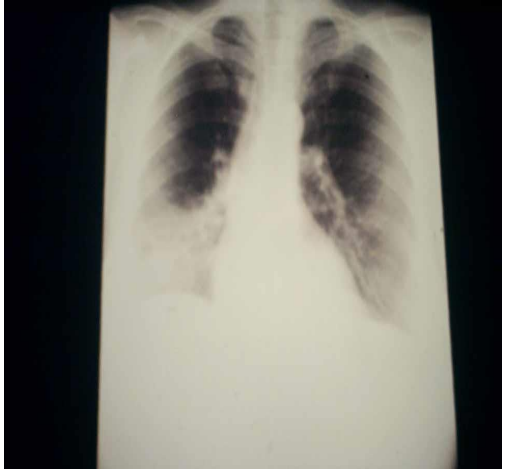

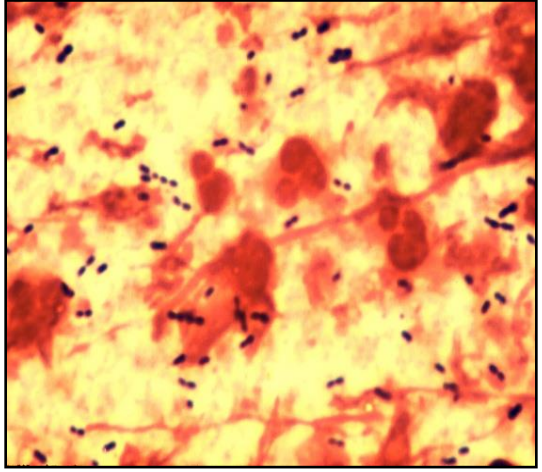

Community-acquired Pneumonia: Test, Target, Treat

Thomas M File Jr. MD, MSc

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Rootstown, Ohio

Learning Objectives

- List differences between empirical and pathogen-directed therapy for community-acquired pneumonia (CAP)
- List advantages of rapid diagnostic methods for CAP

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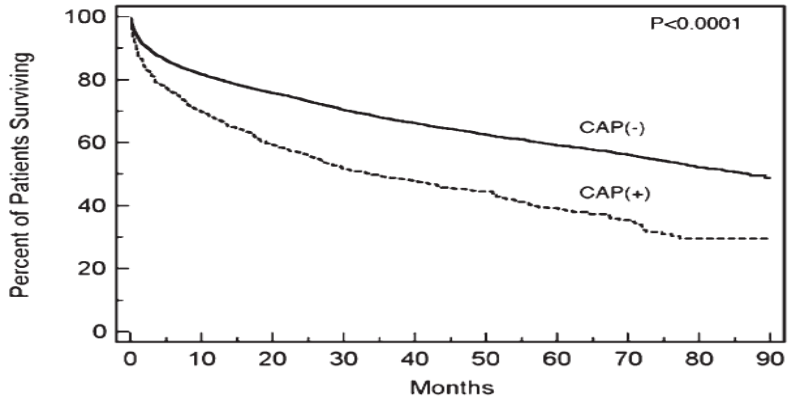
Community-acquired Pneumonia (CAP)

- Leading cause of morbidity and mortality
  - No. 1 cause due to infection
- 5-6 million cases/year
  - Approx. 1 million admissions/year
    - **40% one year mortality; (Kaplan et al. Arch Intern Med 2003; 163: 317-323)**
    - **50% mortality at 30 months (Bordon et al. Chest 2010; 138: 279-83)**



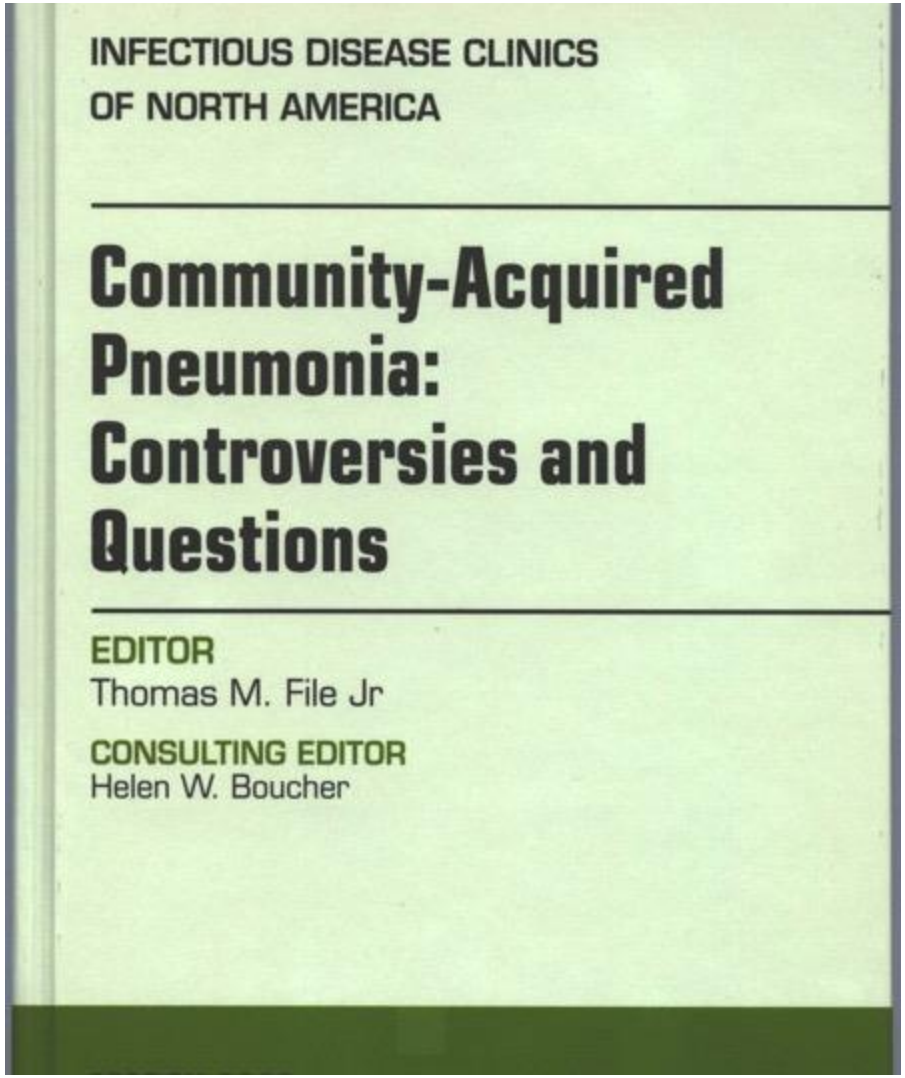
- Cost of treating CAP exceeds $17 billion/year
- Performance Measures

File T. *Lancet* 2003; File and Tan *JAMA* 2005
File T and Marrie T *Postgrad Med*. 2010

Community-acquired pneumonia

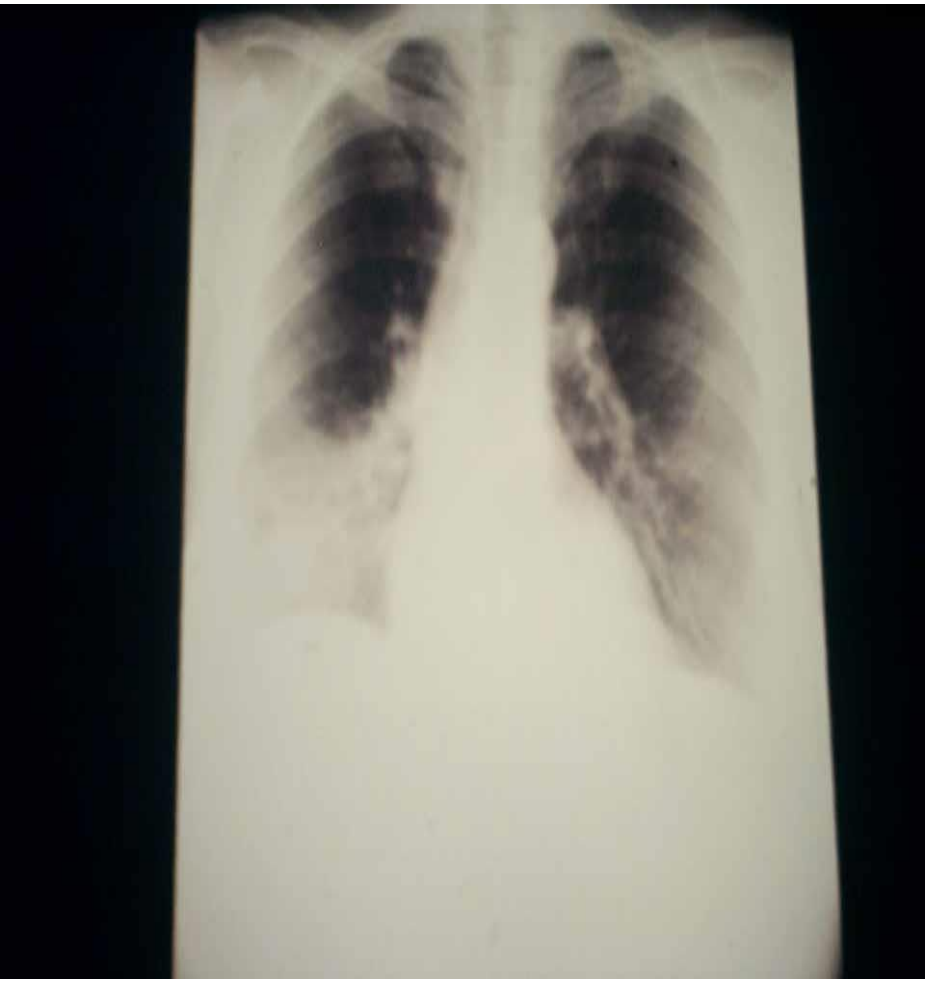
- "Despite remarkable advances in the identification of new microbial pathogens and antimicrobial agents, few diseases are so characterized by disputes about diagnostic evaluation and therapeutic decisions."

  Bartlett J, Mundy L NEJM 1995



March 2013

Community-acquired Pneumonia (CAP): Case



- 56 Y/O MALE
  - Smoker, Diabetes
- Acute fever and cough
- WHAT PATHOGEN?
- WHAT ANTIMICROBIAL?

CXR courtesy of T. File MD

CAP THERAPY: Principles

- TREAT EARLY
- TREAT MOST LIKELY PATHOGENS
  - *S. pneumoniae* (?Drug resistance*); *H. influenzae*
  - Atypicals—studies in North America show high prevalence (even though may not be severe, therapy reduces illness)
  - Others (local epidemiology)
  - Cannot differentiate etiology based on initial findings
- NEW PARADIGM: Pathogen-directed therapy

---

*Recent ATB (Following of ? Relevance: Recent Hospitalization; DayCare; Multiple comorbidities; Age)

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Most Common Etiologies of CAP

Ambulatory Patients	Hospitalized (non-ICU)†	Severe (ICU)†
S. pneumoniae	***S. pneumoniae***	***S. pneumoniae***
M. pneumoniae	***M. pneumoniae***	***S. aureus***
H. influenzae	***C. pneumoniae***	***Legionella* spp.**
C. pneumoniae	***H. influenzae***	**Gram-negative bacilli**
Respiratory viruses††	***Legionella* spp.**	***H. influenzae***
	Aspiration	
	Respiratory viruses‡	

Based on collective data from recent studies; †Excluding *Pneumocystis* spp.
‡ Influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza

File TM. *Lancet*. 2003;362:1991-2001.

Empiric Therapy in CAP: IDSA/ATS

Healthy Outpatient	Outpatient at Risk for DRSP*	Inpatient, non-ICU	Inpatient, ICU†
Macrolide OR Doxycycline	Respiratory fluoroquinolone (Levofloxacin 750 mg; moxifloxacin 400mg daily) OR Beta-lactam plus macrolide	Respiratory fluoroquinolone OR Beta-lactam‡ plus macrolide *OR* *Tigecycline*	Beta-lactam plus azithromycin OR Beta-lactam plus fluoroquinolone

*Recent antimicrobials; comorbidites; Includes healthy patients in regions with high rates of macrolide resistance.
†Treatment of *Pseudomonas* or MRSA is the main reason to modify standard therapy for ICU
‡ Ceftriaxone, cefotaxime, amp/sulbactam, ertapenem, ceftaroline (from CMS list)

Mandell L, et al. *Clin Infect Dis.* 2007;44(Suppl 2):S27-S72; CMS list of antimicrobials.

Performance Measures

- 30-day CAP mortality
- 30-d readmission rate for pneumonia*

*Complements Core Measures as part of the Hospital Readmissions Reduction Program—hospitals with higher than expected 30-d readmission rates for AMI, heart failure, and pneumonia will incur penalties against their total Medicare payments beginning in FFY 2013.

http://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/2014_ClinicalQualityMeasures.html
File TM Jr, personal communication, Sept. 2013. CMS community-acquired pneumonia Technical Expert Panel, 9/19/13.

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Lobar Pneumonia: Diagnosis (1930)

- "It is extremely essential, both from the standpoint of prognosis and treatment, that the physician should know the bacteriological nature of the infectious process. In the first place, is he dealing with a pneumococcus infection?"
- "The bacteriological examination of the sputum usually supplies this information."
  - Agar plates-slow
  - Mouse test-most reliable
- '..frequently the patient has no sputum during the first 48 hours, the time when a bacteriological diagnosis is most important. A blood culture at this time may supply the necessary information."

Cecil R. in Cecil R (ed.) A Text-book of Medicine, 2nd Ed. WB Saunders Co. Philadelphia, 1930

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CHEST Commentary

Rapid Diagnostic Testing for Community-Acquired Pneumonia

Can Innovative Technology for Clinical Microbiology Be Exploited?

Victor L. Yu, MD; and Janet E. Stout, PhD

- "Two nonsynchronous events have affected management of CAP"
  - Spiraling empiricims
    - Broad spectrum antimicrobial therapy with deemphasis of microbiology
      - Just treat for everything
      - Consequence of increase resistance
    - "Golden era" of clinical microbiology
      - Non culture-based (e.g., Urinary Antigen, Molecular tests)
      - Rapid ID of pathogen
      - Offers more specific therapy

(Chest 2009; 136: 1618)

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Empiric vs Pathogen-directed therapy

- Empiric Therapy
  - Treat most likely pathogens
    - Initially then de-escalate (but not often done)
  - Requires broad spectrum antimicrobials
    - Collateral effect
      - Selection of resistance
      - Adverse Effects
- Pathogen-directed therapy
  - ‘Narrow’ therapy
  - Decreased selection resistance
  - Decreased Adverse Effects
  - Decreased Cost

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Reasons to Identify Pathogen

1. Permit optimal antibiotic (ABX) selection against a specific pathogen and limit consequences of ABX misuse
2. Identify pathogens of potential epidemiologic significance (e.g., Legionella, TB)
3. Reduce overuse of Broad-spectrum ABX; which hopefully will reduce selection pressure and antimicrobial resistance
4. Reduce Adverse Events
5. Reduce Cost

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Antimicrobial Resistance

- Serious health threat
  - "Threat to national security" WHO
  - "Healthcare Crisis" CDC
- Overuse of antimicrobials is primary driver
- Need better approaches to optimal antimicrobial therapy
  - Decrease unnecessary and overly broad-spectrum use
  - More rapid identification of pathogen and susceptibiilty

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Optimal management of CAP

- Requires rapid and accurate diagnosis of etiology
- Correct diagnosis enhances appropriate use of antimicrobials and reduces overuse
- Pathogen-directed therapy requires the use of an assay that is FDA-cleared, accurate and completed in a timely manner

Gaydos C. Inf Dis Clinics NA 2013

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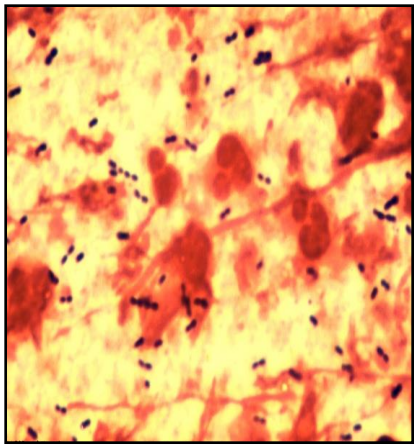
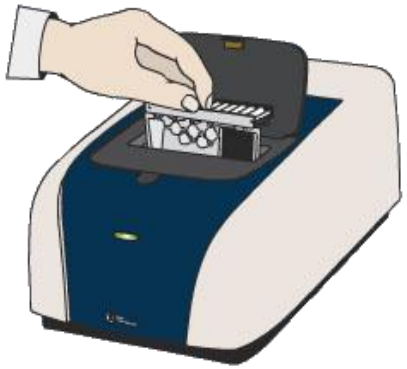
Diagnostic Tests for Etiology in CAP Management

- Standard culture methods (blood, sputum)
  - Low yield, time to results
- Gram stain, urinary antigen testing
  - S pneumoniae, Legionella spp
- Newer molecular tests (PCR, MALDI-TOF)
  - Potential for more rapid diagnosis, greater sensitivity
  - Allows for pathogen-directed therapy
- Biomarkers (Procalcitonin)
  - Differentiate Bacterial vs virus
  - Timely response to bacterial load





PCR, polymerase chain reaction; MALDI-TOF, matrix-assisted laser desorption/ionization Time of Flight mass spectrometry

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2 Recent Hospital CAP FDA Studies

	Ceftaroline vs Ceftriaxone	Solithromycin vs moxifloxacin
# pts	1153	863
PORT	All III or IV	II-IV
Age (mean)	61	61
% 'bacterial' pathogen	26.1%	37.8%
S pneumoniae	12%	17% (3% by Ur Ag only)

Tanaseanu et al. Diag Microb Infect Dis. 2008; 61: 329-338; File et al. Clin Infect Dis. 2016; 63: 1007-16

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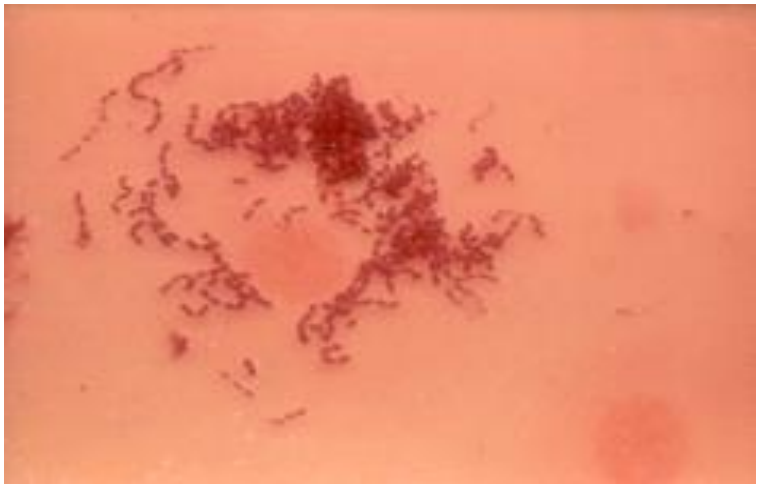
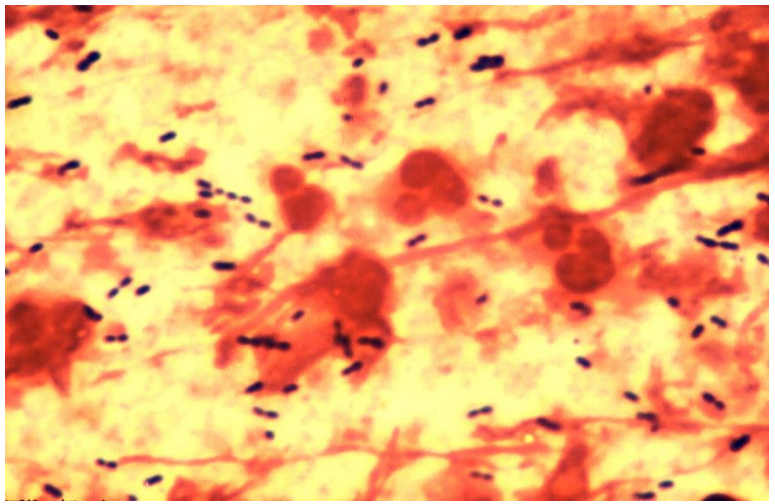
Rapid tests for *S. pneumoniae*: Gram stain

- Yield variable; influenced by quality of process and interpretation
- Adequate sputum-14-50%
- *S. pneumoniae* bacteremia (Musher et al. Clin Inf Dis.2004)
  - Gram stain + 63%; culture + 86%
  - If no prior ATB, Gram stain + 80%
- Lost 'art'
  - Outsourcing of Microbiology





Enrichment of Microbial Etiology- Sputum Grams Stain

- Patients enrolled in six studies of oral Amoxicillin/Clavulanate (2000/125 mg)*
  - *S. pneumoniae* isolated from 15.3% (652/4264) of all patients
  - Inclusion criteria enriched patient populations with *S. pneumoniae*
    - possible bacterial (studies 2,3,5,6): 3.1–13.1% of all patients
    - suspected pneumococcal (studies 1,4): 18.6–20.9% of all patients
      - **Required + Grams Stain or + Urinary Antigen**
- Conclusion: Can enhance % bacterial yield

*File T et al. ICAAC 2005, File T et al. Intern J Antimicrob Agents 25 (2005) 110–119

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Rapid tests for *S. pneumoniae*: Urinary Antigen

- Advantage:
  - 15 minutes, simple, minimal cost
  - Sensitivity 64% non bacteremic (80-90% bacteremic); Specificity > 90% (Gutierrez et al. Clin Infect Dis 2003; Boulware etal. J Infect 2007; Smith et al. J Clin Microb 2009)
  - Increases % of diagnosed pts by 25% (Gutierrez et al. 2000)
  - + after ATB therapy 83% (Smith et al. J Clin Micro 2003)
- Disadvantages
  - No susceptibility; 'False' + in children

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Rapid tests for *S. pneumoniae*: Urinary Antigen (clinical use)

- Management of nonsevere pneumonia using Sp urinary antigen for targeted therapy (Guchev et al. Clin Inf Dis 2005)
  - positive test (22%)--treated with amoxicillin
  - negative test-- treated with clarithromycin
  - allowed targeted therapy with an antibiotic of the penicillin class rather than broader-spectrum antibiotic therapy
    - can be more cost effective; allow broad-spectrum agents to be reserved
    - low level of DRSP in Russia
    - 38% of + Sp Ur Antig also + for 'atypical'
- Usefulness Sp Ur Ag in the treatment of Pts hospitalized for CAP (Stalin et al. Clin Inf Dis 2005)
  - Mean age 75; 45% Fine IV or V
  - positive test supported treatment with narrow-spectrum beta-lactam antibiotics; coverage for atypical pathogens with negative test results
  - No + PCR for atypicals in Sp Ur Ag + patient

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Rapid tests for *S. pneumoniae*: Urinary Antigen (clinical use)

- Prospective randomized study of empirical versus target treatment on basis of urine antigen results in hospitalized patients with CAP (Falguera et al. Thorax 2010)
  - 177 pts
  - Targeted therapy assoc with nonsignificant, slightly higher cost (due to cost of test), reduction in AE and lower exposure to ABX
  - But authors did not "target" therapy until as late as 6 days after initial broad-spectrum therapy (they acknowledge if there had been earlier targeted therapy, may have been economic effect and targeted therapy has potential to lead to less resistance.

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Recent Patient with Flu and Pneumonia

- 88 y/o female admitted with 2 day history of cough and fever
- CXR: Right lower lobe infiltrate
- Labs: Influenza PCR + Influenza A
- Initial Treatment: Oseltamivir, Piperacillin-tazobactam, Vancomycin
- Subsequent Labs: Procalcitonin 4; Blood cultures-no growth; Unable to produce sputum; Urinary Antigens: Legionella-negative; *S. pneumoniae*-Detected
- Intervention: De-escalate antibiotics-Stop Piperacillin-tazobactam and Vancomycin; changed to ceftriaxone.

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New Diagnostic Tests for Pneumonia: What is Their Role in Clinical Practice?

Box 1
Advantages of molecular techniques compared with conventional diagnostic techniques

Advantages

Rapid

Greater sensitivity

Possibility to identify drug resistance

Ability to identify specific clones for epidemiologic assessment

Possibility to test for multiple pathogens simultaneously

Less affected by prior antimicrobial therapy

Able to detect organisms unable to be cultured

File T. Clin Chest Med. 2011

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Enriched PCR Detection of CAP Pathogens

Table 2. Bacterial Yield in the Study Population and the Contribution of Different Methods to the Determination of Etiology with Respect to Their Different Specificity

Pathogen	No. (%) of patients with positive findings (n = 184)	Blood culture (n = 179)	Pleural fluid culture (n = 13)	Urine antigen assay[a]	BAL and/or protected specimen brush culture (n = 12)	Culture and/or PCR from sputum sample for *L. pneumophila* (n = 138)	Culture and PCR from respiratory sample for *M. tuberculosis* (n = 18)	Sputum culture (n = 128)	RQ-PCR from sputum sample (n = 126)	Nasopharyngeal secretion culture (n = 158)	PCR from nasopharyngeal secretion sample[b]	Serology (n = 131)
Streptococcus pneumoniae	70 (38)	27	...	16	...	...	...	10	10	7	...	...
Mycoplasma pneumoniae	15 (8)	...	...	...	...	...	...	...	...	...	8	7
Haemophilus influenzae	9 (5)	...	...	...	...	...	...	4	5	...	...	...
Moraxella catarrhalis	7 (4)	...	...	...	...	...	...	7	...	...	...	...
Staphylococcus aureus	4 (2)	2	1	...	...	...	...	1	...	...	...	...
Legionella pneumophila	3 (1)	...	...	2	...	1	...	...	...	...	...	...
Streptococcus pyogenes	2 (1)	1	...	...	1	...	...	...	...	...	...	...
Streptococcus milleri	1 (0.5)	...	1	...	...	...	...	...	...	...	...	...
Nocardia cyriacigeorgica	1 (0.5)	...	...	...	...	1	...	...	...	...	...	...
Fusobacterium necrophorum	1 (0.5)	1	...	...	...	...	...	...	...	...	...	...
Mycobacterium tuberculosis	2 (1)	...	...	...	...	...	2	...	...	...	...	...
Total	115	31	2	18	1	2	2	22	15	7	8	7

Among the 38 patients who had complete sampling (conventional + molecular assays), a microbial etiology was determined for 89%

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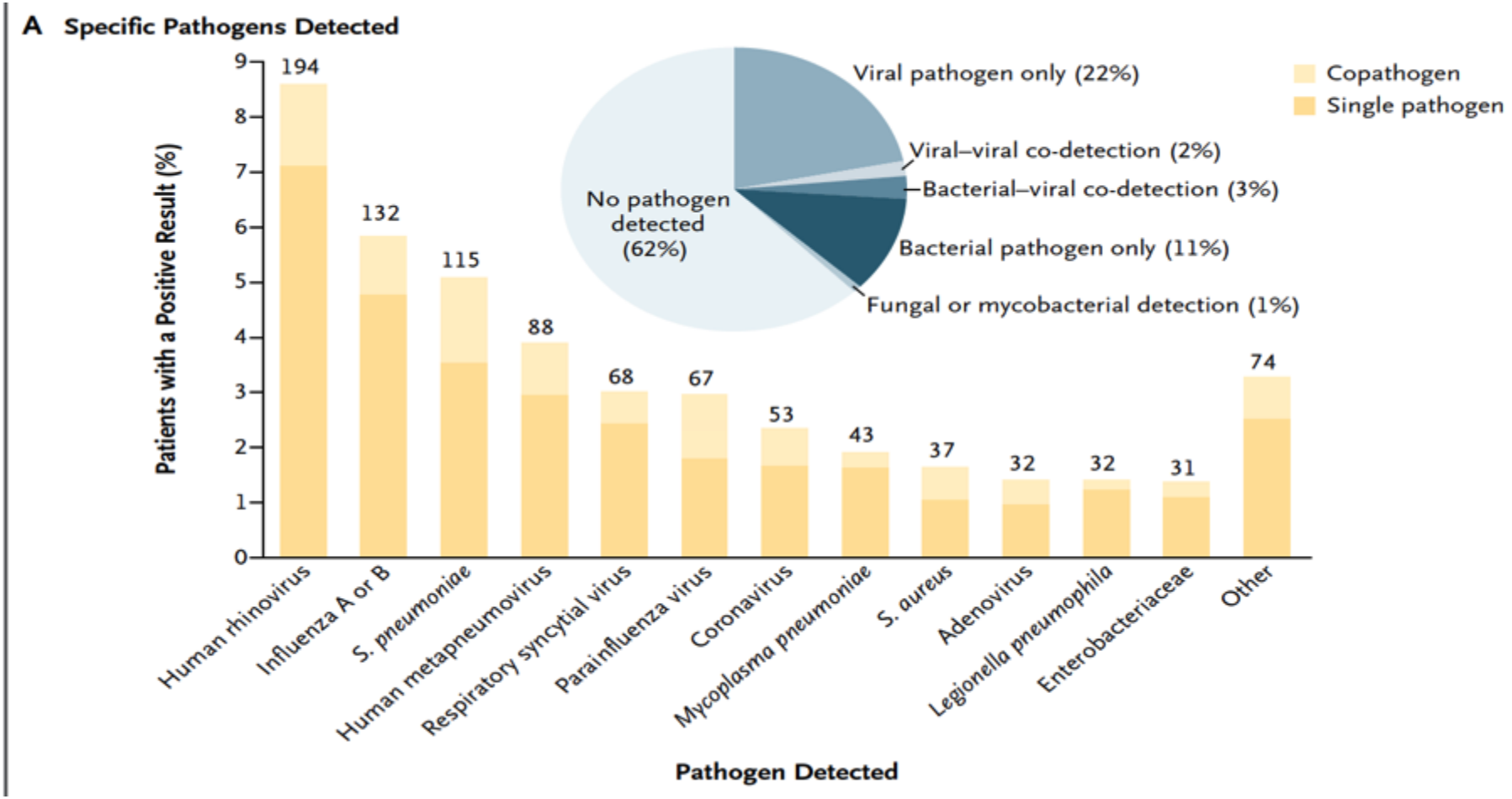
Pathogen Detection among Hospitalized Adults with CAP Enrolled in EPIC Study – Jan 1, 2010–June 30, 2012

2320 pts, 5 sites; Standard cultures, Ur AG, Serology (viral), PCR



Jain S. Self WH, **Wunderink RG** et al. NEJM 2015

Clinical Infectious Diseases

MAJOR ARTICLE

Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia

Naomi J. Gadsby,[1] Clark D. Russell,[1,2] Martin P. McHugh,[1] Harriet Mark,[1] Andrew Conway Morris,[3] Ian F. Laurenson,[1] Adam T. Hill,[4] and Kate E. Templeton[1]

[1]Medical Microbiology, Department of Laboratory Medicine, Royal Infirmary of Edinburgh, [2]College of Medicine and Veterinary Medicine, University of Edinburgh, [3]Department of Anaesthesia, University of Cambridge, and [4]Respiratory Medicine, Royal Infirmary of Edinburgh, United Kingdom

- 323 adults with CAP from 3 UK hospitals
- Sputum or ETA cultured and RT-PCR
- Findings:
  - ID of pathogen 87% (39% by culture)
    - S. pneumoniae 36%; Atypical 4.3%
    - 30% viruses (Rhinovirus 12.7%)
  - Molecular testing had the potential to de-escalation antimicrobials in 77% of patients.

Clin Infect Dis. 2016; 62: 817-23

Clinical Impact: molecular tests

- Oosterheert et al. (Clin Infect Dis 2005)
  - Open RCT to evaluate impact of PCR for detection of respiratory viruses and atypical pathogens
  - Randomized to intervention group (based on PCR results) or control (PCR obtained but not reported).
    - PCR increased diagnostic yield from 21% to 43% (mostly viruses)
    - Decrease of ABX by 11%
      - "no way to exclude bacterial co-infection"
      - Not a standardized algorithm for treatment based on PCR results

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Clinical Impact: Procalcitonin

- Peptide precussor of calcitonin; released by parenchymal cells in response to bacterial-specific mediators (i.e., interleukin [IL]-1b, tumor necrosis factor-a, and IL-6)
  - Up-regulated in bacterial infection
  - Down-regulated in viral infection
  - Differentiates between bacterial and viral infection
  - Advantage: Rapid response to infection (up or down)
    - Repeat at 12-24 hrs if low initially
  - Studies (reviewed in File T. Clin Chest Med. 2011; Gilbert D. Clin Infect Dis. 2011: 52: (Suppl 4))
    - Reduce use of ABX
    - Reduce duration of ABX
- Assist in the discontinuation of empiric antibiotics
  - Stewardship, Sepsis and ATS/IDSA HAP/VAP guidelines

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Use of Procalcitonin for Antimicrobial Stewardship for RTIs

PCT < 0.1 ug/ml	Bacterial Infection VERY UNLIKELY	NO ANTIMICROBIALS	Consider repeat 6-24hrs based on clinical status
PCT 0.1-0.25 ug/ml	Bacterial infection UNLIKELY	NO ANTIMICROBIALS	Use of ABX based on clinical status ('unstable') & judgment
PCT > 0.25-0.5 ug/ml	Bacterial infection LIKELY	YES ANTIMICROBIALS	Repeat PCT day 3, 5, 7 (for Duration)
PCT > 0.5 ug/ml	Bacterial infection VERY LIKELY	YES ANTIMICROBIALS	CONSIDER STOP ABX when 80=90% decrease; if PCT remains high consider treatment failure

File TM Jr. Clin Cherst Med. 2011; modified from Schuetz P. et al. Eur Respir J 2011;37(2): 384–92.

Effect of Introducing Procalcitonin on Antimicrobial Therapy Duration in Patients With Sepsis and/or Pneumonia in the Intensive Care Unit

Annals of Pharmacotherapy
1–7

DOI: 10.1177/1060028014520957
aop.sagepub.com
SAGE

Bryan M. Bishop, PharmD[1], John J. Bon, PharmD[1], Tamara L. Trienski, PharmD[1], Timothy R. Pasquale, PharmD[1], Bradley R. Martin, MD[1], and Thomas M. File Jr, MD[1]

- Observational, historical control to assess impact of PCT in ICU; Education of staff prior to introduction
- 50 patients with PCT at initial suspicion of infection and 48 hrs
  - 50 Control pts--same time frame, diagnosis, gendr, age, APACHE II
- Active ASP in place
- Findings:
  - Duration of ABX decreased by 3.3 days (p=0.0238)
  - Duration in hospital decreased by 4.3 days (p=0.029)
  - Readmission to hospital decreased by 16% (p=0.055)
  - Mortality 2% vs 4% (p=0.5)

The clinical impact of the detection of potential etiologic pathogens of community-acquired pneumonia

Gita Gelfer, James Leggett, Jillian Myers, Luan Wang, David N. Gilbert *

Providence Portland Medical Center, Portland, OR, USA

- Studies (Jan-March 2014)
  - Standard: Blood cult; sput culture; urine AG *L. pneumophila, S. pneumoniae;* nasal for *S. pneumoniae* (in house); *S aureus*
  - FilmArray multiplex respiratory panel; alternate weeks
  - Procalcitonin-all
- Pts with all elements: 28 patients-standard tests; 31 patients- FilmArray
- Findings:
  - **ID of pathogen (proven or presumptive) 78%**
    - **Virus only 30.5%**
    - **Bacterial only 25.5%**
    - **Co-infections 22%**
  - **FilmArray results < 2 hours**
  - **Fewer days of antibiotic therapy, P=0.003, in CAP patients with viral infections and a low serum PCT levels, only 4/18 stopped within 48h**

"Value of rapid diagnostics will only be realized with realtime communication between a member of an antibiotic stewardship team and the treating physicians"

Diagn Microbiol Infect Dis. 2015; 83: 400-6

Effect of rapid molecular diagnostic testing and antimicrobial stewardship on antimicrobial therapy of respiratory infections

File TM Jr, Politis P, Tan M, Kallstrom G. Summa Health, Akron, OH.

Table 1. Effect on duration of antimicrobial therapy (ABX) and hospital length of stay (LOS):

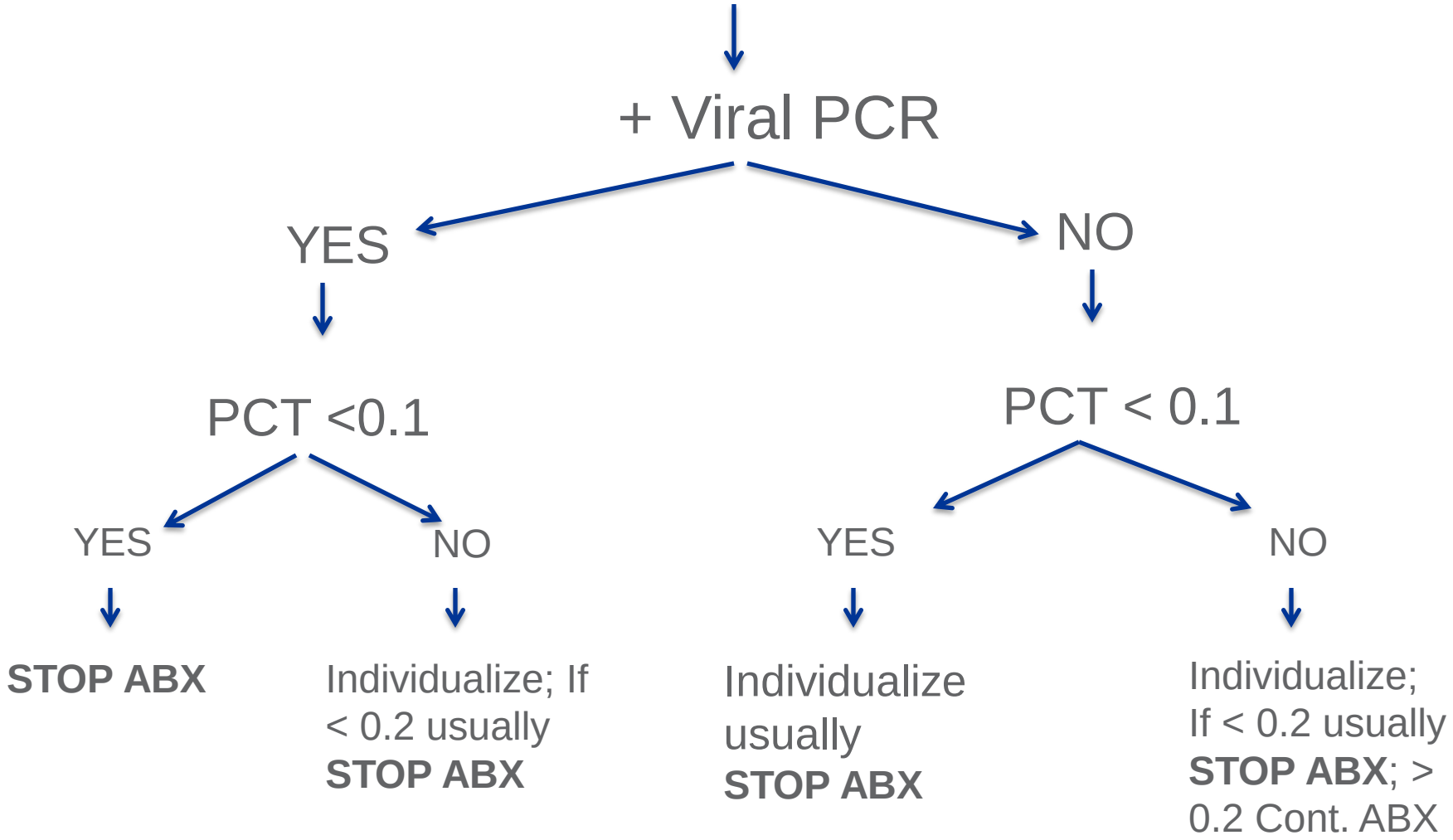
Resp panel result for virus	Mean duration ABX after test result (days)	LOS after test result (days)
Virus + (n=30)	1.6	3.6
Virus – (n=51)	4	4.9
Virus +; PCT < .25 (n=17)	1.2	2.9
Virus +; PCT <.25; AST* (n=10)	0.6	2.7

*AST recommendation. There was no difference in 30-day readmission rates for all groups

- Virus positive without + bacteria identified: median PCT 0.12 (<0.10-0.14); mean duration ABX 2.8 days
- Virus positive with + bacterial culture: median PCT 0.62 (0.1-47); mean duration ABX 6 days

CAP

(empiric ABX; consider epidemiology, host factors; early data: Gram stain, Urinary Antigens)



SUMMA Stewardship

CAP admitted to hospital

61 y/o female; history COPD

Smoker; History-lymphoma

Admitted April 24, 2 days increased dyspnea, NP cough

WBC 4,700; CXR-Bilat infilt

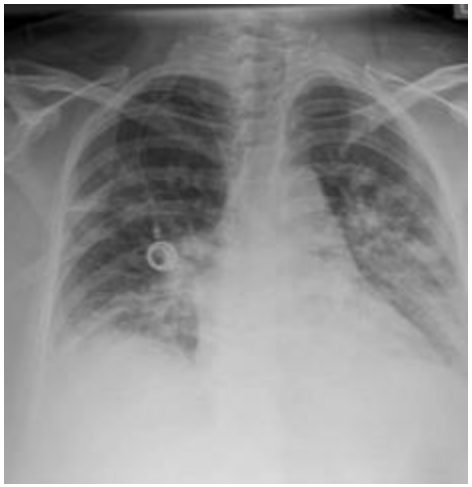
Influenza/RSV PCR neg; PCT <0.10

TX: levofloxacin

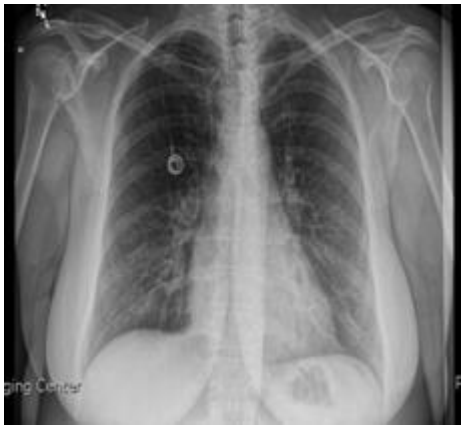
ASP recommended test

- Multiplex Resp Panel + Human Metapneumovirus
- Intervention- STOP ABX (0nly one dose); discharged without ABX

4/24/2017



5/15/2017



Test, Target, Treat: Basis of Antimicrobial Stewardship

- "The primary goal of antimicrobial stewardship is to **optimize clinical outcomes** while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*), and the emergence of resistance…..Effective programs can be financially self-supporting and improve care."*
- Strategies of Stewardship
  - Avoid unnecessary or discordant antimicrobial(s)
  - Pathogen-directed therapy
  - DE-ESCALATE (Switch IV to oral)
  - RIGHT DRUG, RIGHT DOSE, RIGHT DURATION
- **NEED ID of pathogen for optimal therapy**

*Dellit T et al. *Clin Infect Dis.* 2007;44:159-77

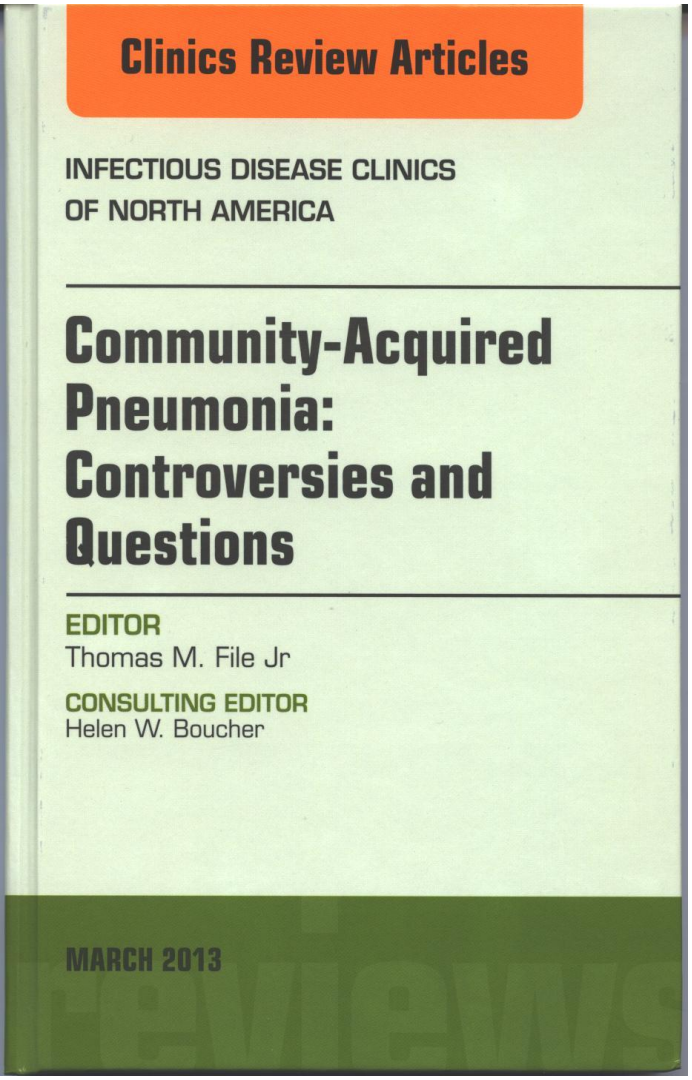
Summa Health

Test, Target, Treat: Basis of Antimicrobial Stewardship

Patient with acute cough and fever; infiltrates on CXR

	Cultures	Urinary AG	PCR	PCT	Target
1	No pathogen	S pn +; Leg -	No pathogen	4	pneumococcus
2	No pathogen	S pn -; Leg -	+ RSV	<0.1; <0.1	RSV
3	No pathogen	S pn -; Leg +	Leg +	2	Legionnella
4	No pathogen	S pn - ; Leg -	No pathogen	2; 0.5	Continue empiric Tx

Conclusions



- CAP is very common and serious
- Despite many advances, controversies and questions remain
- Newer tools are available for rapid pathogen detection
- More 'targeted' therapy is encouraged
  - Better outcomes possible
  - Reduce resistance , Adverse effects, Cost
- New guidelines are under development