Investigating respiratory illness in hospitalised adult patients

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Introduction

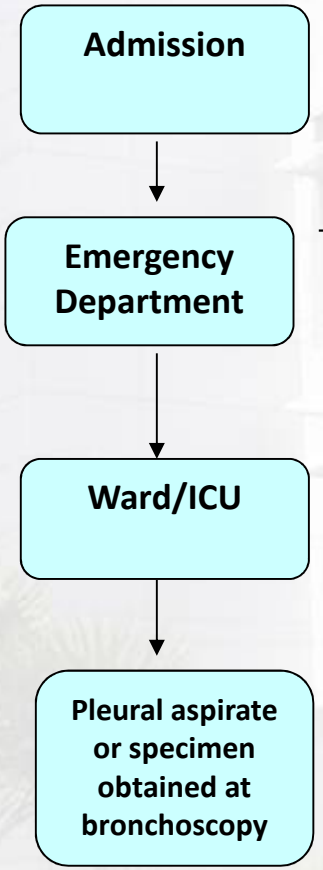
- Community-onset RT infection
  - Excluded hospital-onset infections and infections in immunocompromised hosts
- Likely pathogens
  - More than 20 commonly detected bacterial and viral causes of infection
- Why bother?
- Diagnostic approach
- Preferred specimens
  - “Making a silk purse out of a sow’s ear”
- Future directions

Why diagnose respiratory pathogens?

- Early diagnosis of the aetiological agents enables effective antimicrobial therapy
  - Antibiotics or antivirals
- Allows for the implementation of measures to prevent infection transmission
- Co-infections may cause more severe disease
- Important in immunocompromised patients
- Role in surveillance and vaccination strategies

Templeton K. Why diagnose respiratory viral pathogens? J Clin Virol 2007; 40 (Suppl 1): S2-4

Diagnostic approach

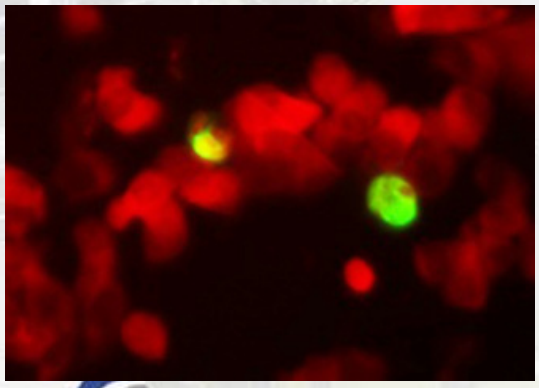


Diagnostic tests (based on clinical context)

- Blood cultures
- Sputum culture
- Legionella culture (not routine)
- Legionella UAT
- Pneumococcal UAT
- Serology
- Viral
  - -Influenza A/B Binax
  - -Immunofluorescence on NPA
  - - (+/- Respiratory viral PCR)
- Direct smear for AFB
- Mycobacterial culture

Rapid Diagnostic Tests

- Antibody-based
  - DFA or Indirect FA
    - Influenza vs multiple viruses
    - Sens 50 to 80% (culture)

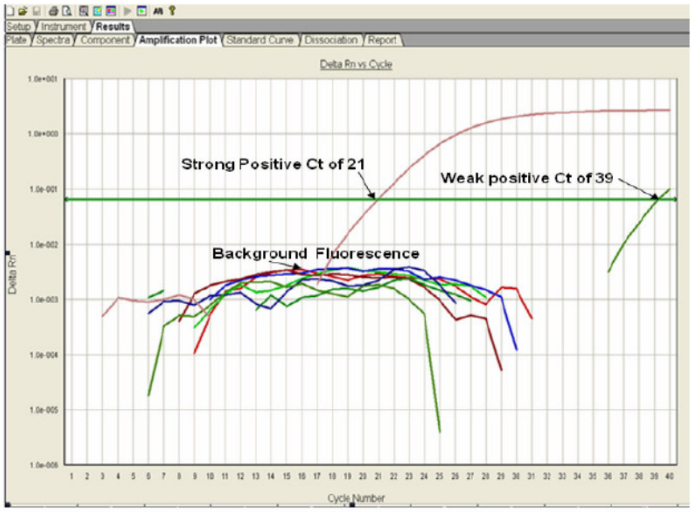


- Antigen-based
  - Binax *S. pneumoniae*
    - Sens 50-80%
    - Spp 90%
    - Carriage vs infection
  - *Legionella pneumophila* serogp 1 (Binax, SA Scientific, Biotest)
    - Sens 60-70% for Pontiac Fever subtype and up to 90% for sporadic cases
    - Spp 99 -99.9%
  - Influenza

Respiratory virus PCR

- Respiratory panel real-time PCR
  - Adenovirus
  - RSV A & B
  - PIF 1 – 3
  - hMPV
  - Rhinovirus
- Other respiratory viruses
  - Coronavirus 229, NL63, OC43
  - Human bocavirus
- Other viruses as clinically warranted

LightCycler 480



Preferred clinical specimens

- Expectorated sputum
  - Subject to oropharyngeal contamination
  - Influenced by prior antibiotic use
- More invasive methods
  - Transtracheal aspiration, transthoracic aspiration or bronchoscopy (BW or BAL)
- Nasopharyngeal swab or aspirate
  - Viral pathogens
  - Pathogen versus coloniser for bacteria?
  - Yield from sputum vs nose or throat swabs (Falsey JCM 2012 50 (1))

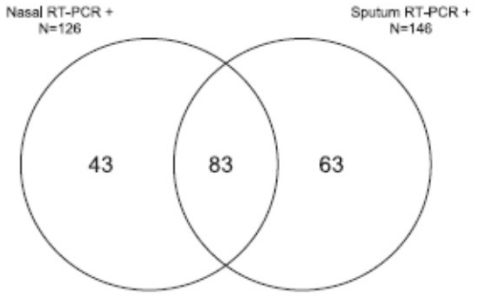


FIG 1 Distribution and overlap of positive diagnostic tests for viral infection diagnosis. Each section of the diagram indicates the number of distinct viral infection diagnoses that were positive for each of the viral assays (NTS RT-PCR and sputum RT-PCR).

	Bacteria	Viruses
Direct detection from clinical specimens: • Stained films • Antigen detection	Gram stain Urinary antigens	Direct fluorescent antibody stains Antigen detection on respiratory specimens
Culture	Blood cultures •30% for *S. pneumo* Respiratory secretions, LRT>URT	Respiratory secretions, URT>LRT (cell culture)
Serology	Atypical bacterial pathogens	Viral pathogens
Molecular methods	PCR	PCR-single target, matrix or multiplex PCR
Yield	Depends on pathogen and specimen	PCR>culture>DFA

Newer tests and aetiology

- With conventional methods <20% of cases of CAP have an aetiology determined
- Adding PCR for both bacterial and viral pathogens results in an increased yield ≈ 67%
  - *S. pneumoniae* leading cause
  - Mixed infections are common

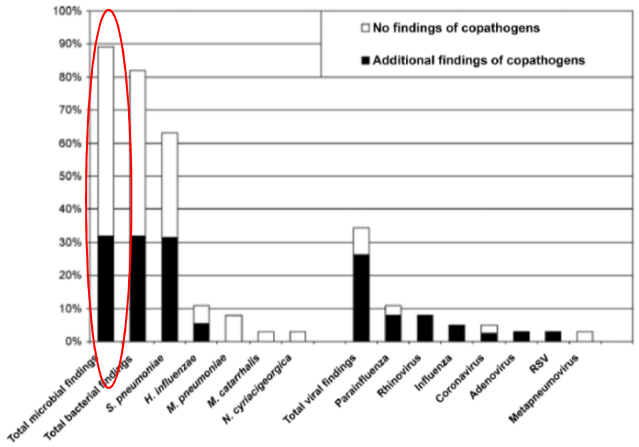


Figure 1. Percentage of patients with complete samples collected ($n = 38$) whose case of infection was etiologically determined and percentage of mixed infections. *H. influenzae, Haemophilus influenzae; M. catarrhalis, Moraxella catarrhalis; M. pneumoniae, Mycoplasma pneumoniae; N. cyriacigeorgica, Nocardia cyriacigeorgica;* RSV, respiratory syncytial virus; *S. pneumoniae, Streptococcus pneumoniae.*

Johansson CID 2010;50: 202-9

Emerging Technologies

- Multiplex PCR
  - Can detect or quantify multiply respiratory pathogens in a single test

Table 1. Summary of Emerging Multiplex Technologies for the Diagnosis of Respiratory Pathogens[a]

	Test System					
Characteristic	RespPlex	Infiniti	Jaguar	FilmArray	STAR	PLEX-ID
Pathogens detected	Viruses and bacteria	Viruses	Viruses	Viruses and bacteria	Viruses	Viruses and bacteria
Degree of multiplexity, no. of targets	>15	>15	2–6	>15	>15	>15
Complexity	High	High	Low	Low	High	High
Fully integrated system (all steps)	No	No	Yes	Yes	No	No
Testing location	Laboratory	Laboratory	Near-patient facility and/or laboratory	Near-patient facility and/or laboratory	Laboratory	Laboratory
Time required for result, h	5-6	6.5–10	1.5–2	1	5-6	6-8
Throughput	Moderate to high	Moderate to high	Moderate	Low	Moderate to high	Moderate to high
Carryover contamination risk	Moderate	Moderate	Low	Low	Low	Low
Quantification	No	No	No	No	Yes	No
Pathogen discovery	No	No	No	No	No	Yes

[a] These data reflect the state of technology as of October 2009; manufacturers may alter their test systems in the future.

Caliendo CID 2011:52 (Suppl4); S326-30

Emerging Technologies

- Potential for high-throughput or rapid POC testing
- Expensive
- Need to determine if cost –effective and improve patient outcomes

Conclusions

- Diagnostic testing has evolved over the last 10 years
  - Rapid POC
  - Newer multiplex PCR strategies
    - “in-house” and commercial platforms
  - Cost effectiveness and improvement in patient outcome is yet to be determined.