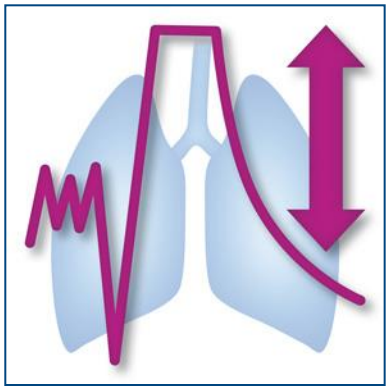
Pneumo Update Europe 2016

24-25 June, Prague

Pneumonia



Mark Woodhead, UK

Contents

- Diagnosis of pneumonia
- Viruses in CAP
- Pathogen detection
- Time to first antibiotic
- Empirical antibiotic therapy
- Steroids in CAP & Influenza
- Long term effects of CAP

Diagnosis of Pneumonia

Diagnosis of Pneumonia
State of the Art

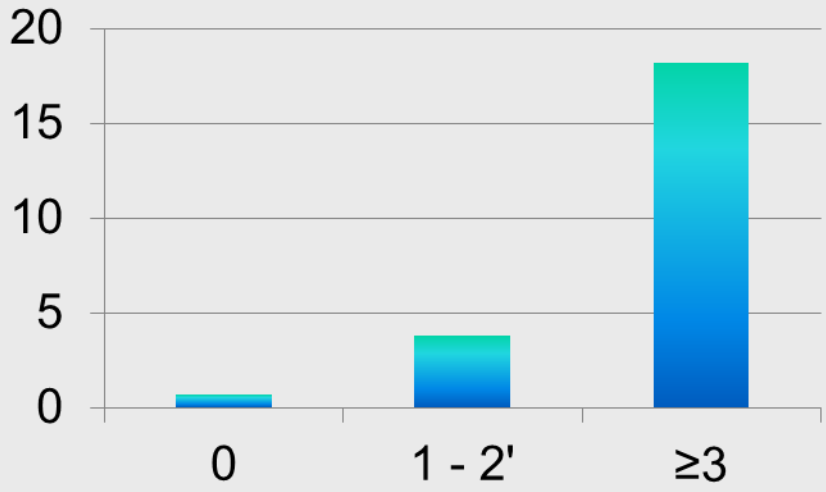
- LRTI is common, pneumonia is rare
- LRTI is self-limiting, Pneumonia=antibiotic
- Overuse of antibiotic for LRTI=resistance
- Diagnosis of pneumonia outside hospital is difficult especially when no CXR
- GPs rely on signs and symptoms
- Prediction rules may assist diagnosis

Van Vugt Model for CAP Prediction

Score x 1 for each of

- Absence of runny nose
- Raised pulse (>100/min)
- Breathlessness
- Fever (temperature >37.8°C)
- Crackles
- Raised CRP (>30 mg/L).
- Diminished vesicular breathing

Score	No of Patients	Pneumonia
0	572 (20.3)	4 (0.7)
1-2	1902 (67.4)	73 (3.8)
≥3	346 (12.3)	63 (18.2)



van Vugt et al. BMJ. 2013; 346:f2450–f2450. doi: 10.1136/bmj.f2450

Meta-analysis: 6 ‘Rules’; 8 Datasets

Pneumonia (%): 5,5,12,13,13,20,21,43

	pooled AUC (95% CIs)
van Vugt et al.	0.79 (0.74–0.85)
Heckerling et al.	0.72 (0.68–0.76)
Diehr et al.	0.65 (0.61–0.68)
Singal et al.	0.64 (0.61–0.67)
Melbye et al.	0.56 (0.49–0.63)
Hopstaken et al.	0.53 (0.5–0.56)

Schierenberg A, et al. (2016) PLoS ONE 11(2): e0149895. doi:10.1371/journal.pone.0149895

Take-Home Message

- Pneumonia diagnosis remains difficult
- Prediction rules may help
- Van Vugt model may be the best
- ? Guides when to withold antibiotic
- CXR remains *gold standard*

Viruses in CAP

Viruses in CAP - State of the Art

- Previously difficult to diagnose
- real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) – new standard
- What does + ve result mean?
  - subclinical infection,
  - persistent shedding after a prior infection
  - infection restricted to the upper respiratory tract,
  - or infection involving the lower respiratory tract

Viruses in CAP

- Asymptomatic controls
  - Children 531 (144 age <2)
  - Adults 238
- CAP
  - Children 832
  - Adults 192
- Nasopharyngeal and oropharyngeal swabs

Self et al *Journal of Infectious Diseases* 2016:213:584-591

Viruses in CAP

- rRT-PCR. Cycle threshold <40
- human rhinovirus (hRV)
- respiratory syncytial virus (RSV)
- human metapneumovirus (hMPV)
- adenovirus (AdV)
- influenza A and B (influenza)
- parainfluenza (PIV) virus types 1, 2, and 3
- coronavirus(CoV) 229E, HKU1, NL63, and OC43

Self et al *Journal of Infectious Diseases* 2016:213:584-591

Viruses in CAP

Virus-specific attributable fraction (**AF**)

An estimate of the proportion of patients with CAP positive for a virus who have symptomatic illness due to that virus

Self et al *Journal of Infectious Diseases* 2016:213:584-591

Viruses in CAP - children

AF = attributable fraction; NC = not calculated)

	Asymptomatic	CAP	Pvalue	AF
Any virus	127 (24.4)	572 (68.8)	< 0.01	NC
hRV	90 (17.3)	182 (21.9)	0.04	0.12
RSV	**10 (1.9)**	**221 (26.6)**	**< 0.01**	**0.93**
hMPV	**8 (1.5)**	**126 (15.1)**	**<0.01**	**0.90**
AdV	16 (3.1)	53 (6.4)	<0.01	0.44
Flu A, B	**0**	**28 (3.4)**	**<0.01**	**NC**
PIV	10 (1.9)	39 (4.7)	0.01	0.56
CoV	8 (1.5)	36 (4.5)	<0.01	0.68

Self et al *Journal of Infectious Diseases* 2016:213:584-591

Viruses in CAP - adults

AF = attributable fraction; NC = not calculated)

	Asymptomatic	CAP	Pvalue	AF
Any virus	5 (2.1)	47 (24.5)	<0.01	0.93
hRV	**2 (0.8)**	**21 (10.9)**	**<0.01**	**NC**
RSV	0	3 (1.6)	.09	0.93
hMPV	**1 (0.4)**	**8 (4.2)**	**.01**	**NC**
AdV	0	3 (1.6)	.09	NC
Flu A, B	**0**	**5 (2.6)**	**.02**	**NC**
PIV	0	3 (1.6)	.09	NC
CoV	2 (0.8)	6 (3.1)	.14	0.69

Self et al *Journal of Infectious Diseases* 2016:213:584-591

Viruses in CAP – children – 2

- 121 cases, (93 cases WHO criteria for radiological pneumonia), and 240 controls.
- Viruses in 81% (56% of the controls).
- Influenza virus, metapneumovirus and respiratory syncytial virus in 60% of cases and were significantly associated with CAP with ORs >10.
- no association with parainfluenza virus, human enterovirus or rhinovirus
- coronavirus and bocavirus were negatively associated with CAP

Rhedin S, et al. Thorax 2015;70:847–853. doi:10.1136/thoraxjnl-2015-206933

Viruses in CAP - Take-Home Message

- Virus infection much less important in adults
- Detections of influenza, respiratory syncytial virus, and human metapneumovirus among patients with CAP of all ages probably indicate an aetiologic role,
- detections of parainfluenza, coronaviruses, rhinovirus, and adenovirus, especially in children, requires further scrutiny
- ? Implication for anti-virals and vaccines

Pathogen Detection

Pathogen detection - State of the Art

- Many microbial causes of CAP
- Antibiotic therapy should be directed to causal pathogen
- Conventional microbiological tests slow and lack sensitivity
- PCR based detection fast and sensitive

Pathogen Detection

- 323 adults with CAP
- 56% ≥ 65
- 6.3 % CURB65 4 or 5
- 7.4% ventilated, 6.2% died
- Sputum 96%, ET aspirate 4%

Gadsby et al *Clinical Infectious Diseases* 2016;62:817-823

Pathogen Detection

Conventional culture + r-tPCR for 26 pathogens

- Streptococcus pneumoniae;
- Haemophilus influenzae;
- Moraxella catarrhalis;
- Staphylococcus aureus;
- Escherichia coli;
- Klebsiella pneumoniae;
- Pseudomonas aeruginosa;
- Acinetobacter baumannii;
- Mycoplasma pneumoniae;
- Chlamydophila pneumoniae;
- Chlamydophila psittaci;
- Legionella pneumophila;
- Legionella spp.;
- influenza A; influenza B;
- respiratory syncytial virus;
- parainfluenza virus types 1–3;
- adenovirus;
- human coronaviruses 229E, HKU1, NL63, and OC43;
- human metapneumovirus;
- rhinovirus

Gadsby et al *Clinical Infectious Diseases* 2016;62:817-823

Pathogen Detection

		All	Prior Antibiotic
		%	%
Conventional culture	Bacteria	39.3	32.1
r-t PCR	Bacteria	81.1	77.6
Including viruses		86.7	

Gadsby et al *Clinical Infectious Diseases* 2016;62:817-823

Pathogen Detection

Initial empirical antibiotics:

Molecular testing had the potential to lead to:

- De-escalation in number and/or spectrum in 247 (77.2%)
- Escalation in number and/or spectrum in 19 (5.9%) patients
- No change in 54 (16.9%) patients

Gadsby et al *Clinical Infectious Diseases* 2016;62:817-823

Pathogen Detection
Take-Home Message

- r-t PCR has potential to improve antibiotic stewardship

- Will it work in practice?
- Cost effective?

Time to First Antibiotic

Time to First Antibiotic

State of the Art

- Common sense suggests early antibiotic = better outcomes
- Evidence base is poor
- Ethics prevent RCT
- Reliance on retrospective cohort studies
- Mainly one US study restricted to >65s
- Large new cohort study from UK

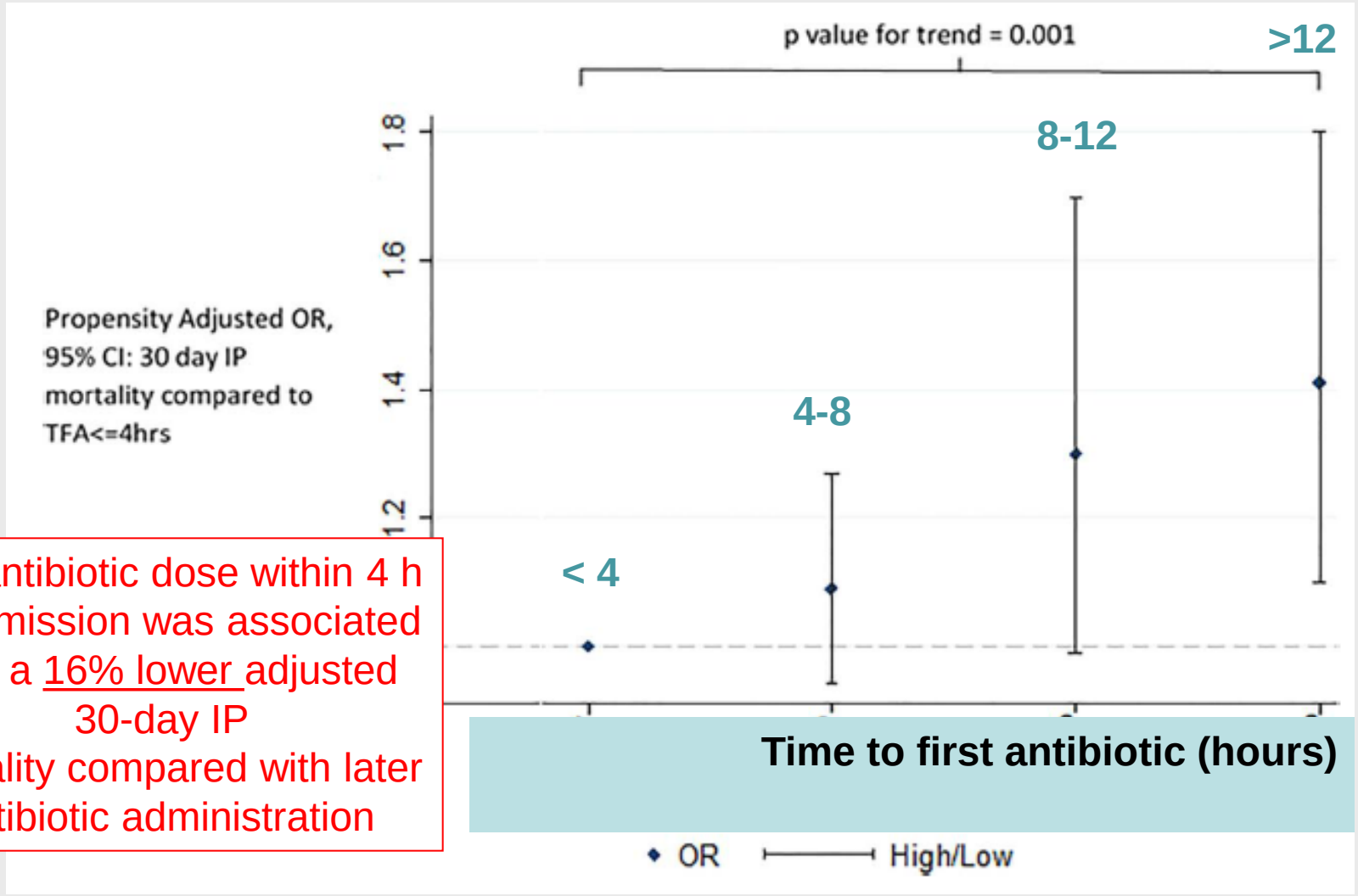
Time to First Antibiotic

- BTS national adult CAP audit during the period from 1 December to 31 January for years 2009/2010, 010/2011, 2011/2012 and 2012/2013
- 188 institutions
- 13,725 adults, median age 75 years (IQR 60.0–85.0)
- CURB65 score ≤1 6045 (44.0%), =2, 4023 (29.3%), ≥3 3657 (26.6%)
- 861 (6.3%) ICU, 30-day IP mortality was 15.0%.
- Median Time to First Antibiotic 3.1 h (IQR 1.8–5.7).
- first dose in ≤4, 4–8, 8–12 and >12 h following hospital admission

in 8642 (63.0%), 2913 (21.2%), 976 (7.1%) ,1194 (8.7%)

Daniel P, et al. *Thorax* 2015;0:1–3. doi:10.1136/thoraxjnl-2015-207513

Time to First Antibiotic



first antibiotic dose within 4 h of admission was associated with a 16% lower adjusted 30-day IP mortality compared with later antibiotic administration

Daniel P, et al. *Thorax* 2015;0:1–3. doi:10.1136/thoraxjnl-2015-207513

Time to First Antibiotic
Take-Home Message

- Reduced mortality with earlier antibiotic
- Retrospective study
- ? Antibiotic effect
- ? Marker for better overall care

- Aim should be to deliver antibiotic as soon as possible after diagnosis

Empirical Antibiotic Therapy

Empirical Antibiotic Therapy – State of the Art

- Whether to cover atypical organisms or not?
- Stratify by place of management or severity?
- B-lactam or B-lactam+macrolide or other?

Empirical Antibiotic Therapy – State of the Art

US

B-lactam + macrolide for all in hospital

Europe

B-lactam alone for non-severely ill

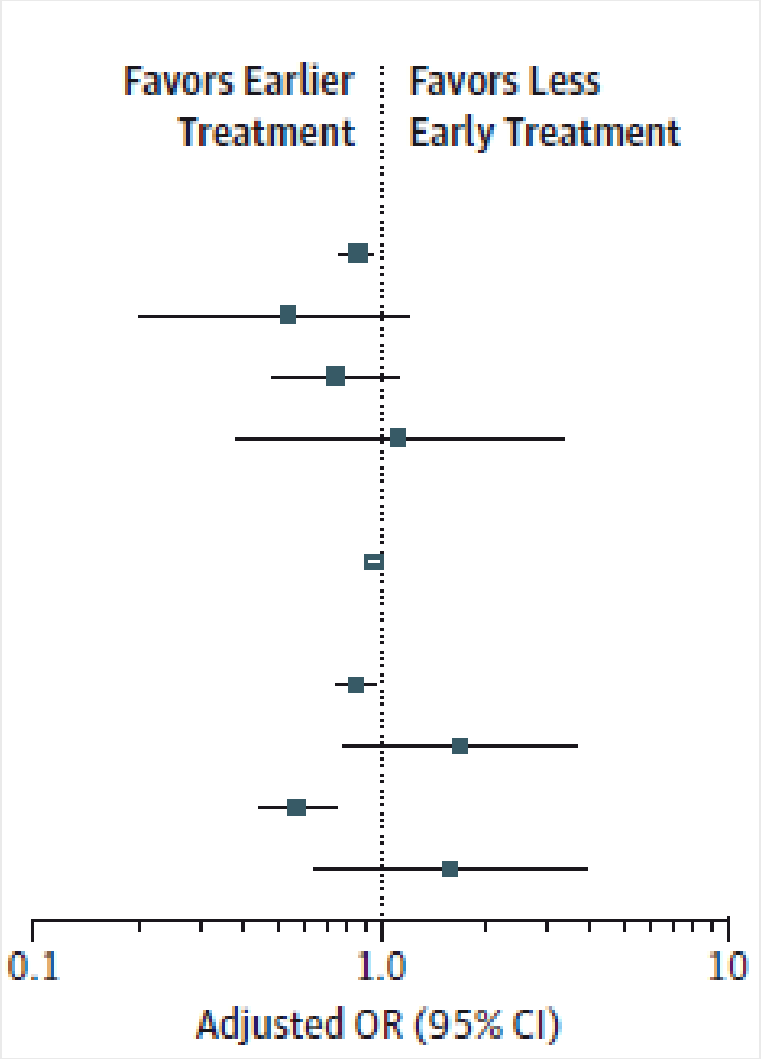
B-lactam + macrolide for severely ill

Antibiotic Therapy for Adults Hospitalized With Community-Acquired Pneumonia
A Systematic Review

Jonathan S. Lee, MD; Daniel L. Giesler, MD, PharmD; Walid F. Gellad, MD, MPH; Michael J. Fine, MD, MSc

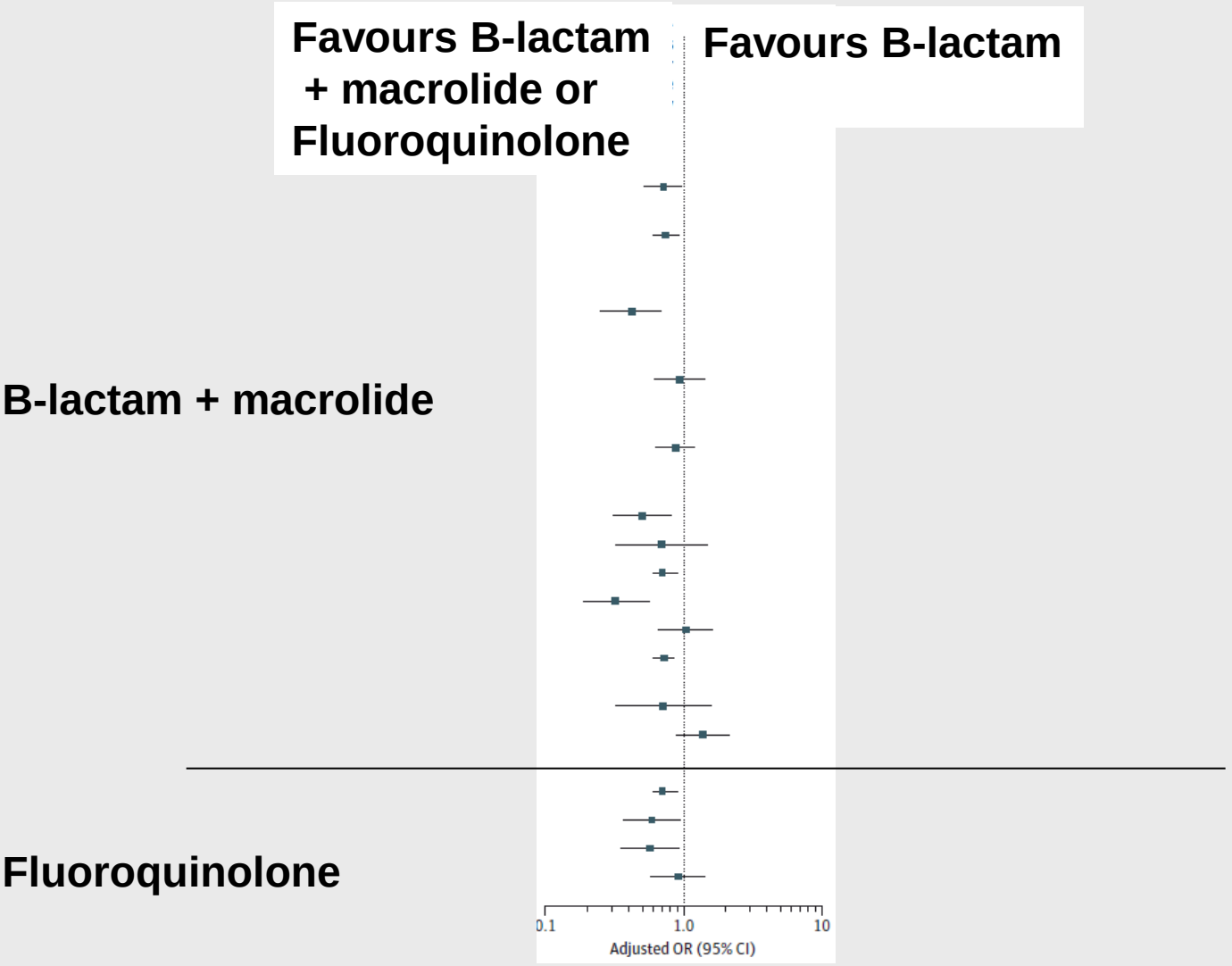
Lee et al *JAMA* 2016;315:593-602

Time to first antibiotic



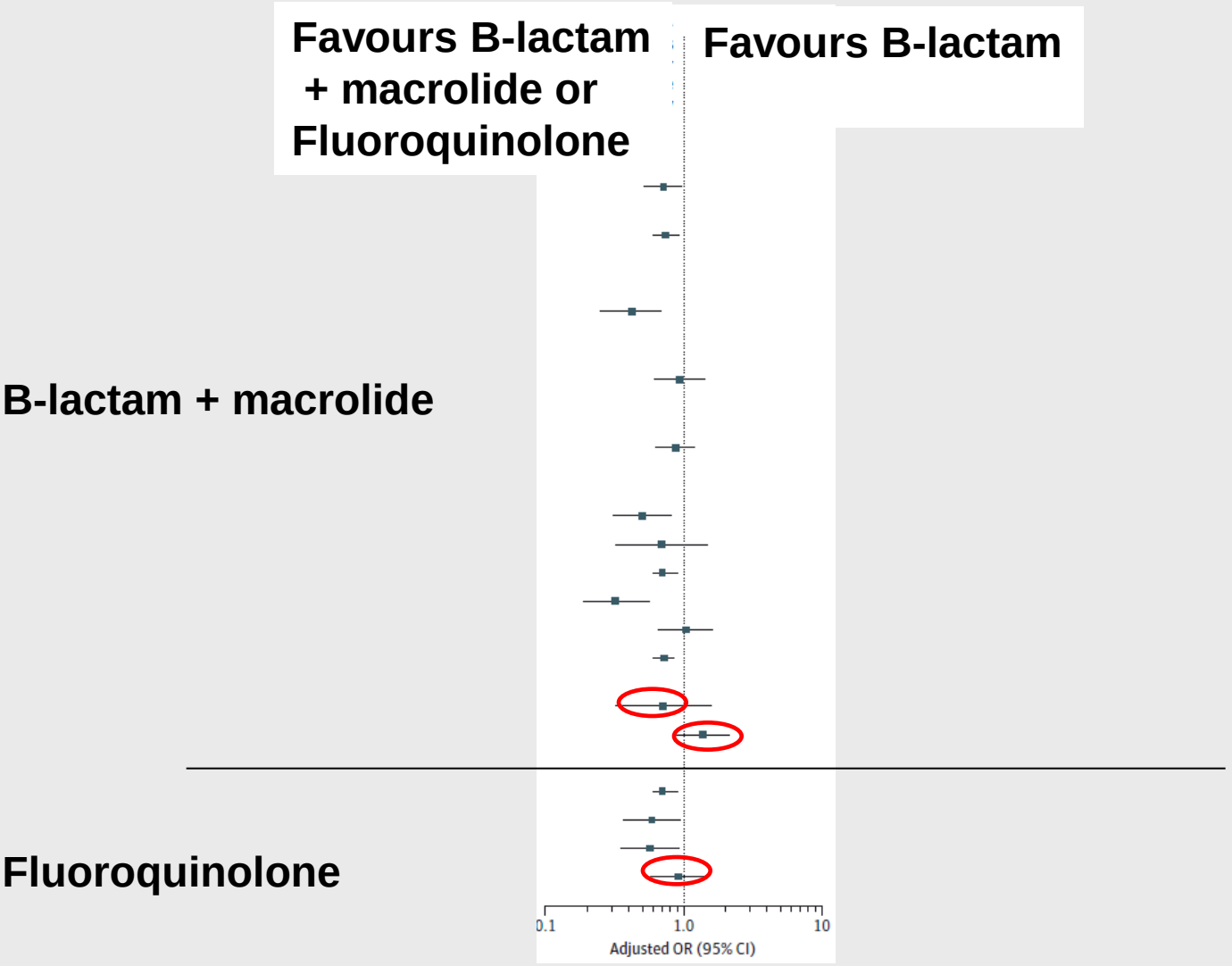
Lee et al *JAMA* 2016;315:593-602

Empirical Antibiotic Therapy



Lee et al *JAMA* 2016;315:593-602

Empirical Antibiotic Therapy



Lee et al *JAMA* 2016;315:593-602

Empirical Antibiotic Therapy
Take-Home Message

- Few RCTs – very low quality evidence
- Absence of objective quality/bias assessment
- Non-RCTs biased by intention
- Mortality 3.4 – 10.2 % (23% in one study)
- Inadequate assessment of harms

Lee et al *JAMA* 2016;315:593-602

Empirical Antibiotic Therapy
Take-Home Message

- Non-severe - evidence for better outcomes with dual therapy is not convincing

  ? Use B-lactam alone

- Severe - use B-lactam + macrolide

Lee et al *JAMA* 2016;315:593-602

Corticosteroids in Community-acquired Pneumonia & Influenza

Steroids in CAP - State of the Art

- Not a current standard of care
- Widely used ? as rescue when Rx failing
- Meningitis and Pneumocystis
- ? benefit in severe CAP, but trials small and biased
- 2 new studies, 4 new systematic reviews and many editorials!

Correspondence

Prednisone for community-acquired pneumonia: not yet time

Varadarajan Baskar[a], Chee Fang Sum[a], Su Chi Lim[a]

Corticosteroids for Severe Community-Acquired Pneumonia: Time to Change Clinical Practice

Marcos I. Restrepo, MD, MSc; Antonio Anzueto, MD; and Antoni Torres, MD, PhD

Systemic corticosteroids and community-acquired pneumonia—cautious optimism or wishful thinking?

Grant Waterer[1,2]

[1]University of Western Australia, Crawley WA, Australia; [2]Northwestern University, Chicago, USA

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Baskar et al. *Lancet* 2015 Aug 1;386(9992):431
Restrepo et al. *Ann Intern Med*. 2015 Oct 6;163(7):560-1. doi: 10.7326/M15-1805.
Waterer G *J Thorac Dis*. 2015 Dec;7(12):E622-4. doi: 10.3978/j.issn.2072-1439.2015.12.22.

Steroids in CAP: 2015 Systematic Reviews

Horita (10 RCTs)
shortens the length of hospital stay
length to clinical stability
without increasing severe adverse effect
lowers the mortality of severe CAP cases

Marti (14 RCTs)
reduction of length of stay,
time to clinical stability,
and severe complications,
effect on mortality remains uncertain

Siemieniuk (12 RCTs)
hospital stay by approximately 1 day
need for mechanical ventilation by approximately 5%
reduce mortality by approximately 3%

Wan (9 RCTs + 6 Cohort studies)
reduce the risk of ARDS
shortening the length of the disease

Horita, N. et al. *Sci. Rep*. 5, 14061; doi: 10.1038/srep14061 (2015).
Marti C et al *PLOS ONE* | DOI:10.1371/journal.pone.0144032 December 7, 2015
Siemieniuk R A C et al *Ann Intern Med*. 2015;163:519-528.
Wan Y D et al *CHEST* 2016; 149(1):209-219

Steroids in CAP: 2015 Systematic Reviews

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

	Intention-to-Treat Population			
	Methylprednisolone Group (n = 61)	Placebo Group, (n = 59)	*P* Value	Difference Between Groups, % (95% CI)
Primary Clinical Outcome				
Treatment failure, No. (%)[a]	8 (13)	18 (31)	.02	18 (3 to 32)
Early treatment failure (0-72 h), No. (%)[b]	6 (10)	6 (10)	.95	0 (−10 to 11)
Early mechanical ventilation	4 (7)	5 (8)	.74	2 (−8 to 11)
Early septic shock	2 (3)	3 (5)	.68	2 (−5 to 9)
Death	2 (3)	2 (3)	>.99	0 (−6 to 7)
Late treatment failure (72-120 h), No. (%)[b]	2 (3)	15 (25)	.001	22 (10 to 34)
Radiographic progression	1 (2)	9 (15)	.007	14 (4 to 23)
Respiratory failure	1 (2)	5 (8)	.11	7 (−1 to 15)
Late mechanical ventilation	1 (2)	4 (7)	.20	5 (−2 to 12)
Late septic shock	0	4 (7)	.06	7 (0 to 13)
Death	0	0		

Torres et al *JAMA*. 2015;313(7):677-686. doi:10.1001/jama.2015.88

Steroids and CAP

- Consecutive adults with CAP, 7 hospitals, 2009-14
- 50 mg prednisolone od or placebo for 7 days

	Prednisolone	Placebo	HR / OR (Cis)	p
n	392	393		
ITT TCS* (d)	3 (2.5-3.4)	4.4 (4.0-5.0)	1.33(1.15-1.5)	<0.0001
PP TCS* (d)	3 (2.5-3.2)	4.4 (4.0-5.0)	1.35(1.16-1.56)	<0.0001
THD** (d)	6 (6.0-7.0)	7 (7.0-8.0)	1.19(1.04-1.38)	0.012
Death	16 (4%)	13(3%)	1.24(0.59-2.62)	0.57

*TCS-time to clinical stability

**THD = time to effective hospital discharge

Blum et al *Lancet* 2015;385:1511-1518

Steroids in Influenza - 1

Corticosteroids as adjunctive therapy in the treatment of influenza (Review)

Rodrigo C,et al.*Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD010406.

Steroids in Influenza - 1

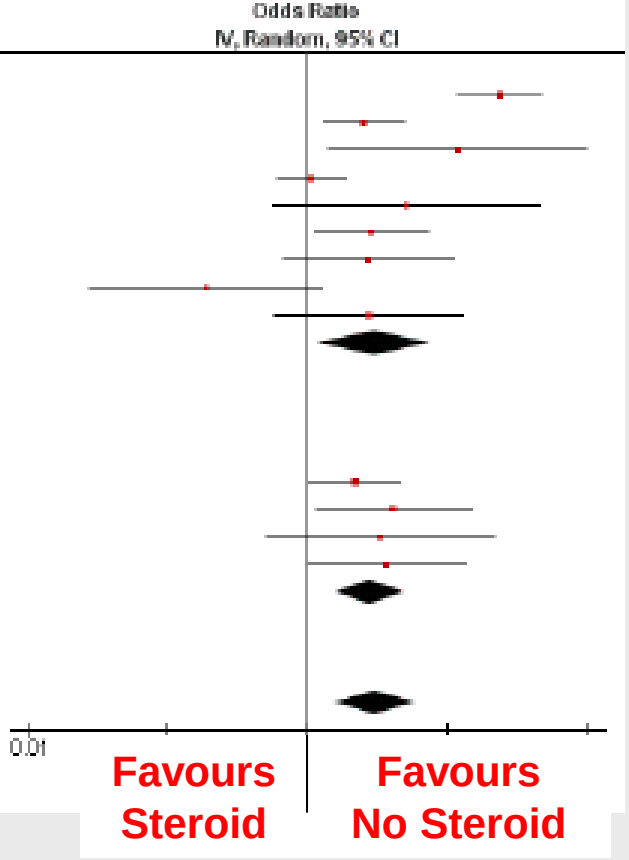
- **No RCTs**
- **19 eligible studies (n=3459), all observational; 13 studies (n=1917) included**
- **12 - 2009 influenza A H1N1 virus (H1N1pdm09).**
- **risk of bias - confounding by indication.**
- **mortality data were of very low quality.**
- **doses of corticosteroids were high**
- **indications for their use were not well reported.**

Rodrigo C,et al.*Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD010406.

Steroids in Influenza - 1

Figure 2. Meta-analysis of studies reporting mortality

Study or Subgroup	log[Odds Ratio]	SE	Corticosteroid group Total	No corticosteroid group Total	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Unadjusted mortality						
Balaganesakumar 2013	3.1676	0.3539	70	210	9.8%	23.75 [11.87, 47.52]
Brun-Buisson 2011	0.9247	0.3334	83	125	9.9%	2.52 [1.31, 4.85]
Chawla 2013	2.4675	1.0825	38	39	5.2%	11.79 [1.41, 98.41]
Diaz 2012	0.0688	0.2802	136	236	10.2%	1.07 [0.62, 1.86]
Li 2012	1.6376	1.1269	27	19	4.9%	5.14 [0.56, 46.82]
Mady 2012	1.0542	0.4731	43	43	9.1%	2.87 [1.14, 7.25]
Patel 2013	1.0116	0.7124	39	24	7.4%	2.75 [0.68, 11.11]
Bertogullarinden 2011	-1.674	0.9789	11	9	5.7%	0.19 [0.03, 1.28]
Vlasua 2011	1.0143	0.7879	37	129	6.9%	2.76 [0.59, 13.03]
Subtotal (95% CI)			484	834	69.1%	**2.99 [1.16, 7.57]**
Heterogeneity: Tau² = 1.66; Chi² = 57.84, df = 8 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 2.31 (P = 0.02)						
1.1.2 Adjusted mortality						
Kim 2011	0.7885	0.3872	107	139	9.6%	2.20 [1.03, 4.70]
Liem 2009	1.4134	0.6543	29	38	7.8%	4.11 [1.14, 14.82]
Linko 2011	1.1939	0.9628	72	60	5.6%	3.30 [0.50, 21.78]
Xi 2010	1.3002	0.6695	52	103	7.7%	3.67 [0.99, 13.60]
Subtotal (95% CI)			260	339	30.9%	**2.82 [1.61, 4.92]**
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 3.83 (P = 0.0003)						
Total (95% CI)			744	1173	100.0%	**3.06 [1.58, 5.92]**
Heterogeneity: Tau² = 1.03; Chi² = 58.81, df = 12 (P < 0.00001); I² = 80%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



Rodrigo C,et al.*Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD010406.

Steroids in Influenza - 1

- corticosteroid therapy was associated with increased mortality (odds ratio (OR) 3.06, 95% confidence interval (CI) 1.58 to 5.92).
- Pooled subgroup analysis of adjusted estimates of mortality from four studies found a similar association (OR 2.82, 95% CI 1.61 to 4.92).
- Three studies reported greater odds of hospital-acquired infection related to corticosteroid therapy;
- all were unadjusted estimates and we graded the data as very low quality

Rodrigo C,et al.*Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD010406.

Steroids in Influenza - 2

- 288 hospital admissions influenza A (H7N9) viral pneumonia
- 204 (71%) high-dose corticosteroids
- > 25mg methyl prednisolone / day
- High-dose corticosteroids were associated with increased mortality and longer viral shedding.

Cao B, et al *Crit Care Med*. 2016 Mar 1. [Epub ahead of print]

Steroids
Take-Home Message

- Evidence does not support use of corticosteroids in CAP or Influenza
- ?subgroup with benefit, ?dose

- Do not use routinely in CAP or Influenza

Long-term Effects of CAP

Long-term Effects of CAP
State of the Art

- Short term effects well known
- Studies suggest long term adverse effects
- Selected populations eg trial, single hospital
- Hospital inpatients
- Not controlled

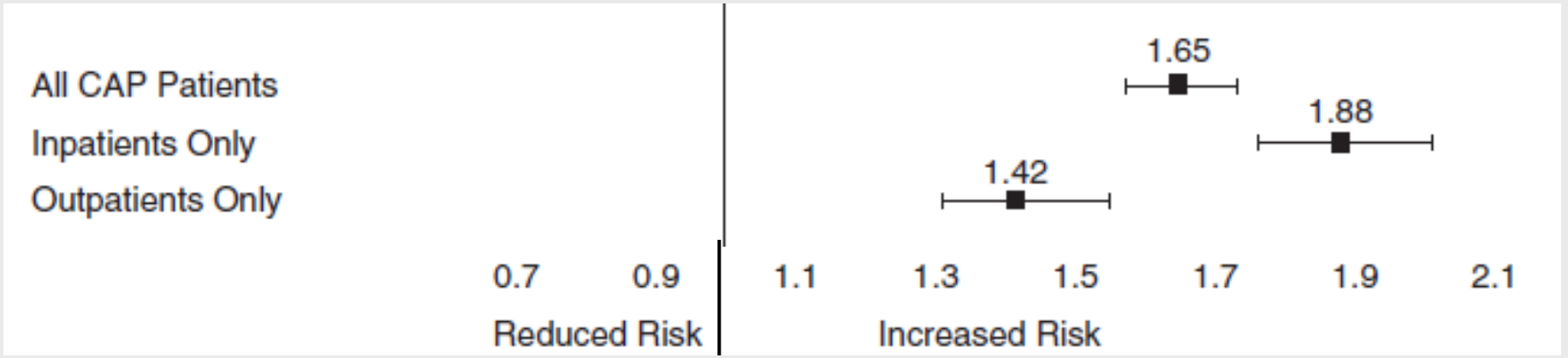
Long-term Effects of CAP

- 2000 - 2002, all CAP >17 years of age
- 6 hospitals or seven ED's, Canada,
- up to 5 age/sex matched controls / case
- follow up to March 2012. Database linkage
- 6078 cases; 29,402 controls

Eurich et al *Am J Respir Crit Care Med* 2015;192, Iss 5:597–604

Long-term Effects of CAP

Death



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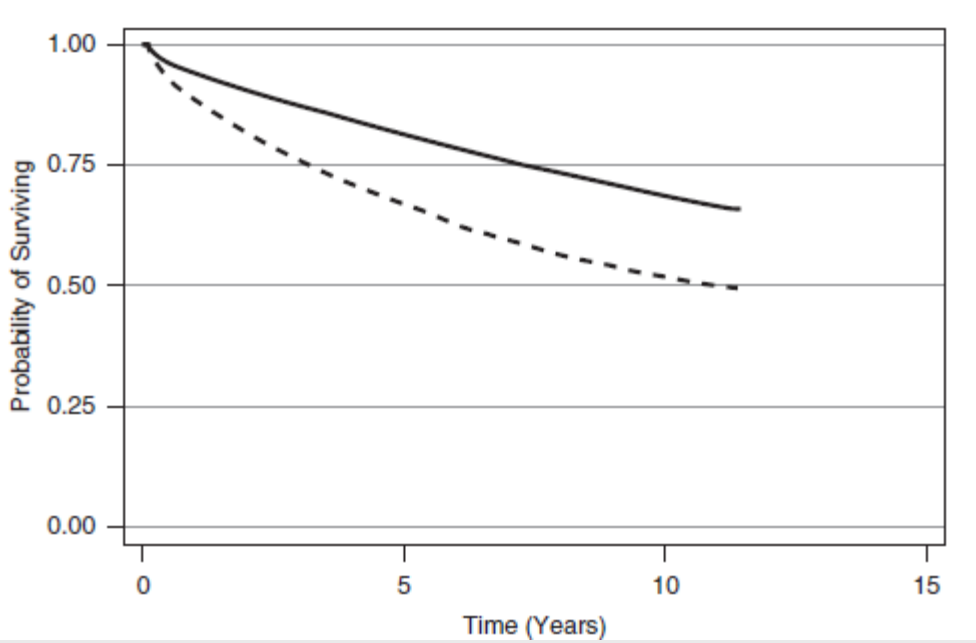
Long-term Effects of CAP

Death



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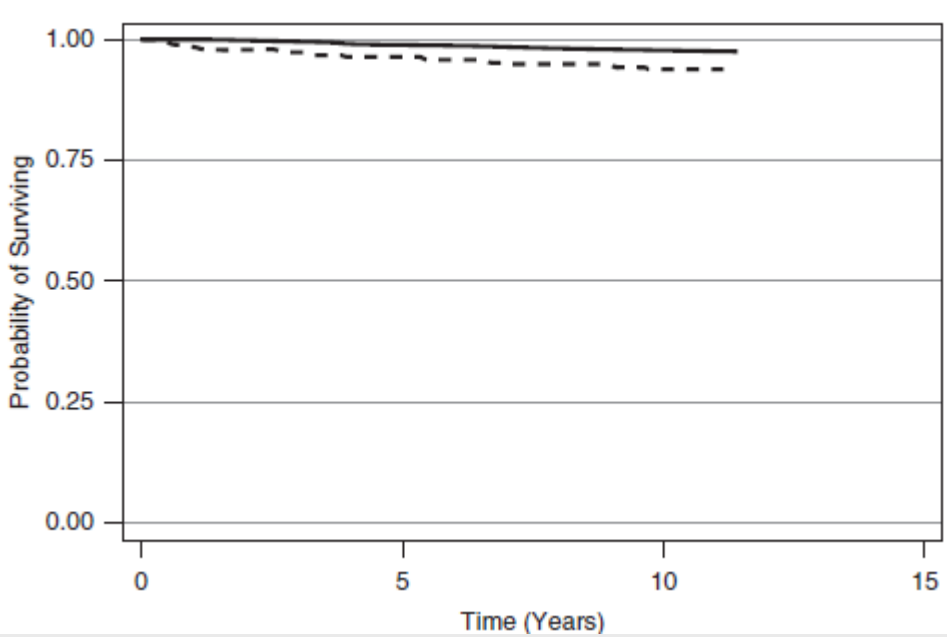
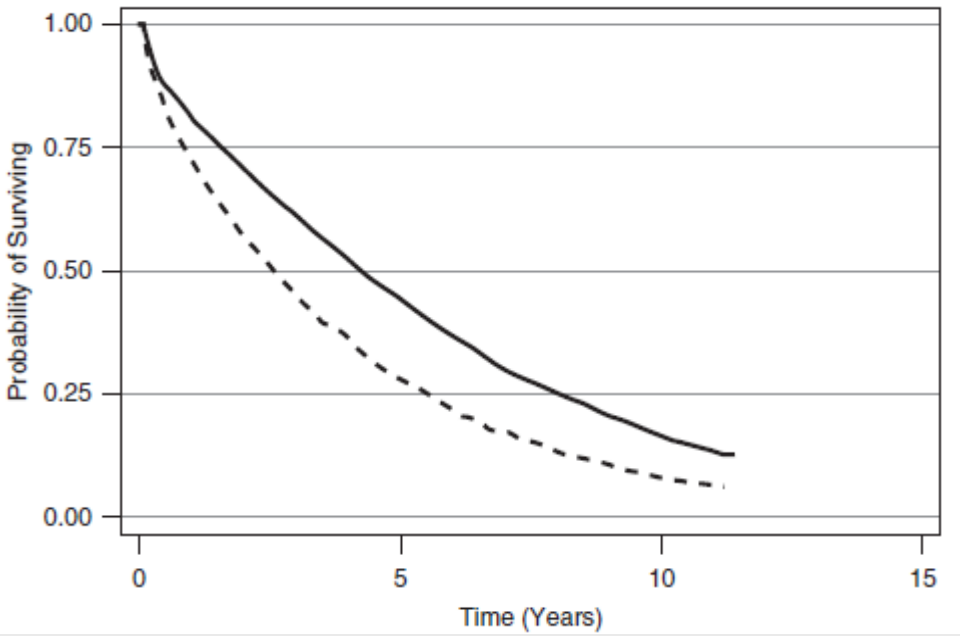
Long-term Effects of CAP

Death





Age ≤ 25

Age > 80

Eurich et al *Am J Respir Crit Care Med* 2015;192, Iss 5:597–604

Long-term Effects of CAP

most common causes of death were:

circulatory system	(35%)
neoplasm	(24%)
Respiratory system	(12%)

Cause of death was similar for patients with CAP relative to control subjects with the exception of respiratory:
CAP 24% vs. control 9% ($P<0.001$).

Eurich et al *Am J Respir Crit Care Med* 2015;192, Iss 5:597–604

Long-term Effects of CAP
Take-Home Message

Excess death after CAP confirmed

- Due to CAP?
- CAP marker of other death risk?

Opportunity for prevention?

Eurich et al *Am J Respir Crit Care Med* 2015;192, Iss 5:597–604

List of References

- van Vugt et al. *BMJ*. 2013; 346:f2450–f2450. doi: 10.1136/bmj.f2450
- Schierenberg A, et al. (2016) *PLoS ONE* 11(2): e0149895.
- Self et al *Journal of Infectious DIseases* 2016:213:584-591
- Rhedin S, et al. *Thorax* 2015;70:847–853. doi:10.1136/thoraxjnl-2015-206933
- Gadsby et al *Clinical Infectious Diseases* 2016;62:817-823
- Daniel P, et al. *Thorax* 2015;0:1–3. doi:10.1136/thoraxjnl-2015-207513
- Lee et al *JAMA* 2016;315:593-602
- Baskar et al. *Lancet* 2015 Aug 1;386(9992):431
- Restrepo et al. *Ann Intern Med*. 2015 Oct 6;163(7):560-1. doi: 10.7326/M15-1805.
- Waterer G *J Thorac Dis. 2015 Dec;7(12):E622-4. doi: 10.3978/j.issn.2072-1439.2015.12.22.*

List of References

- Horita, N. et al. Adjunctive Systemic Corticosteroids for Hospitalized Community-Acquired Pneumonia: Systematic Review and Meta-Analysis 2015 Update. Sci. Rep. 5, 14061; doi: 10.1038/srep14061 (2015).
- Marti C et al PLOS ONE | DOI:10.1371/journal.pone.0144032 December 7, 2015
- Siemieniuk R A C et al Ann Intern Med. 2015;163:519-528. doi:10.7326/M15-0715
- Wan Y D et al CHEST 2016; 149(1):209-219
- Torres et al JAMA. 2015;313(7):677-686. doi:10.1001/jama.2015.88
- Blum et al Lancet 2015;385:1511-1518
- Rodrigo C,et al.Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD010406.
- Cao B, et al Crit Care Med. 2016 Mar 1. [Epub ahead of print]
- Eurich et al Am J Respir Crit Care Med 2015;192, Iss 5:597–604