ESCMID Postgraduate Education Course

Infections in Critically Ill Patients

Athens, Greece
21 – 22 May 2011

Clinical Case 3

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2nd Critical Care Dept

"ATTIKON" Hospital

April, 19 2011

- Previously healthy 23 yo male
- Motor vehicle accident, Rhodes
- Injuries
  - Bilateral hemo-pneumothoraces
  - Lung contusions
  - Fracture of left ribs 5-7
- Main problem respiratory failure
  - Intubation
  - Bilateral chest drains

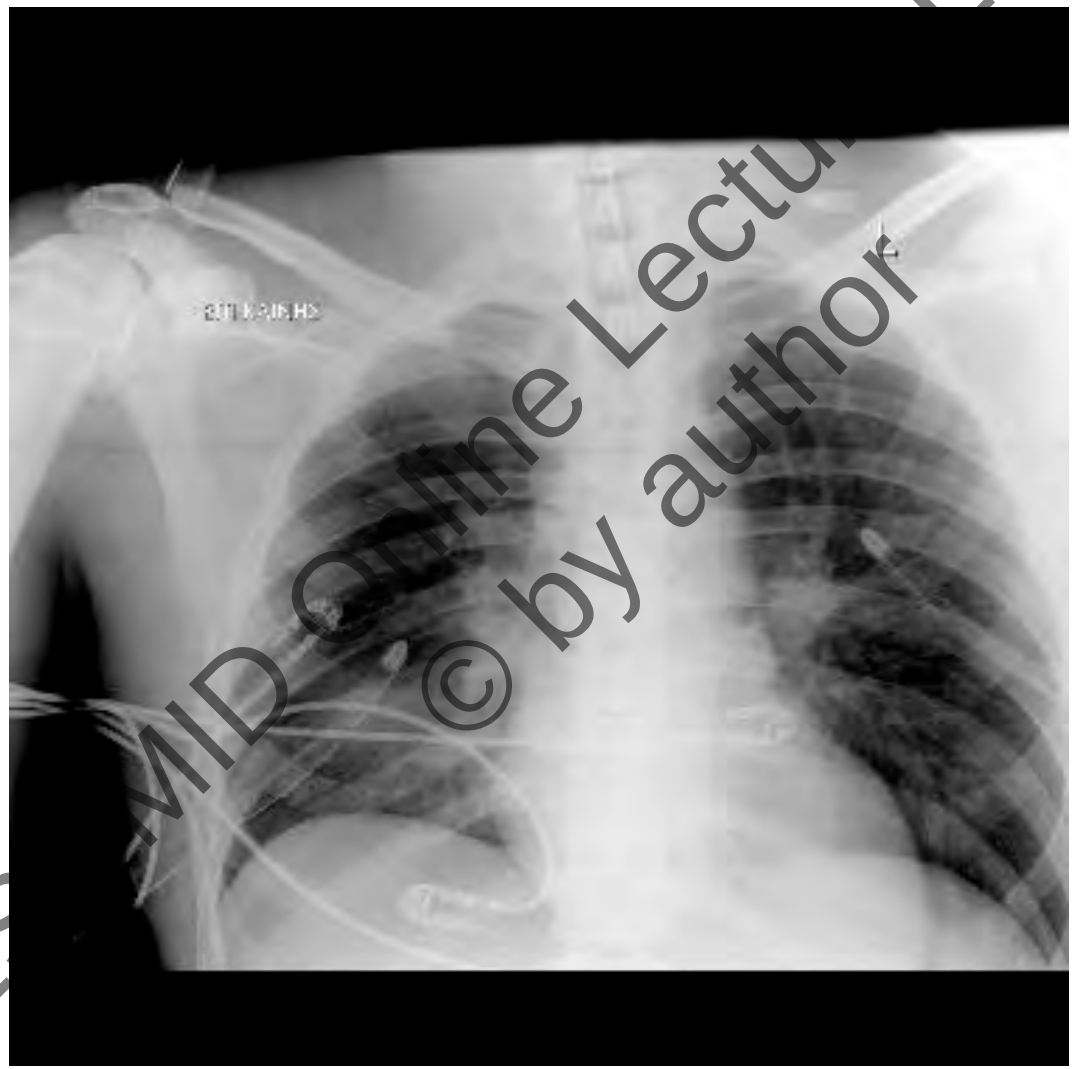
April, 24 2011

- Sedation and conservative treatment
  - Ceftriaxone 2g x2, Clindamycin 600 mg x 4, Linezolid 600 mg x 2
  - No fever
- Respiratory failure better, awakening
  - Paraplegia
  - Total sensory loss (T5 level)
  - CT spine
    - Fracture C5- no spinal compression
    - Fracture-subluxation at the T5-T6 level
- Transfer to Athens for spinal stabilization

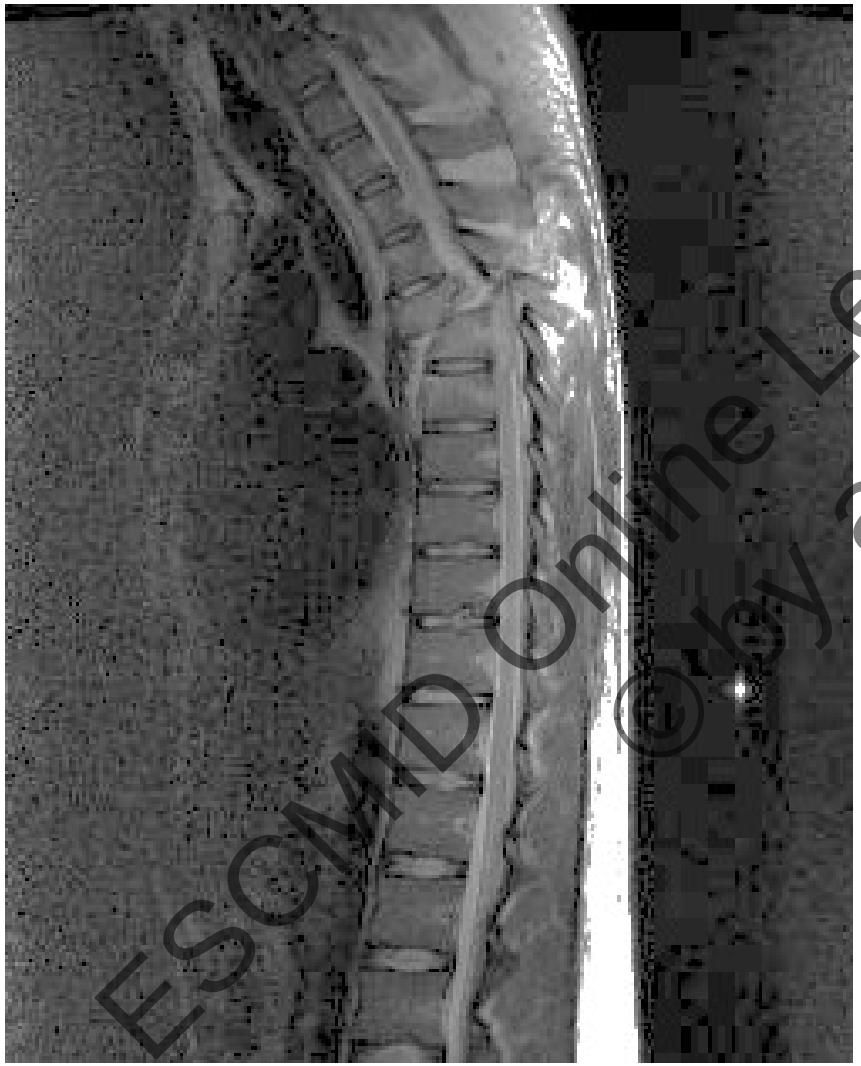
April 26, 2011- Admission

- CNS-Opens eyes, obeys commands, moves arms
- Lungs-Clear lung fields, oxygenation deficit (PaO2/FiO2 150)
- Abdomen- ok
- Rhabdomyolysis (high fluid turnover)
- Fricture burns on right arm- clean, no inflammation
- Labs
  - Hb 8.3 g/dL, WBC 11,200 (77/9/10), Plts 108,000
  - Urea 46 mg/dL, creat 0.9 mg/dL, CPK 2,475 U/L

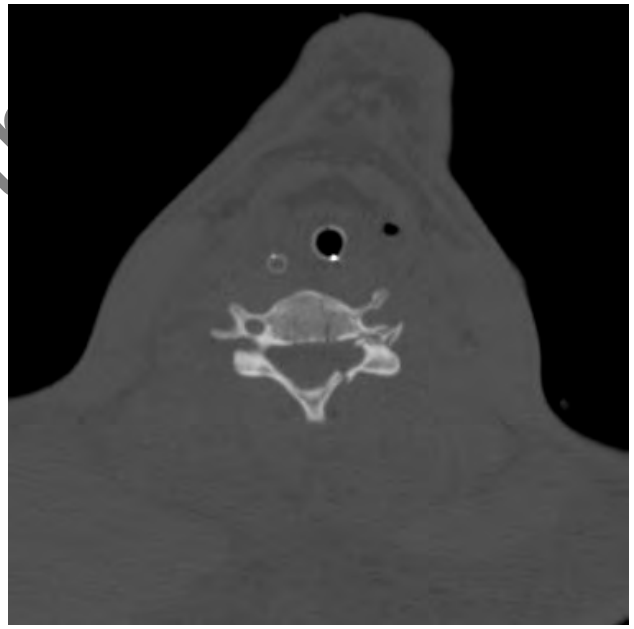
CXR-Admission



Thoracic lesion-MR



Cervical lesion-CT



Working diagnosis-admission

- Respiratory failure
  - Lung contusions
- Complete spinal cord injury (T5 dissection)
  - Late for neurologic salvage
  - Cervical collar, thoracic stabilization
- Treatment
  - New central line (unknown circumstances)
    - Left femoral changed to left subclavian
  - Stop antibiotics
  - Continue sedation/analgesia (dyspnea)

Question 1: Later that night, fever 39.8 °C and hemodynamic instability. What is the most probable etiology of my patient's fever?

1. Ventilator-associated pneumonia
2. Urosepsis
3. Catheter-related bloodstream infection
4. Skin/soft tissue infection
5. Candidemia
6. Non-infectious cause

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Question 2: The patient was covered with piperacillin/tazobactam and vancomycin. What would your choice of empirical therapy be?

1. I agree. Pip/tazo has broad spectrum, incl antipseudomonal, activity against nosocomial pathogens and I would add vancomycin for MRSA

2. The decision is too hasty. I would wait until the diagnosis becomes more clear.

3. I would be more aggressive. I would use meropenem and colistin for gram negatives as well as vanco for MRSA

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Choosing empirical treatment

- Crucial because inadequate empirical rx means mortality

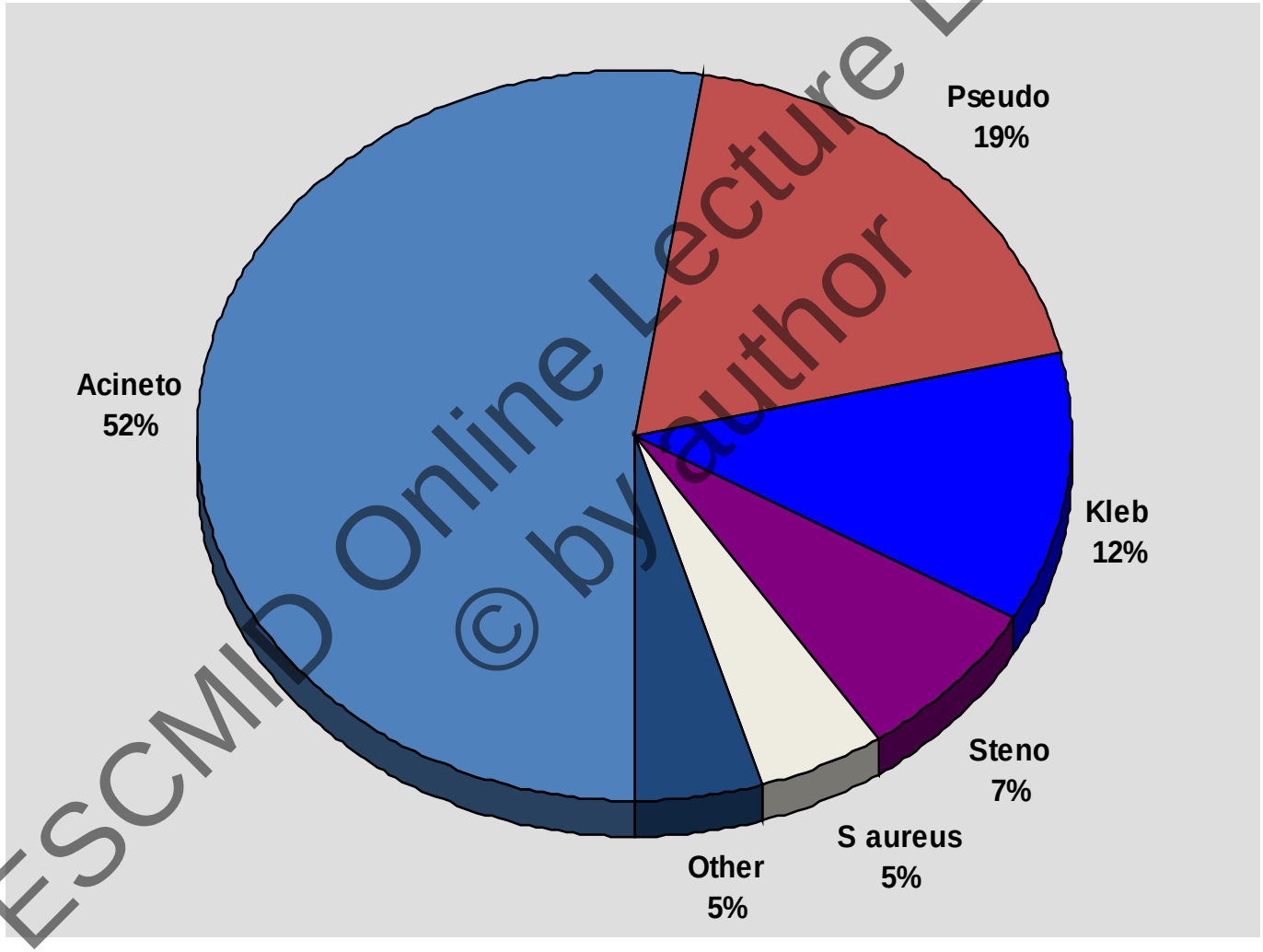
- Factors to consider
  - Risk factors for antibiotic-resistant pathogens
  - Local epidemiology
  - Colonisation status of the patient

Risk factors for MDRs

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

ATS/IDSA guidelines for VAP, Am J Respir Crit Care Med 2005

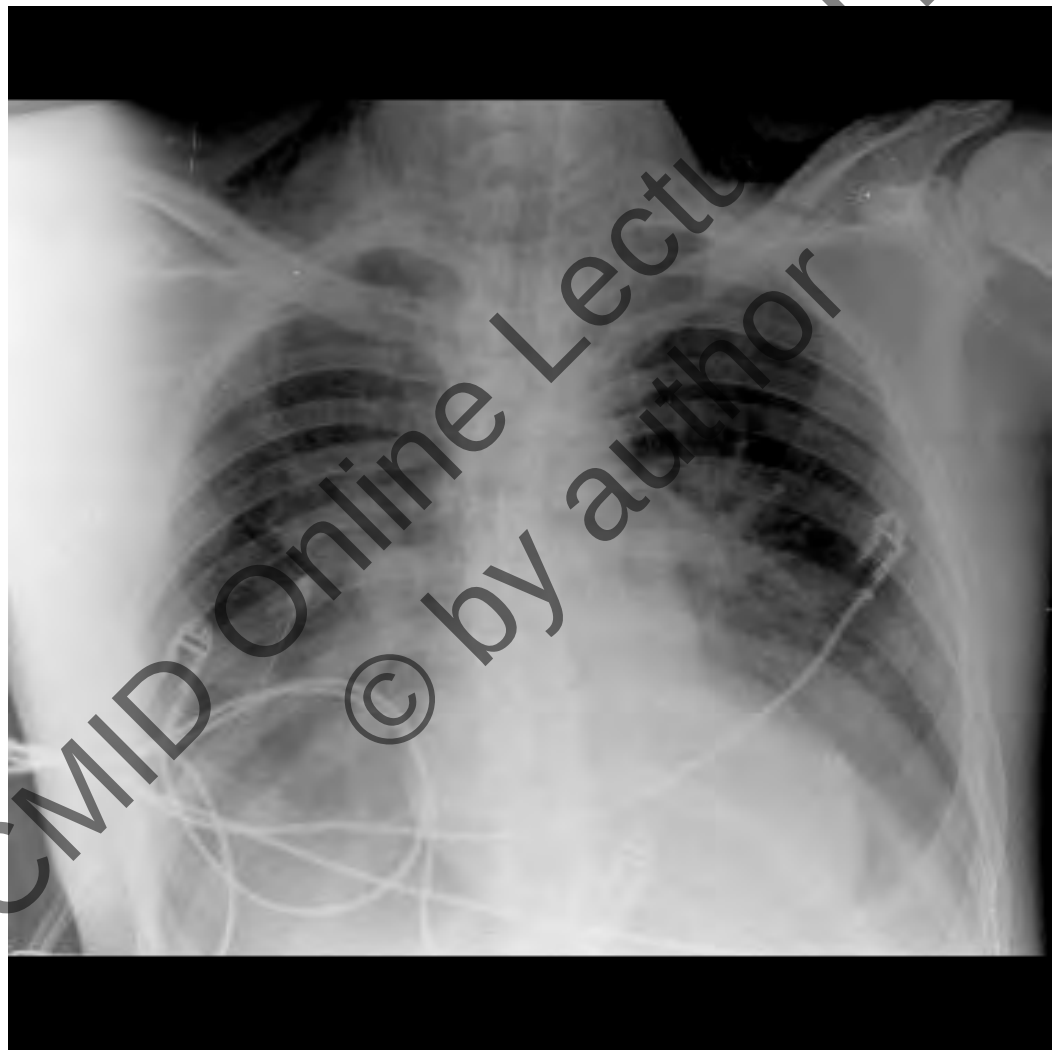
Local epidemiology-VAP



Day 2 (April 27, 2011)

- Fever up to 39 °C, less need for vasopressors
- Worsening oxygenation, PaO2/FiO2 90, not responding to PEEP
  - pH 7.28, pCO2 65 mmHg, pO2 68 mmHg (FiO2 0.8, 7 PEEP)
- Bronchoscopy- purulent secretions bilaterally- BAL peformed RLL
- WBC 10,800/ mL, CRP 130 mg/L

Day 2- Chest X-ray



Question 3: What is your diagnosis?

1. Ventilator associated pneumonia
2. Acute respiratory distress syndrome due to lung contusions and multiple trauma
3. Neurogenic pulmonary edema and neurogenic shock due to spinal cord injury
4. Massive pulmonary embolism
5. Pulmonary hemmorhage from lung contusions
6. Any of the above

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Clinical criteria are sensitive but not specific

Variable or combination of variables	*Sensitivity % (n)*	*Specificity % (n)*	*Positive predictive value % (n)*	*Negative predictive value % (n)*
Chest radiograph (right or left)	92 (12/13)	33 (4/12)	60 (12/20)	80 (4/5)
Chest radiograph (right)	73 (8/11)	33 (4/12)	50 (8/16)	57 (4/7)
Chest radiograph (left)	92 (11/12)	75 (9/12)	79 (11/14)	90 (9/10)
Leucocytosis	77 (10/13)	58 (7/12)	67 (10/15)	70 (7/10)
Fever	46 (6/13)	42 (5/12)	46 (6/13)	42 (5/12)
Purulent secretions	69 (9/13)	42 (5/12)	56 (9/16)	56 (5/9)
Chest radiograph + one of three criteria	85 (11/13)	33 (4/12)	58 (11/19)	67 (4/6)
Chest radiograph + two of three criteria	69 (9/13)	75 (9/12)	75 (9/12)	69 (9/13)
Chest radiograph + all three criteria	23 (3/13)	92 (11/12)	75 (3/4)	52 (11/21)

Fabregas et al, Thorax 1999

Question 4: The calculated CPIS is 5. Does this support a diagnosis of VAP?

1. No, a CPIS≥ 6 is diagnostic for VAP

2. No, I need a second CPIS calculation 48-72 hrs later to diagnose or exclude VAP

3. No, CPIS is not a reliable diagnostic tool for VAP

4. Yes, clinical criteria and CPIS 5 support the diagnosis in this patient

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Clinical Pulmonary Infection Score

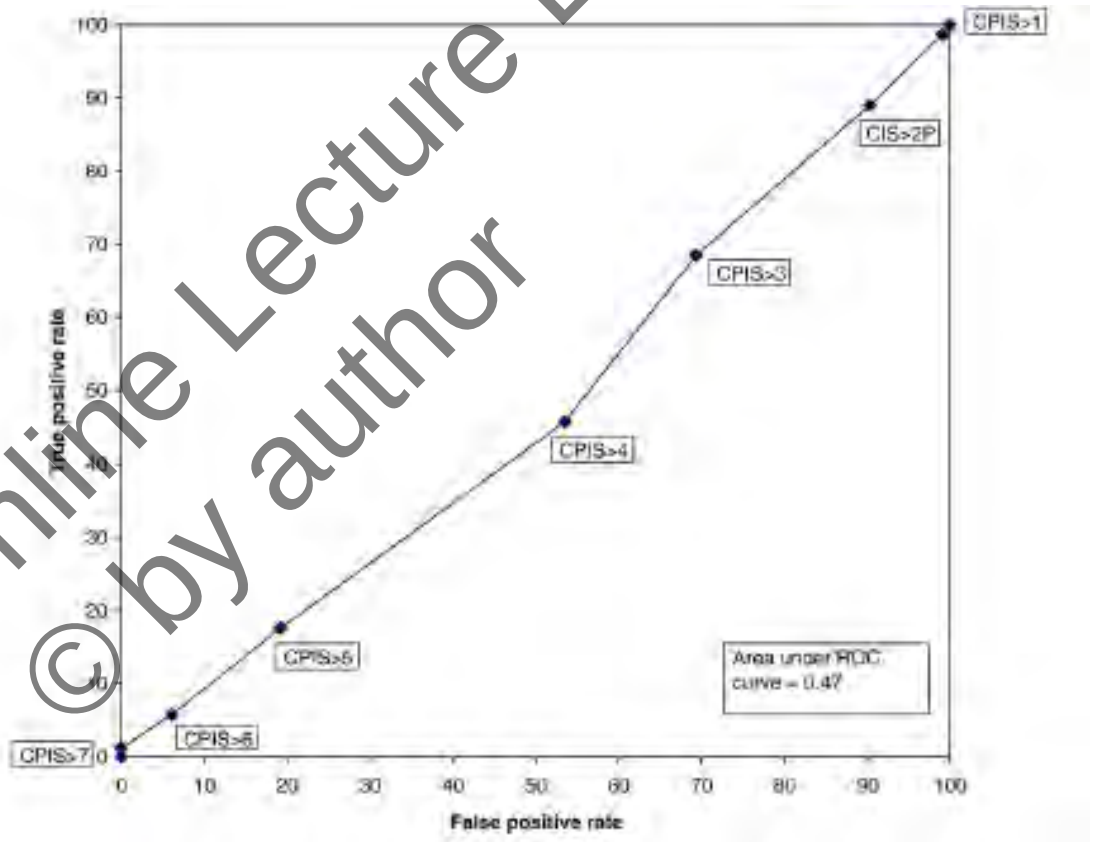
Temperature ^{0} C	**≥ 36.5 and ≤38.4** **≥ 38.5 and ≤38.9** **≥39 or ≤36.4**	**0 points** **1 point** **2 points**
White blood cells (/μL)	**>4000 και < 11000** **<4000 ή > 11000** **> 50% shift to left**	**0 points** **1 point** **+ 1 points**
Tracheal secretions	**Abscence** **Non purulent secretions** **Purulent secretions**	**0 points** **1 point** **2 points**
Oxygenation, PaO_2/ FiO_2	**>240 or ARDS** **< 240 without ARDS**	**0 points** **2 points**
Chest X-ray	**No infiltrate** **Diffuse or multifocal infiltrates** **Localised infiltrate**	**0 points** **1 point** **2 points**
Radiological evolution	**Without radiological worsening** **Radiological worsening (after exclusion of heart failure and ARDS)**	**0 points** **2 points**
Tracheal secretion culture results	**Sterile or pathogens in low growth** **Pathogens in medium/high growth** **Pathogen visible in Gram stain**	**0 points** **1 point** **+ 1 point**

CPIS unreliable for diagnosis

- Canadian Critical Care Trial Group

- 739 ICU patients
- Clinical VAP suspicion
- Modified CPIS calculated (5 parameters) on 1st day of VAP

- No clinically meaningful diagnostic information by CPIS



Lauzier et al, J Crit Care 2008

Question 5:The procalcitonin value is 0.67 pg/mL. Which of the following statements is correct?

1. This is in favor of an active bacterial infection and corroborates VAP diagnosis
2. PCT is low for a patient in shock. Fever and shock are not septic and an alternative diagnosis should be sought (pulmonary embolism, pulmonary hemorrhage)
3. Procalcitonin is not a good diagnostic marker and has no beneficial value in diagnosing VAP.

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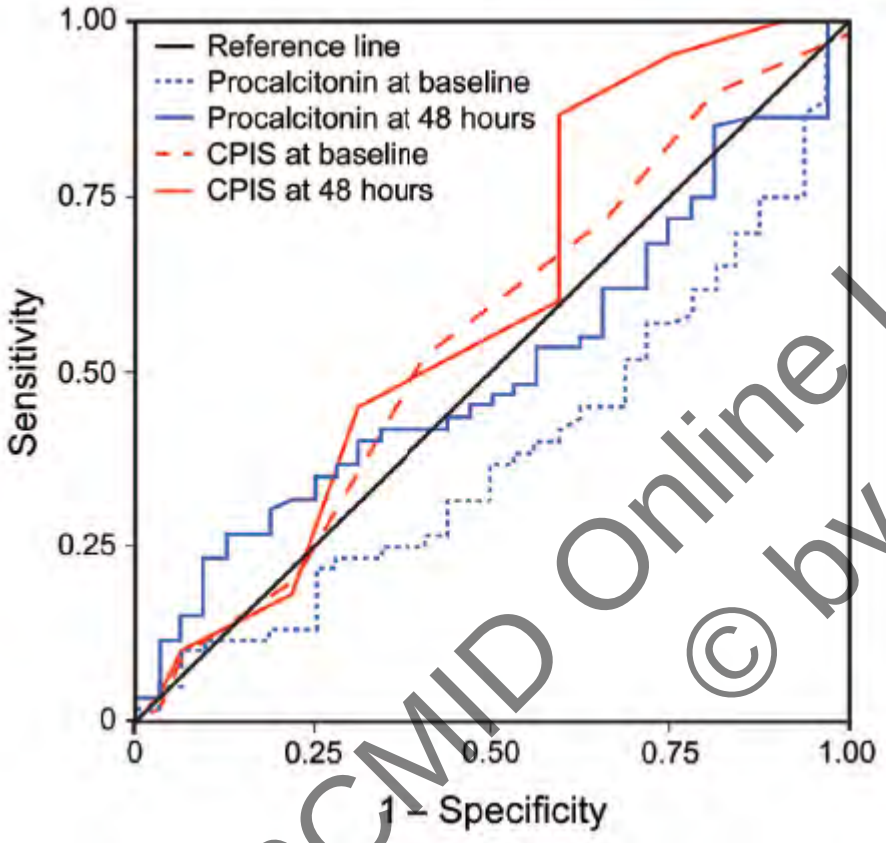
Procalcitonin and VAP



- USA, 8 months
- Med-surg ICU, 104 pts
- Nosocomial pneumonia clinical suspicion (mostly VAP)
- PCT and CPIS in definite vs no pneumonia
- Baseline PCT≥ 1 ng/mL
  - Sens 50%, spec 49%, AUROC 0.51
- CPIS>6
  - Sens 48%, spec 60%, AUROC 0.55
- PCT and CPIS tended to fall in the next 2 days in pneumonia pts, were not diagnostically better

Dallas et al, Respir Care 2011

Question 6: Now, I need samples from the lower respiratory tract to define microbial etiology. The best way to do this is by culturing quantitavely…

1. Tracheal aspirates
2. Bronchoalveolar lavage
3. Bronchoscopic brushing (PSB)
4. Non-invasive lavage techniques
5. No meaningful difference exists between them. Just make sure you take a sample before you start antibiotics

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Invasive and Noninvasive Strategies for Management of Suspected Ventilator-Associated Pneumonia

A Randomized Trial

Jean-Yves Fagon, MD; Jean Chastre, MD; Michel Wolff, MD; Claude Gervais, MD; Sylvie Parer-Aubas, MD; François Stéphan, MD; Thomas Similowski, MD; Alain Mercat, MD; Jean-Luc Diehl, MD; Jean-Pierre Sollet, MD; and Alain Tenaillon, MD, for the VAP Trial Group*

	Quant BAL	Qual EA
14-day mortality	16.2% *	25.8%
28-day mortality	30.9%	38.8%
Antibiotic free days	11.5*	7.5
Inappropriate empirical rx	1%	13%

- Multicenter, randomised trial
- France
- 413 pts with clinical suspicion of VAP
- Quantitative BAL vs non-quantitative EA and algorithm for empiric treatment

Fagon et al, Ann Intern Med 2000

Canadian Critical Care Trial Group

	Quant BAL	Qual EA
Mortality	18.9%	18.4%
Targeted therapy	74.2%	74.6%
Antibiotic free days	10.4	10.6
Organ dysfunction score	8.3	8.6
ICU/hospital length of stay	Similar	Similar

- Multicenter, randomised trial
- 28 ICUs, US+Canada
- 740 pts on MV

- Clinical VAP suspicion, randomised to bronchoscopy and quantitative BAL or simple endotracheal aspirate cultures
- No difference on outcomes
- Pitfall- Staph aureus and Pseudomonas cases were excluded

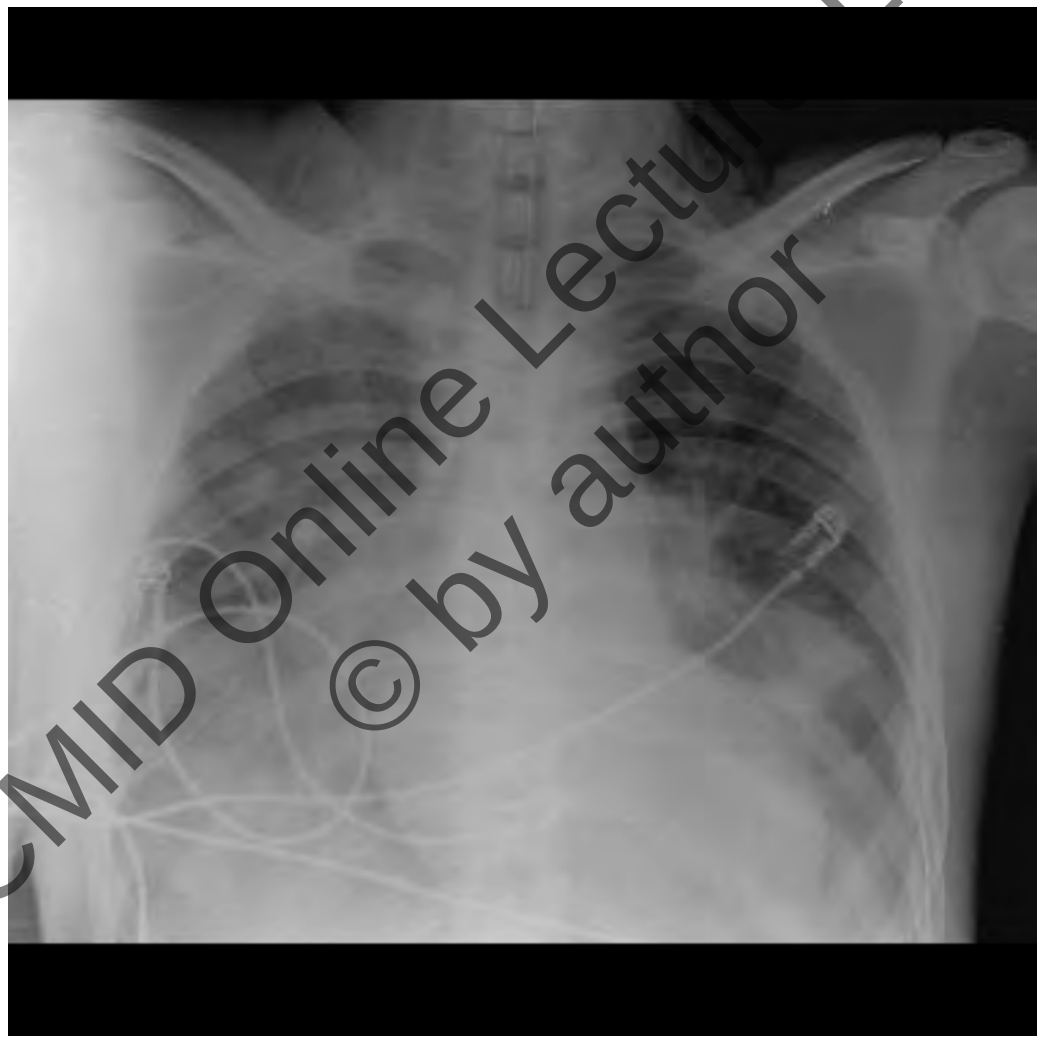
Heyland et al, New Engl J Med 2006

Day 4 (April 29, 2011)

- Fever up to 39, still needs vasopressors
- Worsening respiratory failure
  - pH 7.20, pO2 59, pCO2 82 (FiO2 1, 7 PEEP)
  - Needs muscle relaxants
- WBC 22,760/mL, CRP 254 mg/L

- Culture results **Klebsiella pneumoniae KPC**
  - Bronchial secretions (>10^6) and BAL (>10^4)
  - Sensitive to colistin (MIC ≤ 1 mcg/mL), tigecycline (MIC 2 mcg/mL), gentamycin (MIC 4 mcg/ mL)
  - Resistant to all lactams (meropenem MIC>8) and quinolones

Day 4- Chest X-ray



Question 7: Based on the microbiology results and the patient's clinical condition, how would you adjust your treatment?

1. Continue current regimen (Pip/tazo+Vanco)

2. Stop pip/tazo, vanco and start colistin

3. Stop pip/tazo, vanco and start colistin and tigecycline

4. Stop pip/tazo, vanco and start colistin and gentamycin

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Treating carbapenemase-producing organisms- scarce data

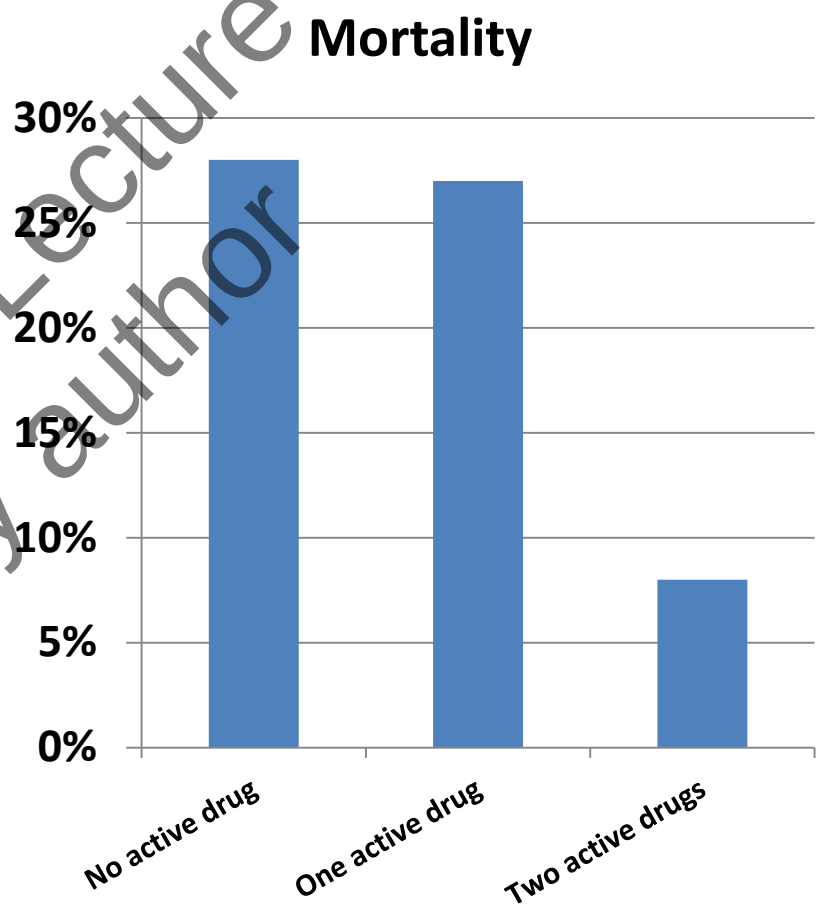
- **Colistin**
  - Mainstay of treatment, alone or combination (carbapenem, rifampicin)
  - Several clinical publications but low level of evidence
  - Unknown lung pharmacokinetics
  - Nephrotoxicity
- **Tigecycline**
  - In vitro active- Good lung penetration
  - Low level of evidence, little experience
    - Retrospective observational study 69% success in MBL-Enterobacteriacae infection (Poulakou et al, J Infect 2009)
  - Off label use
- **Gentamycin**
  - Questionable pharmacokinetics lung
  - Nephrotoxicity
  - Once daily

Carmeli et al, Clin Microbiol Infect 2010

Single drug or combination?

- Combination probably greater activity and delayed development of resistance

- Observational study
  - 67 pts VIM-Klebsiella BSI
  - 49 appropriate empirical rx
  - 18 inappropriate emp rx
  - Mortality lower in two active drug combination empirical rx



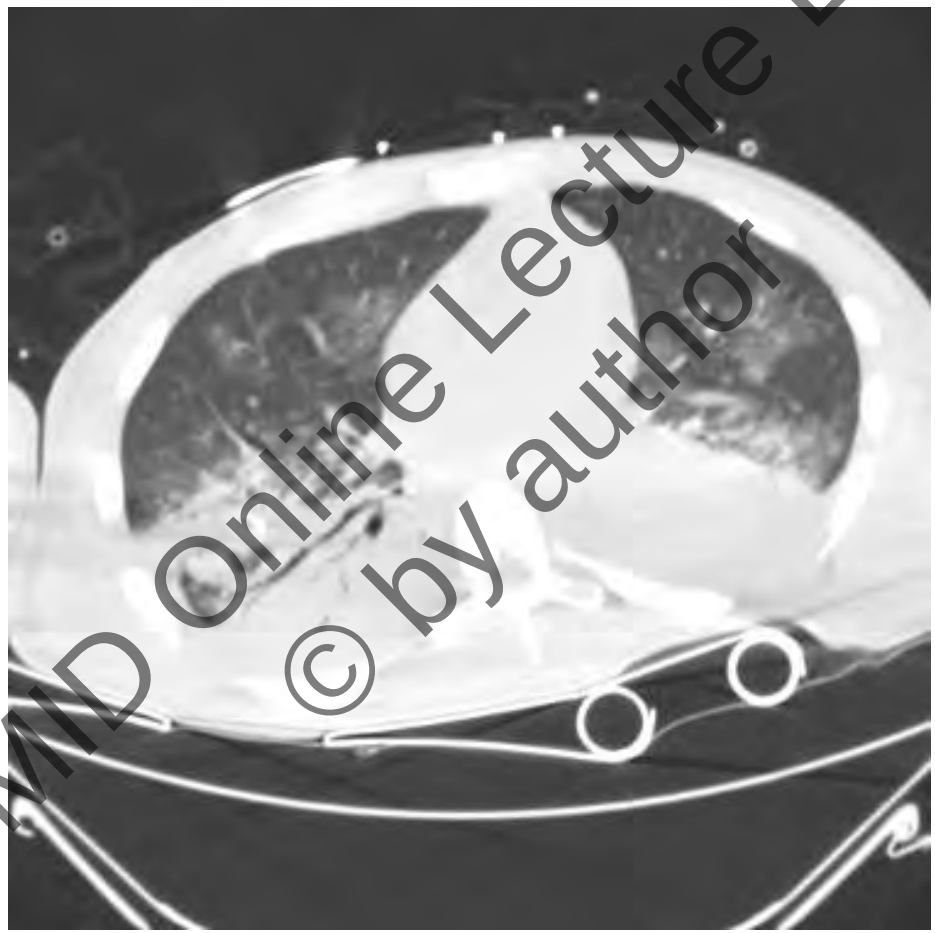
Daikos et al, Antimicrob Agents Chemother 2009

Day 8 (May 3, 2011)

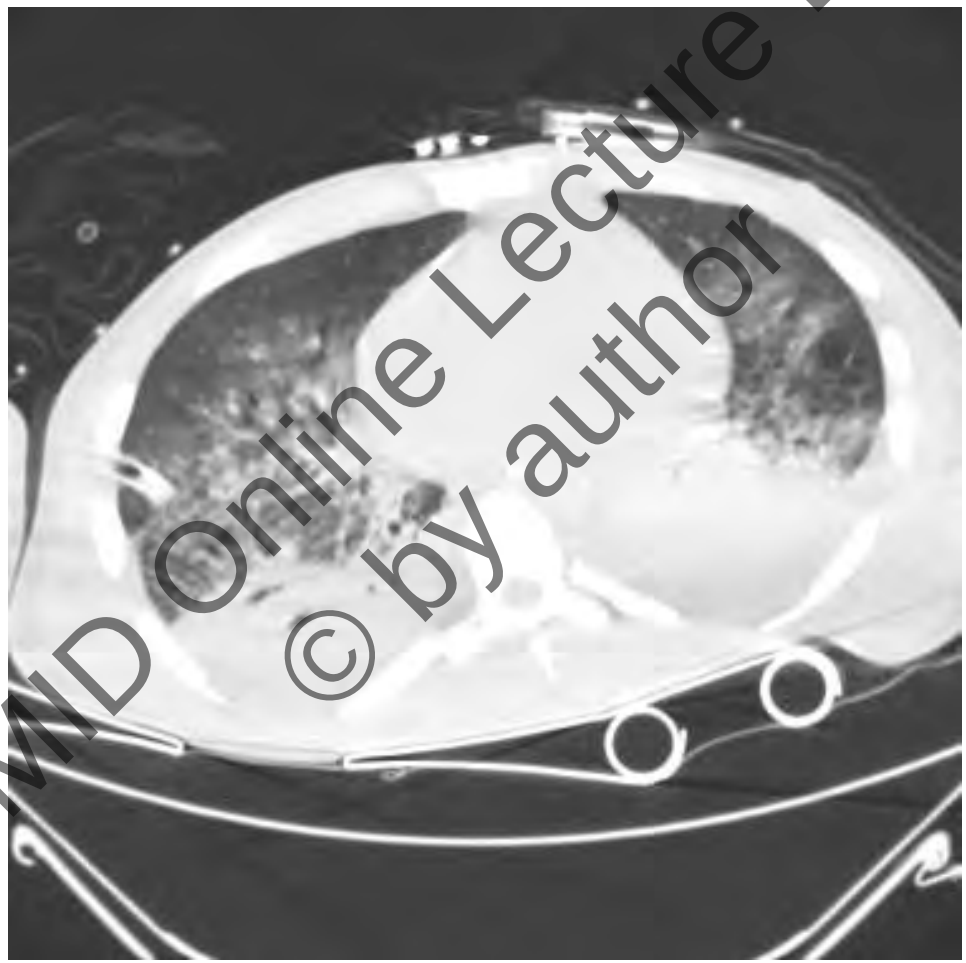
- Patient started on colistin 3 MU tid IV and tigecycline 100 mg loading and then 50 mg bid IV

- On day 8, patient still not responding
  - Feverish, still needs vasopressors
  - ARDS (PaO2/FiO2 80)
- CT chest performed

Day 8- CT chest



Day 8- CT chest



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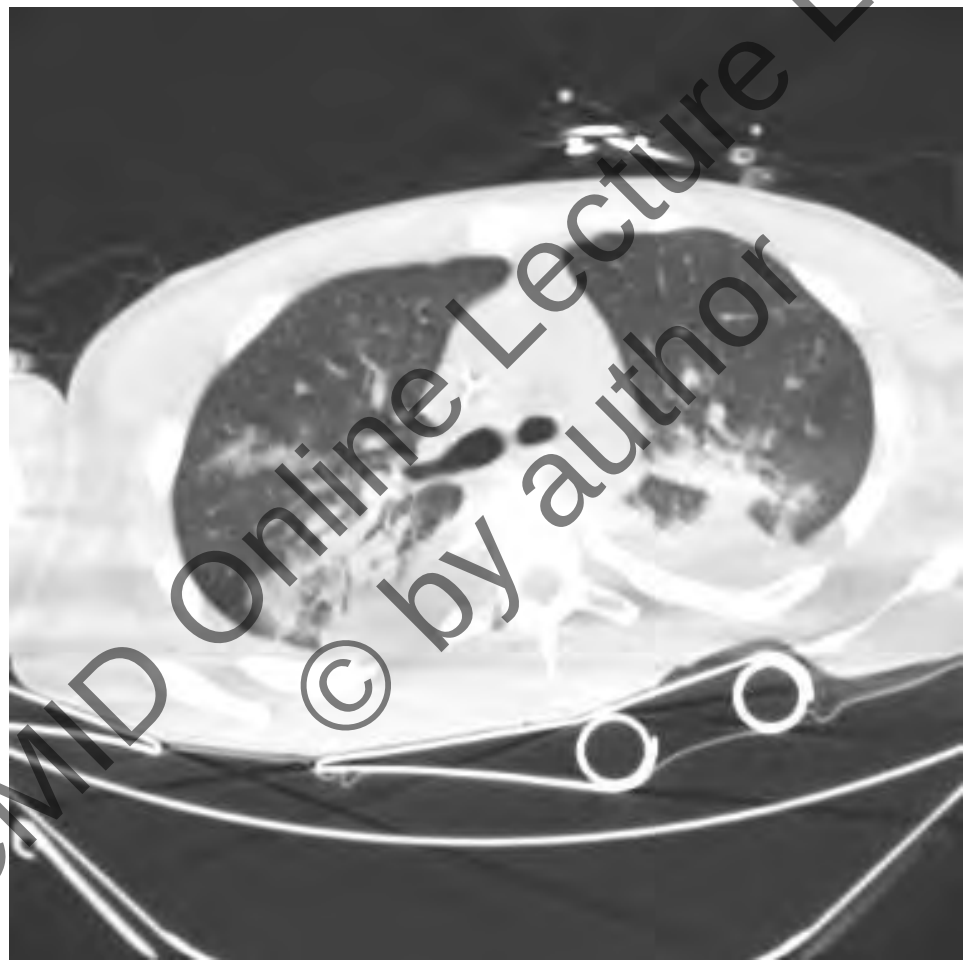

Question 8: The patient seems not to be responding to your treatment, what would you do next?

1. New bronchoscopy
2. Add gentamycin
3. Add antifungal coverage
4. Add genta+antifungal
5. Watchful waiting

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Pattern of VAP resolution

- Improvement during the 48-72 hours of treatment

- Mean time of resolution for
  - Fever (<38) 5 days
  - Oxygenation (PaO_2/FiO_2>250) 6 days
  - Leukocyte count (<10,000) 8 days
  - Bacterial cultures 10 days

Dennesen et al, Am J Respir Crit Care Med 2001

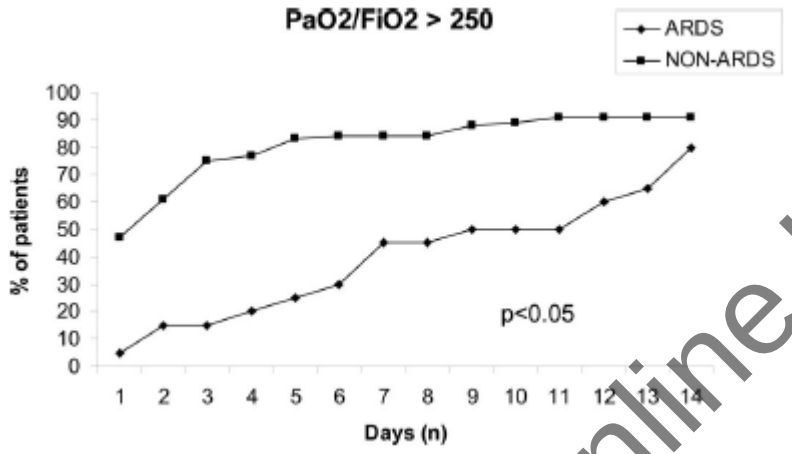
Resolution in VAP with ARDS is much slower

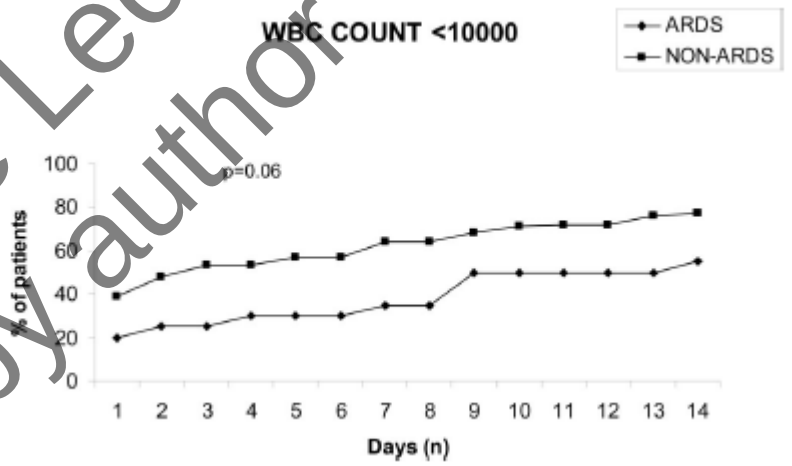
Resolution of clinical parameters 72 hrs after initiation of treatment for VAP

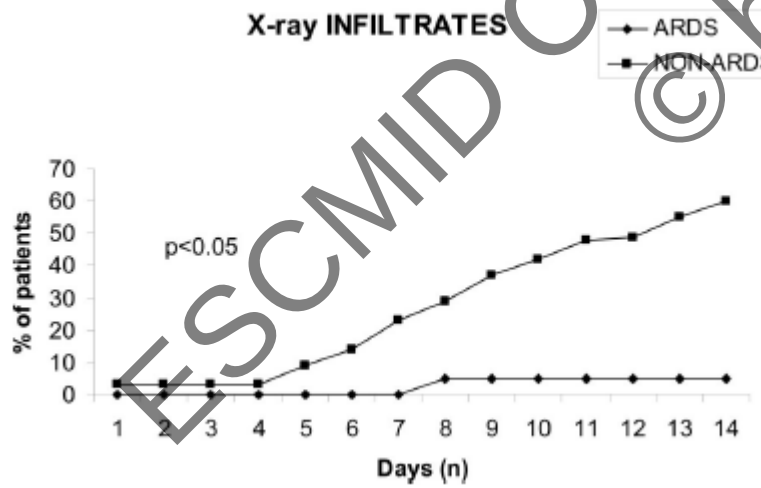
Variable	Overall (n = 95)	ARDS (n = 20)	Non-ARDS (n = 75)	*p* Value
Pao_2/Fio_2 >250 mm Hg	67.4	45	73.3[a]	<.05
Fever <38°C	62.1	15	74.7[a]	<.05
WBC count <10,000	47.4	25	53.3[a]	<.05
Radiographic opacities	2.4	0	3.1	>.20
Clearance of secretions	15.8	15	16	>.20
Failure to improve (two variables)	25.6	65	14.7[a]	<.05

Vidaur et al, Crit Care Med 2005

VAP with ARDS takes twice as long to resolve





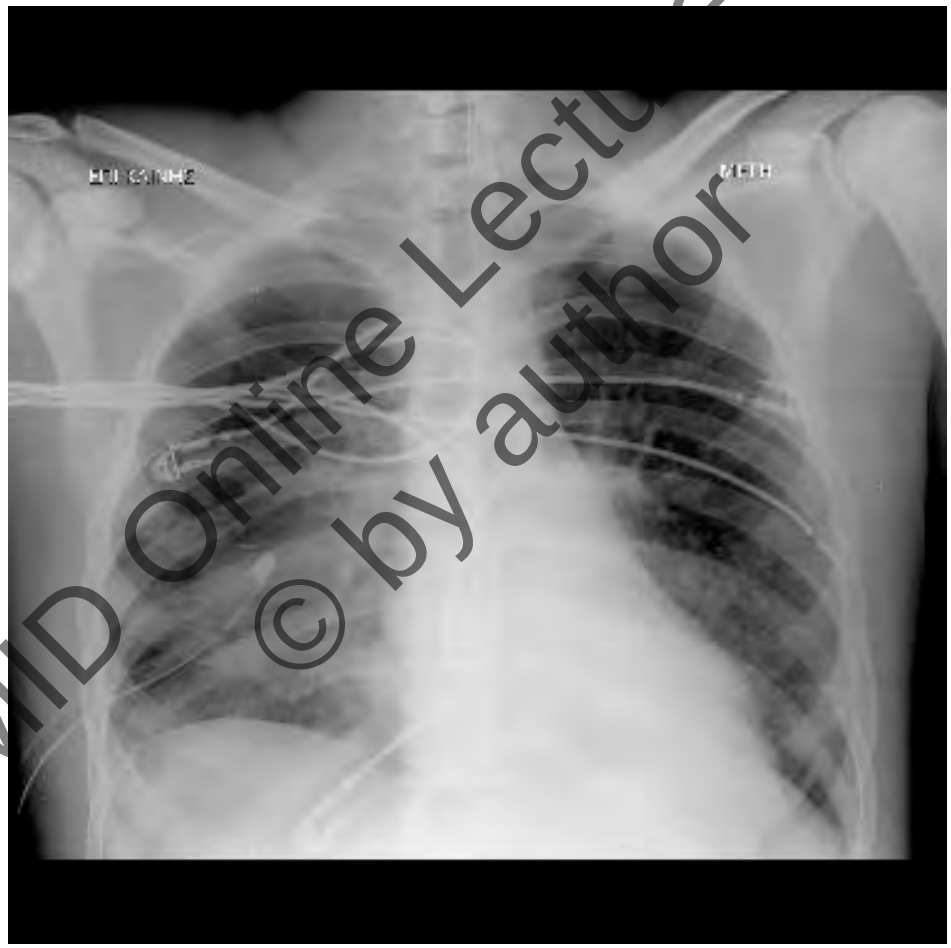


Vidaur et al, Crit Care Med 2005

Day 10 (May 5, 2011)

- On day 8 gentamycin was added 320 mg od for five days
- Fever 39.8
- Better oxygenation and ventilation
  - PaO2/FiO2 120
- WBC 10,280, CRP 686 mg/L
- Empirical change of central lines and new blood cultures

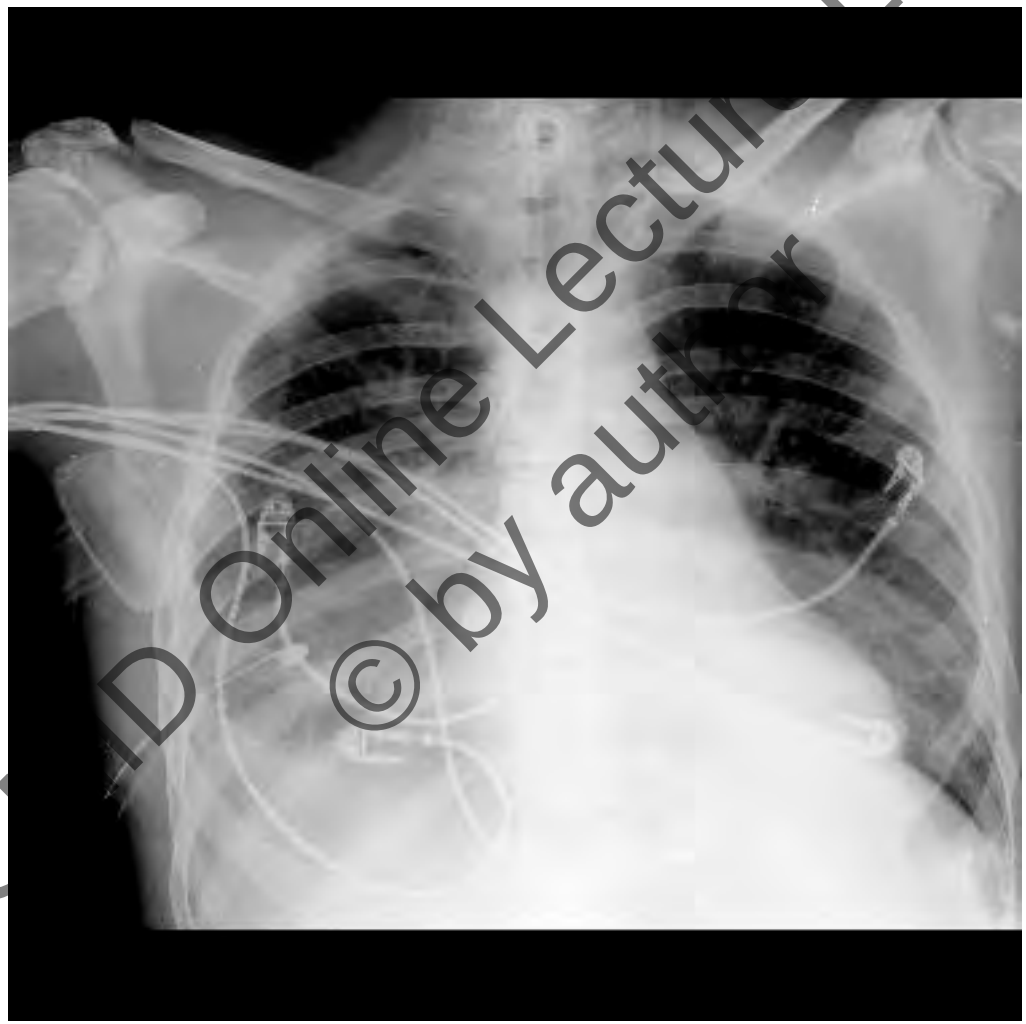
Day 10- Chest X-ray



Day 14 (May 9, 2011)

- Fever better, up to 37.8
- No hemodynamic instability
- Lungs better (PaO2/FiO2 260)
- WBC 9,170, CRP 75 mg/L, PCT 0.23 ng/mL
- Pleurocentesis- exudate, not empyema
- However, non oliguric renal failure developed
  - Urea-148 mg/dL, creat 3.7 mg/dL
  - Needs CVVHDF
- Still on colistin-tigecycline

Day 14- Chest X-ray



Day 21 (May 16, 2011)

- No fever, respiratory function back to normal (PaO2/FiO2 >300)
- Renal failure, still needs CRRT
- Patient awakened
- To be operated on for spinal stabilization