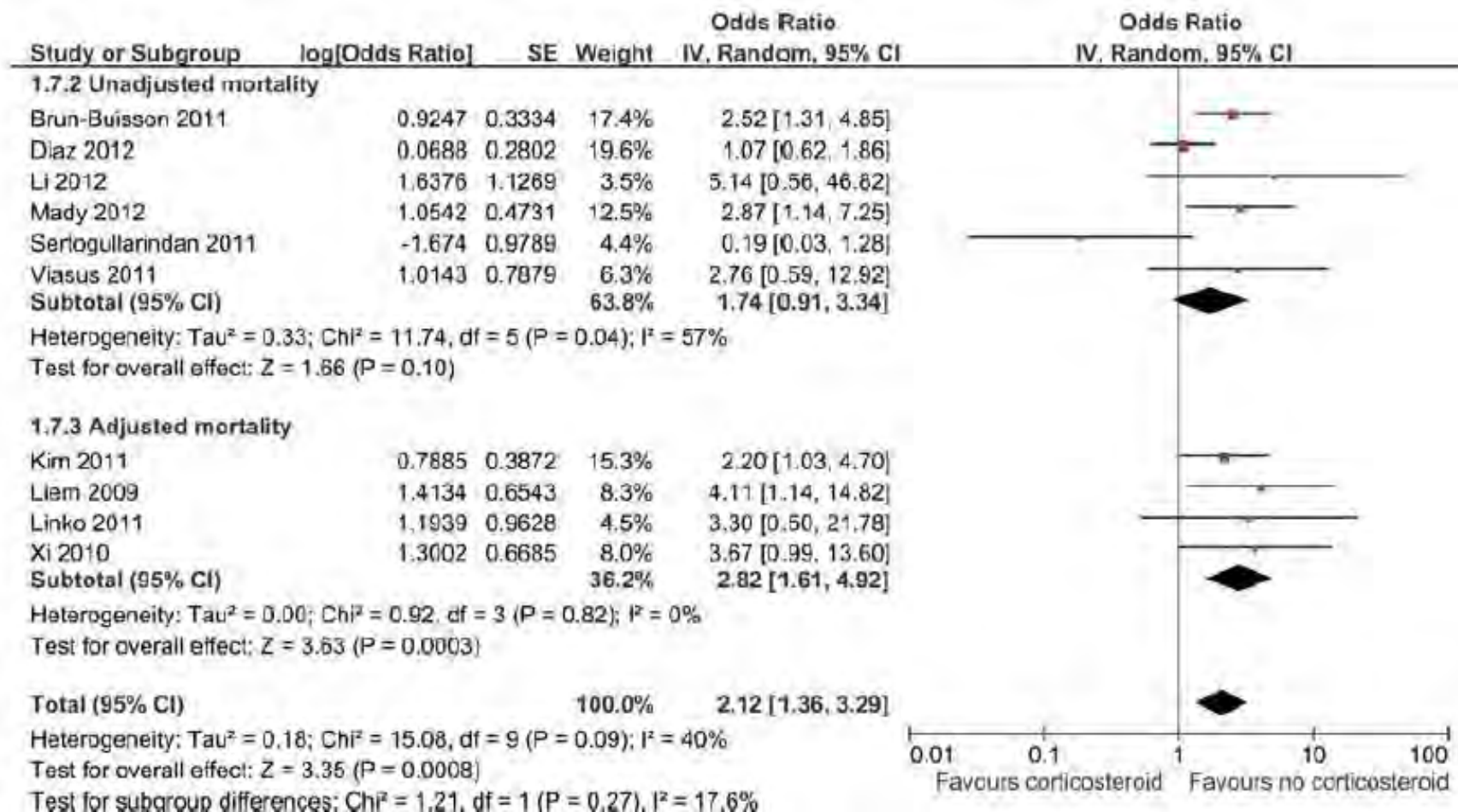
Cochrane review (2015): Steroids in PCP

Mechanical ventilation (3 studies): 6.2% vs 16.4%
RR 0.38 (0.2 to 0.73)



Systematic review: corticosteroids in influenza

No trials. Important concerns – indication bias.



Steroids in pneumonia – summary

- Severe CAP – mortality benefit?? 3 more trials
- Non-severe CAP - no mortality benefit
- PCP - mortality benefit. 21 days steroids
- Influenza - harm? No RCTs.

NICE Pneumonia Guideline Dec 2014

Do not routinely offer a glucocorticosteroid to patients with community-acquired pneumonia unless they have other conditions for which glucocorticosteroid treatment is indicated.

Sepsis Clinical Practice Guideline (BMJ 2018)

Weak recommendation for corticosteroids; both steroids and no steroids are reasonable options.

Typical patient in trials:

- Critically ill (32% mortality)
- Pulmonary infections (44%)
- Most septic shock (refractory to fluids/vasopressors)

Antivirals: current status

Clinical Trials (less bias)

Healthy community patients
Seasonal flu

Symptom benefit (1 day)
Complications?
Hospitalisations?
Mortality?

Cohort studies (more bias)

Hospitalised patients
Pandemic flu

Mortality benefit (20 – 30%?)
Pneumonia?

Antivirals: Cochrane systematic review

Jefferson T et al April 2014

- Time to first symptom alleviation – reduced by 16.8 h (95% CI 8.4 to 25.1 h, $p < 0.0001$), or 7 to 6.3 days.
- Hospitalisations (1.4% v 1.8%) No significant effect
- Harms
 - nausea (11% v 6%, Risk Ratio 1.57, 95% CI 1.14 to 2.15)
 - vomiting (9% v 3%, RR 2.43, 95%CI 1.75 to 3.38)

PRIDE dataset: IPD meta-analysis: cohort study, H1N1 Pandemic, global

- NAls associated with **Mortality reduction** – aOR (95% CI; p value)
- all ages (Treat any time vs none) 0.81 (0.70 to 0.93; p=0.002)
 - Influenza confirmed 0.82 (0.70 to 0.95; p=0.010)
 - A) Adults 0.75 (0.64 to 0.87; p<0.001)
 - B) Adults in critical care 0.72 (0.56 to 0.94; p=0.016)

PHE guidance on use of antiviral agents for the treatment and prophylaxis of influenza (2014-15)

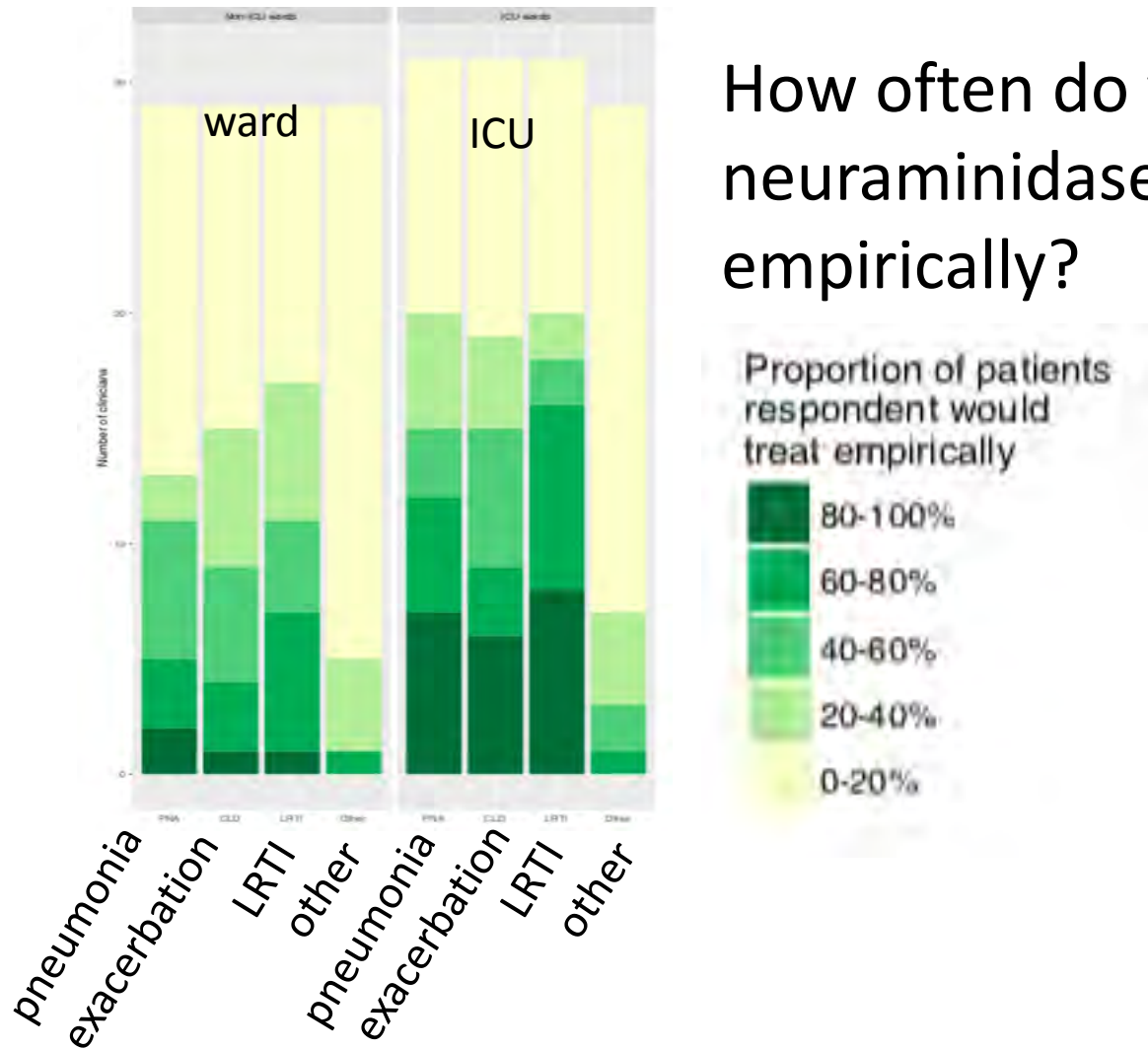
Version 5.1, January 2015

- **All patients with complicated influenza should receive treatment, usually in hospital.**
- **Treatment should be started as early as possible but should always be given, no matter how long after onset of illness. Do not wait for laboratory confirmation.**

PHE Definition of Complicated influenza: Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition

Physicians' attitudes to antiviral use

How often do you prescribe neuraminidase inhibitors empirically?



British Thoracic Society

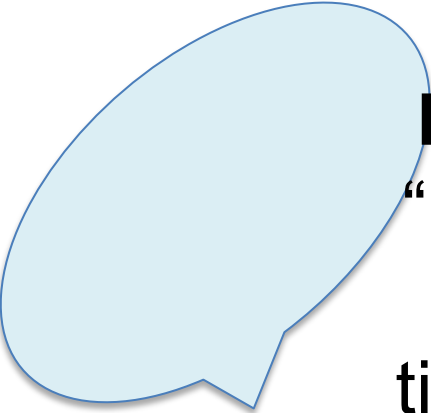
CAP Care Bundle



COST

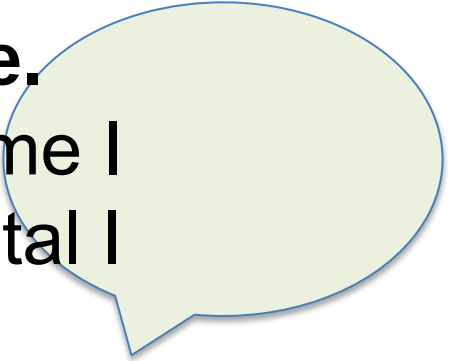
- CXR < 4 hours
- O₂ assessment < 1 hour
- Severity assessment (CURB65 score)
- Timely & targeted antibiotics < 4 hours

?corticosteroids - ?antivirals



Barbara 74: 6 weeks after discharge.
“I'm now nearly back to normal, but I still
"hit the wall" I lose colour and get very
tired my husband tells me to stop and sit
down”

Caren 31: 3 weeks after discharge.
“I'm a strong swimmer but the first time I
swam after coming home from hospital I
only managed 5 lengths and I was
gasping for breath just trying to fill
my lungs.”



Healthcare contact post-discharge

- 3 hospitals East Midlands, n=126.
- Working age adults. Mean age 50 yrs. 89% CURB65 0 – 1.
- Re-consultation 6 weeks n=71 (66%), 90% with GP
- Of 64 pts seen by GP, 37% received antibiotics.
- Readmission n=5 (4.5%) - (3 had seen GP).

<i>Time after hospital discharge</i>	<i>Frequency of healthcare re-consultation visits</i>	
	GP*	Emergency care service
Week 1	20 (33.9)	4 (30.8)
Week 2	21 (35.6)	6 (46.2)
Week 3	4 (6.8)	2 (15.4)
Week 4	12 (20.3)	1 (7.7)
≥Week 5	2 (3.4)	0 (0.0)



The Pneumonia Trust

Improving outcomes in adults with pneumonia

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Recovering From Pneumonia

The time taken to recover from pneumonia will vary on an individual basis, depending on the severity of the illness, presence of chronic health problems and age.

The following time intervals could be expected as a rough guide:

- **1 week-** resolution of fever
- **6 weeks-** improvement in cough and breathlessness
- **3 months-** resolution of most symptoms although tiredness may persist
- **6 months-** return back to normal



[Next: The Pneumonia Diaries](#)



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CXR 2 – 3 months post-pneumonia

	Cohort	Abnormality	Cancer
US (n=618)	Outpatients	3.7%	1.5%
Canada (n=3398)	Hospital 50%		1.1%
NZ (n=302)	Hospital		2%
US (n=40,744)	Hosp, >65yr		2.4%*

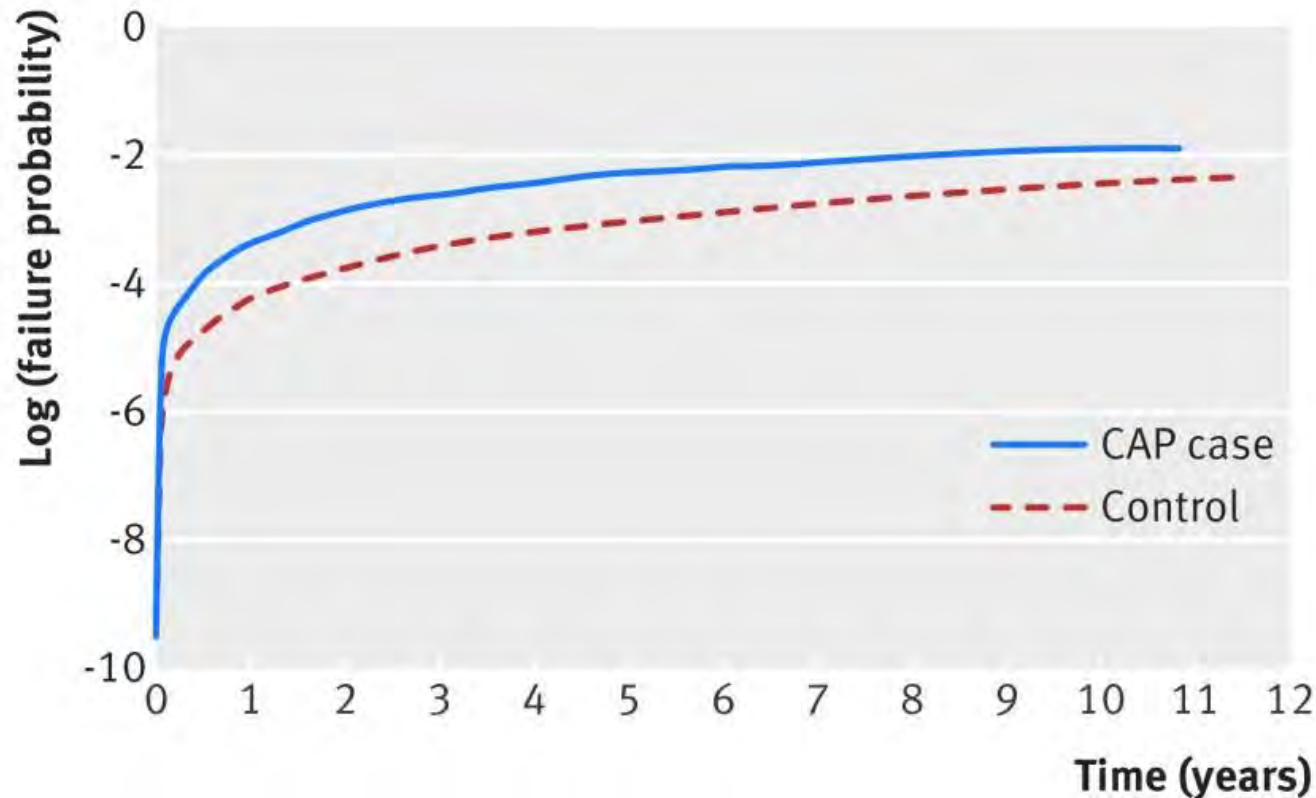
*9.2% had cancer in 5 yr period, median time 297 days.

Factors associated with cancer: chronic pulmonary disease, any prior malignancy, smoking

Cumulative incidence of heart failure post-pneumonia: Canadian cohort over 10 years

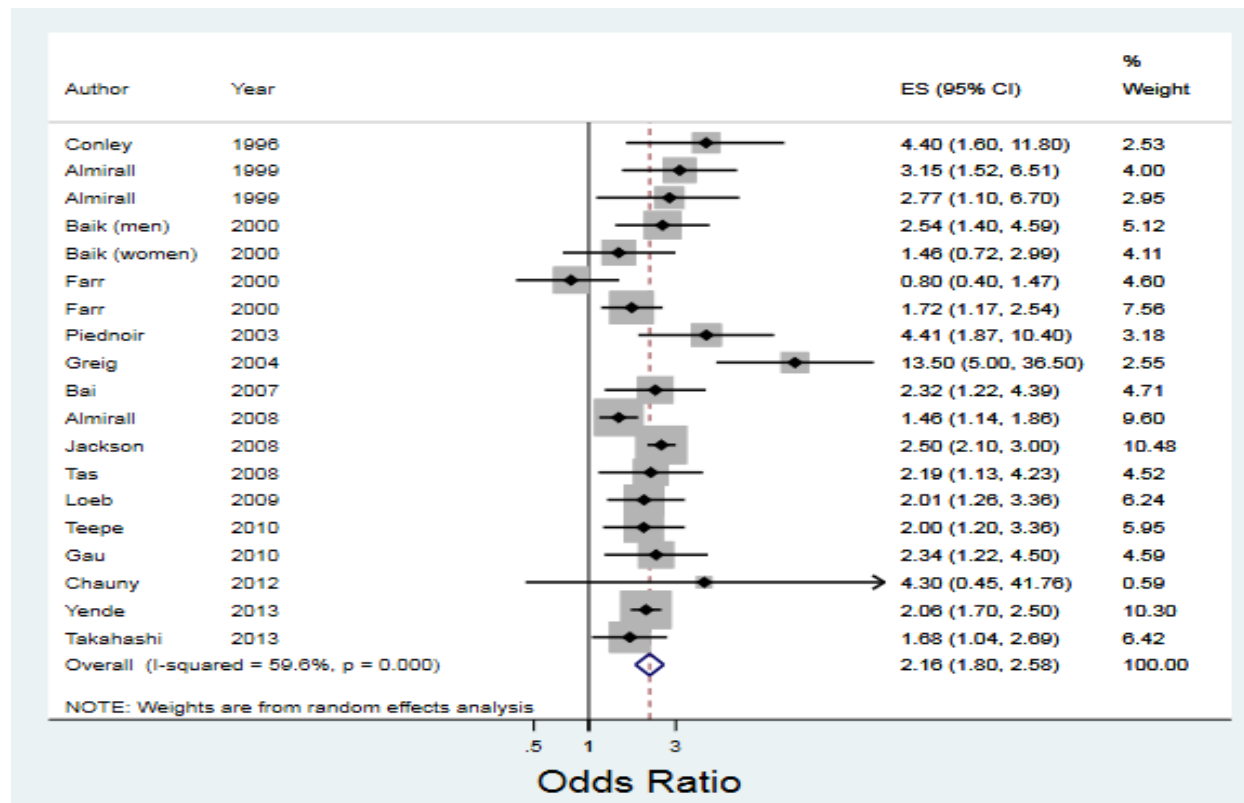
Incident heart failure 12% vs 7%

Adjusted hazard ratio 1.61, 95% CI 1.44 to 1.81



Systematic review of Smoking and CAP

Current smokers are 2x more likely to have CAP
(OR 2.16; 95% CI 1.80-2.58; 18 studies)



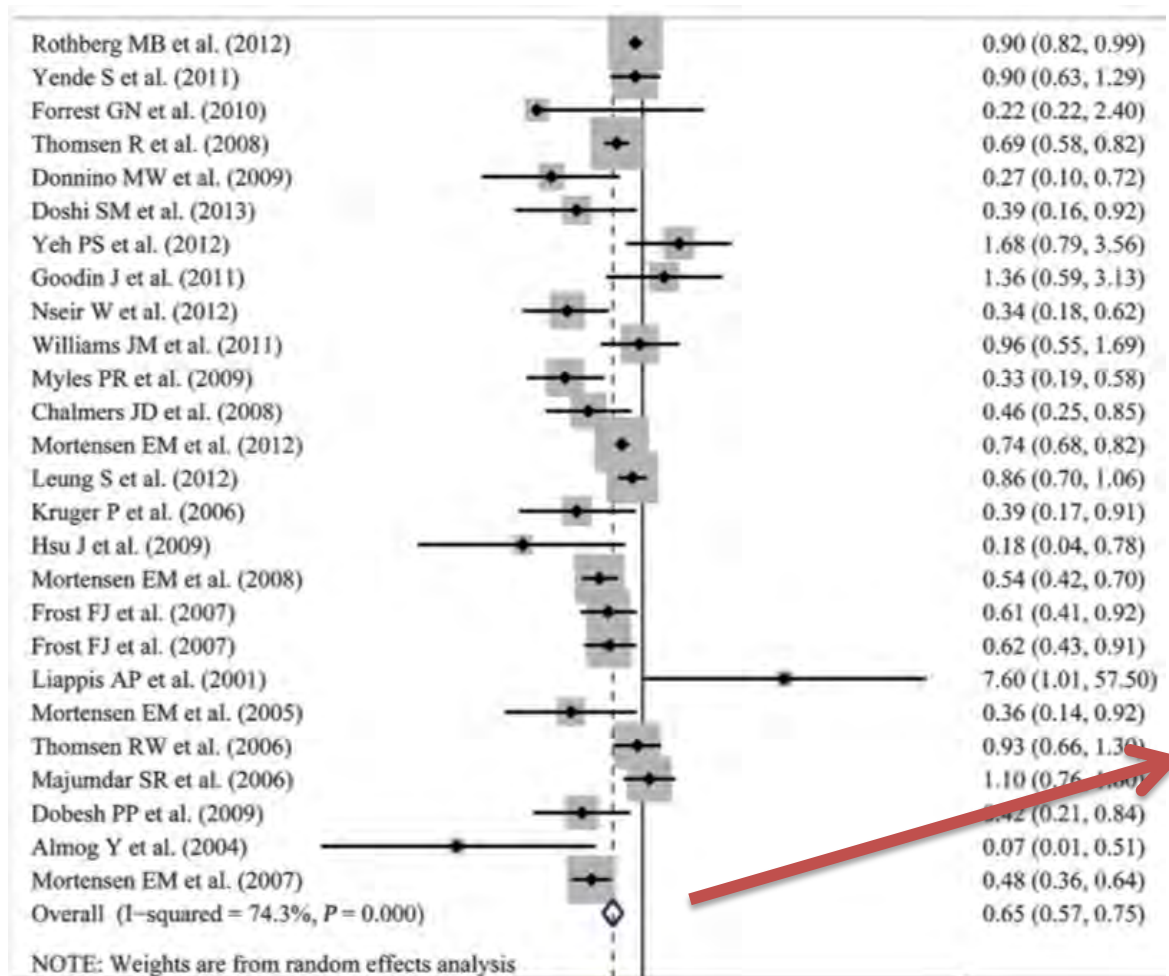
Summary

- Recognise uncertainty → Review diagnosis
- Travel history, HIV
- Consider corticosteroids – for septic shock - ICU
- Consider antivirals – for flu
- Patient information at discharge
- Smoking cessation advice

Thank you

Statins in Infection/Sepsis

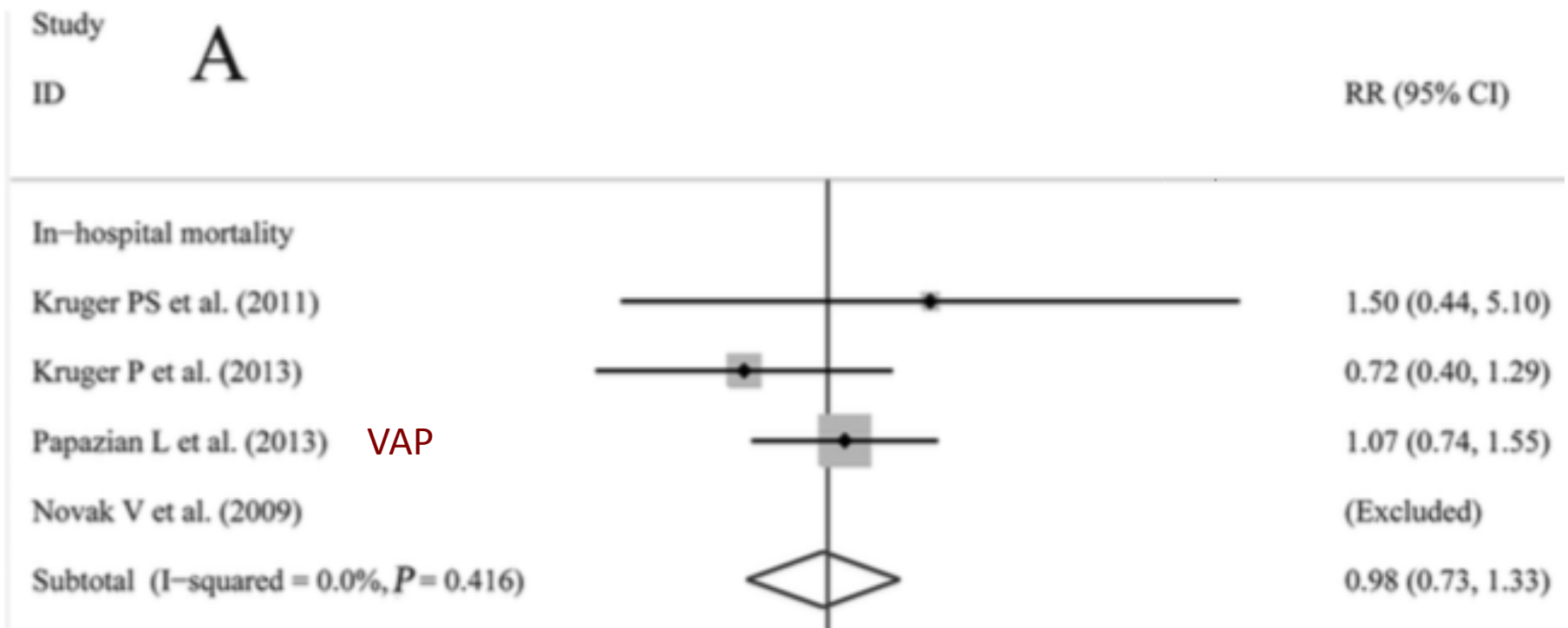
Systematic Review Cohort Studies, n=337,648 (27 studies)



Overall
RR 0.65 (0.57 to 0.75)

Statins in Infection/Sepsis

Systematic Review RCTs, n=867 (5 studies)

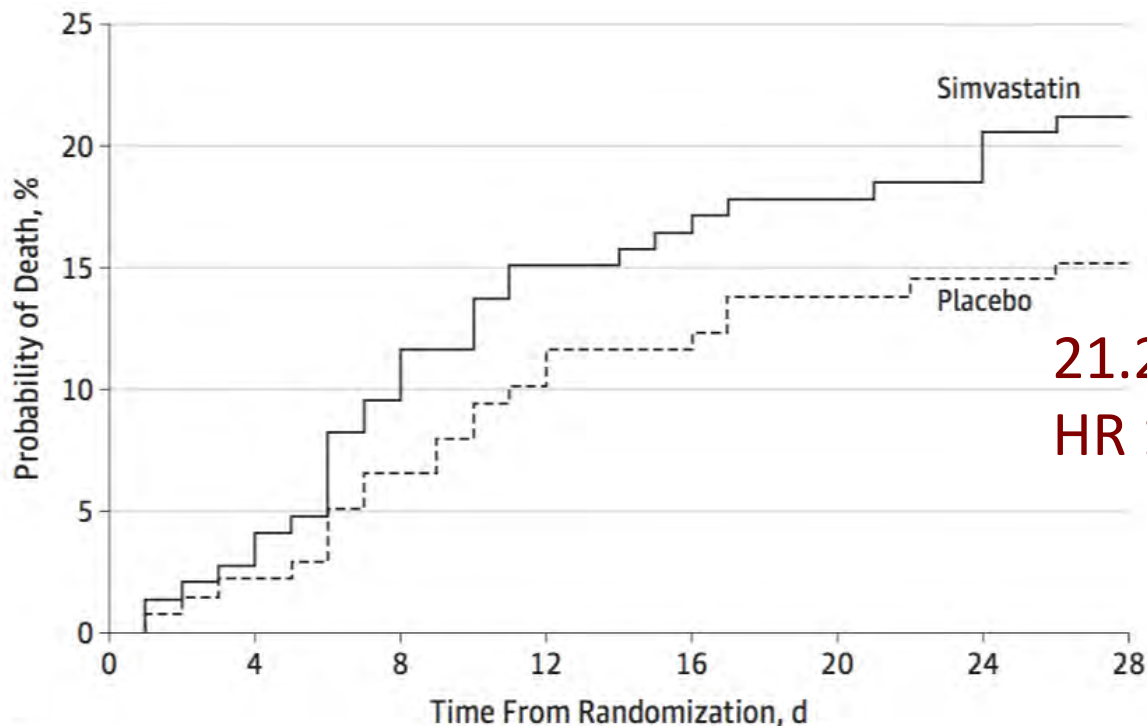


Summary RR 0.98 (0.73 to 1.33)

Simvastatin in Ventilator Acquired Pneumonia

French ICUs. 2010 – 2013. n=251 (planned n=1002)

Simvastatin 60 mg daily, onwards



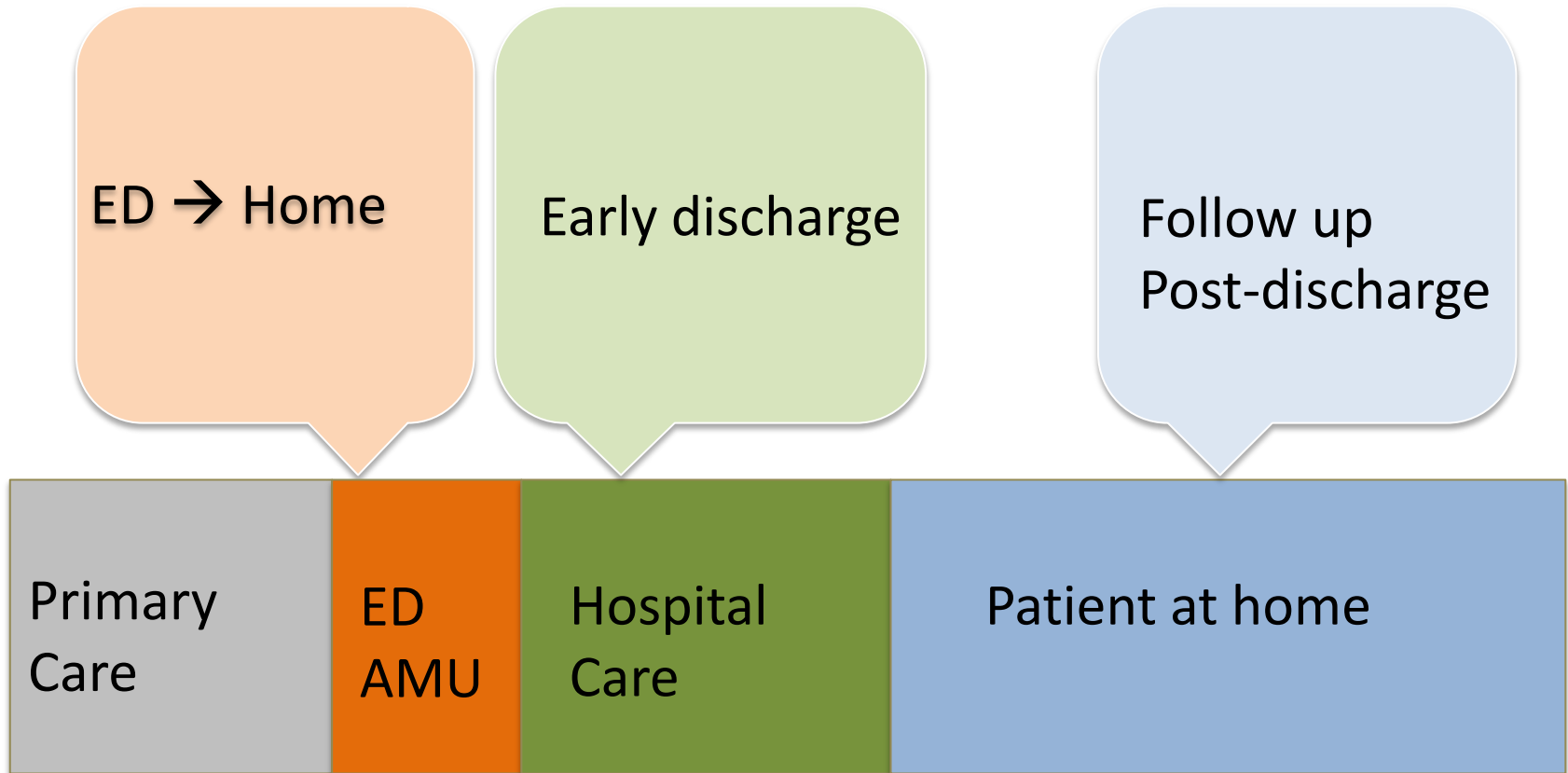
21.2% vs 15.2%

HR 1.45 (0.83 to 2.51)

No. at risk								
Simvastatin	146	142	132	124	122	120	119	115
Placebo	138	135	129	124	122	119	118	117

Statin use in last month: 7% vs 11%

Outpatient management of CAP : a secondary care perspective



Early discharge after admission: role of specialists

Nottingham. Short stay unit – nurse triage.

	Resp Med	Non-specialist	
CAP	n=123	n=174	
LOS d (median)	1.7	3.0	(p<0.01)
Discharged <24h	43%	32%	
Readmission 30d	4%	4%	

Cellulitis	n=229	n=428	
LOS d (median)	2.8	2.6	
Discharged <24h	25%	31%	
Readmission 30d	3.5%	3.5%	

CXR 2 – 3 months post-pneumonia

	Cohort	Abnormality	Cancer
US (n=618)	Outpatients	3.7%	1.5%
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US (n=40,744)	Hosp, >65yr		2.4%*

*9.2% had cancer in 5 yr period, median time 297 days.

Factors associated with cancer: chronic pulmonary disease, any prior malignancy, smoking

NICE Pneumonia Guideline Dec 2014

- Use **clinical judgment in conjunction** with the CURB65 score to guide the management of CAP, as follows:

Consider home-based care for pts with a CURB65 score of 0 or 1.

- Offer a 5-day course of a **single antibiotic** to patients with low-severity CAP. **Consider amoxicillin** in preference to a macrolide or a tetracycline.

CURB65 score

Score 1 point for each feature present:

Confusion

Urea > 7 mmol/l

Respiratory rate ≥ 30 /min

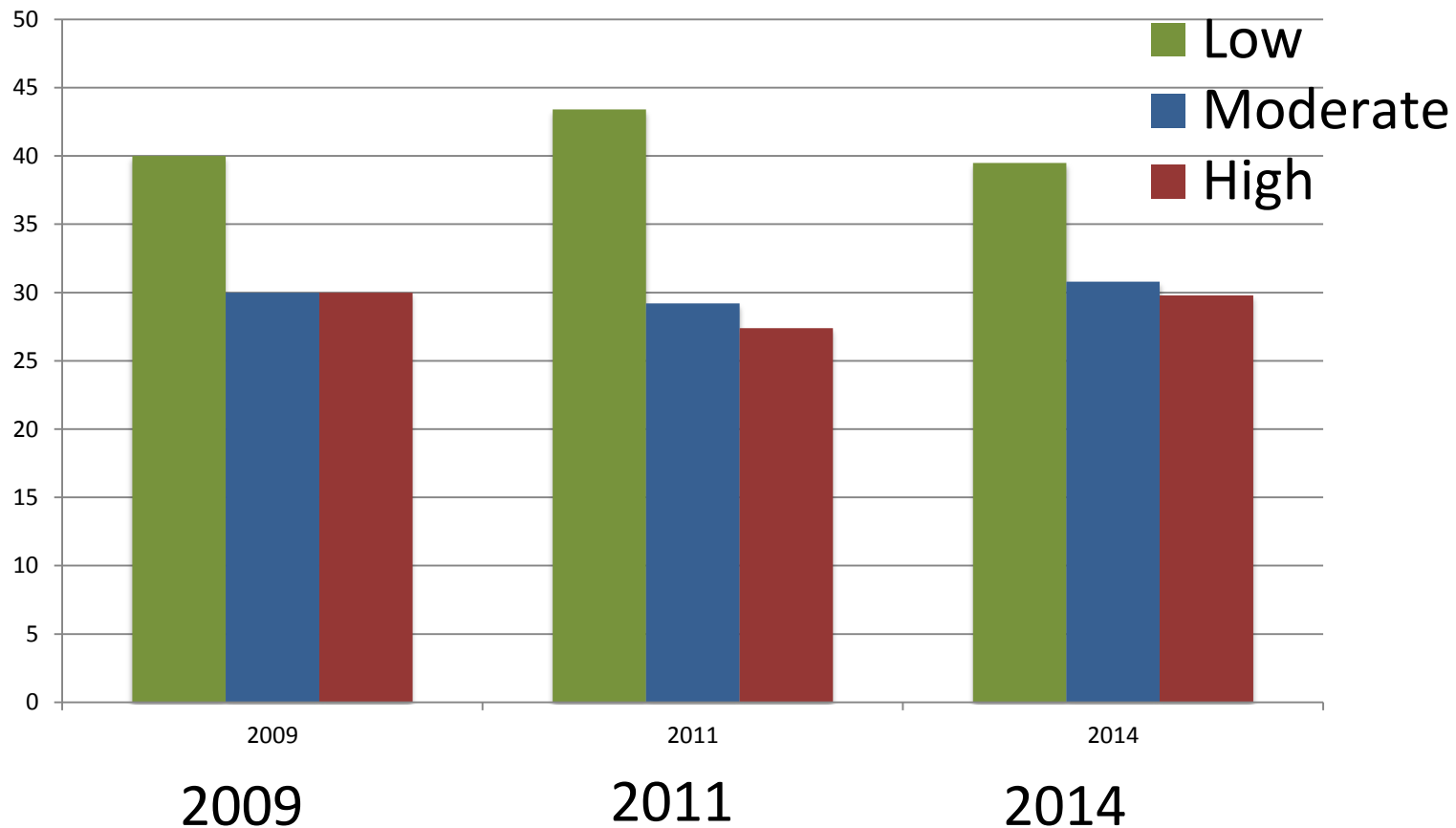
Blood pressure, SBP < 90 or DBP ≤ 60 mmHg

Age ≥ 65 years

Score	0 – 1	2	3 - 5
30-day risk of mortality	<3%	3-15%	>15%

Low-severity CAP – 40%

British Thoracic Society national CAP audit (>6,000 patients)



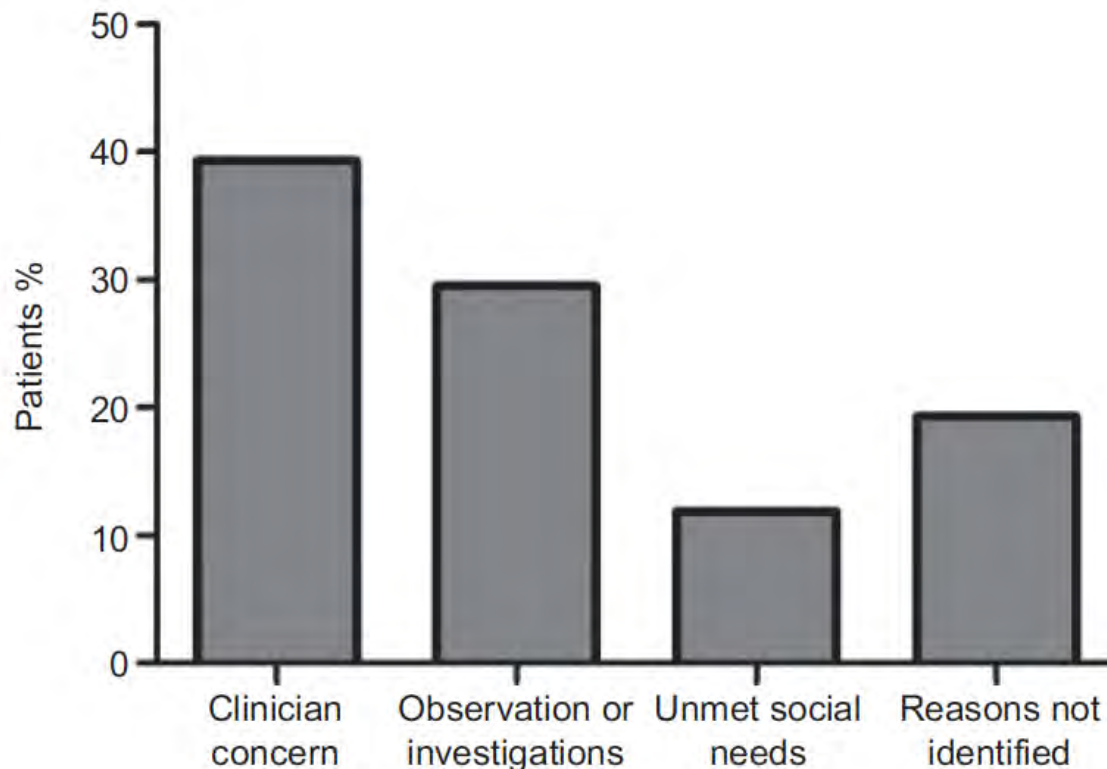
Outpatient treatment from ED

Barcelona (Spain) 17%

Utah (US) 42%

Edmonton (Canada) 56%

Edinburgh (UK) ~ 10% (25% of low-severity CAP)



Cilloniz ERJ 2012, Jones BMC Pul Med 2014,
Eurich AJRCCM 2015, Choudhury ERJ 2011

Reasons for hospitalisation of low-risk patients – 12 US EDs

No (%) low-risk patients (n=249)

Unstable Comorbid illness	178 (71%)
Abnormal symptoms/signs/tests	73 (29%)
Pneumonia more severe than PSI	30 (12%)
Primary care requested hospitalisation	40 (19%)
Patient/family request	24 (10%)
Psychosocial issues	16 (6%)
Problems with outpatient therapy	28 (11%)
Required hospital services	12 (5%)

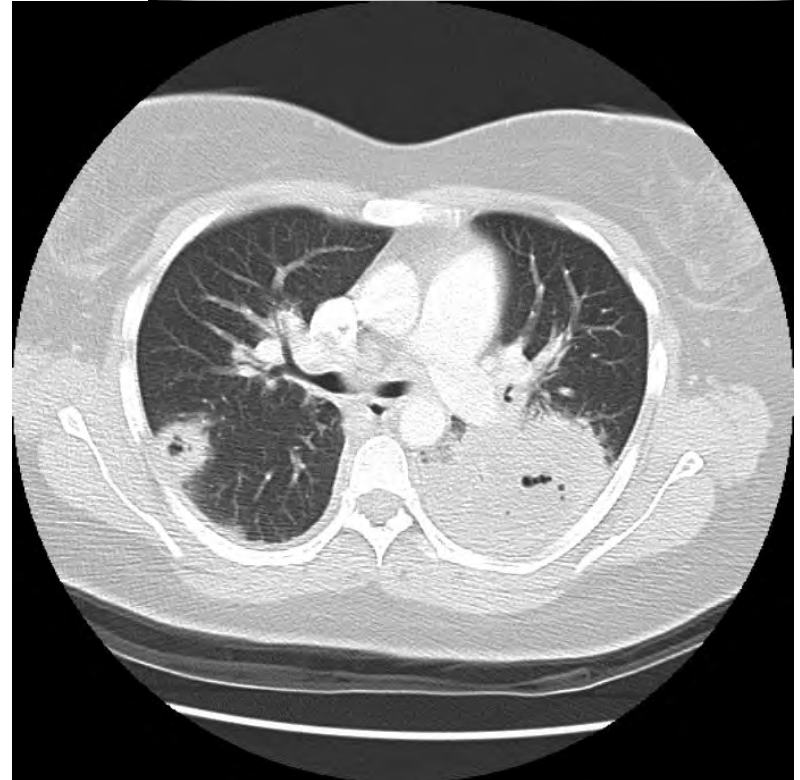
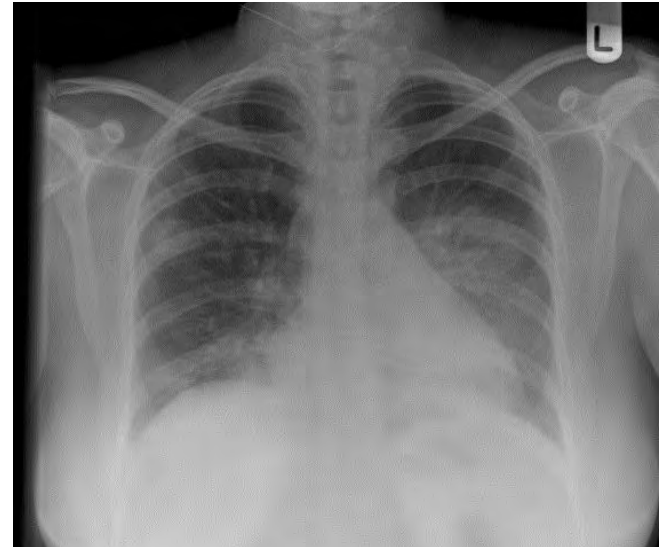
Patients with CAP discharged from ED

Barcelona. Single site. (ED physicians with interest in RTIs)

- 3,223 adults in ED → 568 (17.6%) treated as OP.
- 301 (53.0%) males, mean age 47.2 yrs (19% aged >65 yrs)
- Low-mortality risk (PSI I-III, 97.0%; CURB65 0- 1, 94.7%)
- Pleural effusion: n=30 (5.3%). 5 had empyema → readmitted
- 30-day mortality: n=3 (0.5%).
- Readmitted within 30-days: n=13 (2.3%). 69% comorbidities.

CASE: Cavity in a lady

- 33-year old UK-born Asian lady.
- 4 weeks fever, cough, discoloured sputum. Antibiotics from GP had not helped.
- 2 days prior to admission – haemoptysis.
- No travel outside the UK since birth. No TB contacts.
- WCC 19, CRP 350



Non-infective CAVITIES

Masses

- Cancer – lung, mets
- Wegener's
- Rheumatoid nodules
- Sarcoid

Consolidation

- Infarction
- COP
- Lymphoma
- ABPA

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Head & neck

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CT in suspected CAP

Cohort study, n=319. Hospitalised adults (ESCAPED study)
CT within 4h admission

	Physician CAP Probability Level after Chest CT Scan			
	Definite	Probable	Possible	Excluded
Physician CAP probability level before chest CT scan				
Definite	107	15	10	11
Probable	41	16	13	48
Possible	12	4	7	31
Excluded	2	0	0	2
Total	162 (50.8%)	35 (10.9%)	30 (9.4%)	92 (28.8%)

CT in suspected CAP

Cohort study, n=319. Hospitalised adults (ESCAPED study)

CT within 4h admission

	Total	Changes in Classifications	
		Number	Modification Rates (95% CI)
Physician CAP probability level before chest CT scan			
Definite	143 (44.8%)	36	25.2% (18.1–32.3)
Probable	118 (36.9%)	102	86.4% (80.3–92.6)
Possible	54 (16.9%)	47	87.0% (78.1–96)
Excluded	4 (1.25%)	2	50.0% (1.0–99.0)
Total	319	187	58.6% (53.2–64.0)

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	Number	Modification Rates (95% CI)
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118 (36.9%)	102	86.4% (80.3–92.6)
54 (16.9%)	47	87.0% (78.1–96)
4 (1.25%)	2	50.0% (1.0–99.0)
319	187	58.6% (53.2–64.0)

CT-only pneumonia: pathogens

US multi-centre EPIC cohort (n=2251). Physician directed CT scans (33%)

CT-only pneumonia
n=66

Pneumonia on CXR
n=2185

Any virus	20 (30.3)	570 (26.1)
Influenza	4 (6.1)	126 (5.8)
Parainfluenza virus	1 (1.5)	66 (3.0)
Coronavirus	0 (0)	53 (2.4)
Human metapneumovirus	4 (6.1)	84 (3.8)
Respiratory syncytial virus	0 (0)	68 (3.1)
Human rhinovirus	11 (16.7)	182 (8.3)
Adenovirus	1 (1.5)	31 (1.4)

Bacteria

8 (12)

29 (13.5)