Respiratoire infecties

Academisering 2018-2019

19 december 2018

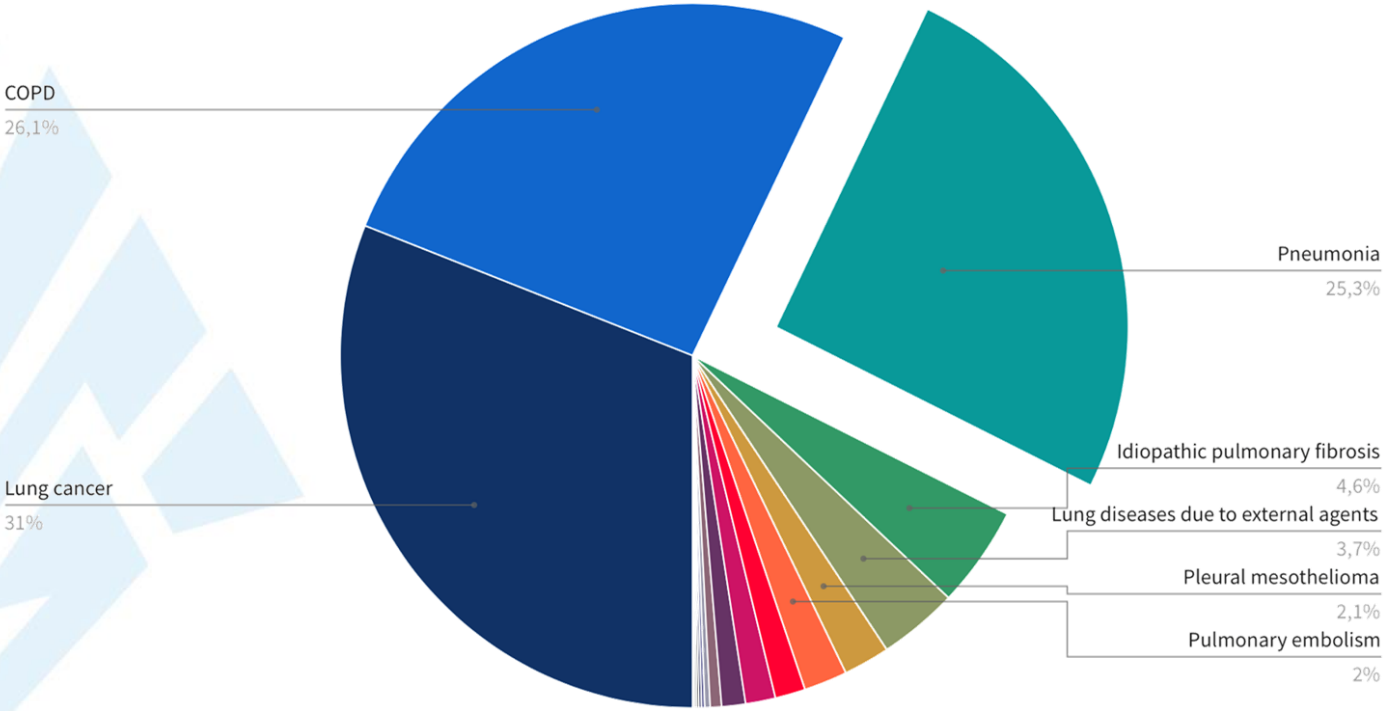
Pascal Van Bleyenbergh, dienst Pneumologie

UZ Leuven | Herestraat 49 B - 3000 Leuven | www.uzleuven.be tel. +32 16 33 22 11 | UNIVERSITY HOSPITALS LEUVEN

Severe pneumonia

CAP: still very high mortality

- Overall mortality rate in hospital is 12% - 20%
- Mortality of severe pneumonia is up to 50%



British Lung Foundation, 2013
Mongardon N et al. *Crit Care* 2012; 16: R155

SURVEILLANCE AND OUTBREAK REPORTS

Euro Surveill. 2014;19(31):pii=20869

Epidemiology and outcome of invasive pneumococcal disease among adults in Belgium, 2009–2011

J Verhaegen (jan.verhaegen@uzleuven.be)[1], J Flamaing[2], W De Backer[3], B Delaere[4], K Van Herck[5,6], F Surmont[7], Y Van Laethem[8], P Van Damme[5], W Peetermans[9]

Category	n	Admission to ICU n (%)	Outcome at discharge			Univariate OLR	
			Cured n (%)	Discharged with persisting symptoms n (%)	Death n (%)	Odds ratio (95% CI)	Overall p value
Total[a]	1,329	434 (33)	884 (67)	237 (18)	208 (16)	–	–
Age in years							
18–49	219	54 (25)	157 (72)	49 (22)	13 (6)	1	0.044
50–64	370	154 (42)	240 (65)	83 (22)	47 (13)	1.42 (0.98–2.04)	
≥65	740	226 (31)	487 (66)	105 (14)	148 (20)	1.52 (1.10–2.12)	

How to improve outcome in severe CAP?

- Optimalization of ICU-admission
  - timely recognition of patients at risk
  - correct indication for admission to ICU
  - *early hemodynamic & respiratory support*
- Optimalization of antimicrobial therapy
- Adjunctive therapy

Waterer GW et al. *Am J Resp Crit Care Med* 2011; 183: 157

Adjunctive therapies

Pneumonia				
Innate immunity			Adaptive immunity	Other
High inflammatory response	Coagulation disorder	Oxidative stress	Lower levels of immunoglobulines	
Corticosteroids Macrolides	Thrombomodulin Aspirine	Vitamin C	Immunoglobulin substitution therapy	Statines Stem cells Pidotimid …

Ceccato A et al. *Clin Chest Med* 2018; 39: 753

Adjunctive therapies

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Ceccato A et al. *Clin Chest Med* 2018; 39: 753

Corticosteroids for CAP

- Most widely used drugs specifically for their immunomodulatory activity
- Multiple mechanisms with broad range of actions
  (effect on PMN, cytokines, chemokines, adhesion molecules, cellular inflammatory receptors, …)

1. Impairment of leukocyte function
2. Downregulation of the inflammatory response
   - widespread
   - largely indiscriminate

Claman HN. *Exp Med Biol* 1988; 245: 203
Barnes PJ. *Eur J Pharmacol* 2006; 533: 2

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

JAMA February 17, 2015 Volume 313, Number 7

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

	Intention-to-Treat Population				Per-Protocol Population			
	Methylprednisolone Group (n = 61)	Placebo Group, (n = 59)	*P* Value	Difference Between Groups, % (95% CI)	Methylprednisolone Group (n = 55)	Placebo Group (n = 57)	*P* Value	Difference Between Groups, % (95% CI)
Primary Clinical Outcome								
Treatment failure, No. (%)[a]	8 (13)	18 (31)	.02	18 (3 to 32)	5 (9)	16 (28)	.01	19 (5 to 33)
Early treatment failure (0-72 h), No. (%)[b]	6 (10)	6 (10)	.95	0 (−10 to 11)	3 (5)	4 (7)	>.99	2 (−7 to 11)
Early mechanical ventilation	4 (7)	5 (8)	.74	2 (−8 to 11)	2 (4)	3 (5)	>.99	2 (−6 to 9)
Early septic shock	2 (3)	3 (5)	.68	2 (−5 to 9)	1 (2)	2 (4)	>.99	2 (−4 to 8)
Death	2 (3)	2 (3)	>.99	0 (−6 to 7)	0	0		
Late treatment failure (72-120 h), No. (%)[b]	2 (3)	15 (25)	.001	22 (10 to 34)	2 (4)	14 (25)	.002	21 (9 to 33)
Radiographic progression	1 (2)	9 (15)	.007	14 (4 to 23)	1 (2)	8 (14)	.03	12 (3 to 22)
Respiratory failure	1 (2)	5 (8)	.11	7 (−1 to 15)	1 (2)	5 (9)	.21	7 (−1 to 15)
Late mechanical ventilation	1 (2)	4 (7)	.20	5 (−2 to 12)	1 (2)	4 (7)	.36	5 (−2 to 13)
Late septic shock	0	4 (7)	.06	7 (0 to 13)	0	4 (7)	.12	7 (0 to 14)
Death	0	0			0	0		
Secondary Clinical Outcomes								
Time to clinical stability, median (IQR), d[c]	4 (3 to 6)	5 (3 to 7)	.28	1 (−0.4 to 2.4)	4 (3 to 6)	5 (3 to 7)	.13	1 (0 to 2)
Length of stay, median (IQR), d								
Hospital	11 (7.5 to 14)	10.5 (8 to 15)	.83	−0.5 (−4.6 to 3.6)	11 (8 to 14)	11.5 (8 to 15)	.70	0.5 (−3.3 to 4.3)
ICU[d]	5 (3 to 8)	6 (4 to 8)	.63	1 (−0.4 to 2.4)	5 (3 to 8)	6 (4 to 8)	.38	1 (0 to 2)
In-hospital mortality, No. (%)	6 (10)	9 (15)	.37	5 (−6 to 17)	3 (5)	7 (12)	.21	7 (−4 to 17)

Annals of Internal Medicine REVIEW

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Ann Intern Med. 2015;163:519-528.

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

13 RCT (through 25 May 2015)

2005 pts

"systemic corticosteroid therapy may reduce mortality by approximately 3%"

- 12 trials -- 1974 pts
- 5,3% vs 7,9% -- OR 0,67
- benefit only in severe CAP

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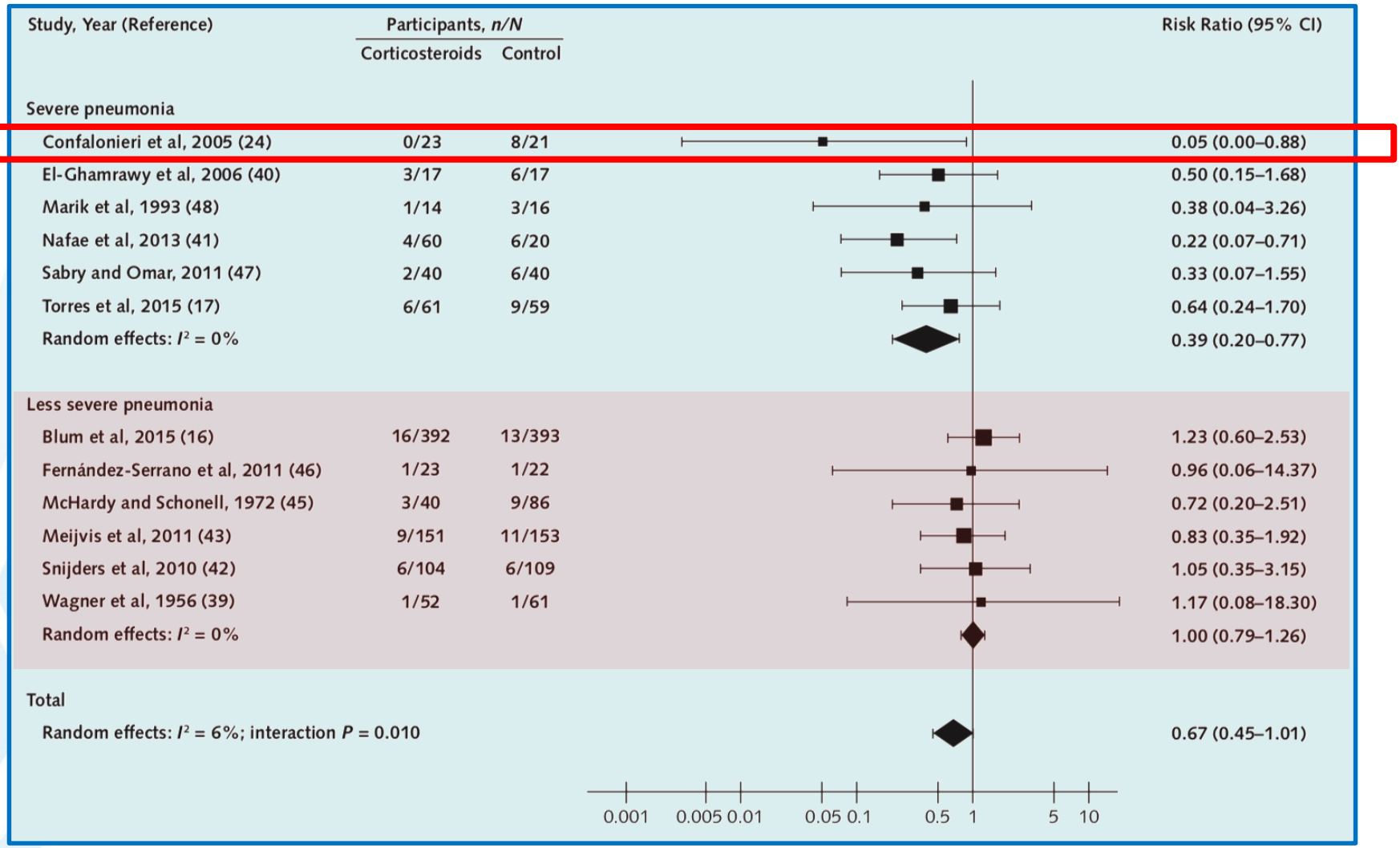

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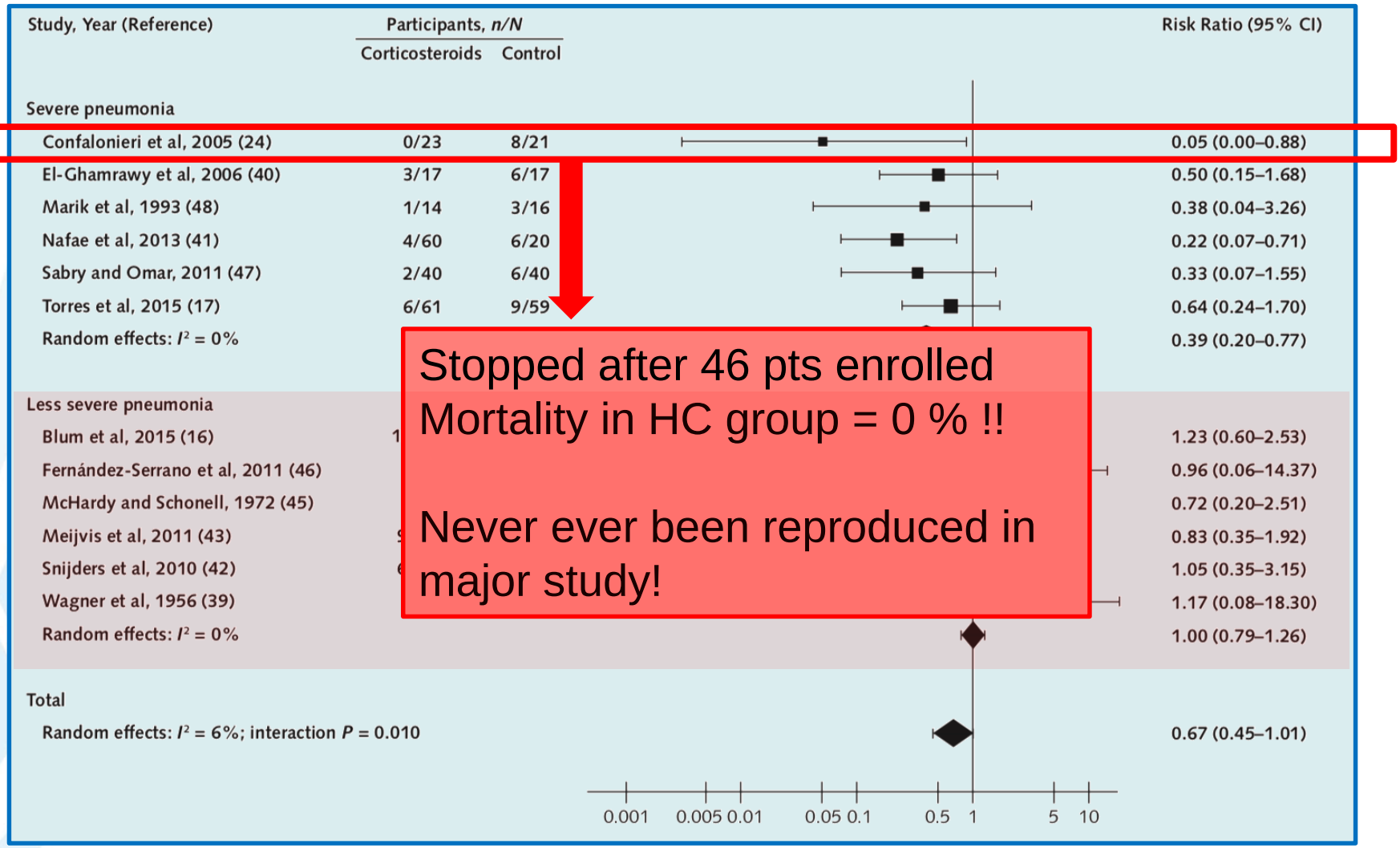

Stopped after 46 pts enrolled
Mortality in HC group = 0 % !!

Never ever been reproduced in major study!

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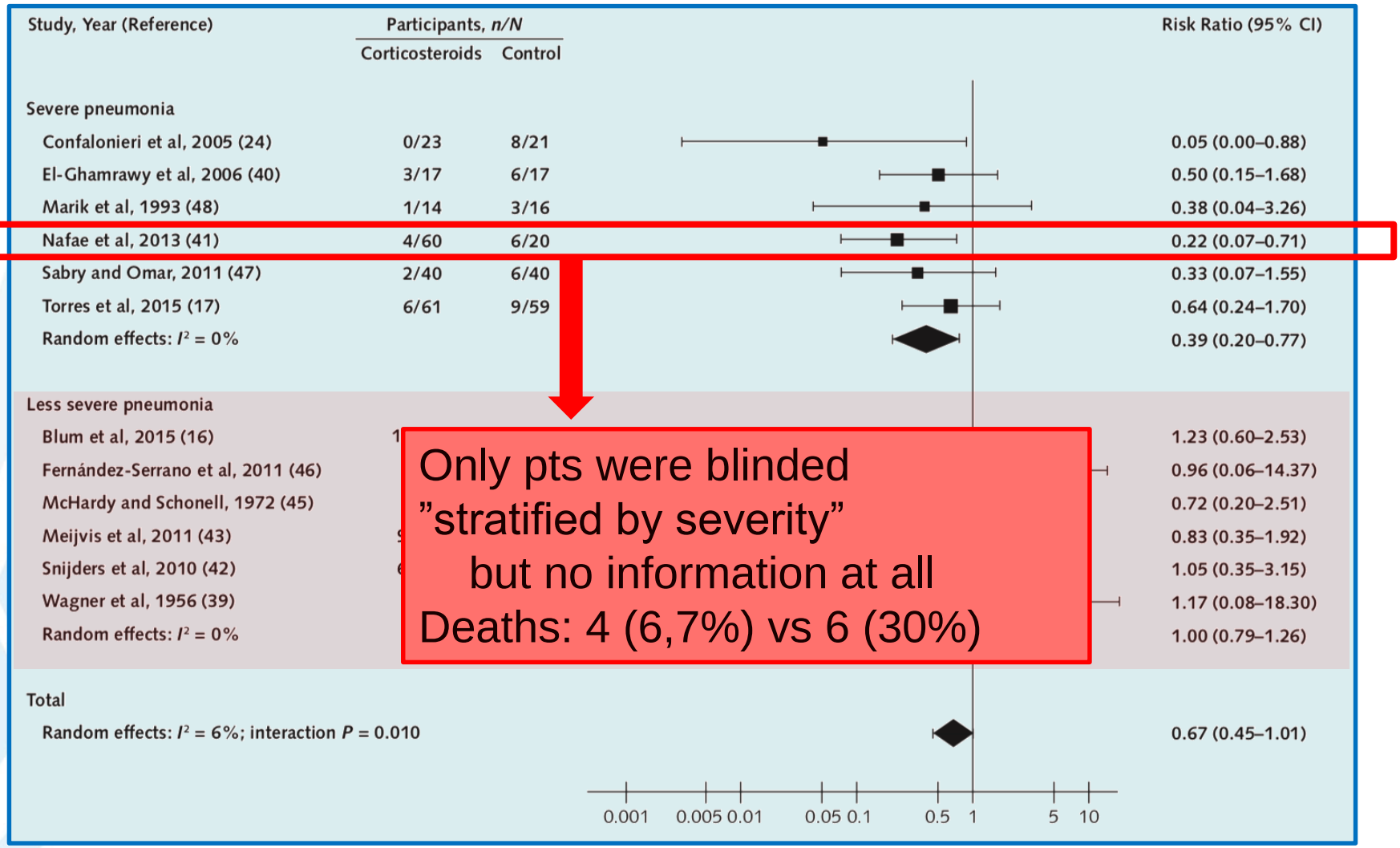

Only pts were blinded
”stratified by severity”
but no information at all
Deaths: 4 (6,7%) vs 6 (30%)

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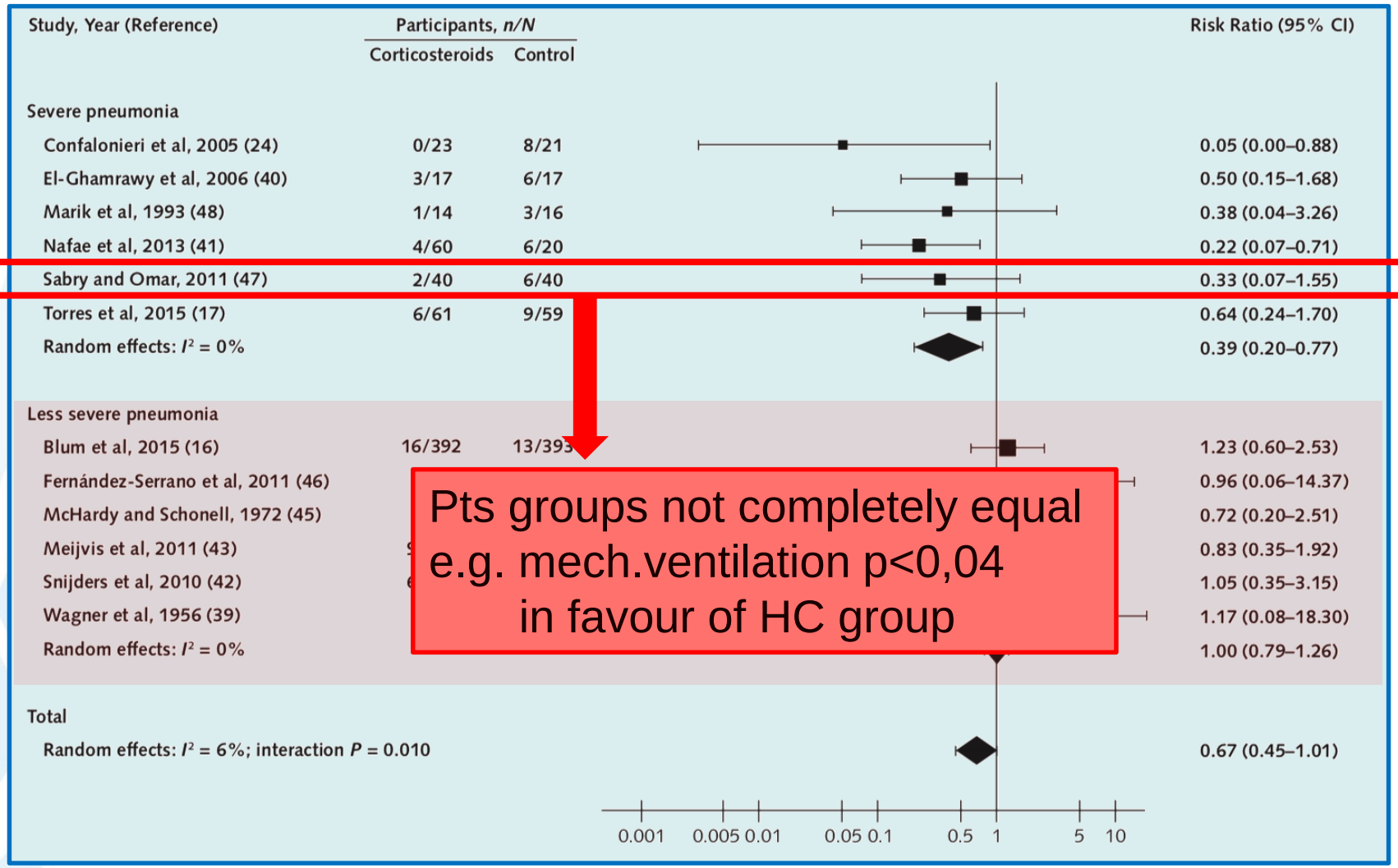

Pts groups not completely equal
e.g. mech.ventilation p<0,04
in favour of HC group

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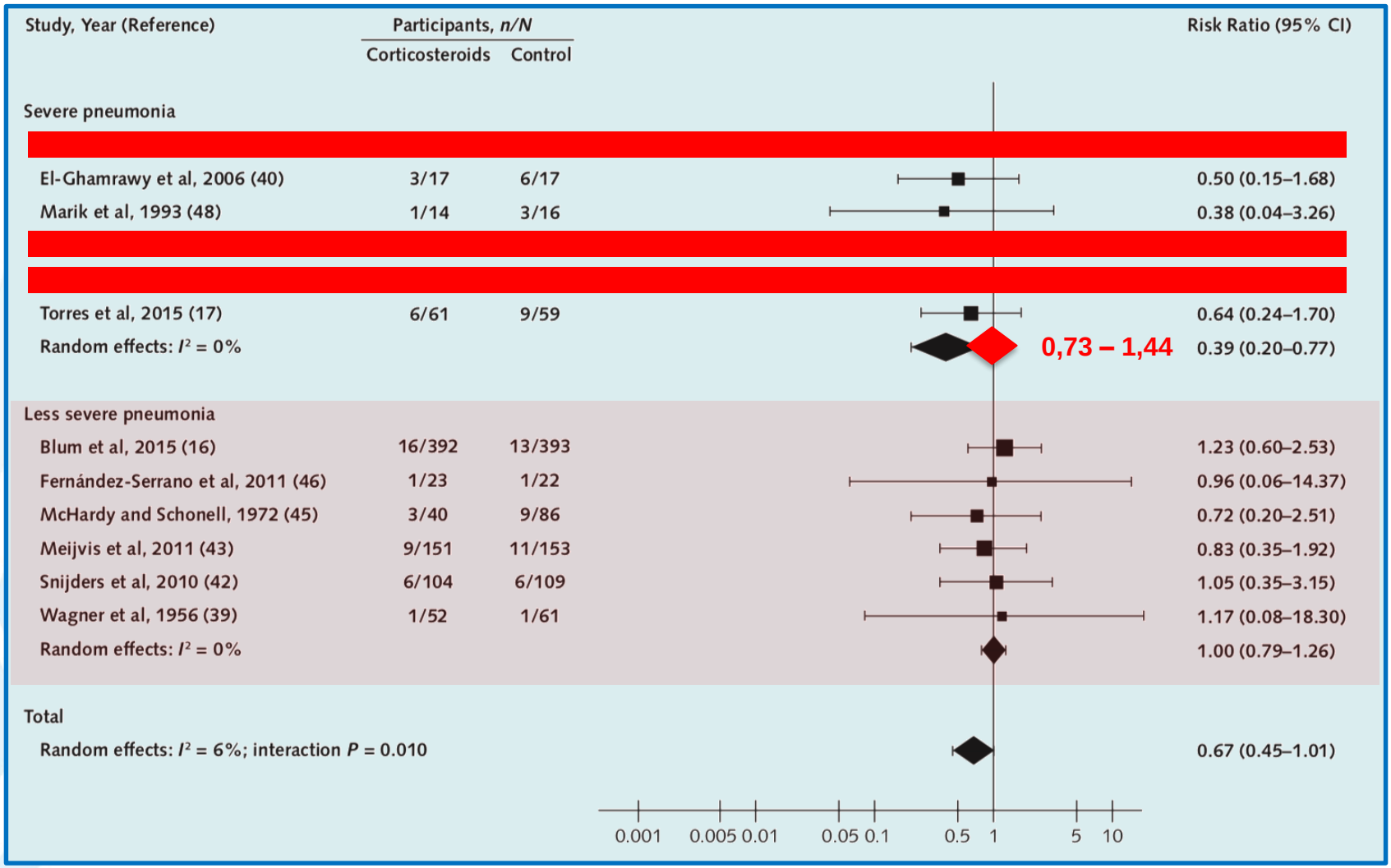


Corticosteroids for CAP

- Net effect is minimal to zero
- Net harm
  - low but not zero

    (hyperglycemia, hypernatremia, VTE, sepsis, fractures, GI hemorrhage)

> **Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study**
>
> Akbar K Waljee,[1,2,3,4] Mary A M Rogers,[2,4,5] Paul Lin,[2] Amit G Singal,[6] Joshua D Stein,[2,7,8] Rory M Marks,[9] John Z Ayanian,[2,5,8] Brahmajee K Nallamothu[1,2,4,10]
>
> *BMJ* 2017;357:j1415

  - cave viral pneumonia (influenza: higher mortality)

> **Corticosteroids as adjunctive therapy in the treatment of influenza (Review)**
>
> 2016, Issue 3. Art. No.: CD010406.
>
> Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS

Corticosteroids for CAP

Corticosteroids for community-acquired pneumonia: a critical view of the evidence

James D. Chalmers

Eur Respir J 2016; 48: 984–986

Major improvements in length of stay, duration of antibiotic therapy and even mortality, greater than those demonstrated with corticosteroids, can be achieved through compliance with high-quality care recommendations, and yet audits show persistently poor compliance with guidelines [1–5]. Doing the simple things well should continue to take priority over the use of corticosteroids, for now.

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock

Critical Care Medicine March 2017 • Volume 45 • Number 3

We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

”Steroids should not be used in septic patients to prevent septic shock!”

Keh D et al. *JAMA* 2016; 316: 1775

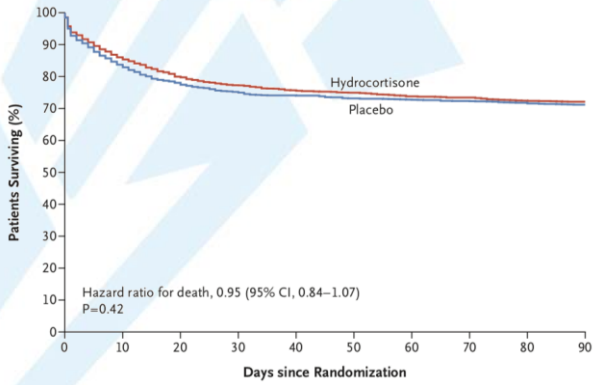
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

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

- 3658 pts
- 35% pneumonia
- 99% MV – 99% VP - APACHE II 24
- HC 200mg ctu infusion
- Mortality 90d:
  27,9% HC vs. 28,8% - RR 0,95 (p 0,50)



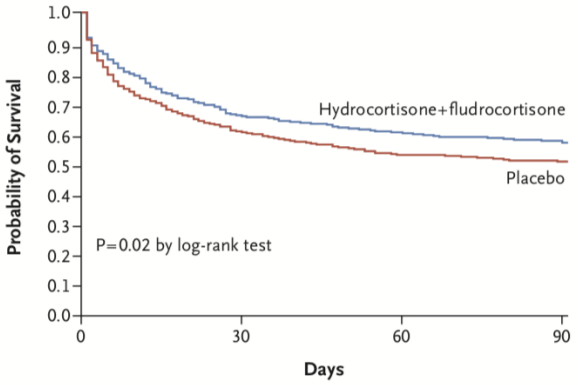
ORIGINAL ARTICLE

N ENGL J MED 378;9 NEJM.ORG MARCH 1, 2018

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

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

- 1241 pts
- 60% pneumonia
- 91 MV – 96% VP - SOFA 12 – SAPS 56
- HC 4x50mg + FC 50µg bolus
- Mortality 90d:
  43,0% HC+F vs. 49,1% - RR 0,88 (p 0,03)



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- 1241 pts
- 60% pneumonia
- 91 MV – 96% VP - SOFA 12 – SAPS 56

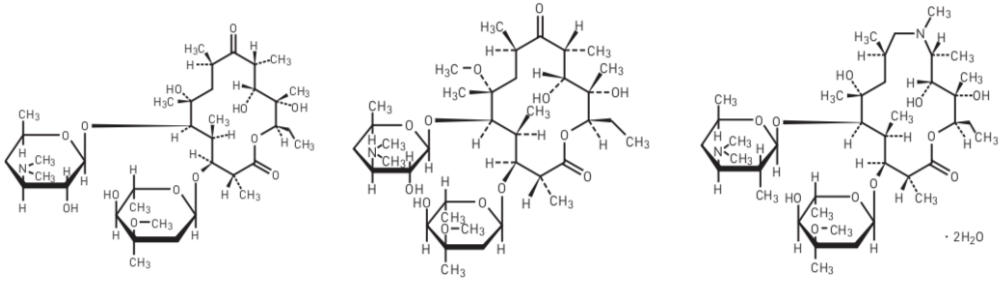
- HC 4x50mg + FC 50µg bolus

Both trials showed
- improved resolution of shock
- more rapid cessation of mechanical ventilation

Benefit of anti-inflammatory therapies may be dependent on the risk of death

Eichacker PQ et al. *Am J Resp Crit Care Med* 2002; 166: 1197
Minneci PC et al. *Clin Microbiol Infect* 2009; 15: 308

Macrolides for CAP

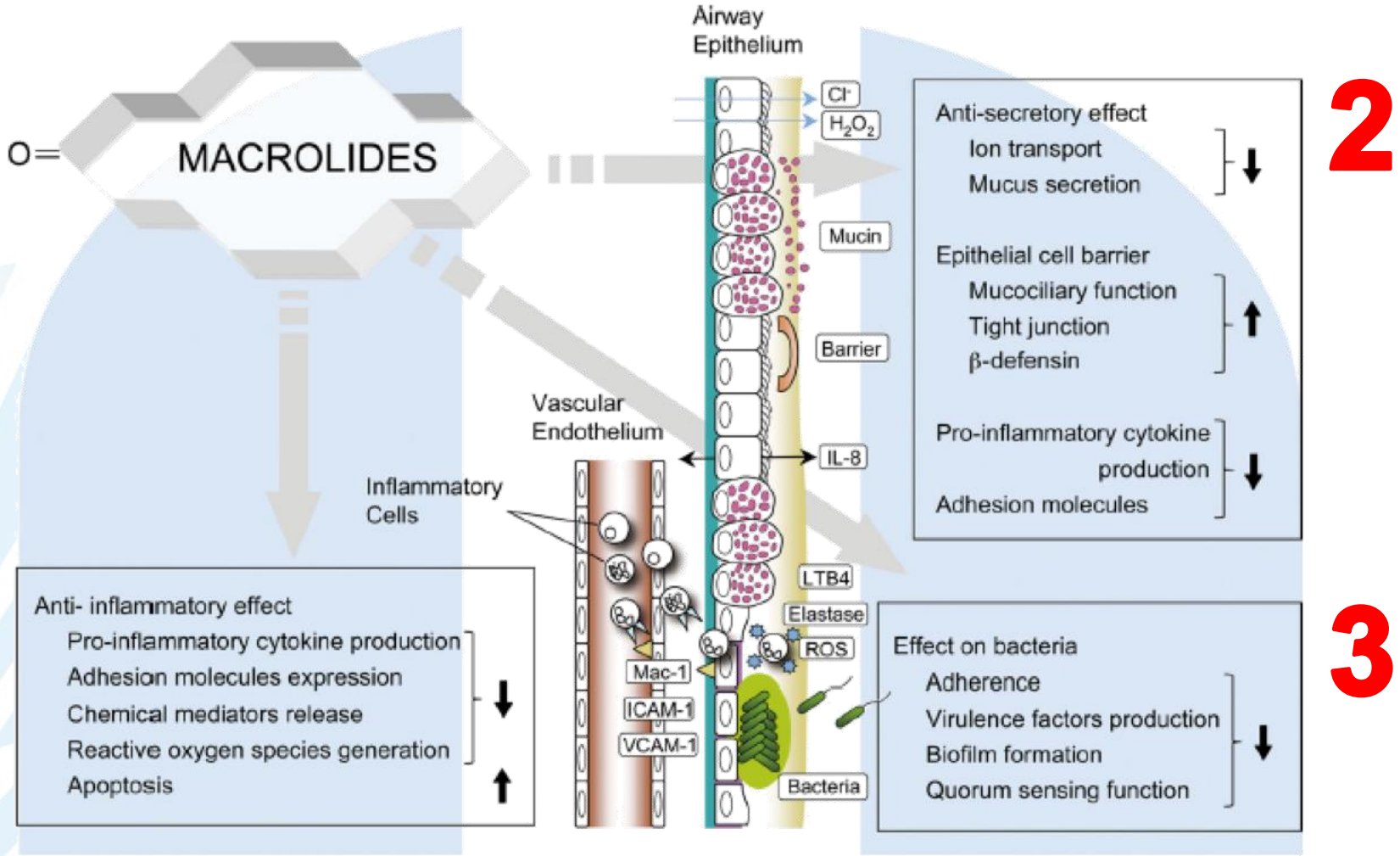


1. Expanding the spectrum of antimicrobial therapy
   → guidelines (IDSA/ATS, BTS/NICE, ERS,…) all recommend coverage of atypical pathogens when treating 'severe CAP'
   ➪ β-lactam + macrolide or fluoroquinolone

Mandell LA et al. *Clin Infect Dis* 2007; 44: 527
Woodhead M et al. *Clin Microbiol Infect* 2011; 17 S6: 1
Wiersinga WJ et al. *Neth J Med* 2012; 70: 90
NICE guidelines 2014; nice.org.uk/guidance/cg191

2. Immunomodulatory therapy
   → still some matter of debate in case of pneumonia
   → as such not included in any of the society guidelines yet…

Macrolides and immunomodulation



Kanoh S, Rubin BK. *Clin Microbiol Rev* 2010; 23(3): 590
Parnham MJ et al. *Pharmacol Ther* 2014; 143: 225

UZ LEUVEN

Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis

NOBUYUKI HORITA,[1] TATSUYA OTSUKA,[2] SHUSAKU HARANAGA,[3] HO NAMKOONG,[4] MAKOTO MIKI,[5] NAOYUKI MIYASHITA,[6] FUTOSHI HIGA,[7] HIROSHI TAKAHASHI,[8] MASAHIRO YOSHIDA,[9] SHIGERU KOHNO[10] AND TAKESHI KANEKO[1]

Respirology (2016) **21**, 1193–1200

- Meta-analysis
- 1975 pts from 2 RCT
  1011 pts from 1 non-RCT interventional study (Blasi et al)
  33332 pts from 11 observational trials
- Substantial inter-subgroup heterogeneity

Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis

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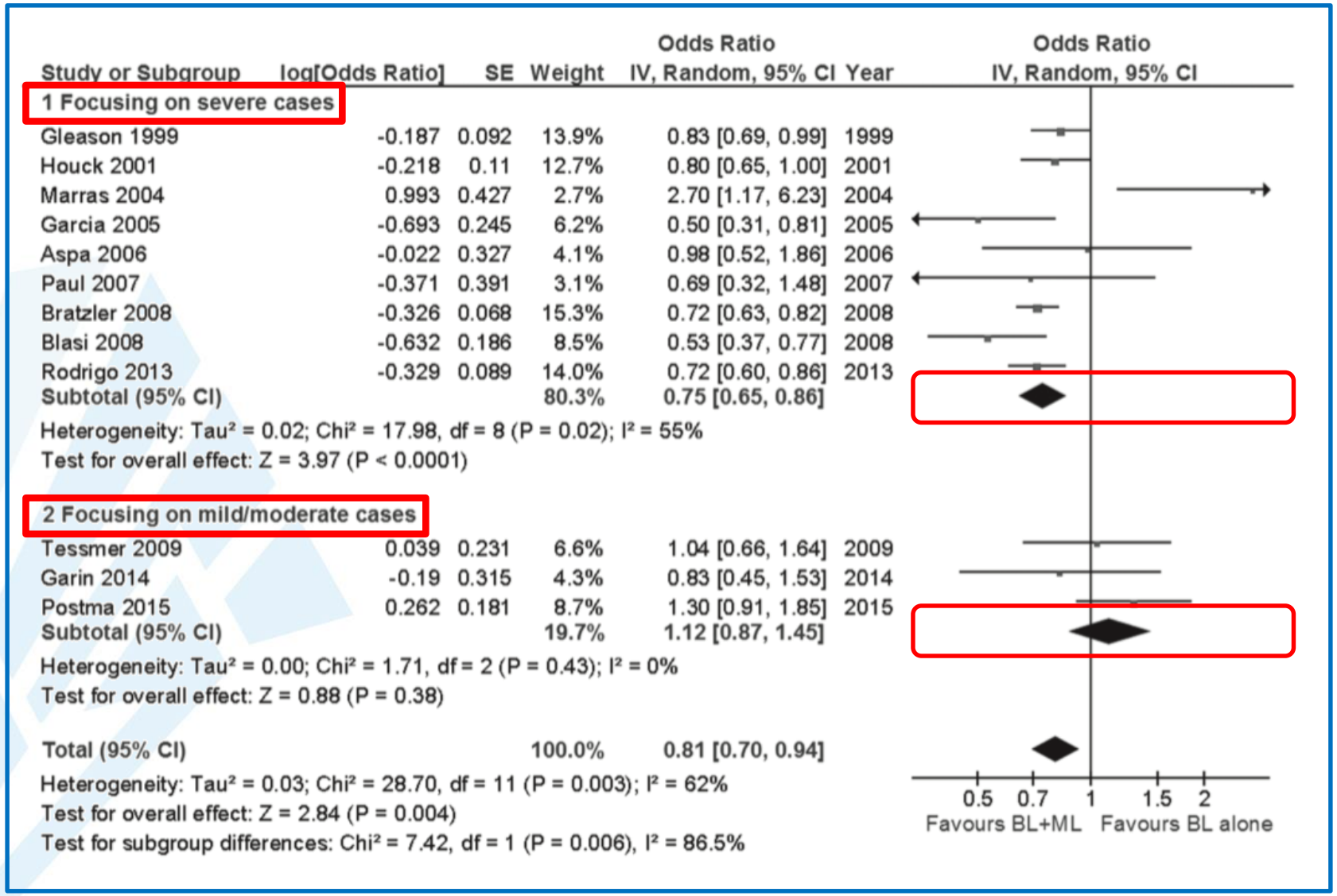
Respirology (2016) **21**, 1193–1200



Macrolide therapy for patients with pneumonia: a triple-edged sword

Anti-infectives and the Lung (ERS Monograph). Sheffield European Respiratory Society, 2017; pp. 206–231

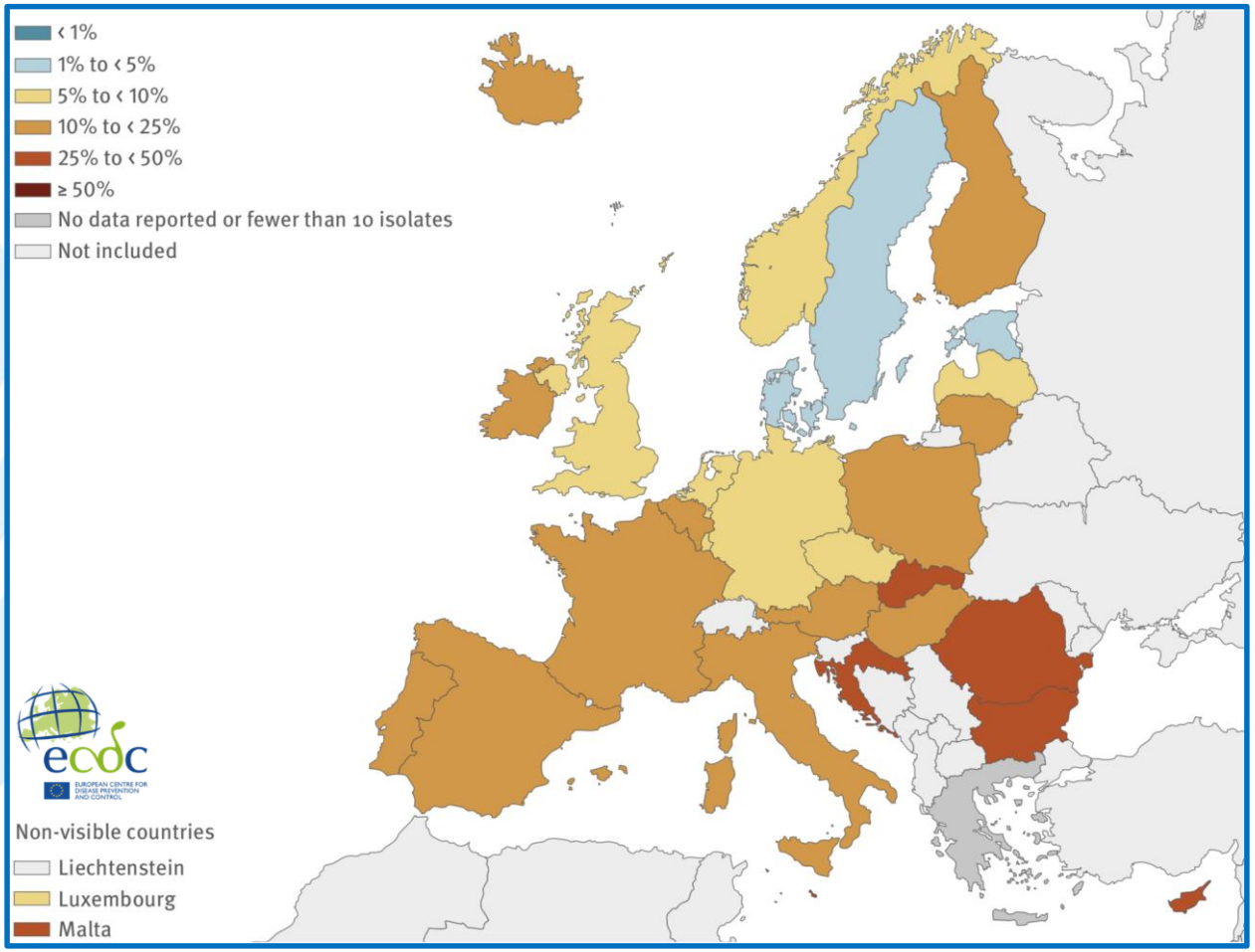
Yuichiro Shindo and Yoshinori Hasegawa

- **Overall hospitalised pts with CAP**
  → both positive and negative results

- **Non-severe vs severe CAP**
  - non-severe: conflicting results – RCT rather negative results!
    "effect of adding macrolides may be minimal in non-severe CAP"
  - severe/bacteremic: mostly positive results (11 POS vs 3 NEG)!
    All observational trials – 1 non-RCT interventional study
    "macrolides are likely to be effective in pts with severe CAP and bacteremia"

Macrolides for CAP: is there harm?

1. Emergence of resistance



ECDC, surv. report, 2017

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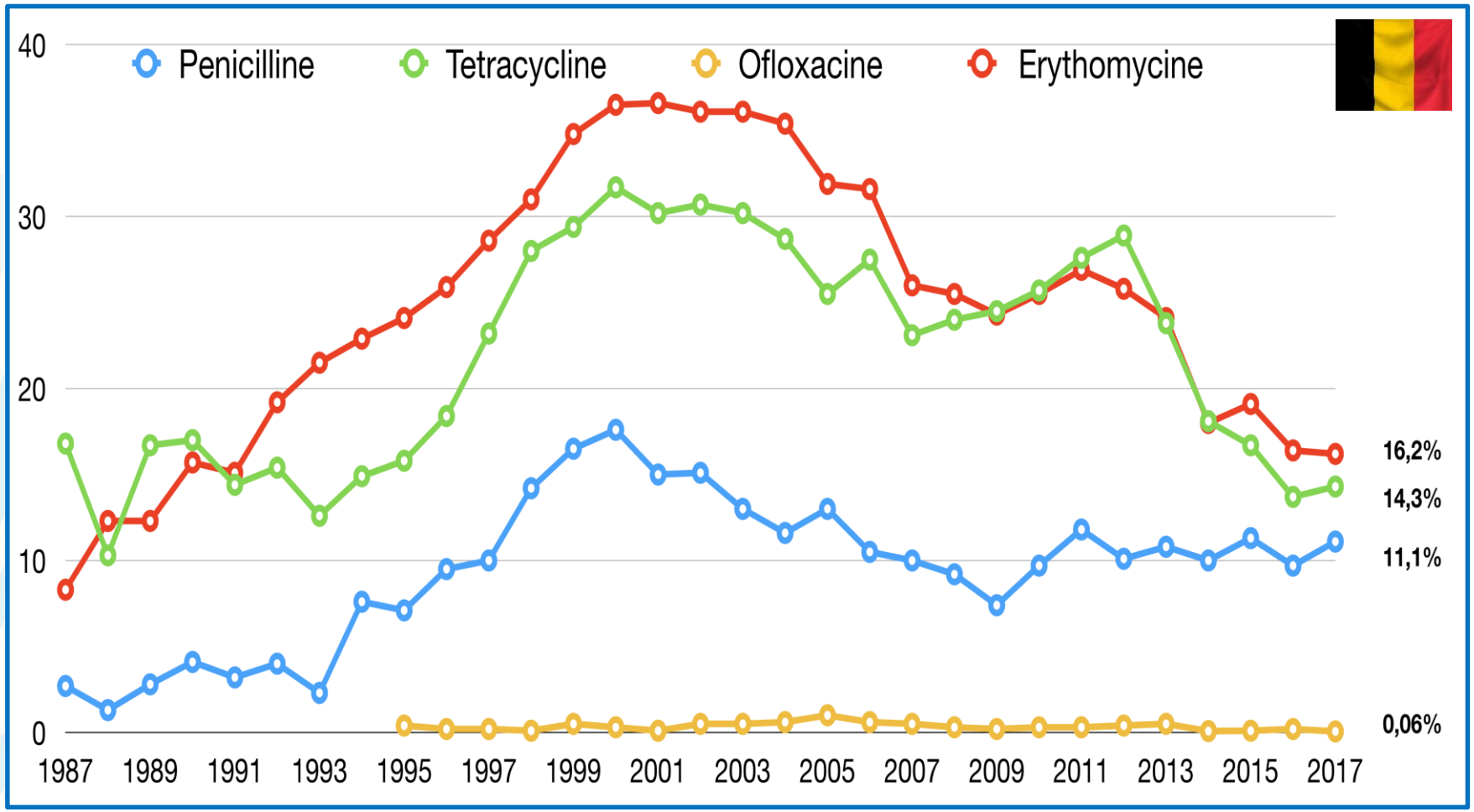


J. Verhaegen, Belgian reference lab, 2017

Macrolides for CAP: is there harm?

1. Emergence of resistance

2. Cardiac events

Azithromycin and the Risk of Cardiovascular Death

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

N Engl J Med 2012;366:1881-90

Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies

BMJ 2013

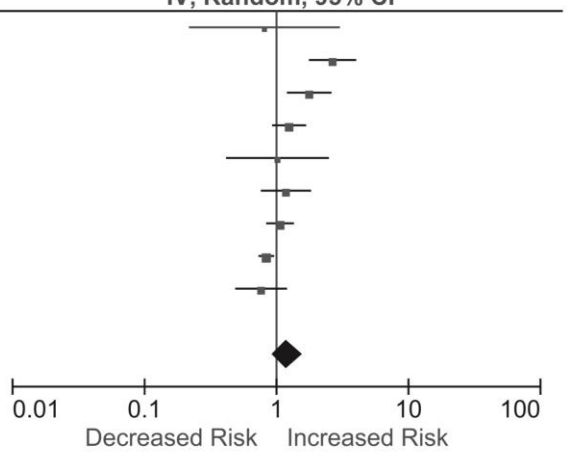
Systematic Review, Meta-analysis, and Network Meta-analysis of the Cardiovascular Safety of Macrolides

Antimicrobial Agents and Chemotherapy®
June 2018 Volume 62 Issue 6 e00438-18

Einat Gorelik,[a,b] Reem Masarwa,[a] Amichai Perlman,[a] Victoria Rotshild,[a] Mordechai Muszkat,[c] Ilan Matok[a]

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Jespersen 2009	-0.211	0.672	3.3%	0.81 [0.22, 3.02]
Zambon 2009	0.978	0.211	11.9%	2.66 [1.76, 4.02]
Rao 2014	0.571	0.199	12.2%	1.77 [1.20, 2.61]
Chou 2015	0.22	0.152	13.7%	1.25 [0.93, 1.68]
Goldstein 2015	0.017	0.458	5.8%	1.02 [0.41, 2.50]
Wong 2016	0.165	0.224	11.5%	1.18 [0.76, 1.83]
Trac 2016	0.062	0.124	14.5%	1.06 [0.83, 1.36]
Berni 2017	-0.178	0.07	15.8%	0.84 [0.73, 0.96]
Trifiro 2017	-0.269	0.231	11.2%	0.76 [0.49, 1.20]
Total (95% CI)			**100.0%**	**1.20 [0.91, 1.57]**

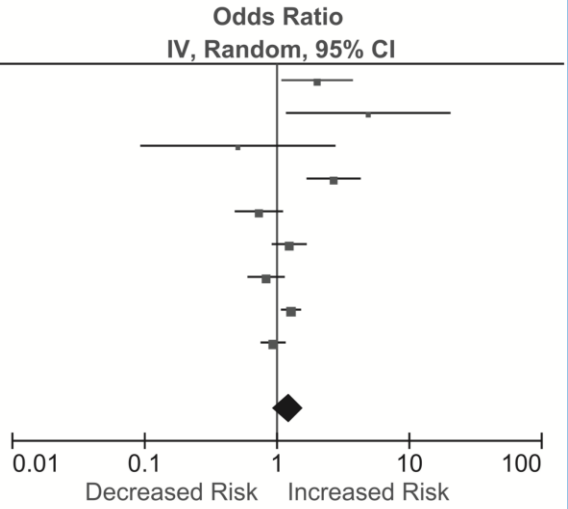
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 40.20$, df = 8 ($P < 0.00001$); $I^2 = 80\%$
Test for overall effect: $Z = 1.31$ ($P = 0.19$)



Odds ratios for arrhythmia in macrolide users versus nonusers.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Ray 2004	0.698	0.318	9.1%	2.01 [1.08, 3.75]
Straus 2005	1.587	0.731	2.9%	4.89 [1.17, 20.49]
Jespersen 2009	-0.681	0.867	2.1%	0.51 [0.09, 2.77]
Ray 2012	0.985	0.241	11.5%	2.68 [1.67, 4.29]
Svanstrom 2013	-0.316	0.215	12.5%	0.73 [0.48, 1.11]
Svanstrom 2014	0.212	0.156	14.6%	1.24 [0.91, 1.68]
Chou 2015	-0.19	0.166	14.3%	0.83 [0.60, 1.14]
Wong 2016	0.243	0.09	16.8%	1.28 [1.07, 1.52]
Quinn 2017	-0.068	0.112	16.2%	0.93 [0.75, 1.16]
Total (95% CI)			**100.0%**	**1.22 [0.94, 1.59]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 33.61$, df = 8 ($P < 0.0001$); $I^2 = 76\%$
Test for overall effect: $Z = 1.50$ ($P = 0.13$)

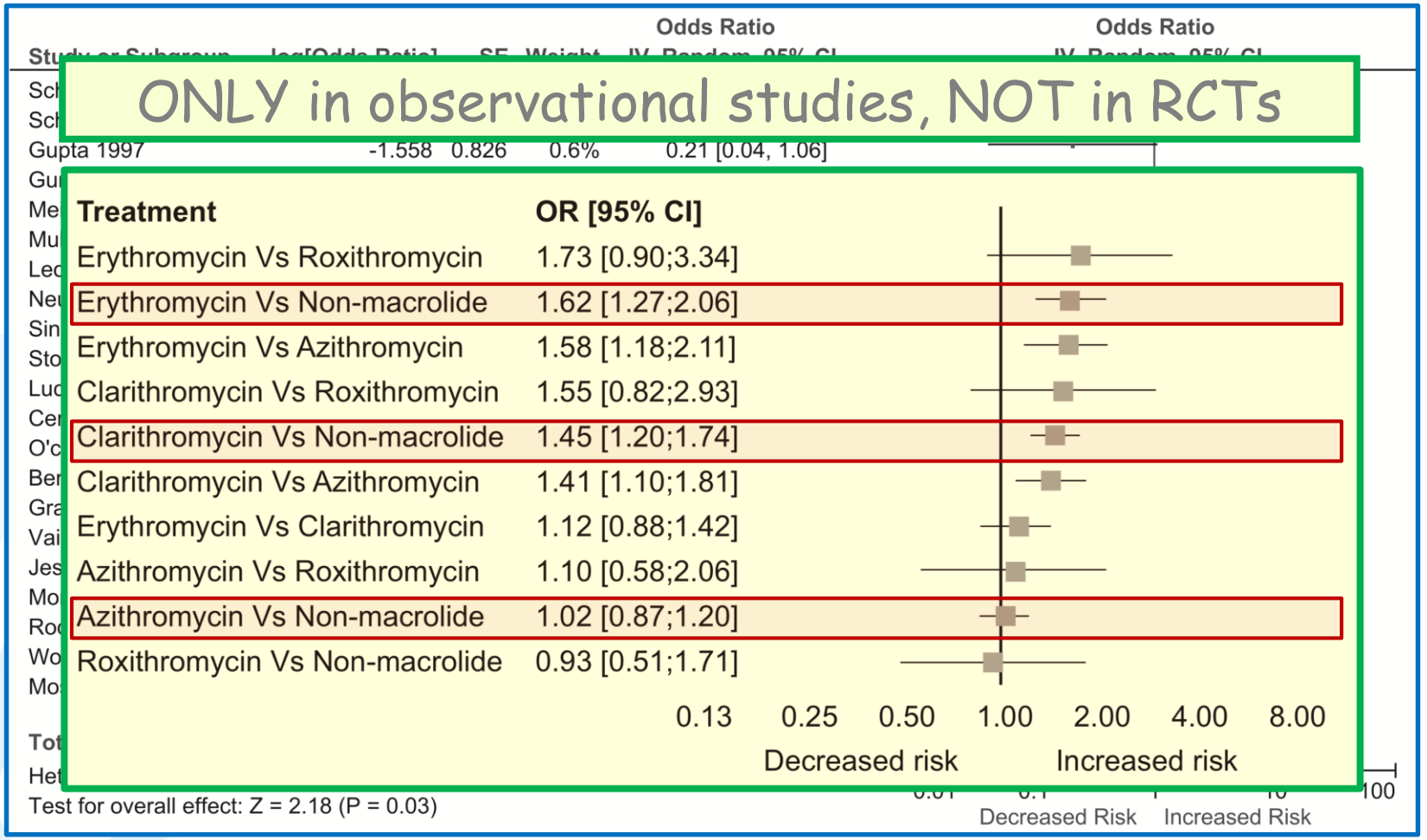


Odds ratios for short-term cardiovascular mortality in macrolide users versus nonusers.

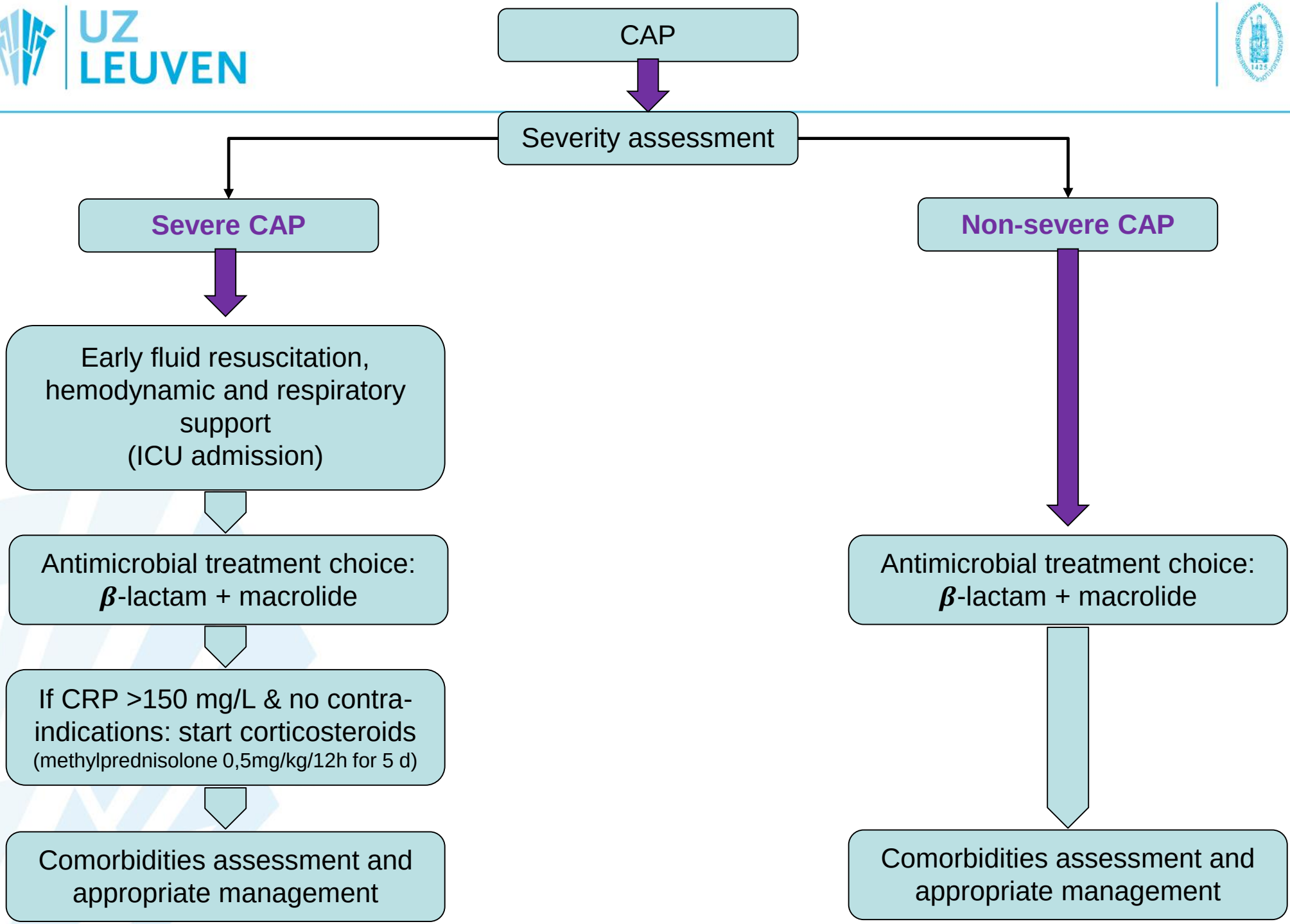
Systematic Review, Meta-analysis, and Network Meta-analysis of the Cardiovascular Safety of Macrolides

Antimicrobial Agents and Chemotherapy®
June 2018 Volume 62 Issue 6 e00438-18

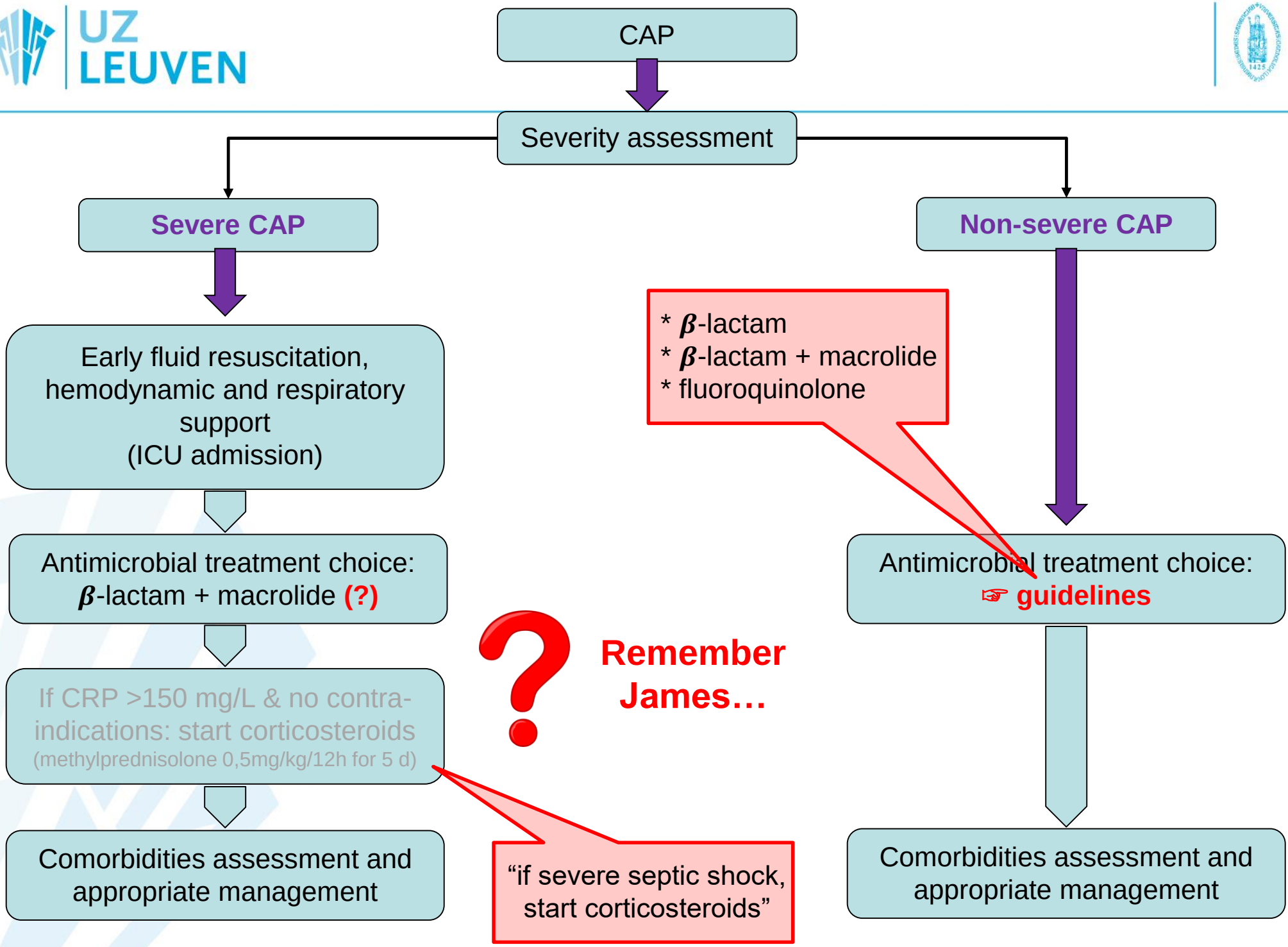
Einat Gorelik,[a,b] Reem Masarwa,[a] Amichai Perlman,[a] Victoria Rotshild,[a] Mordechai Muszkat,[c] Ilan Matok[a]



Odds ratios for MI in macrolide users versus nonusers

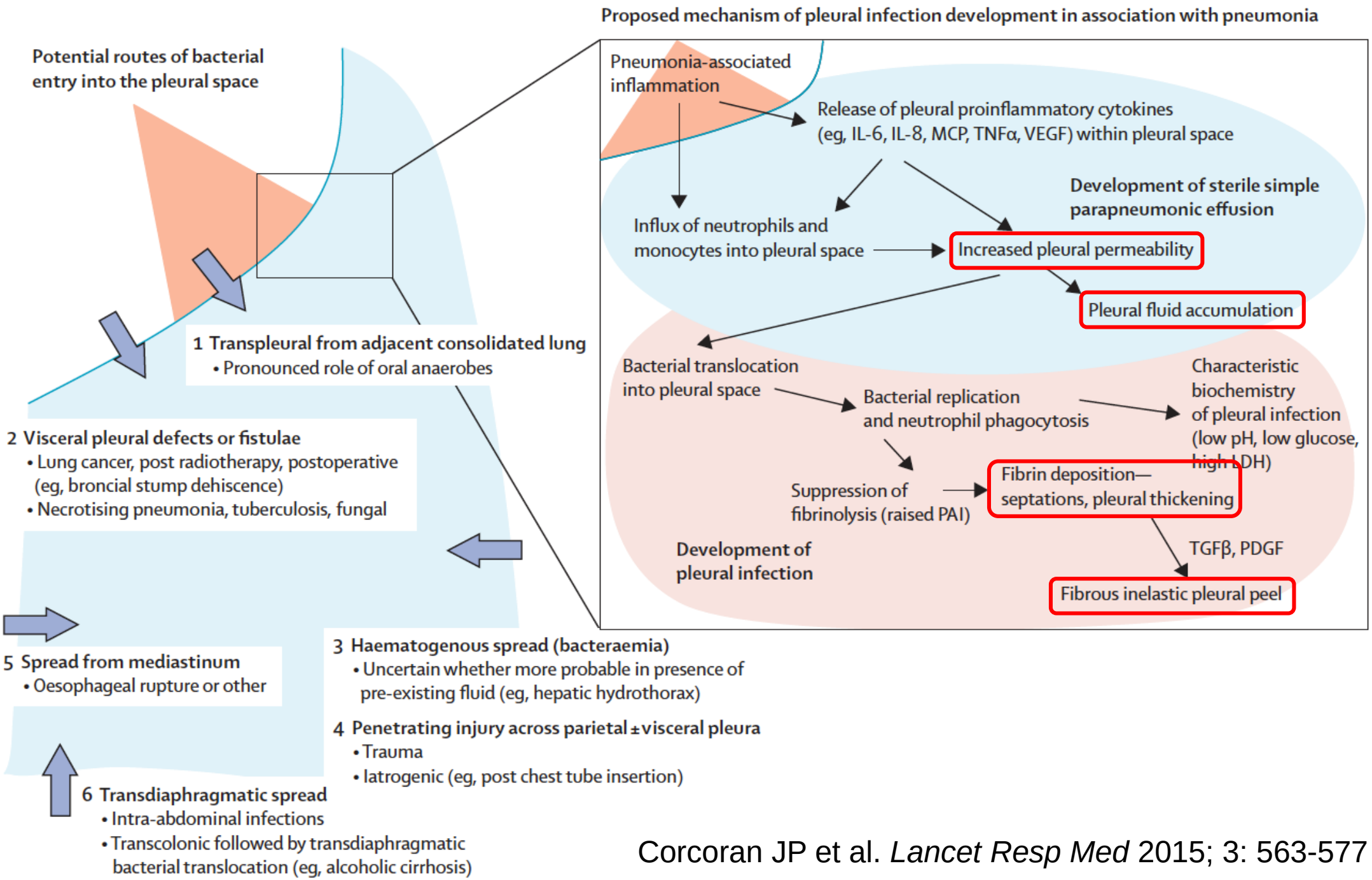


Ceccato A et al. *Clin Chest Med* 2018; 39: 753



Ceccato A et al. *Clin Chest Med* 2018; 39: 753

Pleural infection



Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

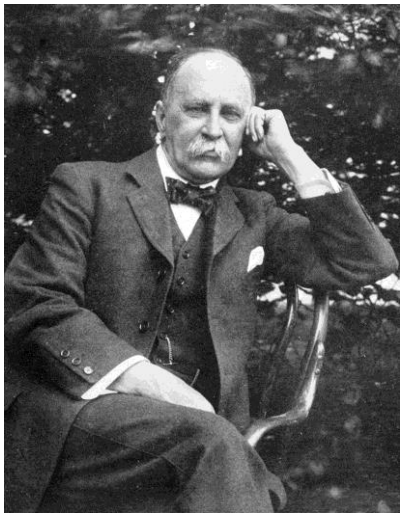
Cause	Number	%
Pulmonary infection	177	55
Thoracic surgery	66	21
Trauma	18	6
Oesophageal rupture	15	5
Spontaneous pneumothorax	7	2
Thoracentesis	6	2
Subdiafragmatic infection	4	1
Sepsis	4	1
Miscellaneous or unknown	22	7
TOTAL	**319**	**100**

Brims FJ et al. Eur Respir Rev 2010; 117: 220-228

Pleurale infectie

- Frequent probleem
  - **50-60%** CAP → pleuravocht ('PPE')
  - **10%** PPE wordt gecompliceerd ('CPE') en/of empyeem

- Belangrijke morbiditeit en mortaliteit
  - Chirurgie noodzakelijk bij **20-40%** CPE/empyeem
  - Mortaliteit 1jaar: **20%**
    - At risk: ≥65jaar, immuunsuppressie, nosocomiaal, …
  - Verblijfsduur: **15dagen** (20% >1md)



sir William Osler
1849-1919

Nielsen J et al. *Scand J Infect Dis* 2011; 43: 430-435
Rahman NM et al. *N Engl J Med* 2011; 365: 518-526

Pleurale infectie

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  - 10% PPE wordt gecompliceerd ('CPE') en/of empyeem

- Belangrijke morbiditeit en mortaliteit

- Purulentie van pleuraal vocht
- Loculaties/septaties (echo)
- Laag aantal WBC
- Bacteriologie
- Vertraging in diagnose
- Vertraging in plaatsen van drain

Davies CW et al. *Am J Resp Crit Care Med* 1999; 160: 1682-1687
Maskell NA et al. *Am J Resp crit Care Med* 2006; 174: 817-823
Marks DJ et al. *PLoS One* 2012; 7: e30074

Pleurale infectie

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  - Chirurgie noodzakelijk bij **20%** CPE/empyeem
  - Mortaliteit 1jaar: **20%**
    - At risk: ≥65jaar, immuunsuppressie, nosocomiaal,…
- Optimale therapie problematisch
  - Laattijdig → meer complicaties!
  - Niet uniform ondanks richtlijnen…

Nielsen J et al. *Scand J Infect Dis* 2011; 43: 430-435
Marks DJ et al. *PLoS One* 2012; 7: e30074

Diagnosis en therapie

Pleural disease 1

Pleural infection: past, present, and future directions

John P Corcoran, John M Wrightson, Elizabeth Belcher, Malcolm M DeCamp, David Feller-Kopman, Najib M Rahman

Pleural space infections are increasing in incidence and continue to have high associated morbidity, mortality, and need for invasive treatments such as thoracic surgery. The mechanisms of progression from a non-infected, pneumonia-related effusion to a confirmed pleural infection have been well described in the scientific literature, but the route by which pathogenic organisms access the pleural space is poorly understood. Data suggests that not all pleural infections can be related to lung parenchymal infection. Studies examining the microbiological profile of pleural infection inform antibiotic choice and can help to delineate the source and pathogenesis of infection. The development of radiological methods and use of clinical indices to predict which patients with pleural infection will have a poor outcome, as well as inform patient selection for more invasive treatments, is particularly important. Randomised clinical trial and case series data have shown that the combination of an intrapleural tissue plasminogen activator and deoxyribonuclease therapy can potentially improve outcomes, but the use of this treatment as compared with surgical options has not been precisely defined, particularly in terms of when and in which patients it should be used.

Lancet Respir Med 2015; 3: 563–77

This is the first in a Series of two papers about pleural disease

See Editorial page 497

See Comment page 505

See Online for a discussion with Nick Maskell and Najib Rahman

Oxford Centre for Respiratory Medicine (J P Corcoran MRCP, J M Wrightson DPhil, N M Rahman DPhil) and Department of Cardiothoracic Surgery (E Belcher PhD), Oxford University Hospitals NHS Trust, Oxford, UK; University of Oxford Respiratory Trials Unit, Churchill Hospital, Oxford, UK (J P Corcoran, J M Wrightson, N M Rahman); NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK (J M Wrightson, N M Rahman); Division of Thoracic Surgery, Northwestern Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (Prof M M DeCamp MD); and Division of Pulmonary and Critical Care Medicine, Johns

Introduction

Despite advances in medical diagnostic and therapeutic strategies, pleural infection (empyema or complex parapneumonic effusion) is an important problem worldwide that continues to be associated with substantial morbidity and mortality. This disorder was reliably described by Hippocrates more than two millennia ago and has claimed many lives since that time, including those of medical luminaries such as Guillaume Dupuytren (1777–1835) and William Osler (1849–1919). The basic principles of treating pleural infection, which include adequate drainage of the infected fluid collection, nutritional support, and an appropriate antibiotic therapy, have remained constant since the mid 20th century.

The incidence of pleural infection in both adult and paediatric populations continues to rise inexorably.[1–5] Postulated reasons for this rise include an improvement in clinical awareness and diagnostics, a replacement phenomenon associated with widening use of multivalent pneumococcal vaccines,[3,6,7] and a vulnerable ageing population living with chronic disease. One in five patients will need surgical intervention to adequately treat their pleural infection,[8,9] whereas the 1-year mortality from the disorder has remained steady at about 20% for more than two decades.[5,8–10] Of particular concern is that the greatest increase in caseload is in patients aged older than 65 years' and immunocompromised patients, whose mortality from pleural infection is above 30%,[1,8,9,11] related to frail health and comorbidity. There are any number of potential reasons for the failure of treatments to have a substantial and lasting effect on key clinical outcomes. These reasons might include variability in clinical practice and disagreement about how these patients are best managed,[12–17] despite the availability of consensus guidelines.[5,18]

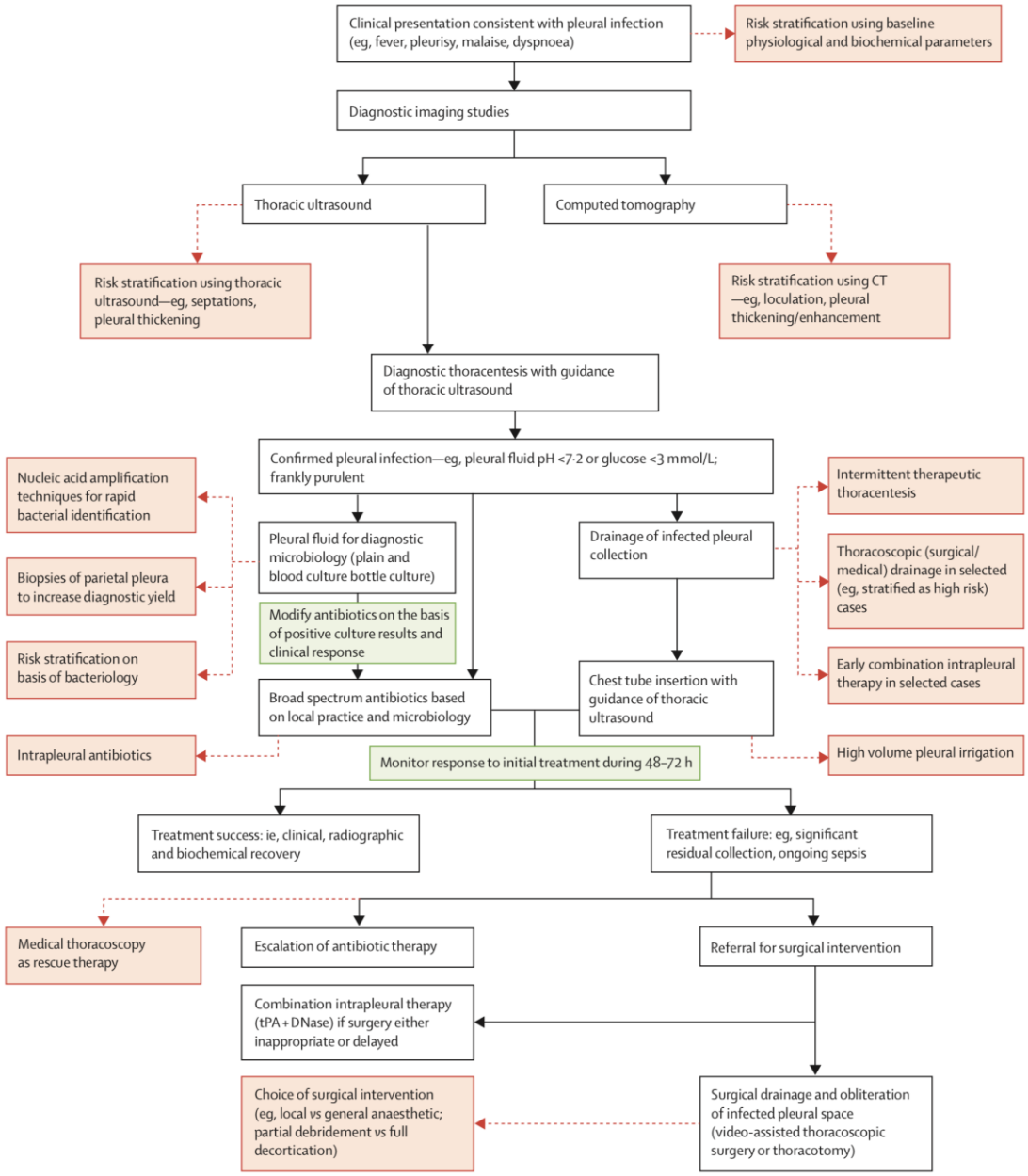
This Series paper addresses our understanding of pleural infection, specifically its pathophysiology, diagnosis, and treatment, together with developments in clinical and laboratory research, and future areas of investigation for management of this disorder.

Pathophysiology

Parapneumonic effusions occur in up to half of all cases of community-acquired pneumonia, with about 10% of these effusions becoming complex due to co-infection of the pleural space.[19,20] The initial formation of a parapneumonic effusion is thought to be caused by increased permeability of the visceral pleural membranes and leakage of interstitial fluid in response to inflammation of the underlying lung parenchyma. The promotion of neutrophil migration together with the release of pro-inflammatory cytokines, including interleukin-6, interleukin-8, and tumour necrosis

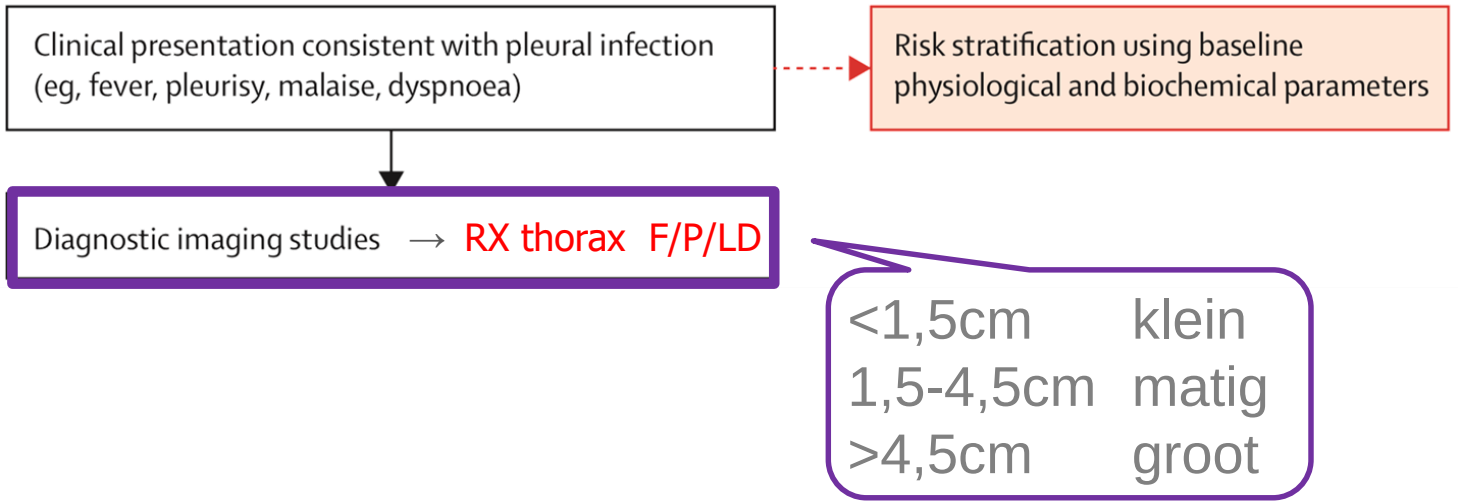
Key messages

- The incidence of pleural infection continues to rise and this disease remains associated with a poor clinical outcome, with up to 20% of patients requiring surgery or dying
- The process by which bacteria translocate the infected lung and multiply in the pleural space is incompletely understood, but there is an increasing understanding of the inflammatory pathways associated with progression from simple to complex, fibrinous infected effusion
- A score to predict clinical outcome at baseline in pleural infection has been derived and might be helpful in the future to plan treatment escalation and invasive interventions
- The microbiological profile of pleural infection suggests a different set of organisms to those seen in pneumonia, with oropharyngeal and microaspiration potential sources
- Conventional microbiological analysis is only slightly sensitive for the identification of causative organism, and this can be improved by the inoculation of pleural fluid into culture media bottles, and potentially in the future by the use of molecular microbiological techniques
- Intrapleural tPA and DNase has been shown to significantly improve drainage and can have important effects on reducing surgical requirement and hospital stay
- Surgery remains a key treatment modality in selected cases, but the precise surgical method of choice, patient selection, and timing are not well defined



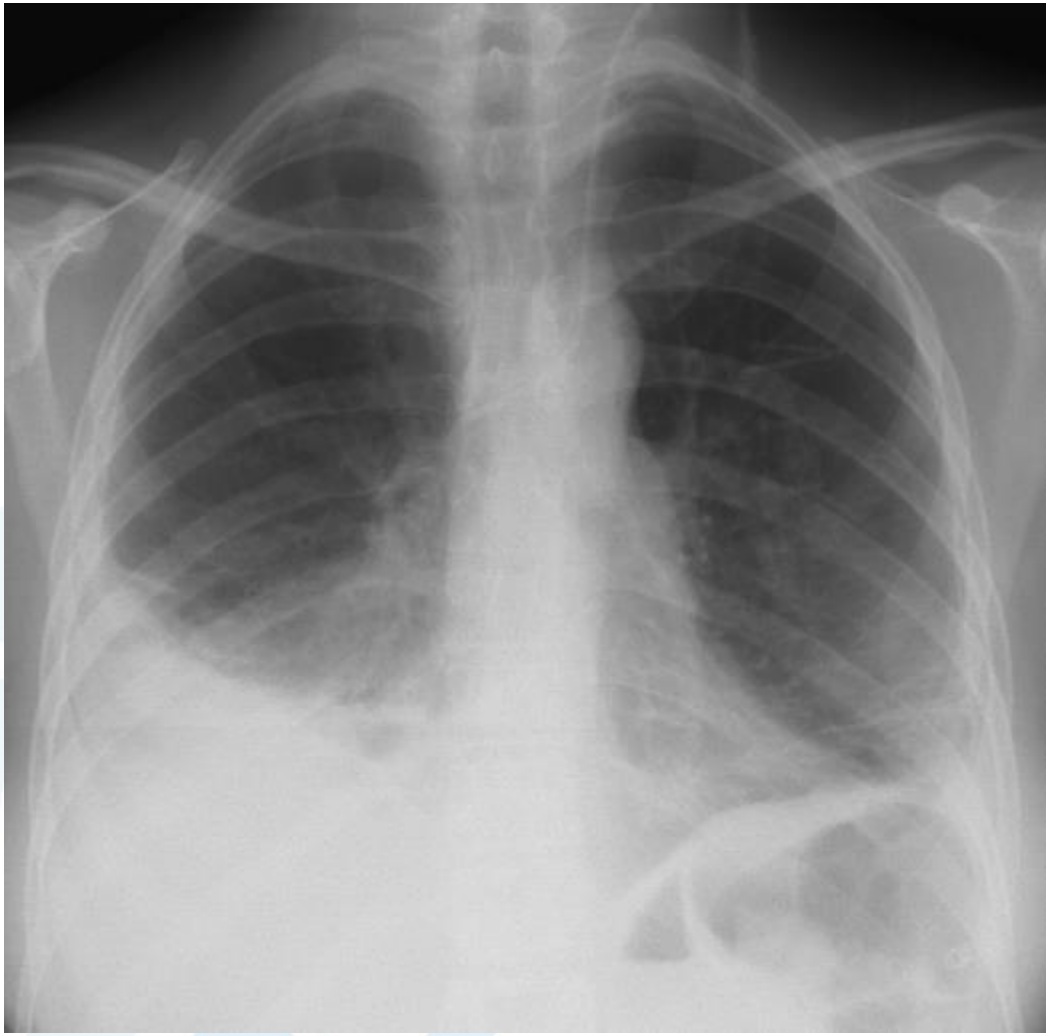
Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

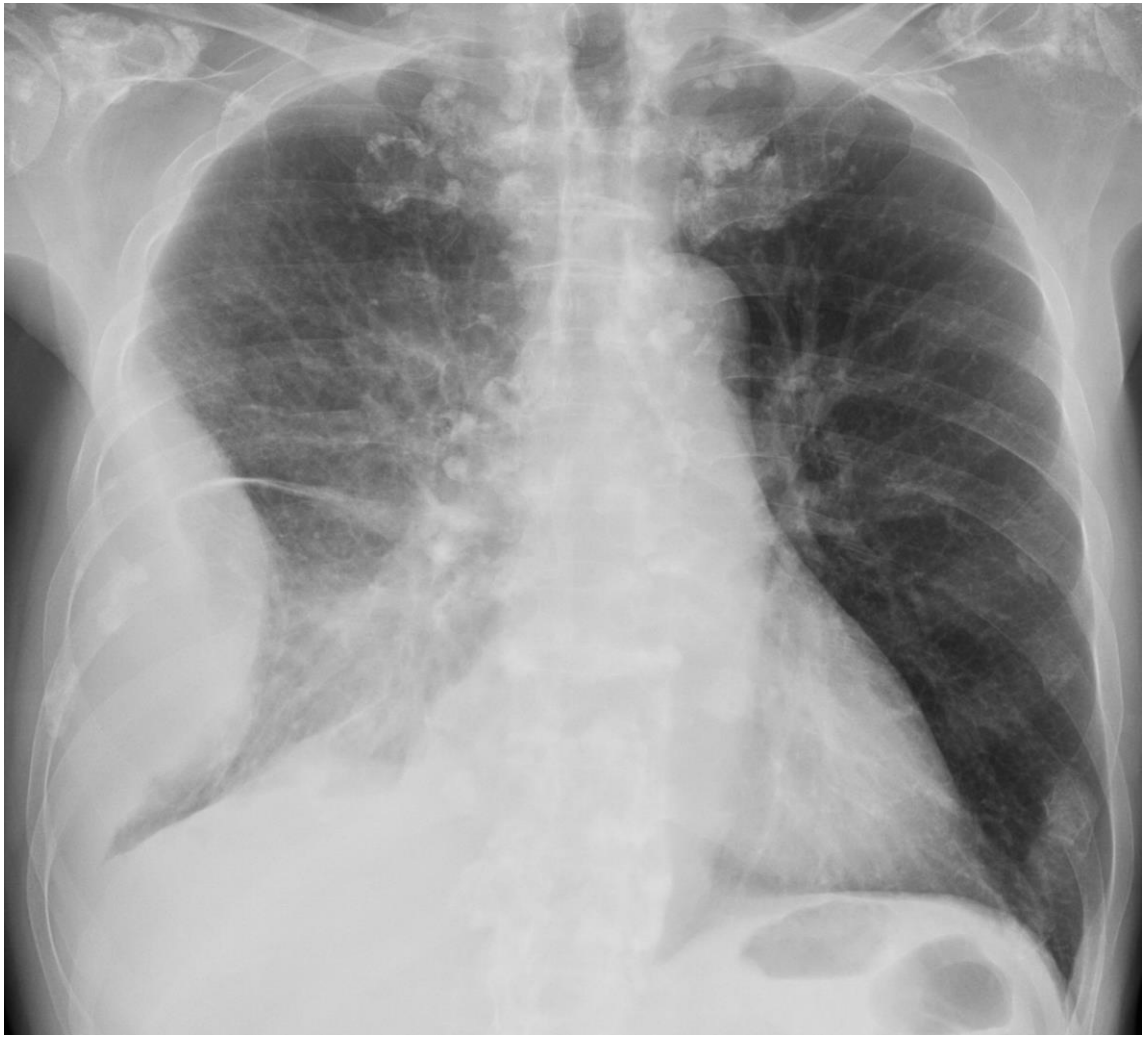
Diagnosis en therapie



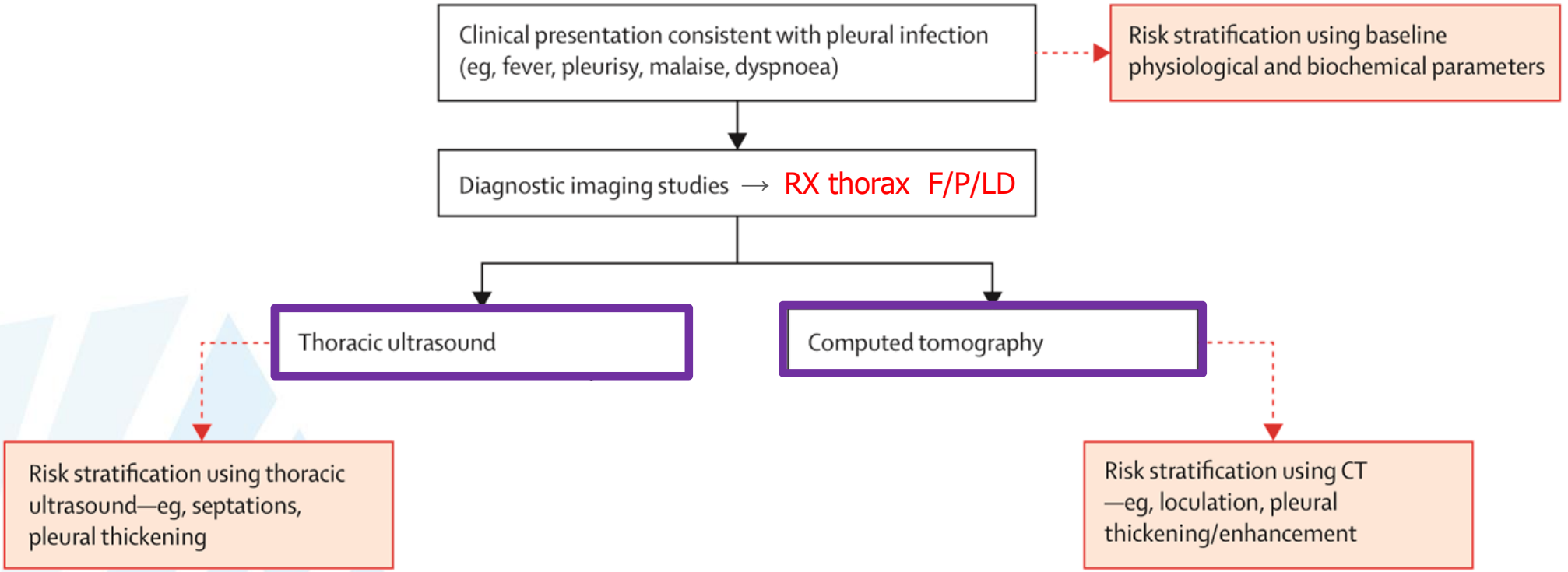
- CPE/empyeem
  - Pleuraal aangelegen opaciteit
  - Stompe hoek met thoraxwand
  - Vormverandering tgv zwaartekracht ('drooping')
  - Niet vrij bewegend in latere decubitus ('no free flow')
  - Zichtbare pulmonale vaten ('filter effect')

Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577





Diagnosis en therapie



Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

Echografie thorax

- Differentiatie massa/vocht
- Exacte locatie van pleuraal vocht
  - → pleurapunctie (geen blinde puncties!)
  - → plaatsen thoraxdrain

CHEST

Patient Safety Forum

Ultrasound Guidance Decreases Complications and Improves the Cost of Care Among Patients Undergoing Thoracentesis and Paracentesis

Catherine J. Mercaldi, MPH; and Stephan F. Lanes, PhD

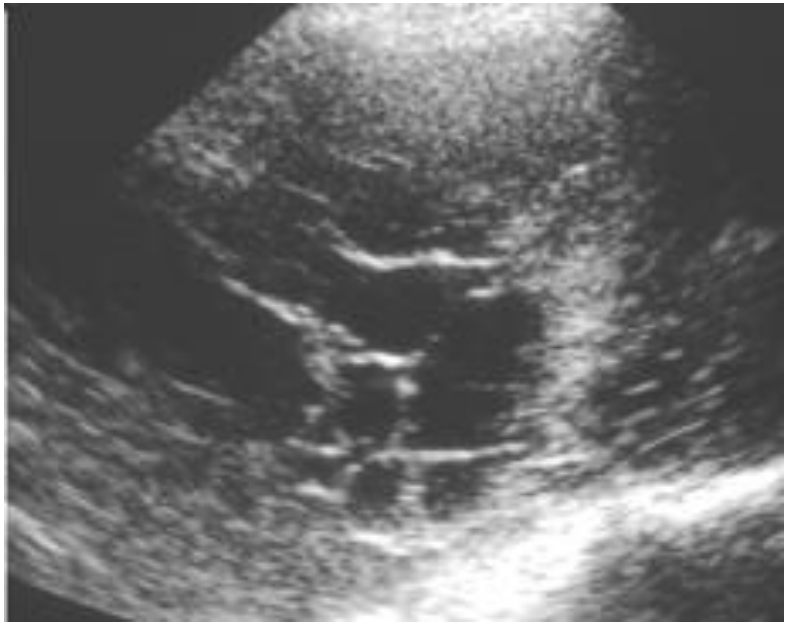
CHEST 2013; 143(2):532–538

Echografie thorax

- Differentiatie massa/vocht
- Exacte locatie van pleuraal vocht
  - → pleurapunctie (geen blinde puncties!)
  - → plaatsen thoraxdrain

- Loculaties/vergroeiingen
  - → echo > CT

  ☞ prognose…

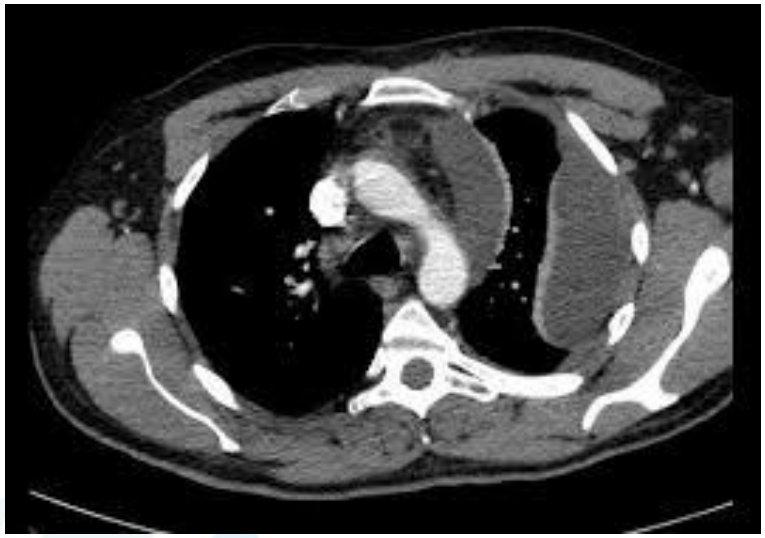


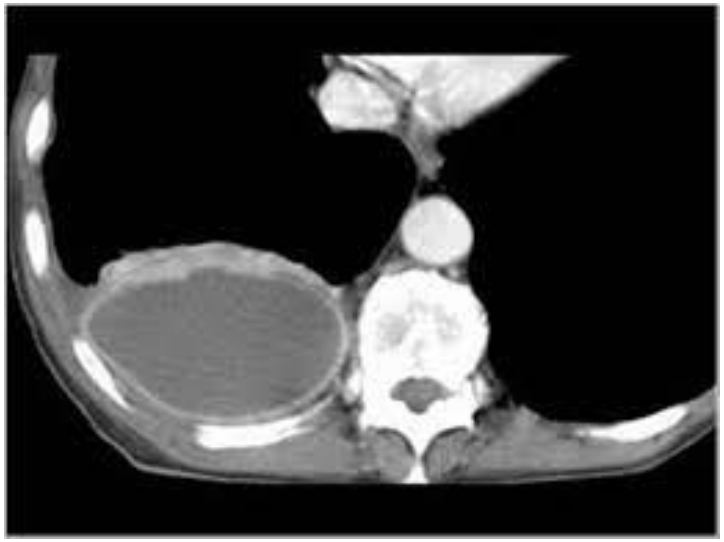
Huang HC et al. *Chest* 1999; 115: 751-756
Chen CH et al. *Ultrasound Med Biol* 2009; 35: 1468-1474
Mercaldi CJ et al. *Chest* 2013; 143: 532-538

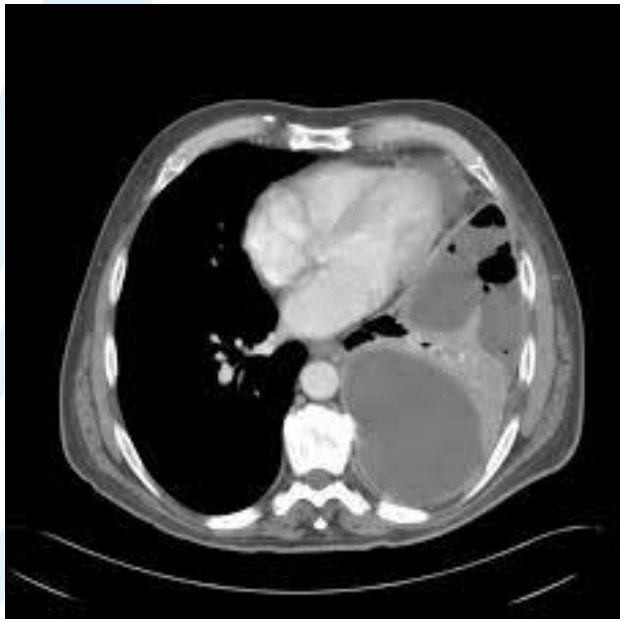
CT thorax

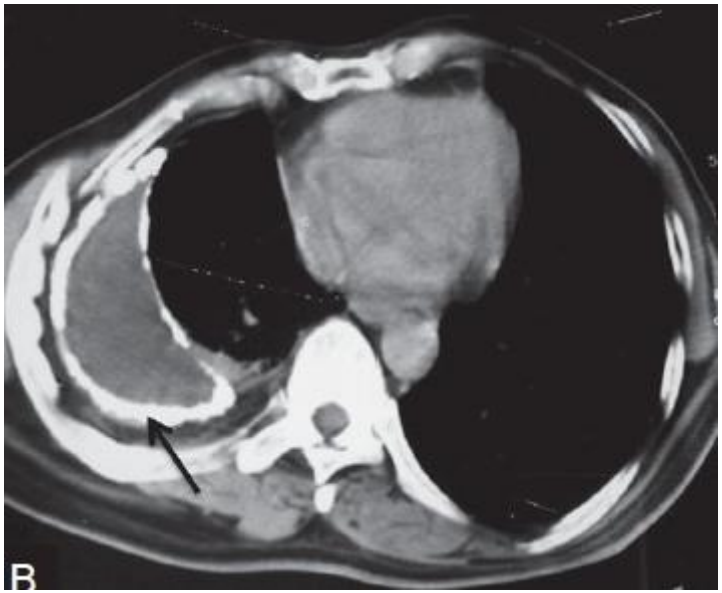
met contrast

- Aankleuring van pariëtale en viscerale pleura ('split pleura sign')
- Vaak ook pleurale verdikking (>3mm)
- Wand vaak wel dunner, minder onderregelmatig dan bij longabces
- Compressie van aanliggende long (geen destructie)
- Stompe hoek met thoraxwand





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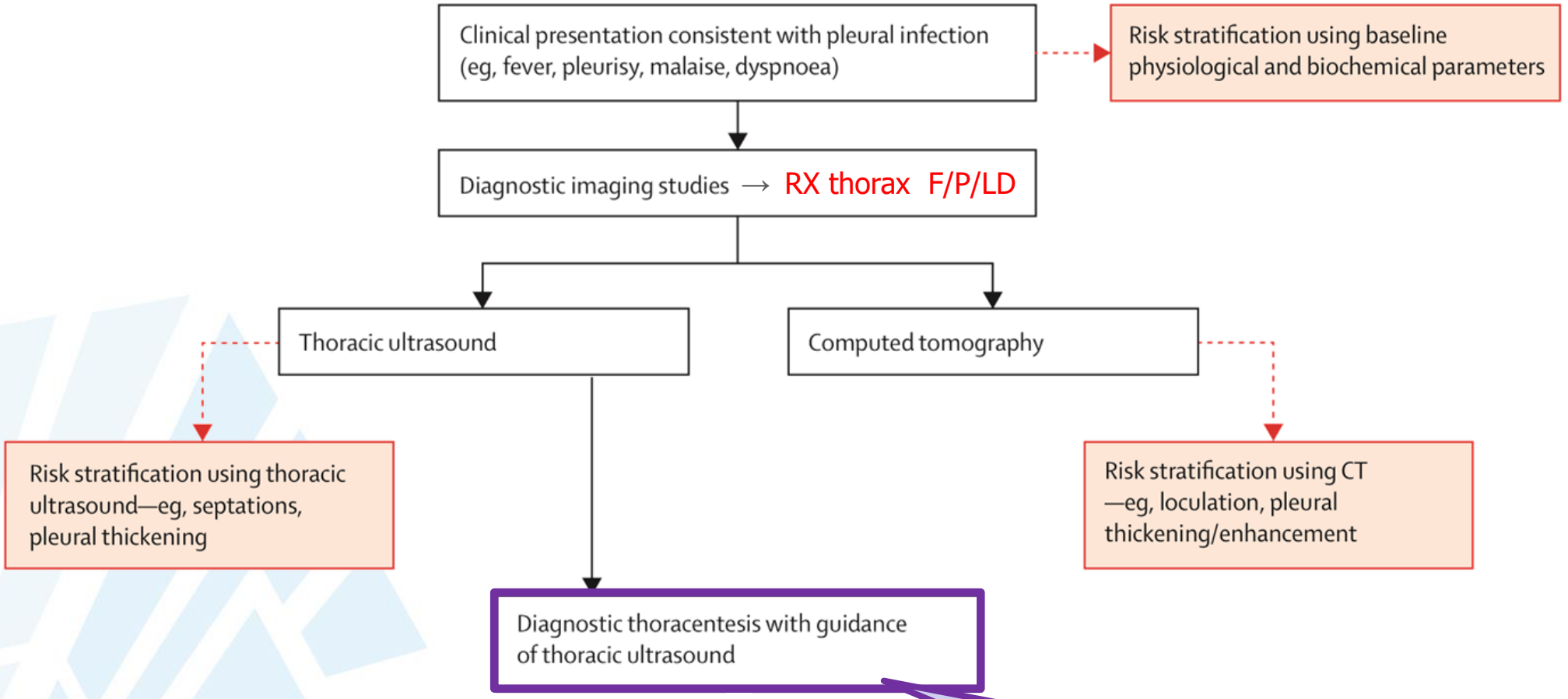
Diagnosis en therapie



- pH (in bloedgasmachine!)
- WBC met differentiatie
- biochemie: eiwit, LDH, glucose
- microbiologie

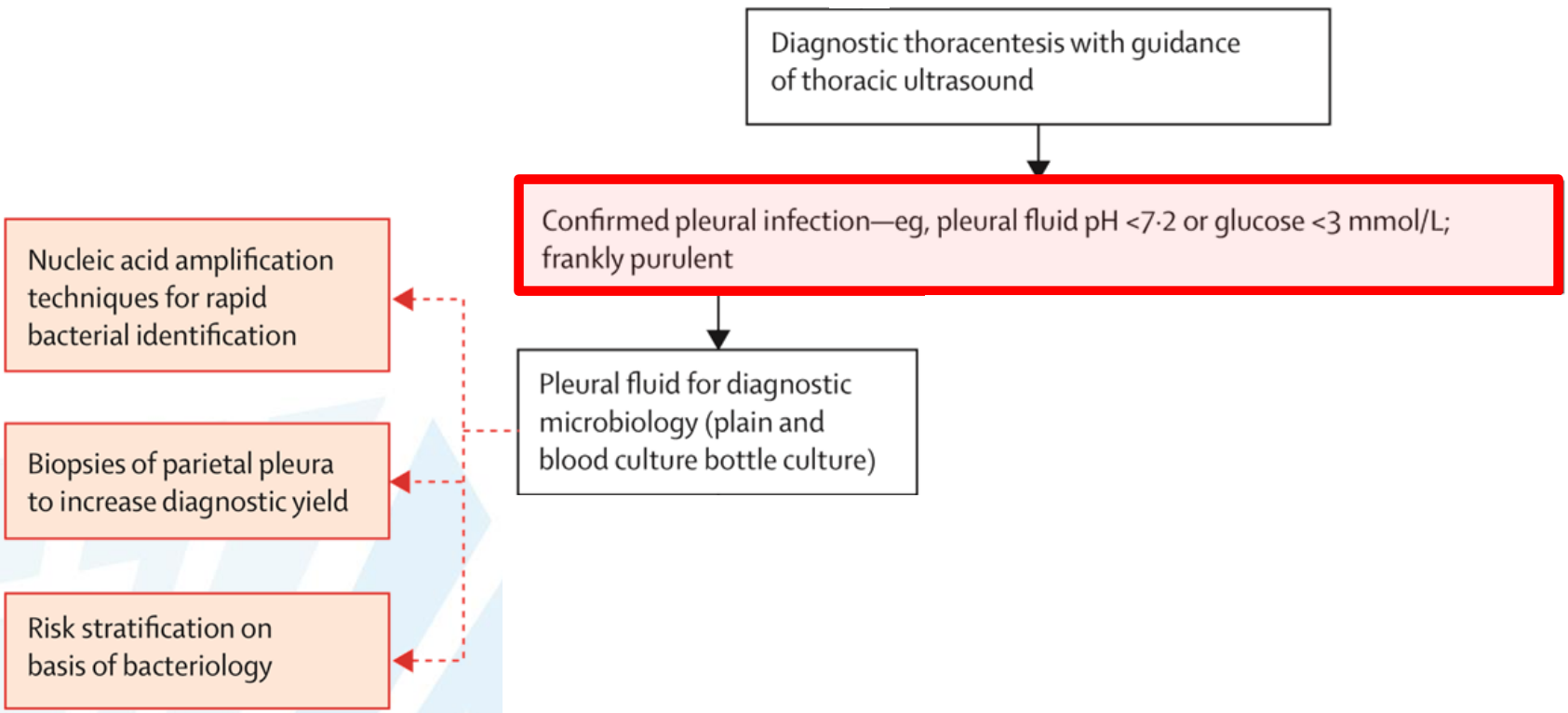
Pleurapunctie

Stages	Macroscopic appearance	Pleural fluid characteristics	Comments
Si pa ex	id	pH>7.2 LDH<1000 Glucose>30	Antibiotics (Drain if required on symptomatic grounds)
Complicated parapneumonic ("fibrinopurulent")	Clear fluid Cloudy/turbid	pH<7.2 LDH>1000 Glucose<30 Gram/cult. +/-	Chest tube drainage (+ …)
Empyema Organising stage (scar tissue, pleural peel)	Frank pus	Gram/cult. +/- No other tests required	Chest tube drainage (+ …) Surgery

- Maligniteit
- Tuberculose
- Rheumatoïde arthritis
- Lupus pleuritis

Davies HE et al. *Thorax* 2010; 65(S2): ii41-ii53
Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

Diagnosis en therapie



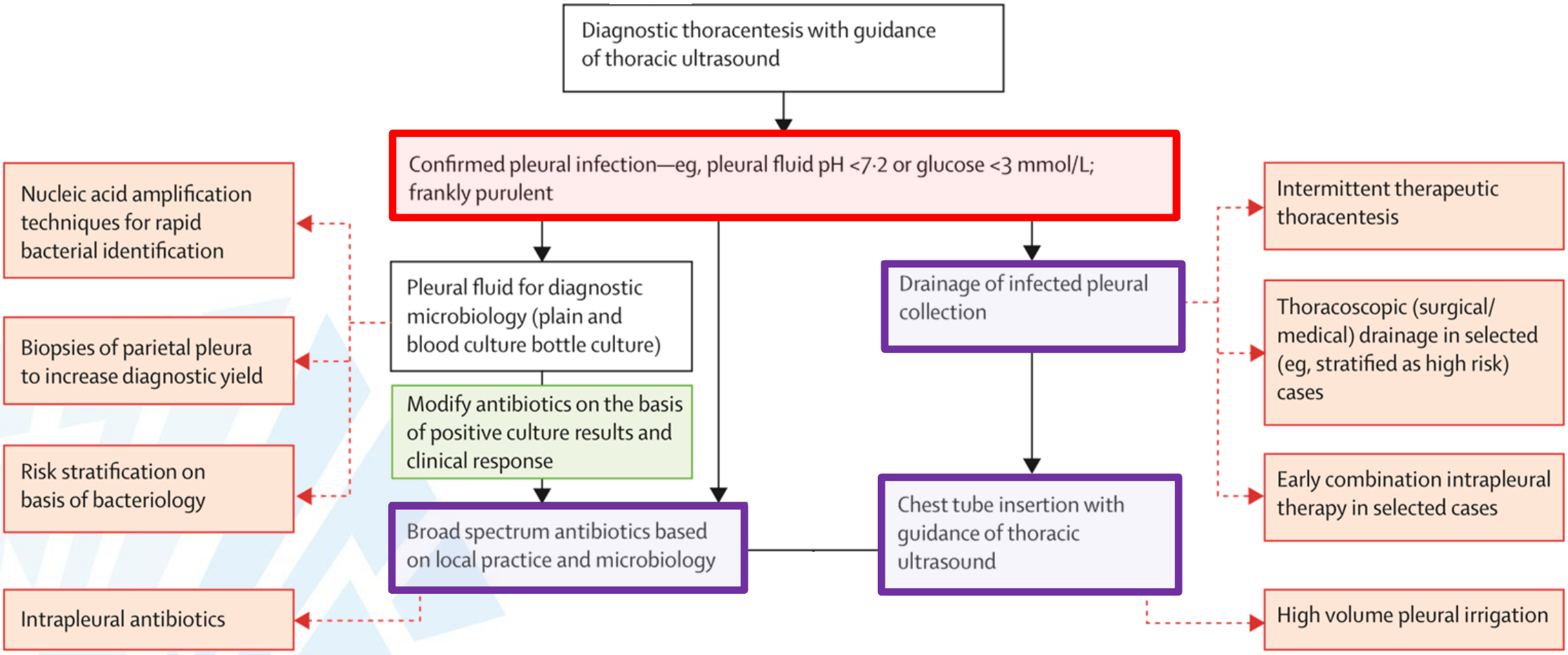
Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

Bacteriologie

Community-acquired	*Streptococcus* spp. (~52%) ► *S milleri* ► *S pneumoniae* ► *S intermedius* *Staphylococcus aureus* (11%) Gram-negative aerobes (9%) ► Enterobacteriaceae ► *Escherichia coli* Anaerobes (20%) ► *Fusobacterium* spp. ► *Bacteroides* spp. ► *Peptostreptococcus* spp. ► Mixed
Hospital-acquired	Staphylococci ► Meticillin-resistant *S aureus* (MRSA) (25%) ► *S aureus* (10%) Gram-negative aerobes (17%) ► *E coli* ► *Pseudomonas aeruginosa* ► *Klebsiella* spp. Anaerobes (8%)

Maskell NA et al. *Am J Respir Crit Care Med* 2006; 174: 817-823

Diagnosis en therapie



Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

Antibiotica

- Altijd noodzakelijk & 'ASAP'
- Empyeem: verdikte pleura, zuur milieu, pus
  - AB concentraties pleura < serum → start IV
  - *Penicillines*, *cephalosporines*, *fluorochinolones*, …: goede penetratie in pleuraal vocht
  - Aminoglycosiden eerder slechtere penetratie & inaktivatie tgv acidose
- Breed spectrum: ook anaërobe dekking …
- Nosocomiaal: + MRSA
- Langdurige therapie: **2-6weken**

Davies HE et al. *Thorax* 2010; 65(S2): ii41-ii53
Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

Antibiotica

Community-acquired infection

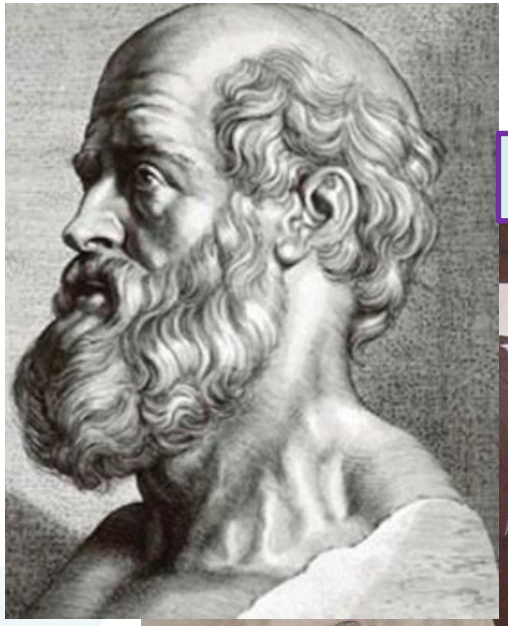
amoxicillin-clavulanate	1g qds
clindamycin	600mg tds
+ levofloxacin	500mg bd

Hospital-acquired infection

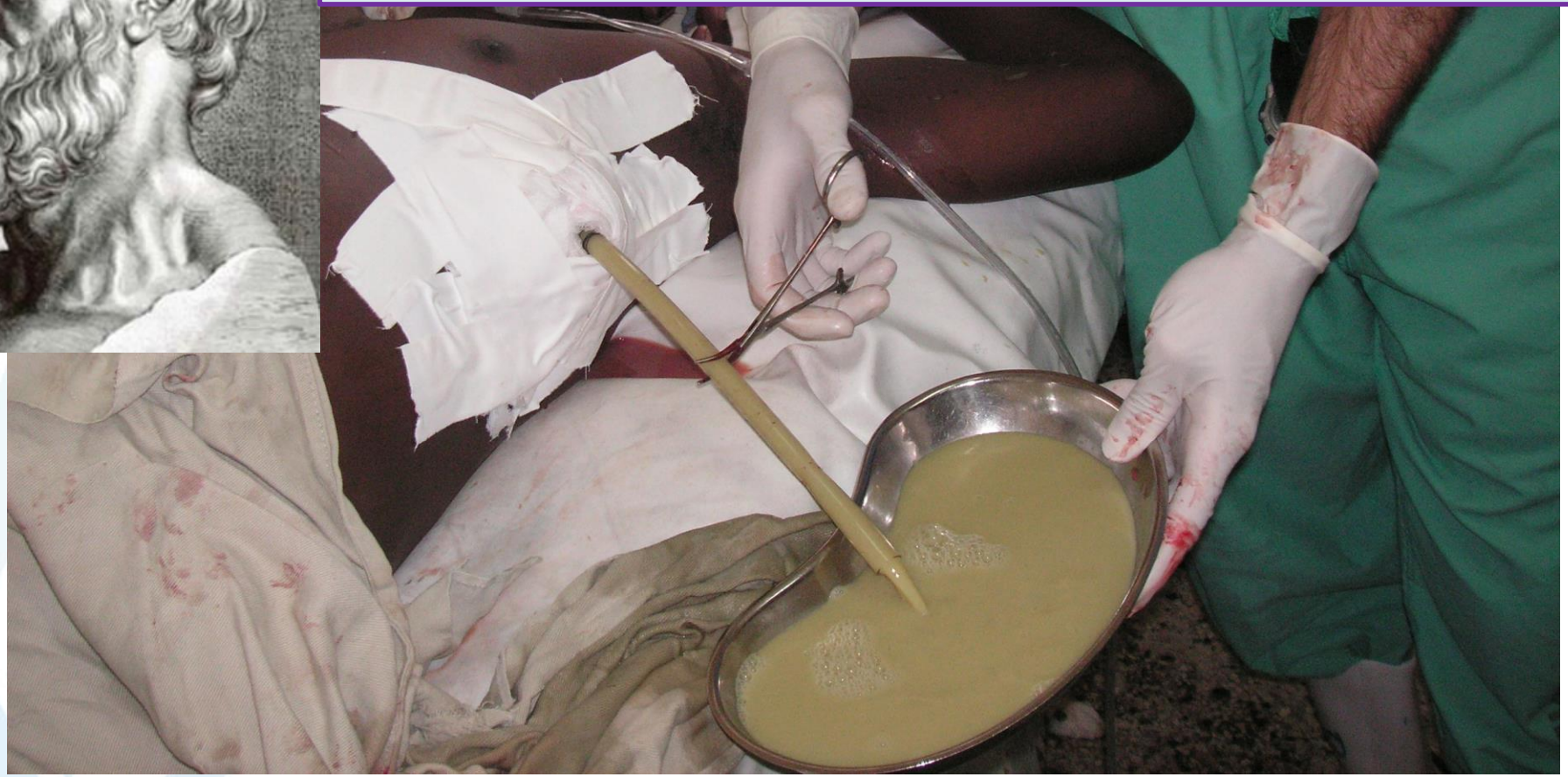
piperacillin-tazobactam	4g tds
ceftriaxone	2g dd
+ ornidazol	1g dd

http://www.uzleuven.be/antibioticagids

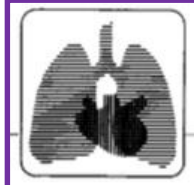
Evacuatie van vocht



"Als het empyema niet doorbreekt, zal de patiënt sterven"



Indicaties voor drainage



aacp consensus statement

Medical and Surgical Treatment of Parapneumonic Effusions*

An Evidence-Based Guideline

CHEST 2000, 18:1158–1171

Gene L. Colice, MD, FCCP; Anne Curtis, MD; Jean Deslauriers, MD; John Heffner, MD, FCCP; Richard Light, MD, FCCP; Benjamin Littenberg, MD; Steven Sahn, MD, FCCP; Robert A. Weinstein, MD; and Roger D. Yusen, MD; for the American College of Chest Physicians Parapneumonic Effusions Panel

Pleural Space Anatomy		Pleural Fluid Bacteriology		Pleural Fluid Chemistry*	Category	Risk of Poor Outcome	Drainage
A_0 minimal, free-flowing effusion (< 10 mm on lateral decubitus)†	AND	B_X culture and Gram stain results unknown	AND	C_X pH unknown	1	Very low	No‡
A_1 small to moderate free-flowing effusion (> 10 mm and < ½ hemithorax)	AND	B_0 negative culture and Gram stain§	AND	C_0 pH ≥ 7.20	2	Low	No‖
A_2 large, free-flowing effusion (≥ ½ hemithorax)¶ loculated effusion,# or effusion with thickened parietal pleura**	OR	B_1 positive culture or Gram stain	OR	C_1 pH < 7.20	3	Moderate	Yes
		B_2 pus			4	High	Yes

Evacuatie van vocht

1. Herhaalde evacuerende punkties

2. Plaatsen thoraxdrain (+ suctie)

3. Spoelen van de pleurale holte
4. Intrapleurale fibrinolytica/mcolytica

5. Medische thoracoscopie

6. Decorticatio
   - VATS
   - Open chirurgie

Seriële puncties

- Attractief want ambulante behandeling mogelijk!
- Geselecteerde gevallen
  → borderline pH, geen loculaties,….
- Succesvolle outcome is gerapporteerd

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- Attractief want ambulante behandeling mogelijk!

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MAAR - weinig case reports
- geen RCT's

Seriële puncties

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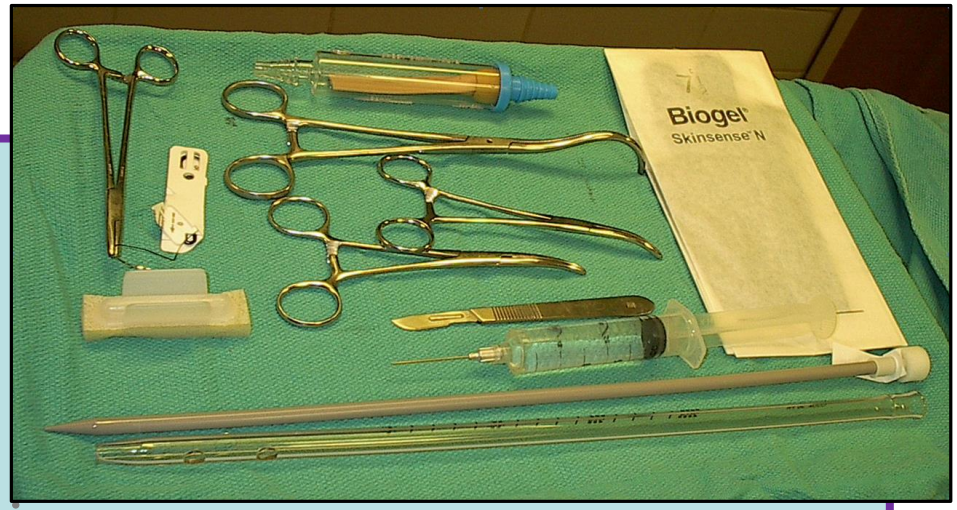
- Geselecteerde gevallen
  → borderline pH, geen loculaties ….
- Succesvolle outcome is gerapporteerd

MAAR - weinig case reports
- geen RCT's

niet aanbevolen in de richtlijnen!

Thoraxdrain

"Ubi pus, ibi evacua"



- Purulent vocht/etter
- pH < 7,2
- Aanwezigheid van pathogene kiemen
- Grote niet-purulente vochtuitstortingen

Thoraxdrain

- Geen consensus omtrent optimale diameter
  - ✓ 'small bore catheters' (10-14F)
    - ⇨ goede resultaten, weinig complicaties
  - ✓ 'large bore catheters'
    - ⇨ dikke etter…

- Kleine diameter → regelmatig doorspoelen!!
  (30mL NaCl 0,9% q6hrs)

- Suctie: geen robuste data, meestal wel toegepast
  (20cm H_2O)

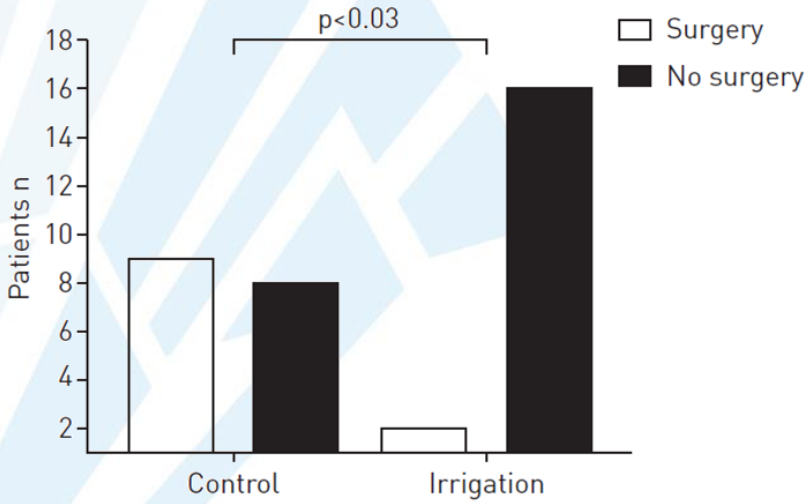
Horsley et al. *Chest* 2006; 130: 1857
Rahman et al. *Chest* 2010; 137: 536
Davies HE et al. *Thorax* 2010; 65(S2): ii41-ii53

Spoeling met NaCl 0,9%

Pleural irrigation trial (PIT): a randomised controlled trial of pleural irrigation with normal saline *versus* standard care in patients with pleural infection

Eur Respir J 2015; 46: 456–463

Clare E. Hooper[1,2], Anthony J. Edey[3], Anthony Wallis[3], Amelia O. Clive[1,2], Anna Morley[2], Paul White[4], Andrew R.L. Medford[2], John E. Harvey[2], Mike Darby[3], Natalie Zahan-Evans[2] and Nick A. Maskell[1,2]



- Betere evacuatie vocht op dag3
  32,3% vs. 15,3% (p<0,04)
- Minder nood aan heelkunde
  11% vs. 47% (p=0,03)

Fibrinolytica/Mucolytica

- Fibrinopurulente stadium
  - inhibitie van fibrinolyse (↑ PAI,…)
  - activatie van stollingscascade

→ vorming van fibrine

⇨ pleurale verdikking
⇨ adhesies, septaties
⇨ loculaties

⊖

Intrapleurale fibrinolyica

* Streptokinase	250.000 IU od/bd
* Urokinase	100.000 IU od
* tPA	10mg bd

Idell S et al. *Am Rev Respir Dis* 1991; 144: 187-194
Cameron R et al. *Cochrane Database Syst Rev* 2004; CD002312
Diacon AH et al. *Am J Respir Crit Care Med* 2004; 170: 49-53

UZ LEUVEN

MIST 1

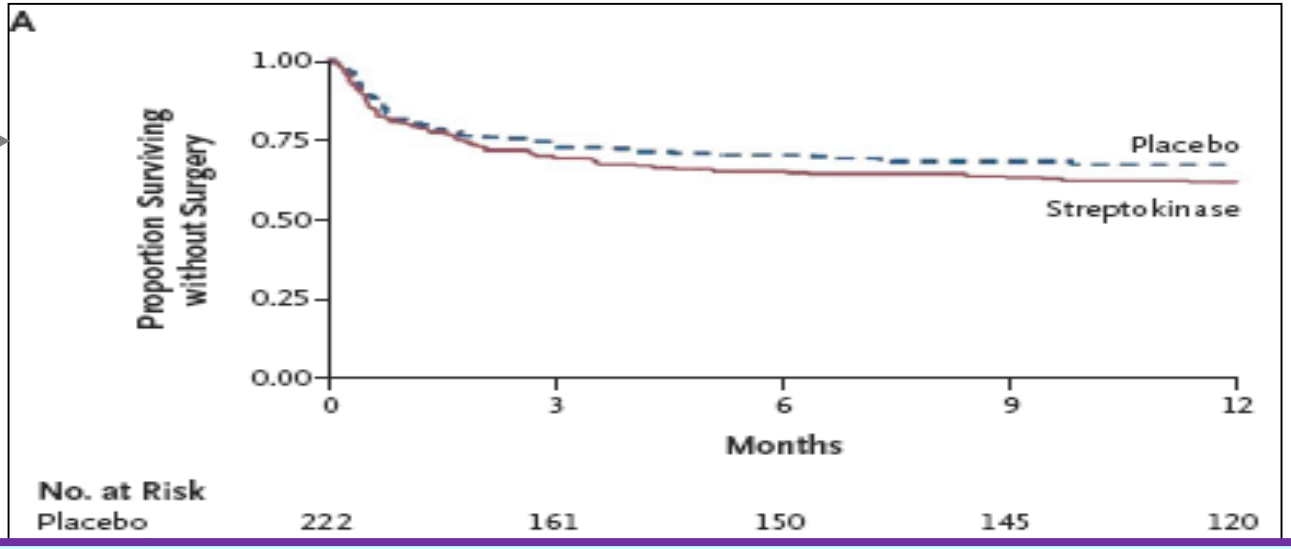
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 3, 2005 VOL. 352 NO. 9

U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection

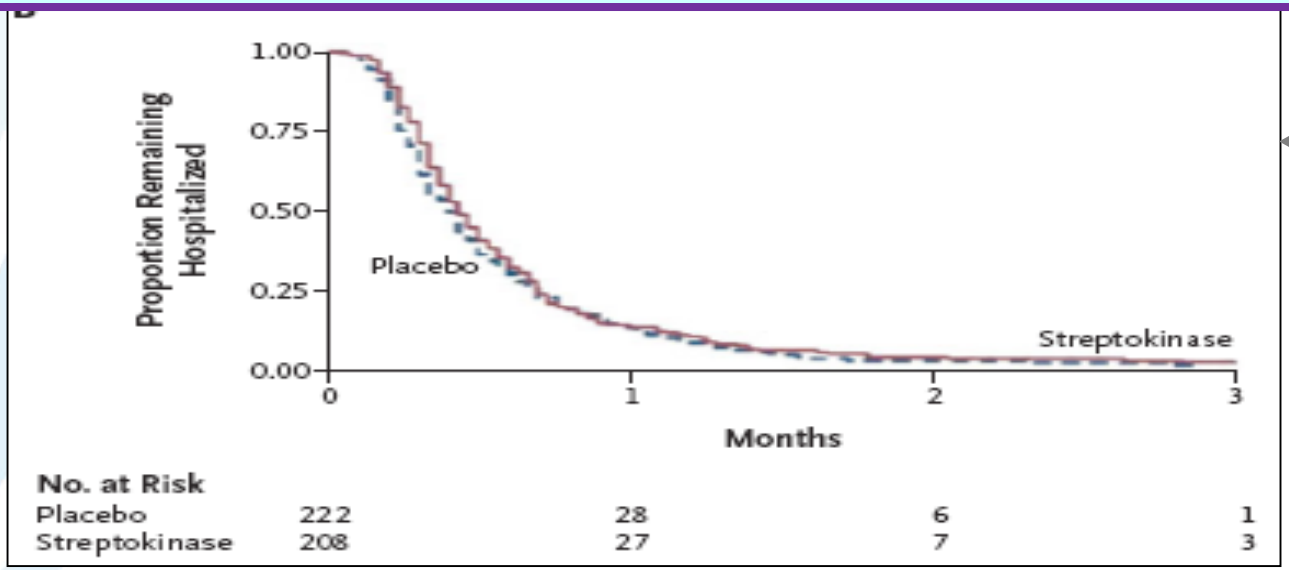
Nicholas A. Maskell, M.R.C.P., Christopher W.H. Davies, M.D., Andrew J. Nunn, M.Sc., Emma L. Hedley, Fergus V. Gleeson, F.R.C.P., Robert Miller, F.R.C.P., Rhian Gabe, M.Phil., Glyn L. Rees, Timothy E.A. Peto, F.R.C.P., Mark A. Woodhead, F.R.C.P., Donald J. Lane, F.R.C.P., Janet H. Darbyshire, M.B., Ch.B., and Robert J.O. Davies, D.M., for the First Multicenter Intrapleural Sepsis Trial (MIST1) Group*

Nood aan chirurgie



CONCLUSIONS

The intrapleural administration of streptokinase does not improve mortality, the rate of surgery, or the length of the hospital stay among patients with pleural infection.



Opnameduur

(13d vs. 12d)

UZ LEUVEN

MIST 2

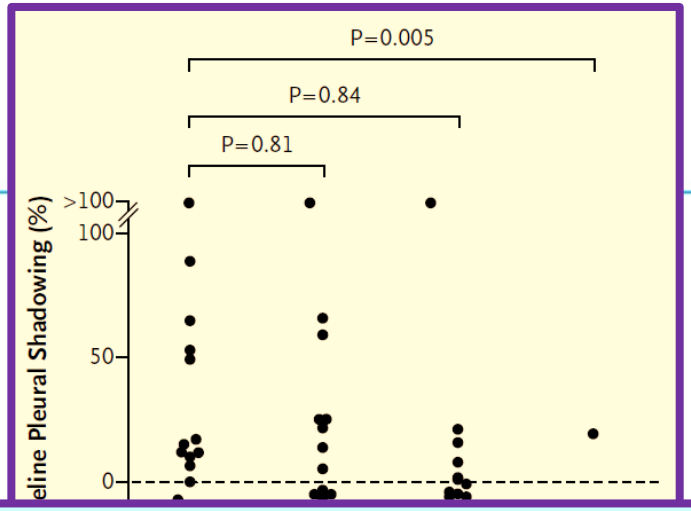
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2011;365:518-26

ORIGINAL ARTICLE

Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection

Najib M. Rahman, D.Phil., Nicholas A. Maskell, D.M., Alex West, M.R.C.P., Richard Teoh, M.R.C.P., Anthony Arnold, M.R.C.P., Carolyn Mackinlay, M.R.C.P., Daniel Peckham, M.D., Chris W.H. Davies, M.D., Nabeel Ali, M.D., William Kinnear, M.D., Andrew Bentley, M.D., Brennan C. Kahan, M.Sc., John M. Wrightson, M.R.C.P., Helen E. Davies, M.R.C.P., Clare E. Hooper, M.R.C.P., Y.C. Gary Lee, Ph.D., Emma L. Hedley, Nicky Crosthwaite, R.G.N., Louise Choo, M.Sc., Emma J. Helm, F.R.C.R., Fergus V. Gleeson, M.D., Andrew J. Nunn, M.Sc., and Robert J.O. Davies, M.D.*



CONCLUSIONS

Intrapleural t-PA–DNase therapy improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. Treatment with DNase alone or t-PA alone was ineffective. (Funded by an unrestricted educational grant to the University of Oxford from Roche UK and by others; Current Controlled Trials number, ISRCTN57454527.)

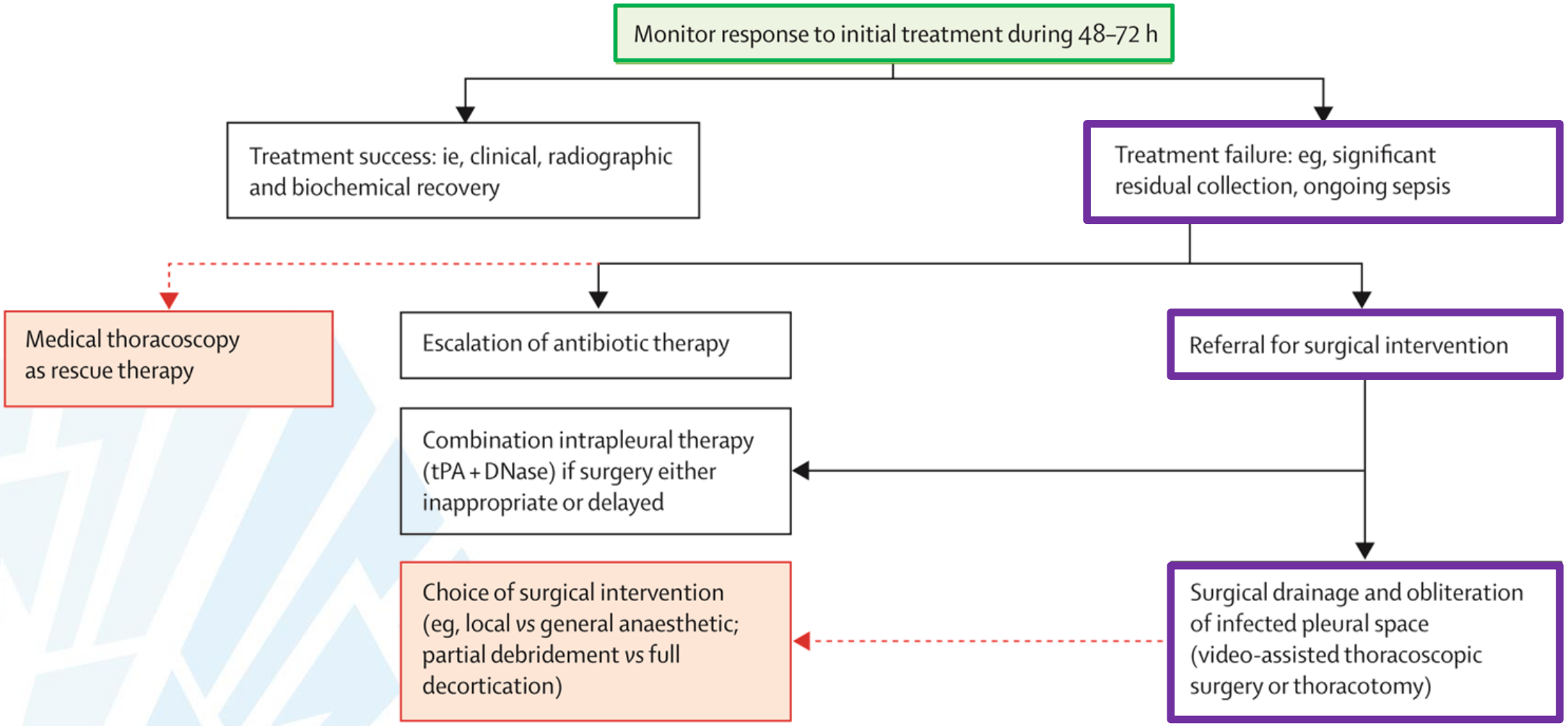
by effusion (primary outc				
Percent difference vs. place				NA
P value				NA
Surgical referral — no. referred				8/51 (16)
Odds ratio vs. placebo (95%				NA
P value				NA
Hospital stay — no. of days				24.8±56.1
Percent difference vs. place				NA
P value	0.21	0.73	<0.001	NA

Chirurgie ↓ 77%
Opnameduur ↓ 6,7d

Klinische verbetering ??
Duur!

géén standaard therapie!

Diagnosis en therapie



Corcoran JP et al. *Lancet Resp Med* 2015; 3: 563-577

Indicatie = 'rescue therapy'

* geen respons op AB en percutane drainage
  (+/- *medische thoracoscopie*)
* progressie tot 'fibrothorax'

20-40%

VATS >> open thoracotomie

→ kortere opnameduur, minder complicaties, even effectief

Tijdige verwijzing indien falen conservatieve therapie: **96u**

Quid VATS als primaire therapie?

→ kortere duur drain & opname, reductie kosten, hogere success rate ??
MAAR studies 'underpowered'...

Lardinois D et al. *Ann Thorac Surg* 2005; 79: 1851-1856
Bilgin M et al. *ANZ J Surg* 2006; 76: 120-122
Chambers A et al. *Interact Cardiovasc Thorac surg* 2010; 11: 171-177


THANK YOU FOR YOUR ATTENTION!
ANY QUESTIONS?