

# **Legionnaires' Disease: It's More Common Than You Think**

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# Objectives

Review the significance of legionellosis

Analyze the means by which legionellosis is spread

Identify the risk groups for legionellosis

Discuss the diagnostic options available for detecting *Legionella*

# General Biology

# Taxonomy

*Legionellaceae* have single genus of *Legionella*

Approximately 50 species

- Most common being *L. pneumophila* (more than 90% of disease), *L. micdadei*, *L. longbeachae*, and *L. dumoffi*

# Description

Gram negative rods

Motile

Mesophilic

Nutritionally fastidious

- Need L-cysteine and iron
- pH 6.7 to 6.9, low salt, . . .

Obligately aerobic

Natural host is amoebae

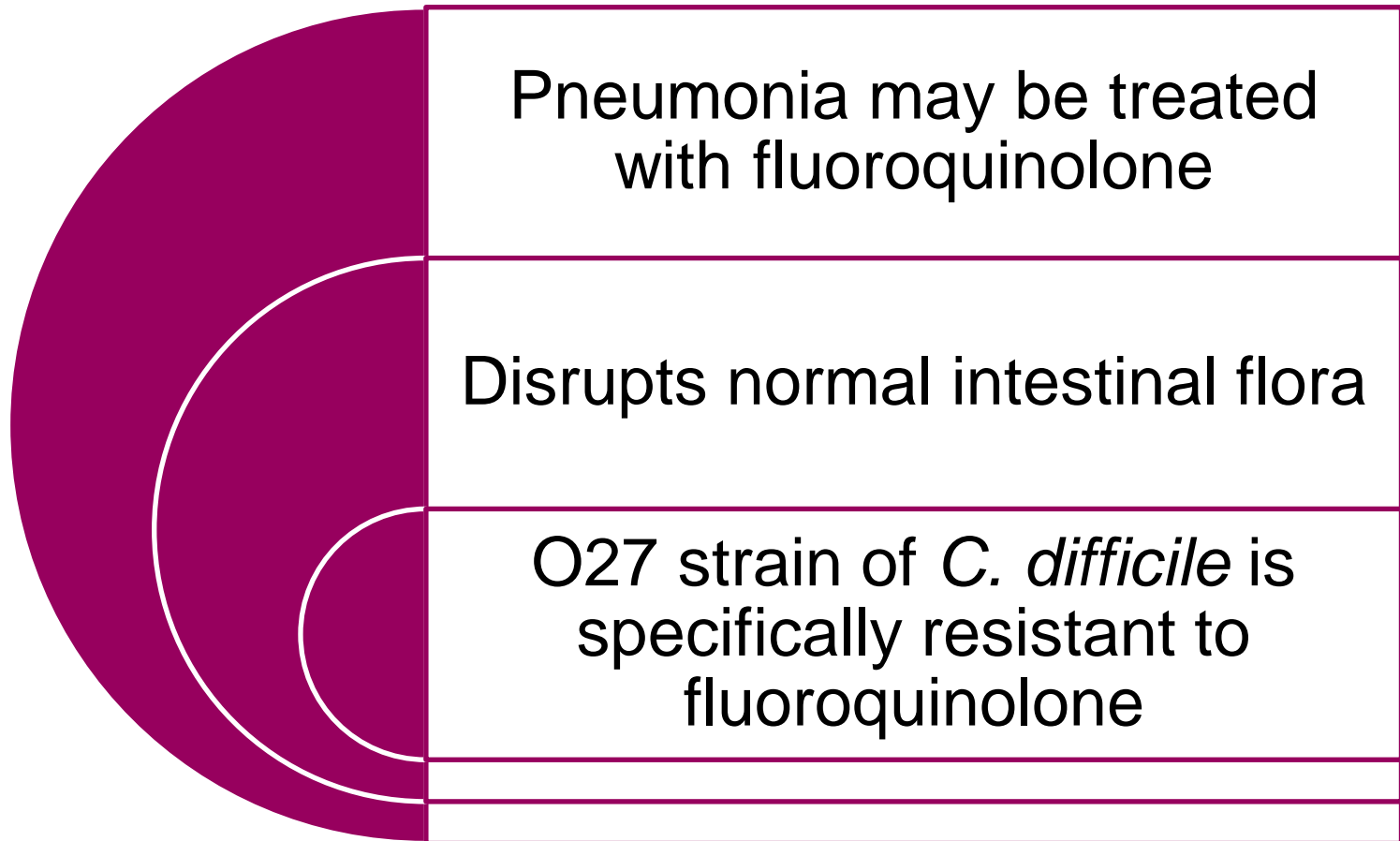
# ***L. pneumonia* Epidemiology**

# Infectious Disease in the US

1970: William Stewart, the Surgeon General of the United States declared the U.S. was “ready to close the book on infectious disease as a major health threat”; modern antibiotics, vaccination, and sanitation methods had done the job.

1995: Infectious disease had again become the third leading cause of death, and its incidence is still growing!

# Misuse of Antibiotics Can Lead to Other Medical Issues





# Diseases Caused by *Legionella*

## Legionnaires' Disease

- Early symptoms include malaise, nonproductive cough, muscle ache, and fever; other symptoms can include vomiting, diarrhea, and mental confusion; final condition is pneumonia
- 2-10 day incubation period

## Pontiac Fever

- Self-limiting 'flu-like illness' which generally clears within one week of onset (without antibiotics)
- 24-48 hour incubation period

# *Legionella* History

**In 1976, reports of illnesses in people who had attended an American Legion convention**

- **Out of 221 people who became ill, 34 persons died**

**Earlier outbreak in 1965 in Washington, D.C. in which 14 of 81 patients died**

# How big a problem is pneumonia?

**Pneumonia is the sixth leading cause of illness and the major cause of death due to infectious disease**

**Half of all pneumonias do not have their etiological agent identified**

# Current Number of Pneumonia Cases (US)

37 million ambulatory care visits per year for acute respiratory infections (physician and ER visits combined)

## Community-Acquired Pneumonia (CAP)

- Each year 2 - 3 million cases of CAP result in ~ 10 million physician visits & 500,000 hospitalizations in the US
- Average mortality is 10-25% in hospitalized patients with CAP

## Hospital-Acquired Pneumonia

- Standard definition: onset of symptoms occurs approx 3 days after admission
- 250,000 - 350,000 cases of nosocomial pneumonia per year
- 25 - 50% mortality rate

**Table 6. Most common etiologies of community-acquired pneumonia.**

Patient type	Etiology
Outpatient	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Haemophilus influenzae</i> <i>Chlamydia pneumoniae</i> Respiratory viruses <sup>a</sup>
Inpatient (non-ICU)	<i>S. pneumoniae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i> <i>H. influenzae</i> <i>Legionella</i> species Aspiration Respiratory viruses <sup>a</sup>
Inpatient (ICU)	<i>S. pneumoniae</i> <i>Staphylococcus aureus</i> <i>Legionella</i> species Gram-negative bacilli <i>H. influenzae</i>

**NOTE.** Based on collective data from recent studies [171]. ICU, intensive care unit.

<sup>a</sup> Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

# How is *Legionella* Transmitted?

**Not by person-to-person contact**

**Aeration of contaminated water droplets**

**Possible by inoculation of surgical wounds with contaminated water**

# Who is at risk for Legionnaires' Disease?

**Smokers, men, diabetics, immunodepressed persons, cancer and AIDS patients, alcoholics, and individuals suffering from end-stage renal disease or an additional pulmonary ailment**

# **Why is more not known about Legionnaires' Disease?**

**Difficult to diagnose - culture may take up to 3 to 10 days**

**10 - 30% of people have nonproductive cough**

**15 - 30% of people have previously received antibiotic therapy**



# Incidence

**Responsible for 2-15% of hospitalized CAP cases in Europe and North America <sup>(1)</sup>**

**Accounts for 17,000 – 23,000 cases of CAP requiring hospitalization each year in the US according to a study published in 1994.<sup>(2)</sup> Some estimates of total cases have been as high as 100,000 per year in the US alone. <sup>(3)</sup>**

***Legionella* species have been shown to colonize 12-85% of hospital water systems <sup>(4)</sup> → contamination of water systems can lead to nosocomial pneumonia (high risk populations in hospitals, tertiary care facilities, etc.)**

# Mortality

**Mortality rates have gone down significantly since the 1980's**

**In 1982 the mortality rate in hospital-acquired cases was 46% and in CAP cases it was 26% (1985)<sup>(1)</sup>**

**In 1998 mortality rates were 14% and 10% in hospital-acquired and CAP cases respectively (CDC averages) <sup>(1)</sup>**

**Decrease due to several factors including use of the urinary antigen test and changes in treatment of hospitalized pneumonia patients <sup>(1)</sup>**

# ***L. pneumonia* – Water Transmission**

# Where has *Legionella* been found?

Homes (6%), cooling towers, spas and whirlpools, humidifiers, decorative fountains, vegetable misters, portable cooling units, faucets and showerheads, ice-making machines, sinks, eyewash stations, dental-unit systems, tub immersion, potting soil, garden soils, compost, intubation tubes, boilers, nebulizers, and windshield wiper fluid.

# Seek and ye shall find

## Study comparing head and neck surgery wards at two hospitals

- First had no reported cases of legionnaires' disease and second had just decontaminated water after 100 cases of nosocomial pneumonia
- First hospital had 30% of nosocomial pneumonias due to *Legionella* and second hospital had 0% (Johnson, 1985)

# Seek and ye shall find

**Three hospitals report no legionellosis**

**First hospital colonized with serogroup 1, second with serogroup 5, and third had no detectable levels**

**9% of nosocomial pneumonia patients in first hospital had legionnaires' disease while none in other two hospitals (Yu, 1987)**

# Outbreak Example

## Dutch flower show

- 188 cases with 133 confirmed and 55 probable
- 20 died giving a mortality rate of 11%
- Room had been kept at  $> 30^{\circ}\text{C}$  for 3 months prior to show

# Outbreak Example

## Melbourne aquarium

- 119 confirmed cases
- 107 occurred among 83,500 visitors (attack rate of 0.13%)
- 77% were hospitalized and 3.4% died



# VA Hospital in Pittsburgh

Outbreak occurred between February 2011 and November 2012

- At least 21 veterans sickened
- At least 5 died

Reported that water system not properly maintained

- Not enough disinfectant
- *Legionella* was found on site visits

# Prevalence in Whirlpool Spas

**458 samples analyzed from 45 different locations including 30 hotels and 15 cruise ships**

***Legionella* was isolated from 5.9% of samples ranging from <1 to 10,000 CFU/mL.**

# Cooling towers

**US - 51% in 1988 to 17% in 1991**

**South Africa, 1999 - 82% of systems contaminated**

**France, 1999 - 75% of systems contaminated**

# International Statistics

## Danish hot-water systems

- Evaluated potable water from 13 apartments, 14 schools, 7 nursing homes, 8 sports centers, 2 industries, and 2 other institutes.
- 41/46 samples were positive with samples ranging from 10 to  $4.9 \times 10^6$  CFU/ml
- Why? Because the water was at 50°C, not 60°C

# International Statistics

## Dental units in Poland

- **63 samples were collected**
- **16 samples positive (rate of 24.2%)**
- **Range was  $1 \times 10^3$  to  $7.2 \times 10^5$  CFU/ml.**

# International Statistics

## Potable water in Turkey

- 139 buildings tested
- 57 samples positive (rate of 41%)
- Range was from 6 to  $2.1 \times 10^4$  CFU/ml
- Concentrations blamed on warm summer weather and iron pipes

# International Case

**Humidifier in a hotel in Cardiff, UK was agent for 5 cases, two of whom died**

# Biofilm formation

**Biofilm may build up when water is cooler ( $<60^{\circ}\text{C}$ ) and stagnant**

***Legionella* can inhabit biofilms as well as be free-living**

***Legionella* can exist in amoebae and get nutrients from biofilm**



# Type of pipe matters!

**Copper doesn't really form biofilms well**

**Stainless steel can harbor *Legionella***

**PVC can form a significant amount of biofilm**

**Plain steel can hold the largest amount of biofilm**

# Suggested *Legionella* guidelines

## Centers for Disease Control

- If find Legionnaires' Disease, then monitor environment

ASHRAE

ISO 11731

# What Water Should be Tested?

**Cooling towers**

**Hot water heating tanks**

**Distal sites such as showerheads, faucets,  
decorative fountains and whirlpools**

**Waters coming into contact with  
immunocompromised persons**

**O-rings in faucets?**

# ***L. pneumonia* Detection Strategies**

# Why Test?

“Legionnaires’ disease has a false but enduring status as an exotic plague. In reality, this disease is a common form of severe pneumonia, but these infections are infrequently diagnosed. Failure to diagnose Legionnaires’ disease is largely due to a lack of clinical awareness. In addition, legionellae, the bacteria that cause this disease, are fastidious and not easily detected.”

No chest X-ray pattern can differentiate this from other pneumonias

- Barry Fields, Robert Benson, and Richard Besser. “*Legionella* and Legionnaires’ Disease: 25 Years of Investigation.” *Clinical Microbiology Reviews*, July 2002; 15: 506-526

# Who to Test?

Patients who have failed outpatient antibiotic therapy

Patients with severe pneumonia, in particular those requiring intensive care

Patients with pneumonia in the setting of a legionellosis outbreak

Patients with a travel history

- Patients that have traveled from home within 2 weeks before the onset of illness

Patients suspected of healthcare-associated pneumonia

# Pediatric Legionellosis

## Review of literature showed 76 cases

- 51.5% were under the age of 2
- 33% mortality rate – higher in immunocompromised children and those under 1 year of age
- 78% had underlying condition
- 46% were community-acquired
- 88% of healthcare-associated had environmental link to contaminated potable water
- 56% of diagnosis made by culture

# Military Recruits

Military recruits highly susceptible to respiratory pathogens during basic training

- Adenovirus, *Mycoplasma pneumoniae*, influenza, etc.

Cluster of 5 recruits seen with *Legionella* from PCR of oropharyngeal swab at Marine Corps Recruit Depot, San Diego

- Occurred in 2007
- All 5 lived together



# Traditional Diagnostic Test Methods

Sputum culture

Direct Fluorescent Antibody (DFA)

Paired serology

PCR

Urinary antigen

- ELISA
- Rapid
  - Note: Blood culture and Gram stain not done for *Legionella* specific testing

# Sample Collection

For culture, expectorated sputum and lower respiratory samples most common

May forgo microscopic qualification of sputum due to limited purulence and minimal/no secretions

- “Up to 80% of specimens culture positive for *Legionella* spp. may be rejected when using the criterion of the presence of sputum purulence for processing specimens”
  - Manual of Clinical Microbiology 9<sup>th</sup> Edition

# Sputum Culture: The “Gold Standard”

**Bacterial culture → Sputum is plated on a specialized media called BCYE (buffered charcoal yeast extract agar). Sample must be pre-treated.**

- Previous antibiotic treatment may affect results

**Typical required incubation period is 4 - 10 days (in very rare cases identifiable growth occurs in 3 days).**

**Specimens used for culture include expectorated sputum, tracheal aspirates, bronchial washes, pleural fluid, lung tissue (necropsy)**

**In one study, only 32% of people could identify a pure culture of *Legionella***

- Edelstein, PH. 1993. Legionnaires' disease. Clin. Infect. Dis. 16: 741-749.

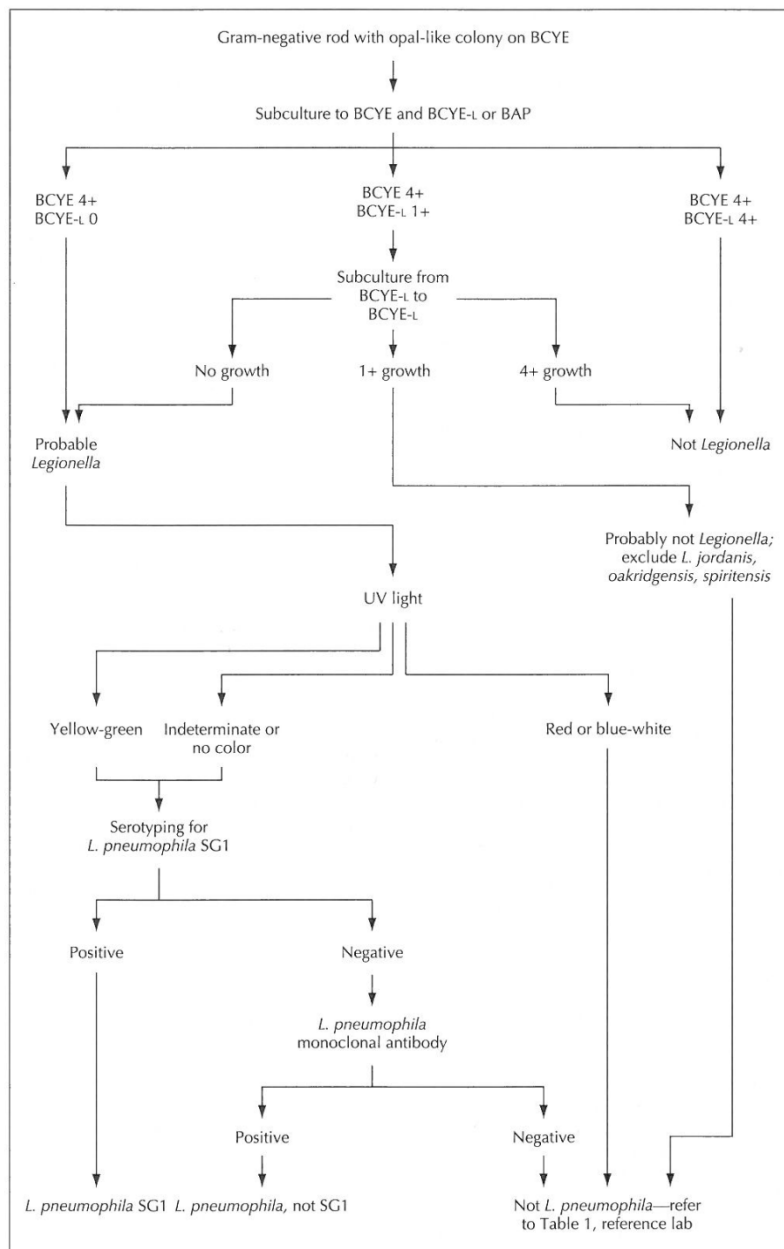


FIGURE 3 Flow scheme for basic identification of *Legionella* spp. grown from a BCYE $\alpha$  plate. Abbreviations: BCYE, BCYE $\alpha$ ; BCYE-L, BCYE $\alpha$  made without L-cysteine; BAP, tryptic soy blood agar; UV light, colony fluorescence and color when illuminated with long-wave (360-nm) UV light. Numbers refer to the amount of growth: 4+, good growth; 1+, poor growth; 0, no growth.

# Serological Tests

## Most patients produce IgG and IgM

- Some produce only IgG, IgM, or IgA
- IgM may last for a year
- In outbreak situations, most patients seroconvert, but only 75% was seen in standard hospital-acquired infections

## Seroconversion takes weeks to months

- Only 50% convert after 2 weeks
- Optimal sensitivity is to collect at weeks 2, 4, 6, 9, and 12

# Direct Fluorescent Assay

Labor intensive

Can pick up multiple serotypes

- Cross-reaction seen when trying to differentiate between serotypes

Poor sensitivity with average around 50% (25% to 75% range)

# Molecular Methodologies

## BD ProbeTec ET *Legionella pneumophila* (LP) Amplified DNA Assay

- Detects *Legionella pneumophila* serogroups 1-14 in sputum
- Retrospective performance vs. culture
  - 91.3% positive agreement
  - 86.7% negative agreement
  - 88% overall agreement

# Urinary Antigen

Carbohydrate gets into urine 1 to 3 days after the onset of symptoms

- Urine is easy to obtain

Available in ELISA and rapid test format

- 95% sensitivity on archived samples with rapid test

Detects serogroup 1 only



# ***L. pneumonia* Guideline Recommendations**

# **Infectious Disease Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**

## **Diagnostic Testing**

- Suggestive clinical features combined with a chest radiograph or other imaging technique is required for the diagnosis of pneumonia
- It is recommended that “patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues.”

# Infectious Disease Society of America/American Thoracic Society CAP Guidelines 2007

## When to apply diagnostic tests

- Optional for outpatients with CAP
- Blood culture and sputum culture for inpatients with productive cough\*
- All adult patients with severe CAP, should have blood culture, sputum culture, *Legionella* urinary antigen and *S. pneumoniae* urinary antigen tests\*
- \*See following chart of conditions

**Table 5. Clinical indications for more extensive diagnostic testing.**

Indication	Blood culture	Sputum culture	<i>Legionella</i> UAT	Pneumococcal UAT	Other
Intensive care unit admission	X	X	X	X	X <sup>a</sup>
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X <sup>b</sup>
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia (anatomic or functional)	X			X	
Recent travel (within past 2 weeks)			X		X <sup>c</sup>
Positive <i>Legionella</i> UAT result		X <sup>d</sup>	NA		
Positive pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X <sup>a</sup>

**NOTE.** NA, not applicable; UAT, urinary antigen test.

<sup>a</sup> Endotracheal aspirate if intubated, possibly bronchoscopy or nonbronchoscopic bronchoalveolar lavage.

<sup>b</sup> Fungal and tuberculosis cultures.

<sup>c</sup> See table 6 for details.

<sup>d</sup> Special media for *Legionella*.

\* Thoracentesis and pleural fluid cultures.

# **IDSA Practice Guidelines for CAP: *Legionella* Urinary Antigen**

**“Preferred diagnostic tests are the urinary antigen assay and culture of respiratory secretions on selective media...**

**The urinary antigen assay for *Legionella pneumophila* serogroup 1 is not technically demanding and reliably and rapidly detects up to 80-95% of community-acquired cases of legionnaires' disease...”**

**Lionel Mandell, et.al. “Update of Practice Guidelines for the Management of Community-Acquired Pneumonia in Immunocompetent Adults,” Clinical Infectious Diseases, 2003;37:1405-33**

# Testing only Severe Pneumonia

Study done in single-center site by culture and/or urinary antigen

Diagnostic testing for *Legionella* was normally tested in less than half of pneumonia cases

If testing only cases under IDSA guidelines, 41% of cases would have been missed.

# British Thoracic Society Guidelines

## Low severity

- Home
  - None routinely
  - PCR, urine antigen or serological investigations may be considered during outbreaks
- Hospital
  - None routinely
  - PCR, urine antigen or serological investigations during outbreaks

# British Thoracic Society Guidelines

## Moderate severity – Hospital

- Blood cultures
- Sputum for routine culture and sensitivity for those not received prior antibiotics
- Pleural fluid, if present, for microscopy, culture, and pneumococcal antigen
- PCR or serology may be considered for Mycoplasma or viral pathogens
- When Legionella is suspected, use a urinary antigen test and a sputum or other respiratory sample for DFA or culture



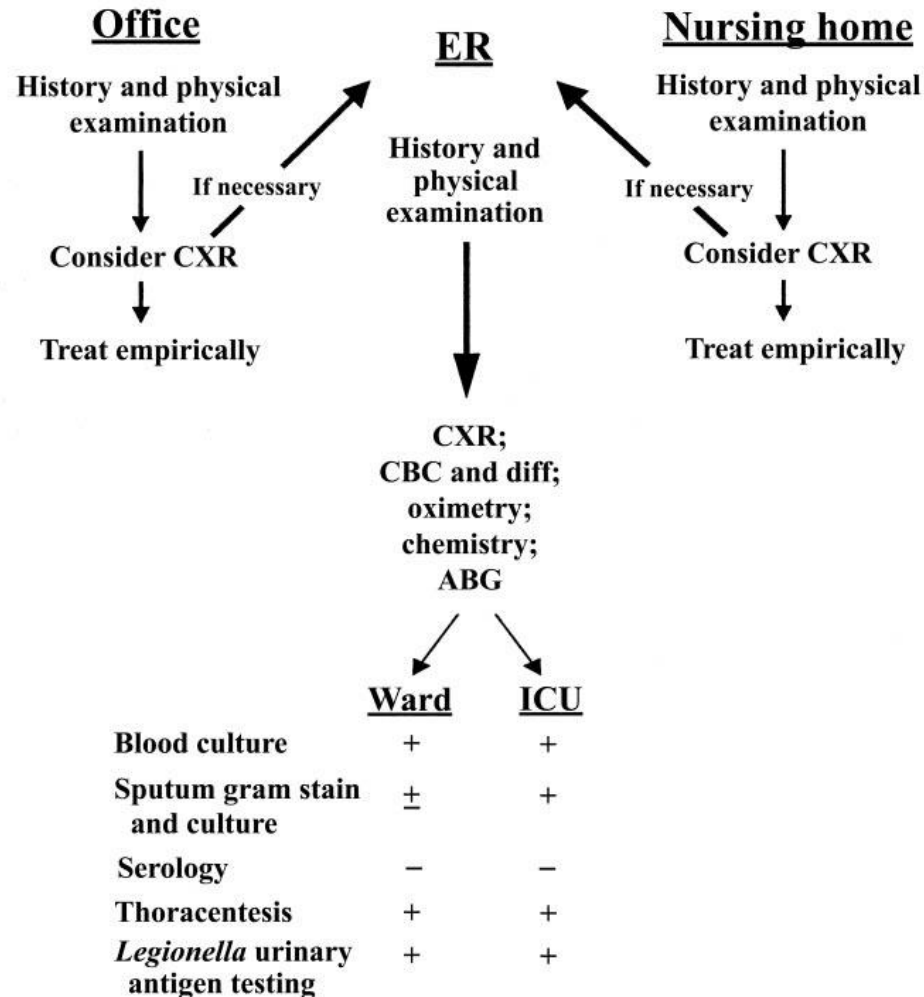
# British Thoracic Society Guidelines

High  
severity  
—  
Hospital

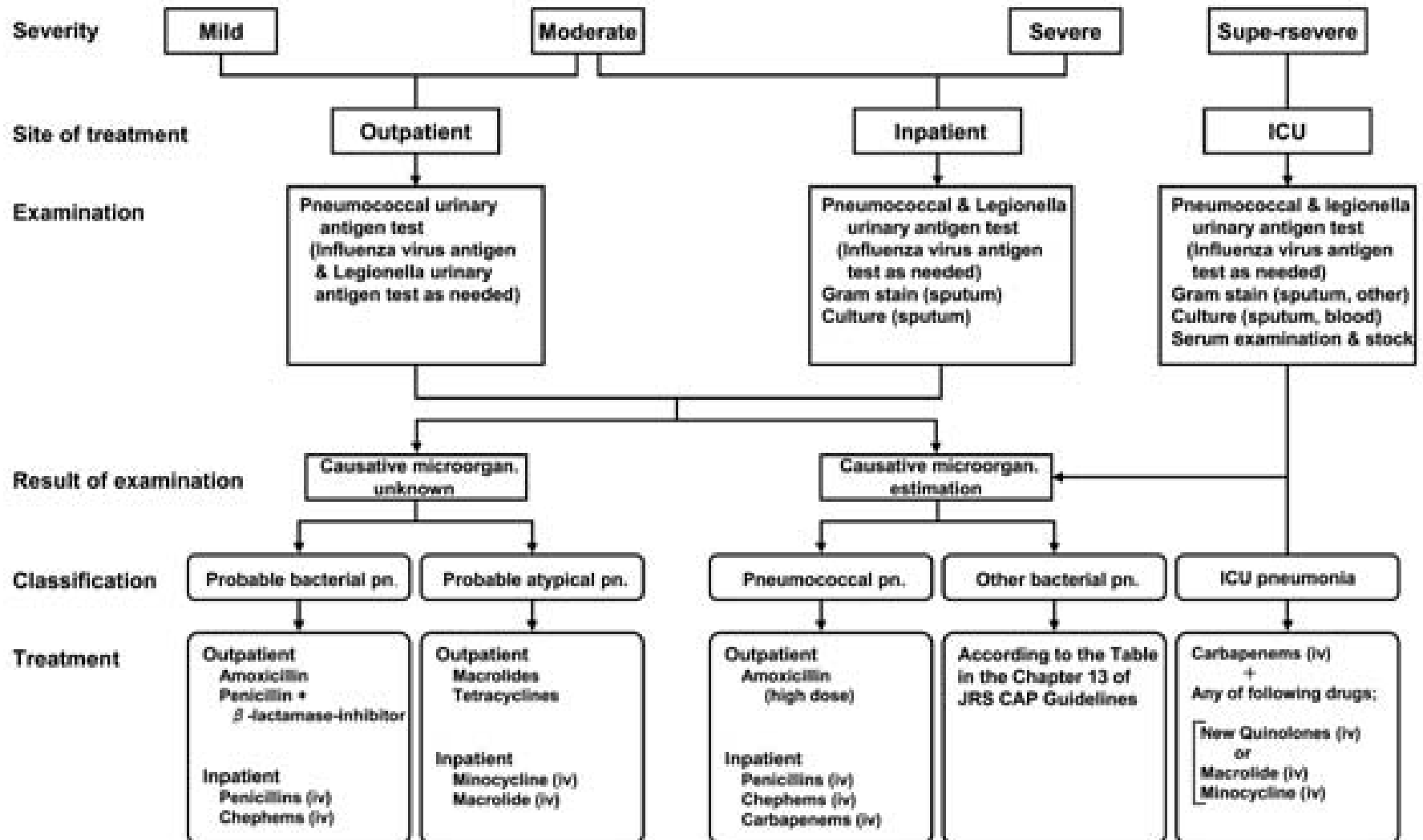
- Blood cultures
- Sputum or other respiratory sample for culture
- Pleural fluid, if present, for microscopy, culture and pneumococcal antigen
- Pneumococcal urine antigen test
- Investigations for Legionella need urinary antigen test and sputum or other respiratory sample for culture or DFA
- For atypical and viral pathogens can use PCR

# Canadian Infectious Disease Society & Thoracic Society

## Diagnostic algorithm for CAP



# Japanese Guidelines



# France

Hospitalized  
- not in  
intensive  
care

- Blood culture & sputum culture
- Urinary antigen tests not recommended immediately
- If patients have symptoms suggestive of Legionnaire's disease, presenting haemodynamic instability and/or hypoxia, or in epidemic setting of CAP

Hospitalized  
– intensive  
care

- Blood culture
- Culture of tracheobronchial secretions taken during intubation
- *Legionella* and pneumococcus urinary antigen tests

# Dutch Association of Chest Physicians

Blood and sputum culture prior to initiation of antibiotics

Legionella urinary antigen testing in case of severe pneumonia

Pneumococcal urinary antigen can be considered

## Brazilian Guidelines

Blood culture, sputum culture, tracheal aspirate culture recommended on all severe CAP as well as urinary antigen tests for *S. pneumoniae* and *Legionella*

- *Legionella* specifically on all who don't respond to initial therapy

**Questions?**