CAP versus TB: The Physician’s Dilemma
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Background

- Two epidemics
- Double trouble
- Combined
- Pandemic
- Is it Bacterial CAP? Is it TB
- Atypical presentations
- Dual and Triple co-infections
- IRIS
- Lack of access to appropriate and essential investigations
Further

- TB: commonest infection in HIV
- HIV/TB co-infection 80%
- Incidence of TB 8.3 times higher with HIV
- Risk of reactivating latent TB 80-200 times higher
- Risk of aggressive disease higher with HIV
More sad stories.......

- CAP incidence higher in HIV population
- Risk increases as CD4 declines
- Epidemiology altered
- TB/PCP competing with Bacterial pathogens
Initial management of CAP is empiric antibiotics
Cover common causes of CAP
TB requires specific anti-TB drugs
Delay in diagnosis:
  progression of disease
  increased morbidity and mortality
  transmission of TB
TB in CAP: pre-HIV era

- Capetown 1980: 6 %
- Maartens et al 1980s: no TB
- Western Europe North America: 2.4 %
- Malaysia: 4.9 %

Multivariate analysis: predictors of TB

- History more than 2 weeks
- Night sweats
- Upper lobe disease
- Cavitation
Medical books rewritten!

- Study from KZN: 39.6% TB
- strep pneumo 35.5%
- HIV negative: 35% CAP due to TB
- Nyamande, Laloo; Int J Tuber Lung Dis 2007
What’s the message?

- Low HIV incidence: TB uncommon as cause of CAP
- Traditional assumptions correct
- In high HIV incidence areas: impossible to differentiate CAP due to bacteria vs CAP due to TB
- Clinical /radiological features same
TB: why atypical presentation?

- Acute rapidly progressive CAP
- Profound immunosuppression
- Low CD\textsubscript{4}
- Qualitative changes in lymphocyte function
- Poverty, malnutrition
Consequences

- Rapidly progressive disease
- Lower lobe infiltrates
- Less cavitation
- Lober and segmental consolidation
- Diffuse infiltrates
- Pleural effusions with intra-thoracic lymphadenopathy
- No or poor granuloma formation: sputum negative
Radiology

- Apical disease
- Cavitation
- Non specific
- No use in HIV
- Kudjawu et al: 10 day course of amoxycillin more useful than any clinical/radiological derived scores
- HRCT chest: more useful
- Nyamande and Laloo: a correct HRCT diagnosis of CAP due to TB, Bacteria, PCP was made in 80 %, 84 % and 100 % of patients respectively (Br J Radiology 2007)
Microbiology

- TB diagnosis: sputum direct microscopy and culture
- Problems: dry cough, too sick, uncooperative, poor quality
- Low sensitivity: 22% - 78%
- Lower with HIV
- Culture of no use in acute rapidly progressive disease
- Issues: reagents, equipment, staff
- Failure to cope with number of samples to process
- PCR: sensitivity and specificity > 95% (in smear positive) but not available
- 40-70% in smear negative
The FBC

- Bacterial CAP: leucocytosis
- Unreliable in HIV
- May occur on TB
The role of biomarkers

- Aetiological diagnosis?
- Separate mild from severe?
- Inform ward versus ICU?
- Predict complications?
- Predict mortality?
Procalcitonin (PCT)

- 13 kDa 116 amino acid
- Prohormone of calcitonin
- Elevated in bacterial infections and sepsis
- Recent studies: distinguishing bacterial from non-bacterial causes of CAP
Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis


Usefulness of Procalcitonin Levels in Community-Acquired Pneumonia According to the Patients Outcome Research Team Pneumonia Severity Index

Mar Masia, MD; Felix Gutierrez, MD; Conrado Shum, MD; Sergio Padilla, MD; Juan Carlos Navarro, MD; Emilio Flores, MD; and Ildefonso Herna´ndez, MD

Chest 2005;128;2223-2229
Box plots showing procalcitonin levels according to the etiology of CAP. The box plots show 25th, 50th, and 75th percentiles, maximal, extremes (*), and outliers (O).
Box plots showing procalcitonin levels according to the etiology of CAP in patients with low PSI risk classes (I-II) [top], and in patients with higher PSI risk classes (III-V) [bottom]. The box plots show 25th, 50th, and 75th percentiles maximal, extremes (*), and outliers (O).
Conclusion

- PCT contribution to the evaluation of CAP varies according to severity.
- While PCT may have a role to predict the microbial aetiology in patients with a low PSI score, in patients classified within high PSI risk classes, it is a prognostic marker rather than a predictor of aetiology.
Procalcitonin and C-reactive protein levels in HIV-positive subjects with tuberculosis and pneumonia

G.K. Schleicher, V. Herbert, A. Brink, S. Martin, R. Maraj, J.S. Galpin and C. Feldman

Box-and-whisker graph of C-reactive protein (CRP) levels in patients with pulmonary tuberculosis (PTB) and pneumococcal community acquired pneumonia (PCAP).
Box-and-whisker graph of procalcitonin (PCT) levels in patients with pulmonary tuberculosis (PTB) and pneumococcal community-acquired pneumonia (PCAP).
Receiver-operating characteristics curve for discrimination between pulmonary tuberculosis and pneumococcal community-acquired pneumonia for procalcitonin ($) and C-reactive protein (#). ——: reference line.
Conclusion

- HIV seropositive patients with pneumococcal CAP had significantly higher PCT and CRP levels than those with PTB. A PCT level >3 ng/dl and a CRP level >246 mg/L were both highly predictive of pneumococcal infection.
Serum procalcitonin distinguishes CAP due to bacteria, *Mycobacterium tuberculosis* and PJP

K. Nyamande, U. G. Laloo
Procalcitonin concentrations in bacterial pneumonia (pneumococcus, *Staphylococcus aureus* and *Haemophilus influenzae*), PJP and PTB. Error bars show mean 1.0 SEM. PJP *Pneumocystis jirovecii* pneumonia; PTB pulmonary tuberculosis; SEM standard error of the mean.
Conclusion

- PCT levels differ significantly in patients with CAP due to TB, PJP, and bacteria. PCT may be important in distinguishing M tuberculosis and PJP in a high HIV prevalence setting where atypical presentations often confound the empirical clinical diagnosis.
Triggering receptor expressed on myeloid cells (TREM-1)

- 30 kDa glycoprotein of the Ig superfamily
- Identified on human chromosome 6
- Expressed on myeloid cells: neutrophils and monocytes
- Induces the secretion of several proinflammatory cytokines and chemokines
- TNF alpha, IL8, MCP-1, GMCSF
- IL-10 suppressed
Unknown ligand → DAP12, TREM-1 → Cell activation markers

Cell adhesion molecules → Tyrosine phosphorylation

IL-1β, IL-8, MCP-1, TNF-α → Ca²⁺ mobilization

MPO → Cell activation markers
Triggering receptor expressed on myeloid cells: role in the diagnosis of lung infections


Eur Respir J 2004; 24: 247–250
Triggering receptor expressed on myeloid cells (TREM)-1 expression on total bronchoalveolar (BAL) cells is significantly higher in patients with community-acquired pneumonia likely to be caused by extracellular bacteria (group A) than in patients with pulmonary tuberculosis (group B; *: pv0.05) or patients with noninfectious interstitial lung diseases (group C; ***: pv0.001). Data are presented as TREM-1 mean fluorescence (MF) of total BAL cells, subtracted from isotype control.
Conclusion

- TREM-1 is selectively expressed in the lungs of patients with pneumonia caused by extracellular bacteria and not in patients with tuberculosis, providing a potential marker for differential diagnosis.
Macrophage migration inhibitory factor (MIF)

- Regulates macrophage migration, localisation and phagocytosis
- High levels of MIF in PTB, sepsis and shock
- High levels in PTB correlate with disease severity and virulence of organism
Serum and BAL macrophage migration inhibitory factor levels in HIV infected Tanzanians with pulmonary tuberculosis or other lung diseases

Gibson S. Kibiki, Andre J.A.M. van der Venb, Anneke Geurts-Moespot, John Shao, Thierry Calandra, Fred C.G.J. Sweep, Wil M.V. Dolmans

Clinical Immunology (2007) 123, 60–65
Median serum MIF and IQR in the four groups: HIV-seropositive with and without PTB and HIV-seronegative with and without PTB. The difference between serum MIF in the HIV infected patients with PTB or without PTB was not statistically significant. Serum MIF in HIV-infected patients with PTB was higher than in HIV-seronegative patients with PTB (p=0.004) as well as without PTB (p<0.0001).
Conclusion

- HIV infection was associated with elevated serum MIF levels regardless of PTB. Low serum MIF levels were associated with high mortality.
Other biomarkers in CAP

- Free and total cortisol
- Pro endothelin-1
- Midregional pro-atrial natriuretic peptide (MR pro-ANP)
- Carboxy-terminal provasopressin (CT-proAVP)
Cortisol

- Cortisol levels are predictors of severity and mortality and correlate with PSI (Christ Crain et al, Am J Resp Crit Care Med; vol 176; 913-920)
- HIV?
- TB versus bacteria in CAP?
ProEndothelin-1 (proET-1)

- In CAP, ProET-1 correlates with disease severity (PSI and CURB65) and is an independent predictor for mortality and ICU admission. (Schuetz P et al, 2008, BMC Infectious Diseases, 8; 22)
- HIV?
- TB vs bacterial CAP?
Midregional pro-atrial natriuretic peptide

- MR–proANP correlates with PSI and CURB65 scores and predicts likelihood of complications
- Helpful for individual risk assessment (Pat C et al, 2007; Journal of Infection; 55; 400-407)
- HIV
- Levels in TB vs bacterial CAP
Carboxy-terminal provasopressin (CT-proAVP)

- Levels correlate with PSI severity of infection; independent predictor of death (Masia M et al, 2007; Clinical Chemistry; 53, 12; 2193-2201)
- ?HIV
- ?levels in PTB vs bacterial CAP and PCP?
Summary

- PCT most promising
- Easily measured
- Cheap
- Available
- Most studied
- Large multicentre studies required
Others

- Lagging behind in terms of well designed, good, large studies
- Pro-ET₁; CT-proAVP; MR proANP not yet out of the starting blocks!
Meanwhile

Back to the good Professors!
Diagnostic approach?
AN APPROACH TO MANAGEMENT OF CAP IN A HIGH HIV
PREVALENCE HIGH TB INCIDENCE POOR RESOURCE SETTING

Symptoms and Signs of CAP

CXR

Diffuse infiltrate

Empiric antibiotics + high dose cotrimoxazole for PCP

No response by day 5
Add TB treatment

Negative sputum consider referral for bronchoscopy

Sputum mcs + Ziel Neelsen staining for AFB

Adjust treatment according to results

Good clinical response.
AFB stains negative

Follow-up in 4-6 weeks to check TB culture results

AFB +
Add TB treatment
Check TB culture report
Add TB treatment
Check sensitivity results for drug resistance

Infiltrate and or focal consolidation

Sputum mcs + Ziel Neelsen staining for AFB

Start empiric antibiotic treatment according to local guidelines

No response, remains ill or deteriorates
Dual infection

- Polymicrobial infections unusual pre HIV
- 2-5%
- HIV: mixed infections common
- As high as 16% in Sub-Saharan Africa
- Commonest combination: MTB and Strep pneumoniae
- Mortality high: 38%
- Isolation of one pathogen not end of story
Red flag!

- Failure to show expected clinical progress
- Failure to improve
- Improve then deteriorate
- Check results of all microbiological specimens.
Empiric antibiotic treatment in CAP

- Pitfalls
- Fluoroquinolones, macrolides, azalides in algorithms
- Activity against mycobacteria!
- Transient improvement in patients with TB
- Partial MTB treatment
- Missed diagnosis
- Delayed diagnosis
- Can be catastrophic
Summary

- HIV/TB present dilemmas in CAP
- Limited resources
- Changing aetiology of CAP
- Severe immnosuppression
- Atypical presentations
- No typical and radiological features anymore
- Challenge: recognize and treat TB early
- Empiric full anti TB treatment may be the only option