Epidemiologia, clinica e diagnosi delle polmoniti

Maddalena Peghin MD, PhD
Clinica di Malattie Infettive
Presidio ospedaliero di Udine Azienda Sanitaria Universitaria Integrata di Udine

BUON USO DEGLI ANTIBIOTICI NELL'ERA DELLE RESISTENZE

Come far si che il miracolo continui

15 giugno 2019

AZIENDA OSPEDALIERO UNIVERSITARIA
Santa Maria della Misericordia di Udine

Mr. C clinical case

- Mr. C is a 70 year old male who presents to the medical clinic where you work the day 15 January
- He is accompanied by his daughter
- Mr. C’s daughter states that Mr. C has a bad cold with a cough and that he has been confused. He fell as he was getting dressed this morning
- Previous contact with a grandson with a cold

Mr. C Past Medical History

- Coronary artery disease
- Recovering alcoholic
- Class I obesity (BMI 34 kg/m^2)
- Depressive syndrome
- Vascular ulcer lower limb, wound care at hospital twice a week
- No recent immunisations

Mr. C’s physical assessment

- T 37.8. BP 138/70, HR 90 RR 34. pulse ox 90%
- Using accessory muscles to breath. Crackles in the left lower lobe
- He reports pain on inspiration

After clinical assessment you have found several cinical findings indicative of suspected pneumonia
How would you classify it?

1. Hospital acquired pneumonia (HAP)
2. Community acquired pneumonia (CAP)
3. Health Care-associated Pneumonia (HCAP)
4. I don’t know

After clinical assessment you have found several cinical findings indicative of suspected pneumonia
How would you classify it?

1. Hospital acquired pneumonia (HAP)
2. Community acquired pneumonia (CAP)
3. Health Care-associated Pneumonia (HCAP)
4. I don’t know

After clinical assessment you have found several cinical findings indicative of suspected pneumonia
How would you classify it?

1. Hospital acquired pneumonia (HAP)
2. **Community acquired pneumonia (CAP)**
3. Health Care-associated Pneumonia (HCAP)
4. I don’t know

Classification by site of origin

- **Hospital acquired pneumonia (HAP) :** acquired after at least 48 hours of admission to hospital
- **Health Care-associated Pneumonia (HCAP)** : 2005 ATS/IDSA Guidelines
  - hospitalized in an acute care hospital for two or more days within 90 days of the infection
  - resided in a nursing home or long-term care facility
  - received recent IV antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection
  - attended a hospital or haemodialysis clinic
- **Community acquired pneumonia (CAP)**

- **HCAP** was thus expected to predict a higher frequency of Gram-negative and MDR bacteria >>different empirical antibiotic therapy to that for CAP

Am J Respir Crit Care Med 2005;171:388–416.

However…HCAP : new avenue or just a cul-de-sac?

- Similar frequency and spectrum of causative pathogens in HCAP and CAP
- HCAP for the identification of pneumonia patients with a worse prognosis >>worse outcome related to patient factors
- **HCAP should not be used to direct empirical antibiotic therapy:**
  - opposite effect to that intended
  - promote the development of bacterial antibiotic resistance
- 2016 ATS/IDSA Guidelines on HAP/VAP: removal of the concept of HCAP
- Recommendations regarding coverage for MDR pathogens among CAP based on validated risk factors for MDR pathogens

Khalil et al. Clinical Infectious Diseases 2016;63(5):e61–111

Woodhead et al. Thorax 2013;68:985–986.

Overview on Community-acquired pneumonia (CAP)

CAP is a leading cause of hospitalization and death worldwide

- The annual estimated CAP burden in USA : 5 million cases
  - 80% of these cases are treated as outpatients (1% mortality)
  - 20–25% treated in the hospital setting (23% mortality)

Gramegna et al. BMC Infectious Diseases (2018) 18:677

Why is Mr. C at increased risk for developing CAP?

Primary host factors [4▪]	Increasing age, male sex
Modifiable risk factors [4▪]	High alcohol intake >40 g/day, smoking, malnutrition/decreased body weight, low vitamin D levels [6]
Respiratory compromise [4▪]	COPD, asthma, pulmonary malignancy, bronchial obstruction, preceding or concurrent viral respiratory infection, recent bronchoscopy, nasogastric tube placement within last year, ciliary dyskinesis [7]
Chronic medical conditions [4▪]	Heart disease, cerebrovascular disease/stroke, dementia, dysphagia, diabetes, renal disease, liver disease, rheumatoid arthritis, epilepsy [8]
Immune suppression [4▪]	TNFα inhibitors, HIV infection, asplenia
Medications	Proton pump inhibitors [9], oral or inhaled steroids [8], amiodarone [8], *N*-acetylcysteine [8], oxygen therapy [8], benzodiazepines [10], zopiclone [10]
Socioeconomic factors [4▪,5]	Low-income household, crowded living conditions
Other [8]	Poor dental hygiene, contact with pets, contact with children

Remington et al. Curr Opin Pulm Med 2014, 20:215–224

To Admit or Not?

Pneumonia Severity & Deciding Site of Care

To Admit or Not?
Pneumonia Severity & Deciding Site of Care

- Using objective criteria to risk stratify & assist in decision re outpatient vs inpatient management
- PSI (pneumonia severity index)
- CURB-65
- Caveats
  - Other reasons to admit apart from risk of death
  - Not validated for ward vs ICU
  - Labs/vitals dynamic

CURB-65

Prediction Rule to Assist in Determining Site of Care

- **C**onfusion (disorientation to person, place or time)
- **U**rea (BUN > 7 mmol/L)
- **R**espiratory Rate (RR > 30 breaths/minute)
- **B**lood Pressure (systolic< 90 mmHg-diastolic< 60 mm Hg)
- **65** (years of age or greater)

One point for each prognostic variable
0-1 treat as outpatient, 2 general inpatient admission,
3-5 intensive care admission

CURB-65

Prediction Rule to Assist in Determining Site of Care

- **C**onfusion (disorientation to person, place or time)
- **U**rea (BUN > 7 mmol/L)
- **R**espiratory Rate (RR > 30 breaths/minute)
- **B**lood Pressure (systolic< 90 mmHg-diastolic< 60 mm Hg)
- **65** (years of age or greater)

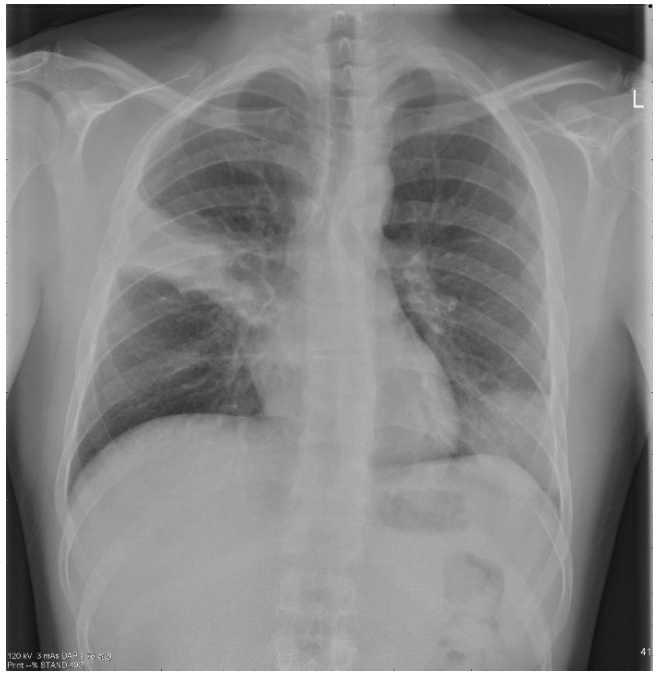
One point for each prognostic variable
0-1 treat as outpatient, 2 general inpatient admission,
3-5 intensive care admission

E.R.

Due to the baseline risk factors and clinical and physical assessment the patient is referred to the emergency room

Laboratory and radiographic findings

- RADIOGRAPHIC FINDINGS



- LABORATORY FINDINGS

- WBC count: 13,500 cells/µL (with 82% polymorphonuclear cells and 11% band forms, lymphocytes 7%), platelets; 180,000 cells/mL
- CRP 223 mg/L
- AST 18 IU/L; ALT 23 IU/L
- Sodium 135 mEq/L; Potassium 4.2 mEq/L Chloride 99 mmol/L Calcium 8 mg/dL
- BUN 19 mg/dL Creatinine 1.9 mg/dL
- Glucose 116 mg/dL

Which pathogen/s would you suspect?

1. Respiratory virus
2. *Staphylococcus aureus*
3. *Streptococcus pneumoniae*
4. *Legionella pneumophila*
5. All of the above

Microbiology of CAP

- **Causative organism of CAP established**
  - 60% in research setting
  - 20% in clinical setting

- **“Typical”**
  - S. pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Group A streptococci, Moraxella catarrhalis, anaerobes, and aerobic gram-negative bacteria
- **“Atypical”**
  - Legionella spp, Mycoplasma pneumoniae, Chlamydophila (formerly Chlamydia) pneumoniae, and C. psittaci
  - Mainly distinguished from typical by not being detectable on Gram stain or cultivable on standard media

Gramegna et al. BMC Infectious Diseases (2018) 18:677

Major respiratory virus

Virus	Genome	Diversity
Rhinovirus	RNA	A, B, C, >100 types
Coronavirus	RNA	OC43, E229, HKU1, NL63
Influenza virus	RNA	A, B, C / H3N2, H1N1pdm
Respiratory syncytial virus	RNA	A and B
Parainfluenza virus	RNA	1, 2, 3 and 4
Metapneumovirus	RNA	A1, A2, B1, B2
Adenovirus	DNA	7 species, > 50 serotypes

Diagnostic tests for CAP

- **Culture of respiratory tract specimens (sputum, tracheoaspirate, BAL):**
  - very low sensitivity for atypical bacteria and RV
- **Blood cultures**
  - yield 5-15% ; stronger indication for severe CAP
- **Direct fluorescent antibody (DFA) assay for atypical bacteria and RV**
  - suboptimal sensitivity
- **Serologic assays: antibodies to for atypical bacteria and RV**
  - fourfold rise in either IgM or IgG titer is needed to confirm active disease
    repeat 4-6 weeks later
- **S.pneumoniae and L. pneumophila urine antigen**
  - S.pneumoniae urine antigen: Sensitivity 60-75%, specificity : 95-99%
  - L. pneumophila urine antigen: Legionella serogroup 1-specific (80%) >>>>>not useful for other serogroups
- **Molecular testing**

Arnold et al. Semin Respir Crit Care Med 2016;37:819–828

The list of pathogens causing CAP is evolving
Who seeks finds…

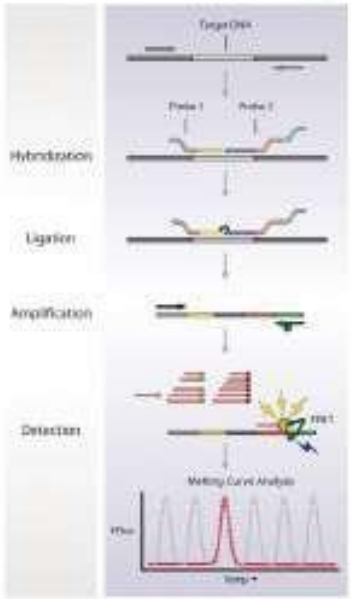
- Most patients do not have the CAP pathogen identified
  - effective antimicrobial agents available to treat CAP
  - lack of perceived need to know the pathogen, unless no response to empiric therapy

- Improvements in the sensitivity and availability of molecular testing influence understanding of the causes of CAP

- Better diagnostic tests
  - to reduce overall antibiotic use
  - to improve the targeted use of antibiotics

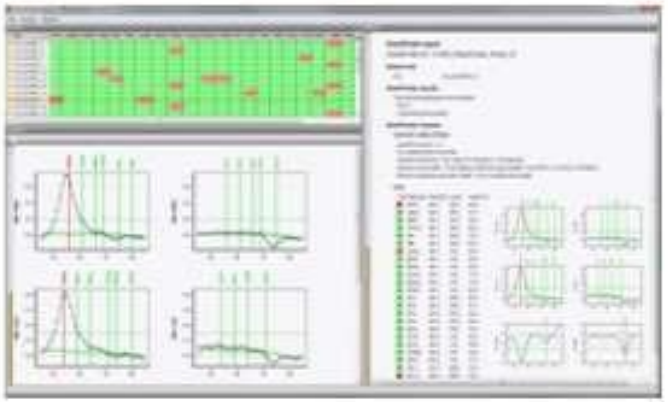
Some commercialized molecular multiplex assays for >3 pathogens (*M. pneumoniae, C. pneumoniae, L. pneumophila, B. pertussis, resp. viruses)*

RespiFinder ,
Pathofinder



Mx RT amplification
no sample prep
melting curve analysis
Up to 25 targets
TAT 6 hr

RespiFinder SMART 22 Fast



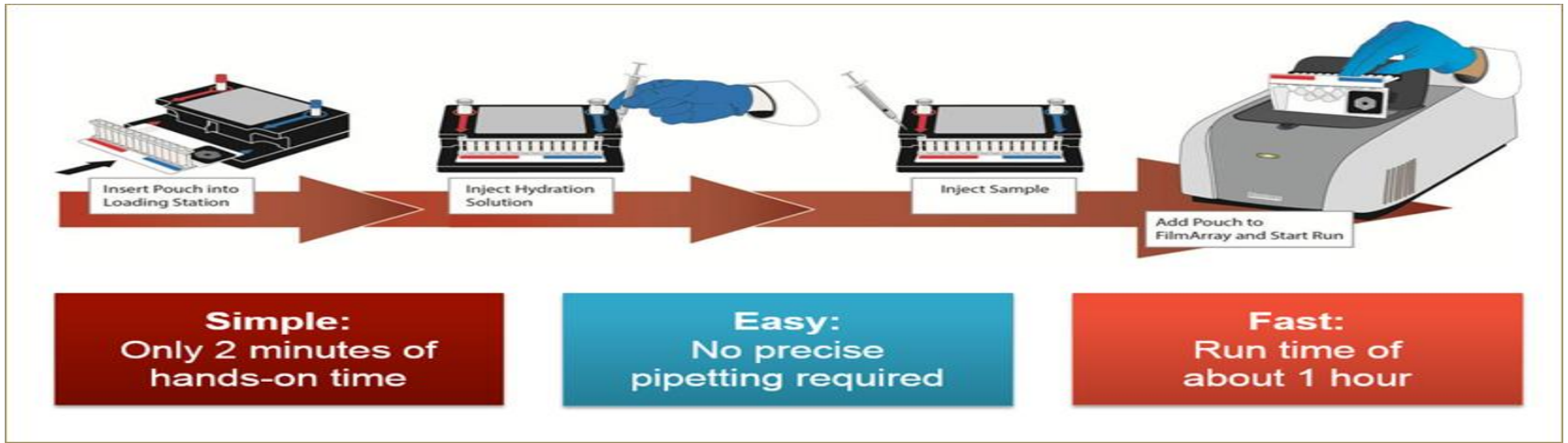
Mx RT amplification
no sample prep
melting curve analysis
22 targets
TAT 4 hr
multiple samples/instrument

FilmArray RP, BioMérieux

Mx amplification
Sample prep included
Up to 20 targets
TAT VP 1 hr
1 sample/instrument

Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia

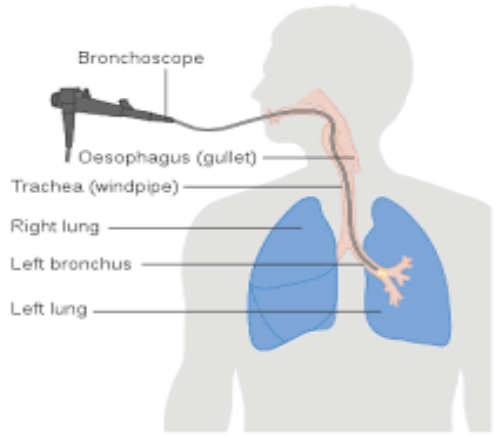
Typical bacteria	Atypical bacteria	Respiraotry viruses
Streptococcus pneumoniae;	Mycoplasma pneumoniae	Influenza A
Haemophilus influenzae	Chlamydophila pneumoniae	Influenza B
Moraxella catarrhalis;	Chlamydophila psittaci	Respiratory syncytial virus
Staphylococcus aureus;	Legionella pneumophila	Parainfluenza virus types 1–3;
Escherichia coli	Legionella spp	Adenovirus
Klebsiella pneumoniae		Coronaviruses
Pseudomonas aeruginosa		Metapneumovirus
Acinetobacter baumannii		Rhinovirus



Type of samples

NASOPHARYNGEAL SWABS

SPUTUM



BAL

Epidemiology-atypical pathogens

- increased trend of atypical pathogens over the last 15 years, with prevalence ranging from 6 to 40% in both Europe and USA

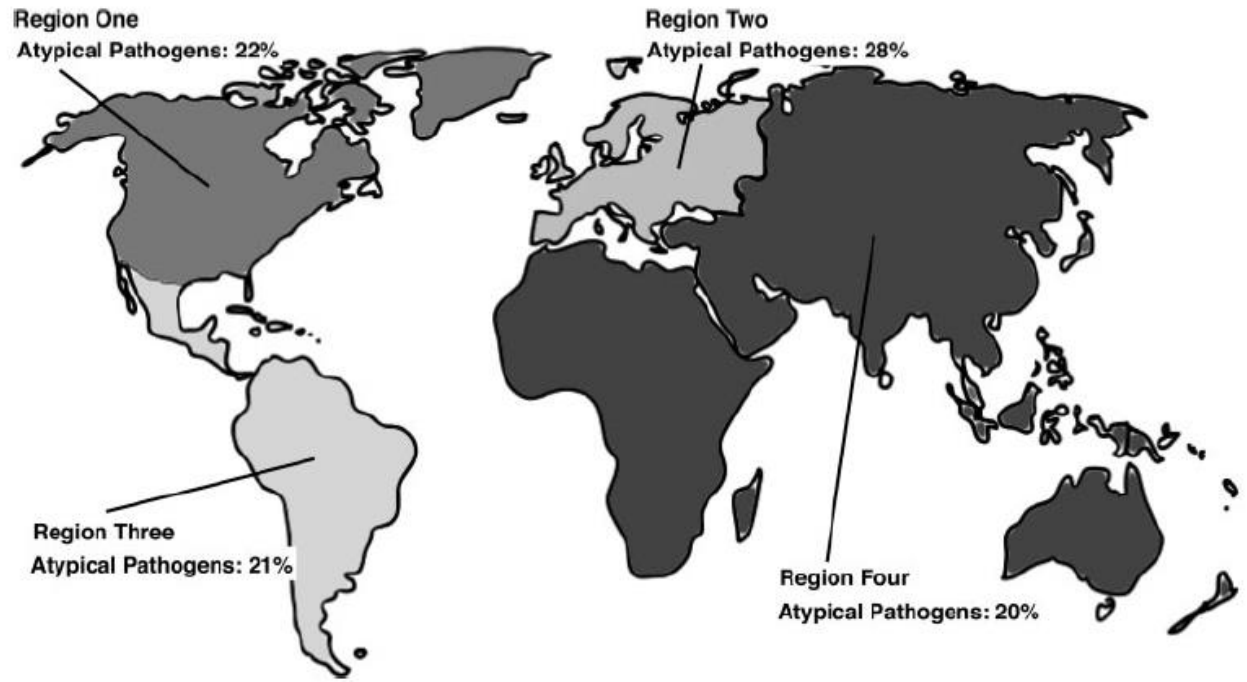


Fig. 1 Regions of the community-acquired pneumonia organization and world incidence of atypical pneumonia.

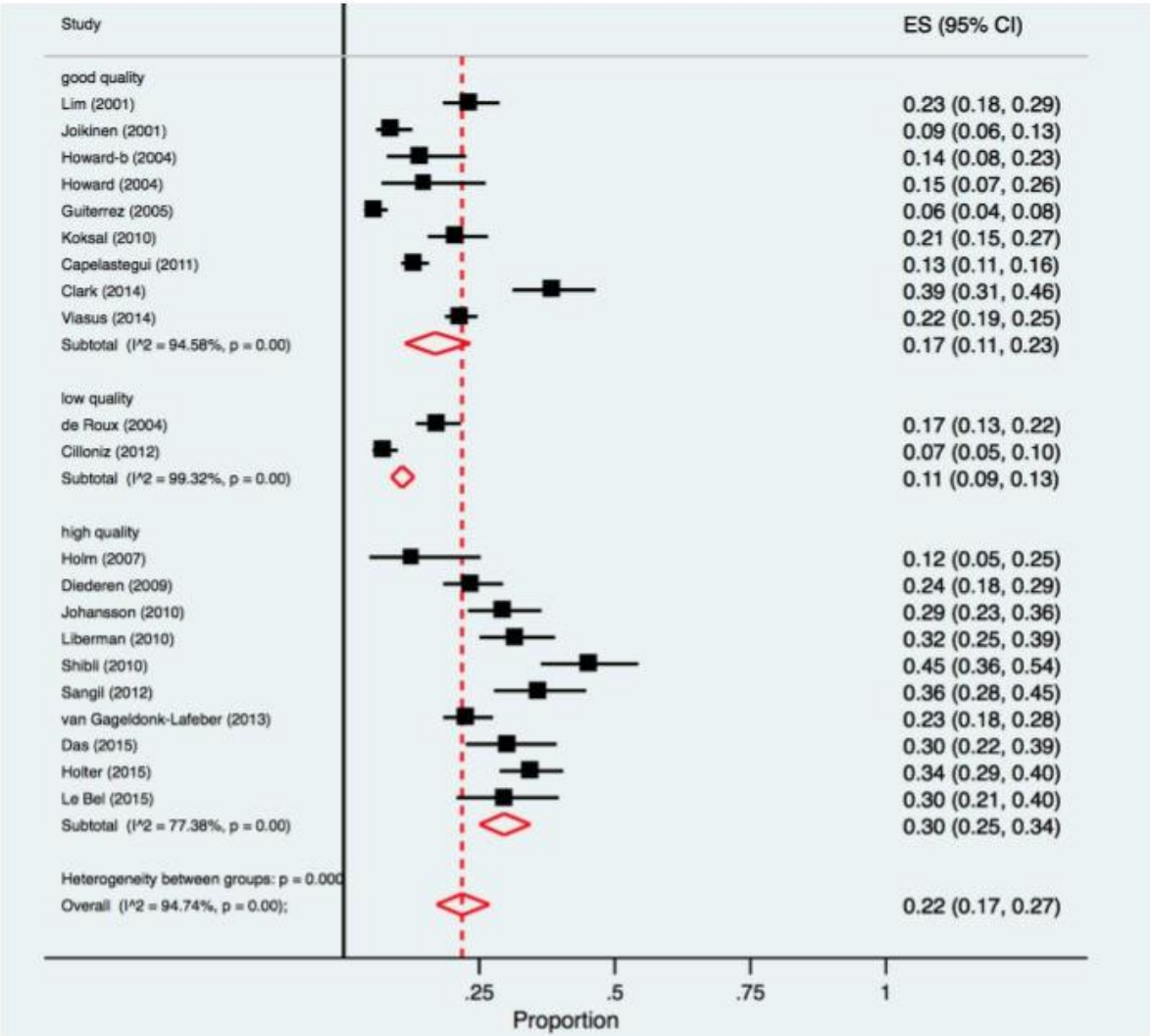
Viral pneumonia in adults

Author	Cases	Etiology	Bacteria	Viral	Mixed	Year & Source
Templeton	105	52	44	50	27	CID 2005
Marcos	198	57	57	33	10	Ant Ther 2006
Jennings	304	58	48	29	30	Thorax 2008
Johnstone	193	39	51	39	11	Chest 2008
Johansson	184	67	58	29	23	CID 2010
Sangil*	131**	70	60	23	17	EJCMID 2012
Luchsinger	356	65	40	35	26	Thorax 2013
Total	1115	65	52	25	23	

Sangil A, et al. Eur J Clin Microbiol Infect Dis 2012;31(10):2765–72

Systematic review of respiratory viral pathogens identified in adults with CAP in Europe

21 studies



- Proportion of patients with identified RV: 29.0% (25.0%–34.0%) in studies with PCR
- Influenza virus was the most frequently detected RV 9% (7%–12%) of CAP

Alimi et al. Journal of Clinical Virology 95 (2017) 26–35

What treatment would you start?

1. Beta-lactam plus macrolide/levofloxacin
2. Beta-lactam plus levofloxacin plus oseltamivir
3. Beta-lactam plus macrolide plus oseltamivir
4. Beta-lactam alone

What treatment would you start?

1. Beta-lactam plus macrolide/levofloxacin
2. **Beta-lactam plus levofloxacin plus oseltamivir**
3. **Beta-lactam plus macrolide plus oseltamivir**
4. Beta-lactam alone

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

OUTPATIENT EMPIRIC CAP

- **Healthy; no abx previous 3 months**
  - Macrolide e.g. azithromycin
  - 2nd choice: doxycycline

- **Comorbidities; abx previous 3 months (use alternative abx)**
  - Respiratory fluoroquinolone: Moxifloxacin, levofloxacin, gemifloxacin
  - Beta-lactam + macrolide

Regions with >25% high-level macrolide-resistant *S. pneumoniae*, consider alternative agents

2007 IDSA/ATS Guidelines for CAP in Adults

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

INPATIENT EMPIRIC CAP

- **Inpatients Ward**
  - Respiratory fluoroquinolone
  - ß-lactam + macrolide

- **Inpatients ICU**
  - ß-lactam (cefotaxime/ceftriaxone or ampicillin/sulbactam) + macrolide
  - Respiratory fluoroquinolone for PCN-allergic pts

- **Special pathogens**
  - ***Pseudomonas*** anti-pseudomonal ß-lactam + cipro/levofloxacin or aminoglycoside and azitromycin
  - **MRSA** add vancomycin or linezolid

2007 IDSA/ATS Guidelines for CAP in Adults

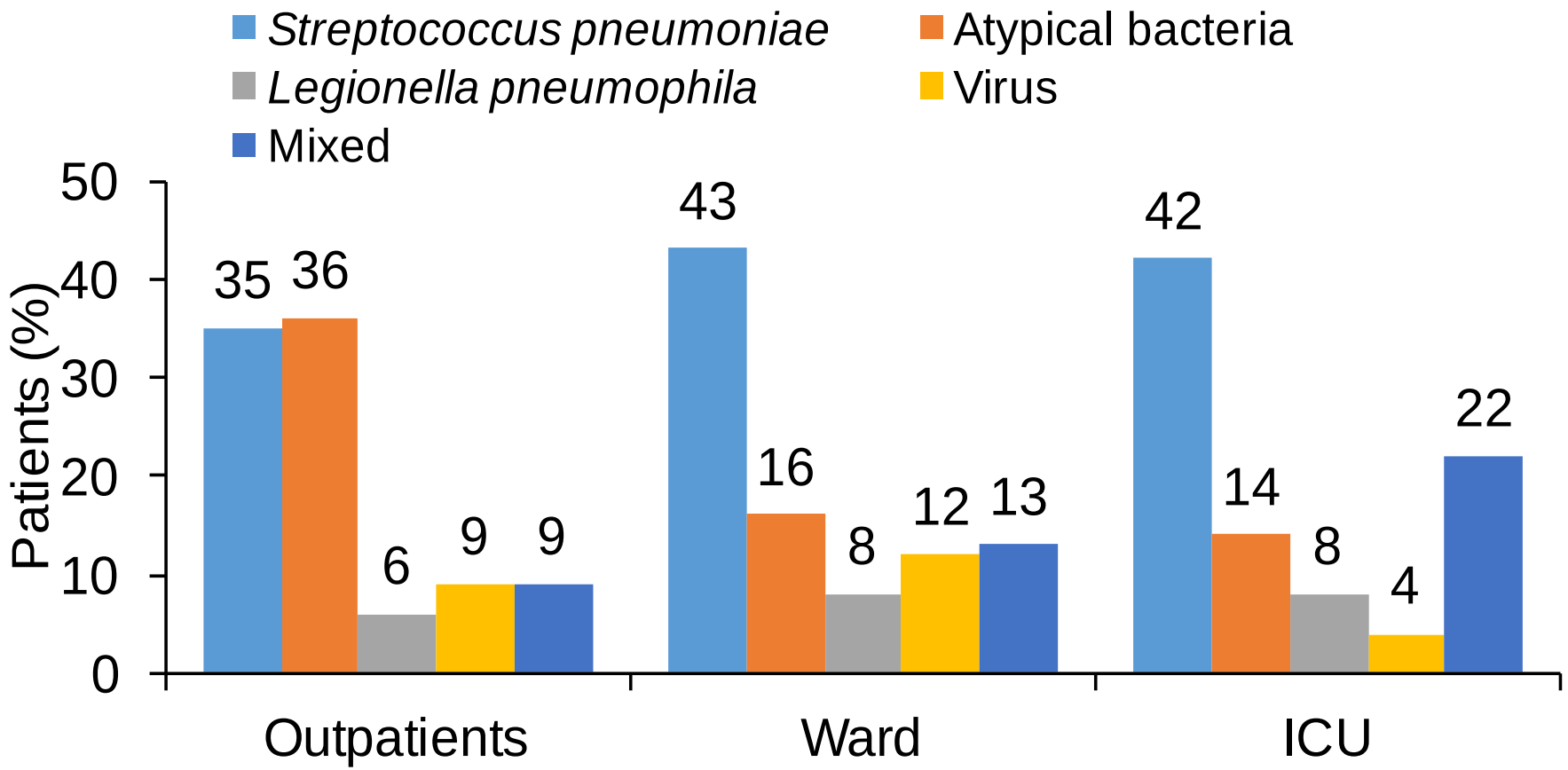
Mr. C in ICU

- Worsening condition with need for mechanical ventilation and BAL performed
- Microbiological results
  - **BAL: RT-PCR positive for influenza A , culture negative**
  - Sputum culture: negative
  - Blood culture: negative
  - Urine antigen negative for *S. pneumoniae* and *Legionella*
  - **Influenza testing nasopharyngeal swab: RT-PCR positive for influenza A**

STOP betalactam AND macrolide
Therapy was de-escalated to oseltamivir

Microbial aetiology of CAP and its relation to severity

3523 patients
Microbiological diagnosis 1463



Cilloniz C et al Thorax 2011; 66: 340-346

The burden RV in pneumonia associated with acute respiratory failure an underappreciated Issue

- 364 patients with CAP and HAP requiring MV
- RV was the sole pathogen in 79 cases (21.7%):
  - rhinovirus/enterovirus (n 20)
  - influenza A (n 12)
  - respiratory syncytial virus (n 11)

Viruses represent a major cause of pneumonia in critically ill patients requiring MV
Identifying such subjects presents an opportunity for discontinuing antibiotics

Shorr et al Chest 2017; 66: 340-346

After discharge

- The patient is sent home with recommendation of seeing the family doctor and planning antipneumococcal vaccination and influenza vaccination

- However the patient complains that in previous years he got vaccinated but he developed fever after vaccination and he still got the flu ...

The family doctor explained to the patient that…

1. Flu like syndrome can be caused by respiratory virus other than influenza virus : rhinovirus, coronavirus…
2. Influenza vaccine does not reduce the risk of complications
3. Influenza vaccine reduce the risk of complications in adults hospitalized with Influenza
4. The family doctor agrees with him

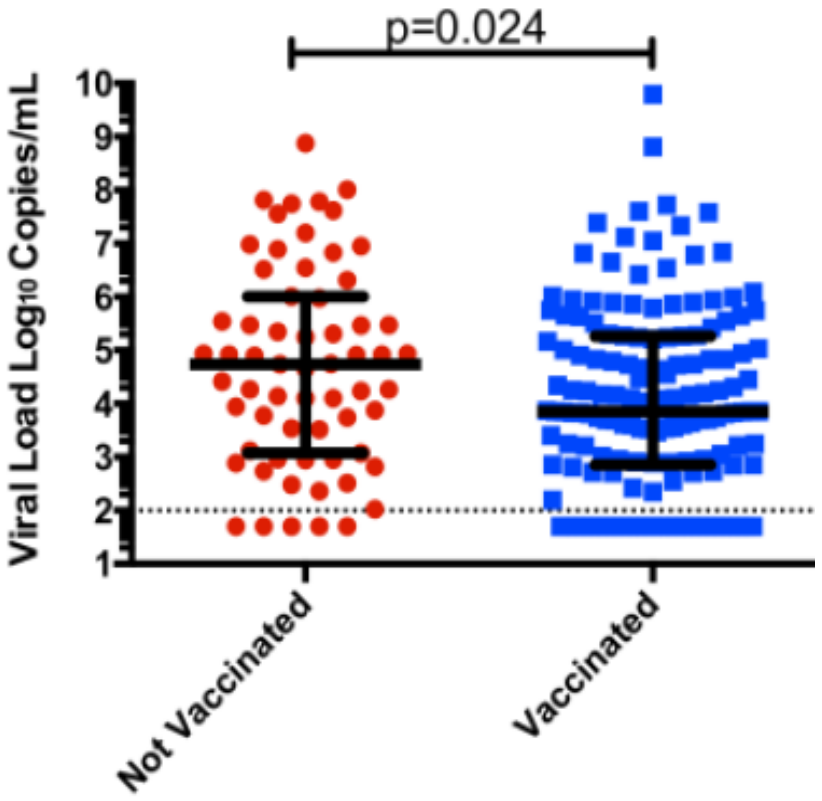
Influenza vaccination modifies disease severity among adults hospitalized with Influenza

- Influenza season attenuate adverse outcome among adults hospitalized with laboratory-confirmed influenza:
  - reduces hospital mortality due to influenza in all age categories
  - reduces the rate of hospitalizations and the duration of ICU hospitalization

Arriola C et al. Clin Infect Dis. 2017 Oct 15;65(8):1289-1297.

The receipt of vaccine in the same influenza season is associated with a decrease in disease severity in immunocompromised SOT and HSCT

- Lower pneumonia (OR 0.34 (95%CI 0.21-0.55), p<0.001) and ICU admission (OR 0.49 (95%CI 0.26-0.90), p=0.023)



Kumar et al Clinical infectious disease 2018 Oct 15;67(9):1322-1329

Mr. BW clinical case

Mr. BW clinical case

- Mr. BW is a 66 year old male who presents to the cardiac surgery clinic the day 19 of september 2018

- Past Medical History
  - Heart transplant 30.07.2017 , treatment with cyclosporine, mycophenolate and steroids
  - Diabets

- He reported fever, dry cough and progressive dyspnoea of 1-week duration

- The family doctor prescribed amoxicillin/clavulanate 875/125 mg every 8 hours for one week without benefit

What would you do in this situation?

1. Start empirical coverage for atypical bacteria with azithromycin or a fluoroquinolone

2. You will take the day after a chest X ray and blood test

3. Ask for an urgent ID consultation

4. The patient must be hospitalized

What would you do in this situation?

1. Start empirical coverage for atypical bacteria with azithromycin or a fluoroquinolone

2. You will take the day after a chest X ray and blood test

3. **Ask for an urgent ID consultation**

4. **The patient must be hospitalized**

Be aware of clinically significant antibiotic drug interactions

- Cyclosporine, mycophenolate and steroids
- Warfarin
- Antiarrhythmic agents…

Prevalence and etiology of CAP in immunocompromised patients

- 3.702 patients with CAP
  - in 652 (17.6%) patients at least one risk factor for immunocompromised
  - 312 patients (8.4%) had more than one risk factor for immunocompromise

- Most frecuent risk factors:
  - chronic steroid/s use (45.0%)
  - hematological malignancy (25.0%)
  - chemotherapy (22.0%)

Pasquale MF et al. Clin Infect Dis 2018

Pathogen	Immunocompetent (n = 2626)	Immunocompromised (n = 596)	*P* Value
Pathogens covered by CAP therapy			
Streptococcus pneumoniae	218 (8.3)	50 (8.4)	>.99
Atypical	50 (1.9)	13 (2.2)	.78
Legionella	21 (0.8)	10 (1.7)	.08
MRSA	83 (3.2)	12 (2.0)	.17
MSSA	73 (2.8)	20 (3.4)	.53
Pseudomonas aeruginosa	98 (3.7)	35 (5.9)	.02
Haemophilus influenzae	65 (2.5)	10 (1.7)	.31
Klebsiella pneumoniae	89 (3.4)	22 (3.7)	.81
Influenza virus	126 (4.8)	28 (4.7)	>.99
Pathogens not covered by CAP therapy			
Non-CAP bacteria			
Acinetobacter baumanii	33 (1.3)	7 (1.2)	>.99
Nocardia spp.	0 (0.0)	4 (0.7)	<.001
Mycobacteria			
Mycobacterium tuberculosis	21 (0.8)	5 (0.8)	>.99
NTM	2 (0.1)	5 (0.8)	.002
Fungi			
Aspergillus fumigatus	10 (0.4)	8 (1.3)	.01
Actinomyces	2 (0.1)	0 (0.0)	>.99
Cryptococcus	3 (0.1)	0 (0.0)	.94
Pneumocystis jirovecii	5 (0.2)	13 (2.2)	<.001
Viruses			
Adenovirus	5 (0.2)	0 (0.0)	.62
Coronavirus	3 (0.1)	3 (0.5)	.047
Metapneumovirus	3 (0.1)	2 (0.3)	.51
RSV	7 (0.3)	6 (1.0)	.03
MDR pathogens	231 (8.8)	54 (9.0)	.54

Specific risk factors independently associated with

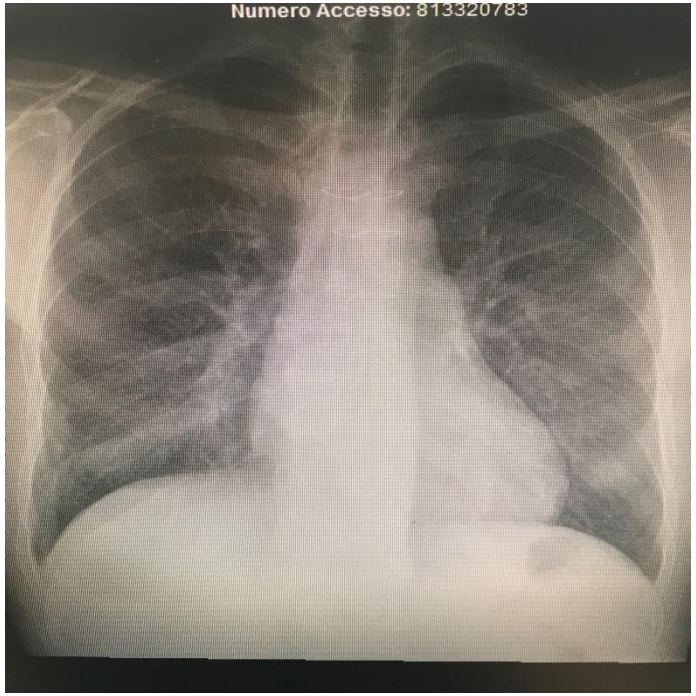
- **fungal infections** (OR for AIDS and hematological cancer, 15.10 and 4.65, *P* = .001)
- **mycobacterial infections** (AIDS; *P* = .006)
- **viral infections other than influenza** (hematological cancer, 5.49; *P* < .001)

Finding should be considered by clinicians in prescribing empiric antibiotic therapy for CAP in immunocompromised patients

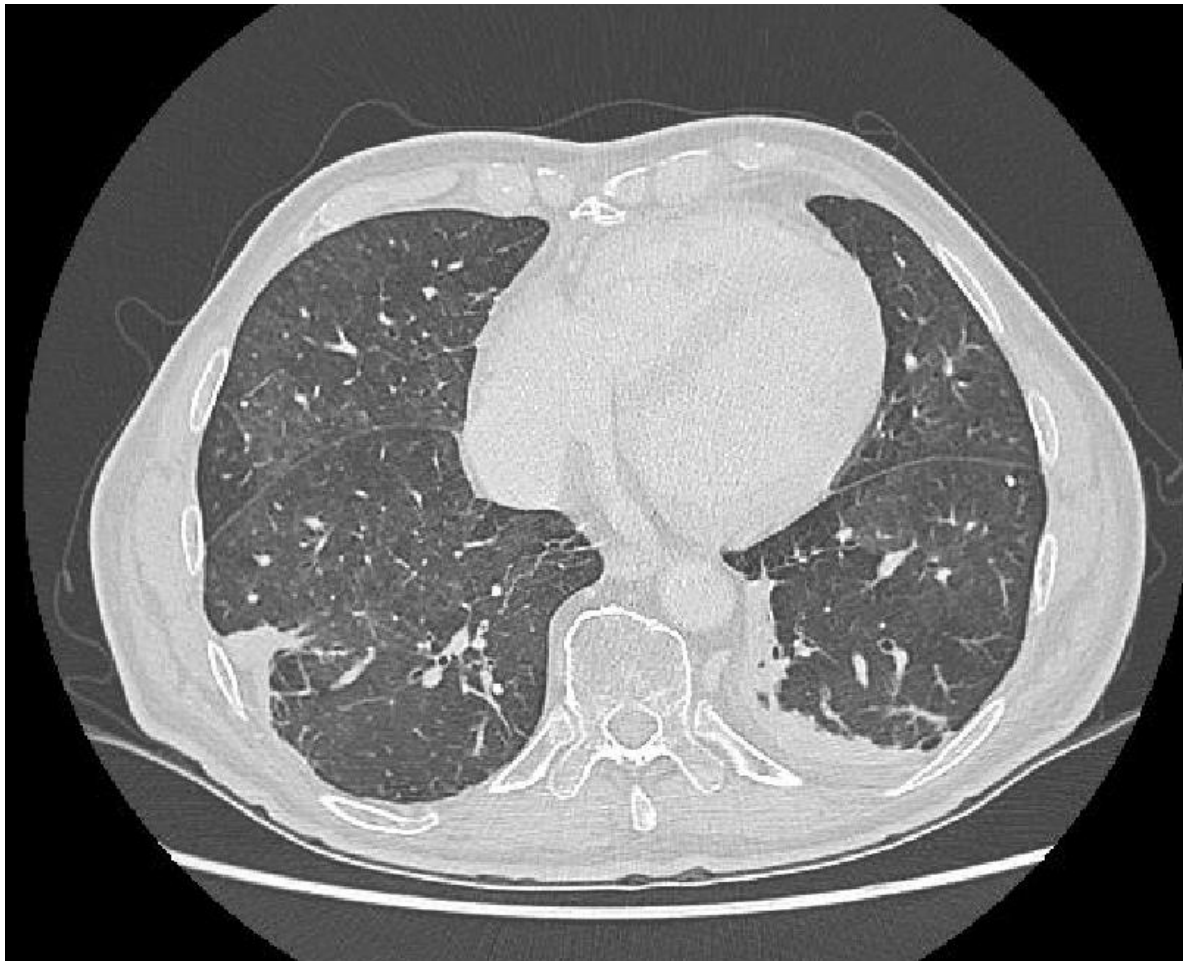
Pasquale MF et al. Clin Infect Dis 2018

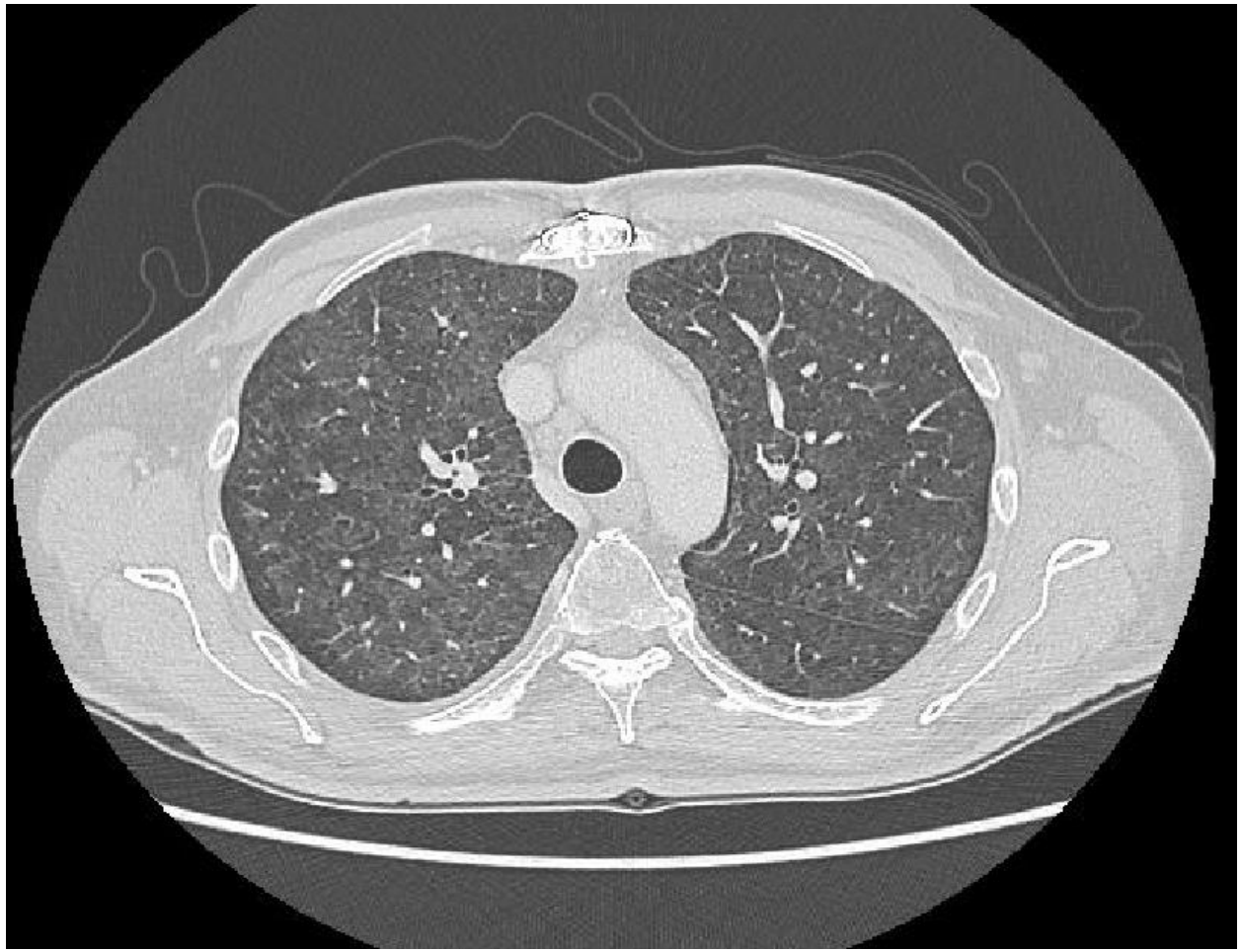
Mr. BW clinical case

- Physical examination: **tachypnoic (RR 20/min)**, Sat 95-96% , bilateral **lung crackles**. No other localizing signs of infection
- Blood analysis: LDH **600 U/L**
- ABG: pH 7,37, pCO2 36 mmHg, **paO2 64 mmHg**, BE 1



Mr. BW clinical case
CT of the thorax





Imaging technology is challenging the clinical diagnosis of CAP the role of CT scanner

- 319 prospectively enrolled patients with suspected CAP:
  - Chest XR parenchymal infiltrate in 188/319 (59%).
  - CT scan: infiltrate in 40 (33%) of the patients without infiltrate on chest radiograph and excluded CAP in 56 (29.8%) of the 188 with parenchymal infiltrate on chest film

- The increasing availability of CT scanners in ED and a modern generation of CT scanners

- Ultrasonography to confirm the presence of infiltrates and distinguish between parenchymal and pleural abnormalities

Ohana M et al. Rev Pneumol Clin 2017;73:3-12

Claessens et al. Am J Respir Crit Care Med. 2015 Oct 15;192(8):974-82

Mr. BW clinical case : microbiological investigation

- Virus?

CMV: negative, EBV: negative, Nasopharingeas swab for respiratory virus: negative

- Bacteria?

Blood and urine culture: negative, Quantiferon: negative, Nasopharingeas swab for Pneumotris: negative, Urinary antigen for Legionella and Pneumococcus: negative

- Fungi?

Blood culture: negative, Ag Galattomannan: negative**, Beta D Glucan: 210 ng/mL**

- Parasites?

Toxoplasma Ab: negative

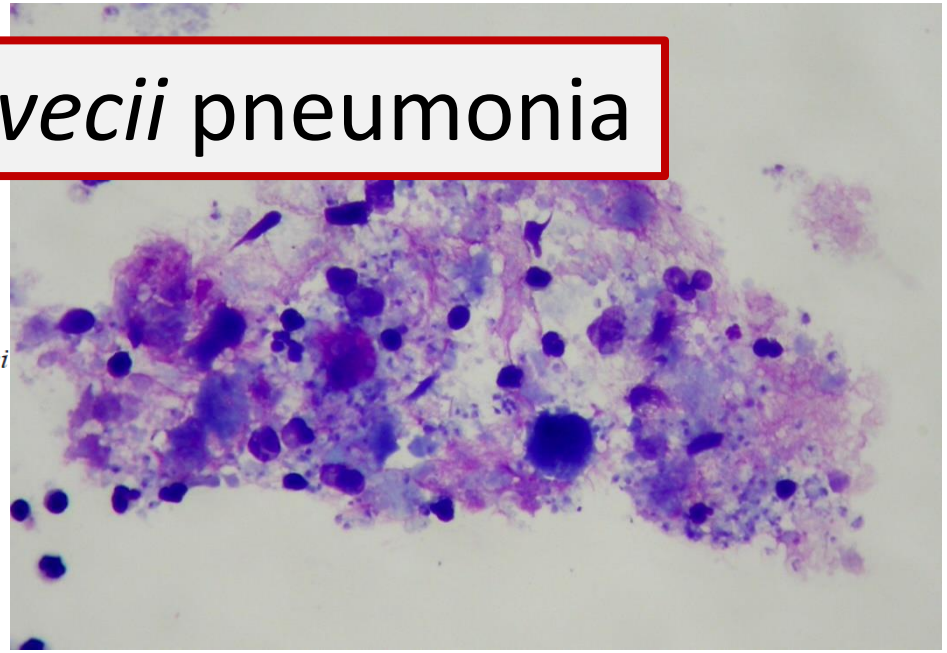
Mr BW clinical case : diagnosis

- Underwent to diagnostic bronchoscopy
- Broncoalveolar lavage:

Materiale: Broncolavaggio

Esame microscopico	
Leucociti	
Cellule epiteliali	
Colturale per batteri aerobi e	**germi patogeni**
Colturale per miceti	**Nessuno sviluppo**
Esame colturale Legionella	**Nessuno sviluppo**
Ricerca Pneum.carinii-jirovecii(IF)	**Positivo**
	Oocisti di Pneumocystis jiroveci
Pneumotris PCR	
Ricerca Clamydia pneumoniae (PCR)	**Negativa**
Ricerca Mycoplasma pneumoniae (PCR)	**Negativa**
Ricerca Legionella (PCR)	**Negativa**
Ricerca Nocardia species	**Nessuno sviluppo**
Ricerca Actinomyces species	**Nessuno sviluppo**

Pneumocystis jirovecii pneumonia



Take home messages

- Removal of the concept of HCAP
- Changing epidemiology of CAP: new diagnostic methods and their impact in management
- Emerging role of respiratory viruses in CAP
- The role of prevention and influenza vaccination
- Empiric antibiotic therapy for CAP should not be prescribed in immunocompromised patients

GRAZIE

BE ANTIBIOTICS AWARE

SMART USE, BEST CARE