U.S. FOOD & DRUG ADMINISTRATION

Clinical Considerations for Procalcitonin-Guided Evaluation and Management of Lower Respiratory Tract Infections and Sepsis

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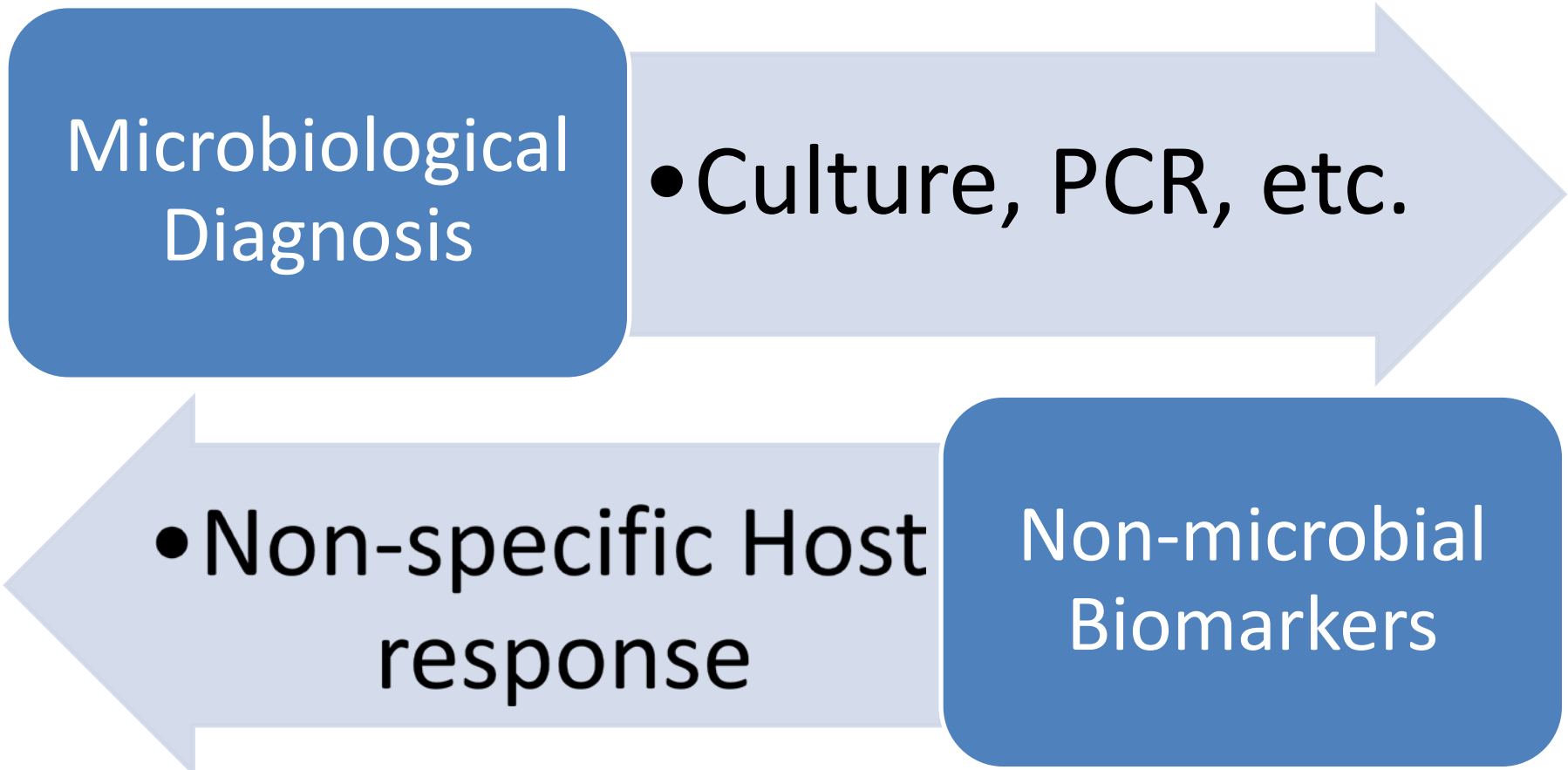
Original Indications for Use

- To aid in the **risk assessment** of critically ill patients on their first day of ICU admission for **progression to severe sepsis and septic shock**
- To aid in assessing the **cumulative 28-day risk of all-cause mortality** for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission

Proposed Indications for Use

- To aid in decision making for **antibiotic therapy** for inpatients or outpatients, with suspected or confirmed **lower respiratory tract infections** (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)
- To aid in decision making for **antibiotic discontinuation** for patients with suspected or confirmed **sepsis**

Diagnostic Approaches

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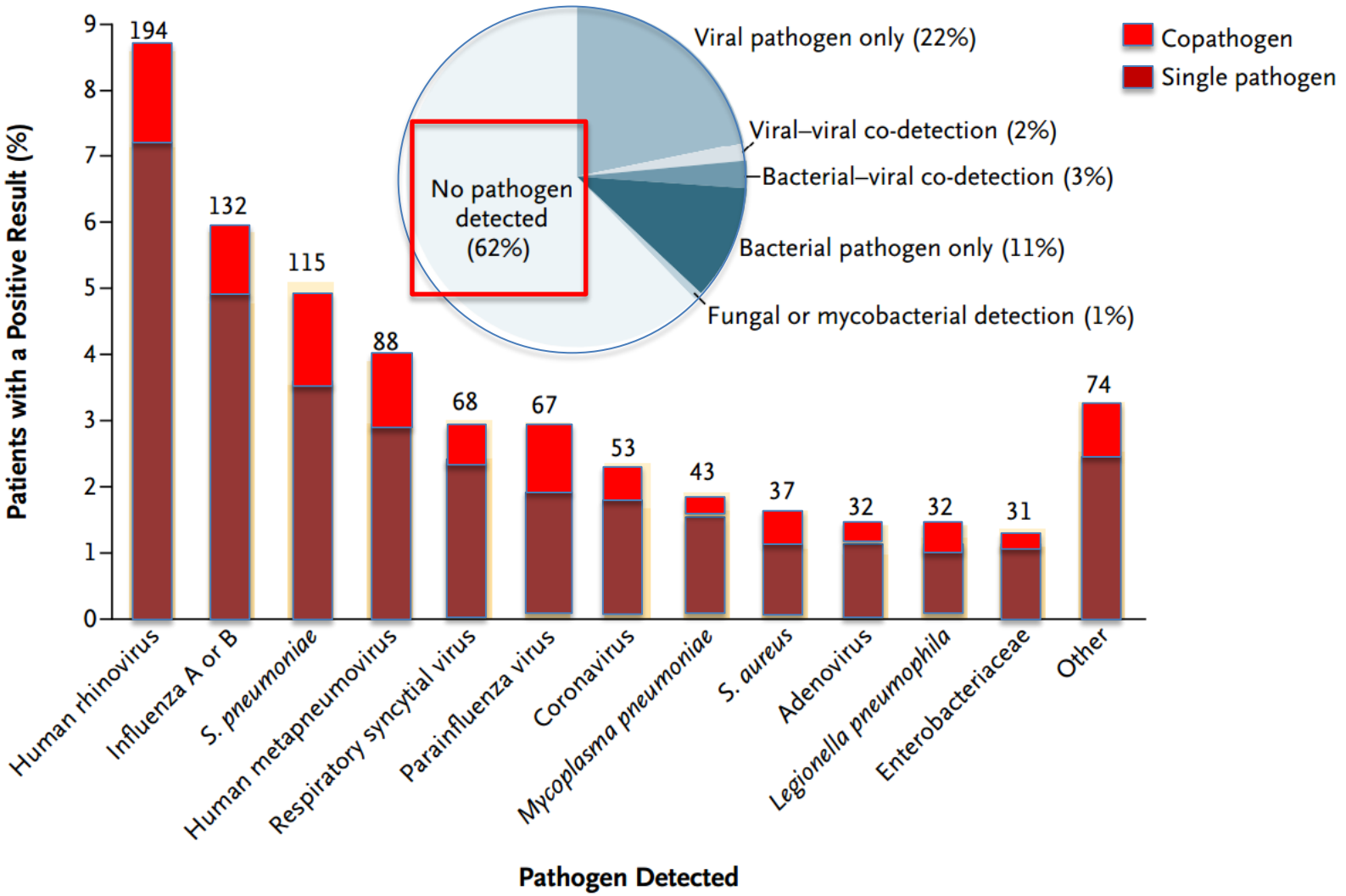
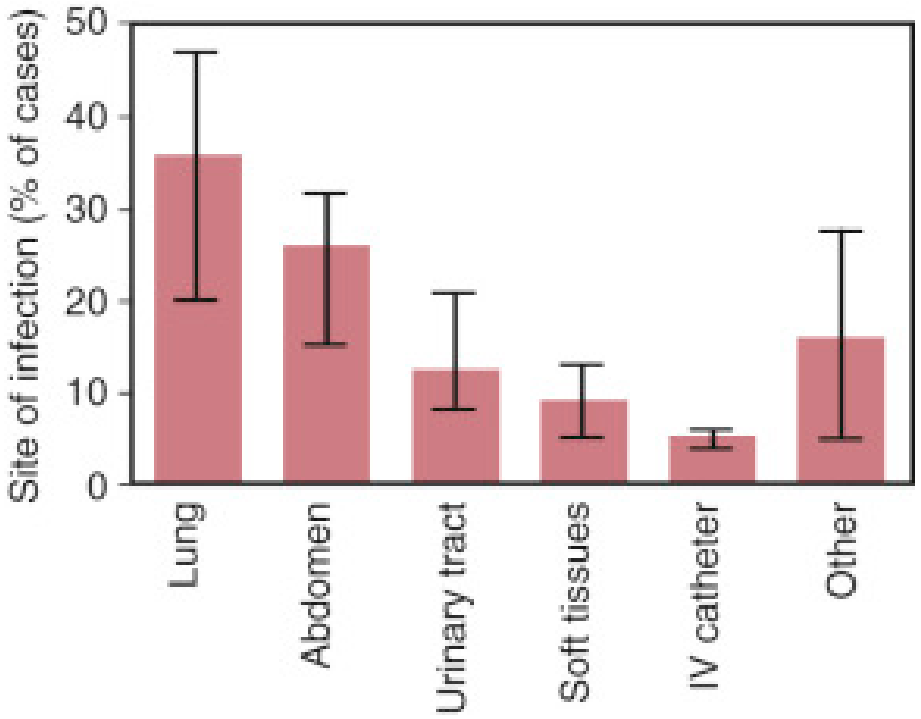
CDC EPIC Study



(Jain, Self et al. 2015)

Presumed sites of infection in patients with culture-positive severe sepsis.



Munford, Robert S.; Suffredini, Anthony F. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Updated Edition. Published January 1, 2015.

Microbiological Assays

- A retrospective analysis of antibiotic use among adults admitted with acute respiratory symptoms who subsequently received a diagnosis of viral RTI
- 196 subjects enrolled with or influenza A/B, adenovirus, RSV or parainfluenza infection
  - 64% continued to receive antibiotics after viral diagnosis for a median of 8 days
  - 63% had normal CXRs
  - 6% developed *C. difficile* diarrhea
  - Antibiotic use associated with increased length of stay, not powered for mortality/readmission

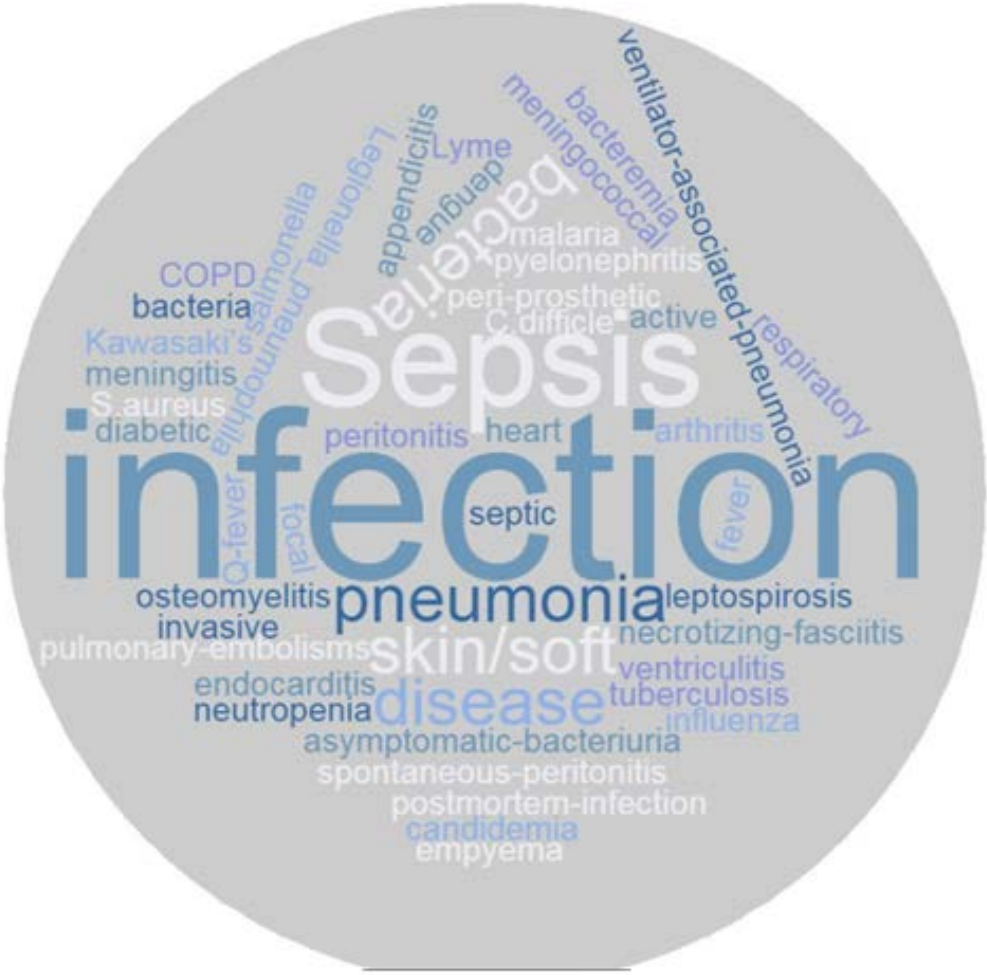
(Shiley, Lautenbach et al. 2010)

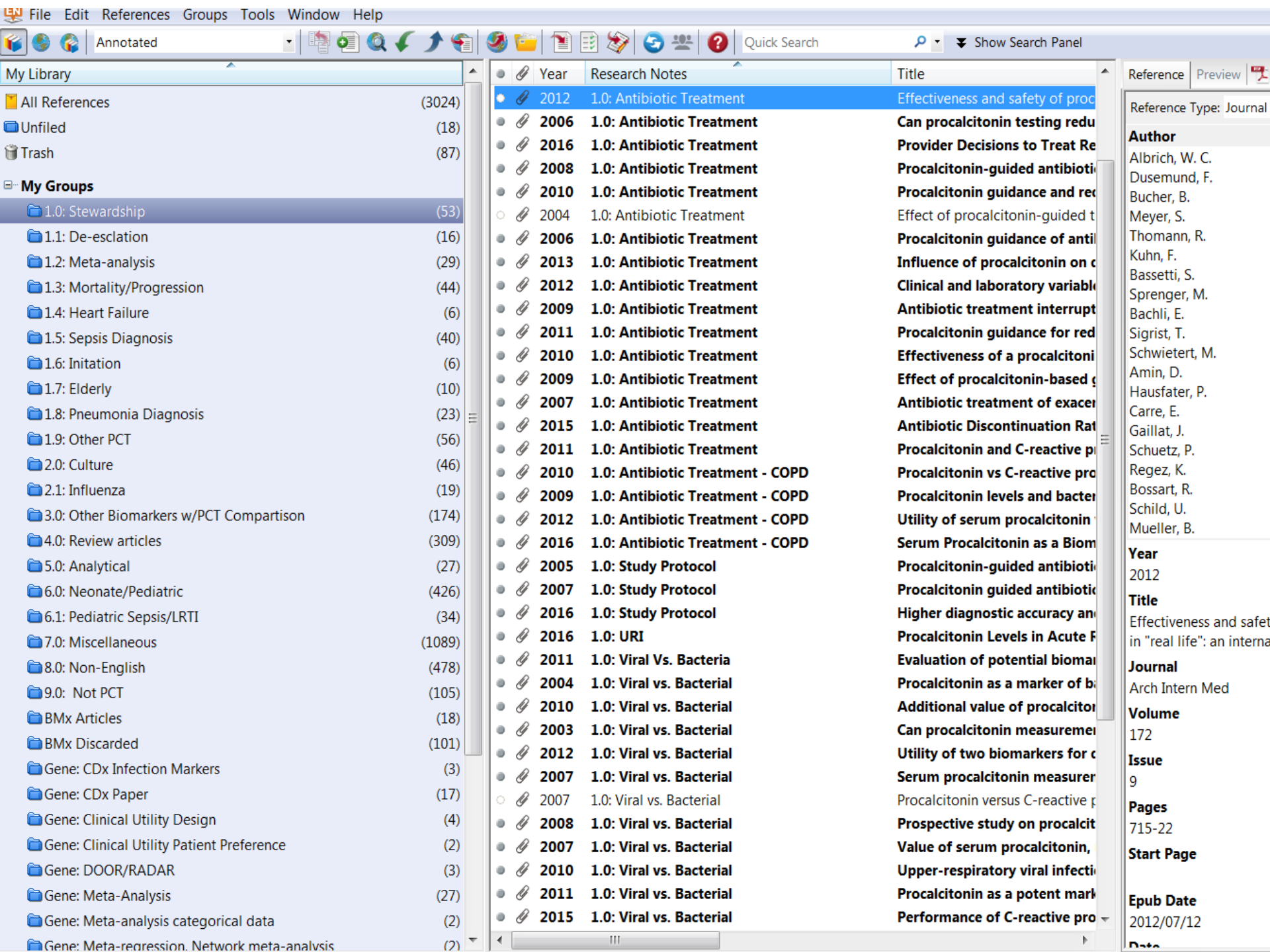
Non-microbial Biomarkers

- Not biologically tied to a specific microorganisms or family of microorganisms.
- Associated with the host response to infection.
- Hypothesized to distinguish between colonization, contamination and infection.
- Diagnostic accuracy variable with imperfect comparator method.

Procalcitonin Literature

- More than 3000 peer-reviewed articles involving procalcitonin published since 2004
  - >25 meta-analyses since 2009
  - >300 review articles
  - Many prospective randomized clinical trials

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1.0: Stewardship (53)
1.1: De-esclation (16)
1.2: Meta-analysis (29)
1.3: Mortality/Progression (44)
1.4: Heart Failure (6)
1.5: Sepsis Diagnosis (40)
1.6: Initation (6)
1.7: Elderly (10)
1.8: Pneumonia Diagnosis (23)
1.9: Other PCT (56)
2.0: Culture (46)
2.1: Influenza (19)
3.0: Other Biomarkers w/PCT Compartison (174)
4.0: Review articles (309)
5.0: Analytical (27)
6.0: Neonate/Pediatric (426)
6.1: Pediatric Sepsis/LRTI (34)
7.0: Miscellaneous (1089)
8.0: Non-English (478)
9.0: Not PCT (105)
BMx Articles (18)
BMx Discarded (101)
Gene: CDx Infection Markers (3)
Gene: CDx Paper (17)
Gene: Clinical Utility Design (4)
Gene: Clinical Utility Patient Preference (2)
Gene: DOOR/RADAR (3)
Gene: Meta-Analysis (27)
Gene: Meta-analysis categorical data (2)
Gene: Meta-regression, Network meta-analysis (2)
Year
Research Notes
Title
2012 1.0: Antibiotic Treatment Effectiveness and safety of proc
2006 1.0: Antibiotic Treatment Can procalcitonin testing redu
2016 1.0: Antibiotic Treatment Provider Decisions to Treat Re
2008 1.0: Antibiotic Treatment Procalcitonin-guided antibioti
2010 1.0: Antibiotic Treatment Procalcitonin guidance and red
2004 1.0: Antibiotic Treatment Effect of procalcitonin-guided t
2006 1.0: Antibiotic Treatment Procalcitonin guidance of anti
2013 1.0: Antibiotic Treatment Influence of procalcitonin on c
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2015 1.0: Antibiotic Treatment Antibiotic Discontinuation Rat
2011 1.0: Antibiotic Treatment Procalcitonin and C-reactive pr
2010 1.0: Antibiotic Treatment - COPD Procalcitonin vs C-reactive pro
2009 1.0: Antibiotic Treatment - COPD Procalcitonin levels and bacter
2012 1.0: Antibiotic Treatment - COPD Utility of serum procalcitonin
2016 1.0: Antibiotic Treatment - COPD Serum Procalcitonin as a Biom
2005 1.0: Study Protocol Procalcitonin-guided antibioti
2007 1.0: Study Protocol Procalcitonin guided antibiotic
2016 1.0: Study Protocol Higher diagnostic accuracy an
2016 1.0: URI Procalcitonin Levels in Acute F
2011 1.0: Viral Vs. Bacteria Evaluation of potential biomar
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2011 1.0: Viral vs. Bacterial Procalcitonin as a potent mark
2015 1.0: Viral vs. Bacterial Performance of C-reactive pro
Reference
Preview
Reference Type: Journal
Author
Albrich, W. C.
Dusemund, F.
Bucher, B.
Meyer, S.
Thomann, R.
Kuhn, F.
Bassetti, S.
Sprenger, M.
Bachli, E.
Sigrist, T.
Schwietert, M.
Amin, D.
Hausfater, P.
Carre, E.
Gaillat, J.
Schuetz, P.
Regez, K.
Bossart, R.
Schild, U.
Mueller, B.
Year
2012
Title
Effectiveness and safet
in "real life": an interna
Journal
Arch Intern Med
Volume
172
Issue
9
Pages
715-22
Start Page
Epub Date
2012/07/12

Current Recommendations for Procalcitonin

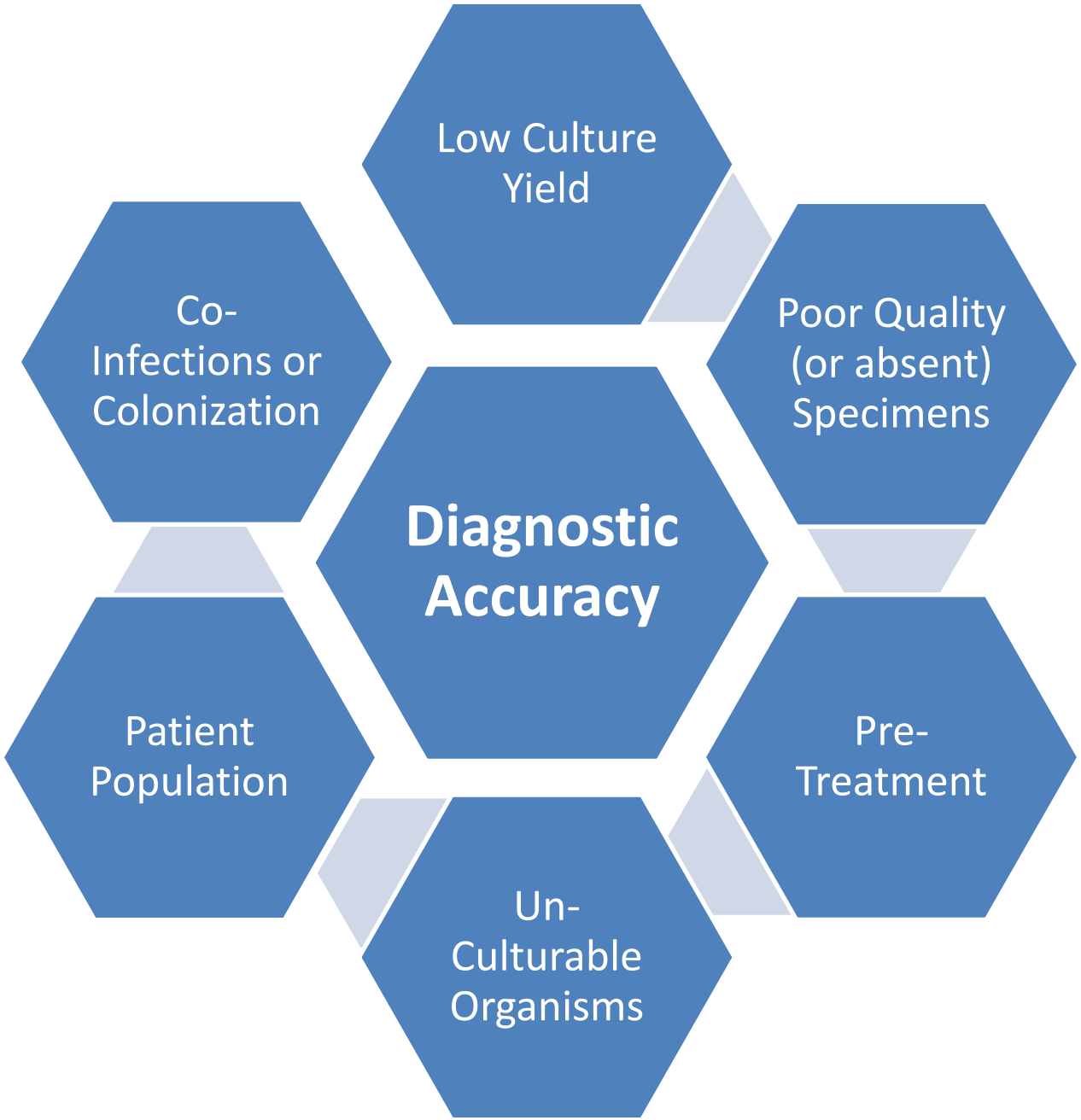
	LRTI Initiation	LRTI Discontinuation	Sepsis Discontinuation
AHRQ (2012)	Recommended (high quality evidence)	Recommended (high quality evidence)	Recommended (high quality evidence)
IDSA* (2013/2016)	Not recommended (moderate quality evidence)	Recommended (low quality evidence)	Recommended (weak quality evidence)
NICE (2014/2016)	Recommended (moderate quality evidence)	Recommended (moderate quality evidence)	Not recommended – More research needed

*IDSA: includes recommendations from Surviving Sepsis Campaign and SHEA . LRTI recommendations limited to HAP/VAP.

Limitations

- Generalizability of benefit
  - Existing stewardship programs
  - Facilities with low baseline duration of antibiotic treatment.
  - Limited US data
- Appropriate patient population
  - Patients with lingering diagnostic uncertainty
- Diagnostic Accuracy
  - Failure to meet a priori goals for sensitivity and/or specificity

Can we establish an accurate measurement of sensitivity/specificity for non-microbial biomarkers in the absence of an adequate comparator method?


Low Culture Yield
Co-Infections or Colonization
Poor Quality (or absent) Specimens
Diagnostic Accuracy
Patient Population
Pre-Treatment
Un-Culturable Organisms

What is the appropriate clinical trial approach?

Possible Clinical Trial Approaches

Diagnostic Accuracy Study		Clinical Outcome Trial	
Pro	**Con**	**Pro**	**Con**
• Allows for estimation of diagnostic accuracy • Identifies potential clinical limitations (e.g. chronic renal failure, influenza, atypical bacteria) • Informs clinical decision making • Easier study logistics	• Variable reference methods • Difficult to compare studies	• Evaluate impact of diagnostic on patient management and outcomes	• May not be able to determine accuracy of test • Variable endpoints • Expensive

Can we use pragmatic clinical trial evidence to establish safety and effectiveness?

Initiation:

PCT Result	<0.10 ng/mL	0.10-0.25 ng/mL	0.26-0.50 ng/mL	>0.50 ng/mL
Interpretation	Antibiotic therapy strongly discouraged. Indicates absence of bacterial infection.	Antibiotic therapy discouraged Bacterial infection unlikely.	Antibiotic therapy encouraged. Bacterial infection possible.	Antibiotic therapy strongly encouraged. Suggestive of presence of bacterial infection.
Follow-up	For inpatients, if antibiotics are withheld, repeat PCT measurement within 6-24 hours. For outpatients, reassess and/or repeat test if symptoms persist/worsen. In all cases, antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted.		Follow up samples should be tested at regular intervals and antibiotic therapy may be adjusted using the discontinuation table below:	

Discontinuation:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.25 ng/mL or if the ΔPCT > 80%.

- PCT_{Peak}: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\triangle PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \times 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray or ongoing/increasing toxicity.

If PCT remains high, consider treatment failure.

Proposed PCT Sepsis Algorithm

Discontinuation:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.50 ng/mL or if the ΔPCT > 80%.

- PCT_{Peak}: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\triangle PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \text{ X } 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray or ongoing/increasing toxicity.

If PCT remains high, consider treatment failure.

Potential Limitations

- False Negatives
  - **Localized infections**
  - **Early measurement**
  - **Steroid use**
  - **Atypical bacteria**
- False Positives
  - Some oncological process
  - Pancreatitis
  - Heat stroke
  - Trauma/burns/surgery
  - **Influenza/URIs**
- Understudied Populations
  - Children/neonates
  - Chronic renal failure
  - Immunocompromised


Risks
Benefits

Benefits

- The clinical data indicates that patients will experience benefit from PCT-guided management
  - Decreased antibiotic duration
  - Decreased antibiotic initiation
  - Decreased antibiotic side effects
  - Decreased antimicrobial resistance?

Risks

- Is the clinical data sufficient to determine if a reduction in antibiotic duration or initiation will increase risk to patients?
  - Increased mortality
  - Increased length of stay
  - Increased recurrence of infection
  - Prolonged symptoms/decreased quality of life

How does adherence affect the evaluation of safety and effectiveness of PCT-guided care?

Adherence

- Under-estimation of efficacy?
- Over-estimation of safety?
  - Reflection of Clinical Practice
  - Extrapolation to outpatient population
  - Evaluation of patient subgroups
- Can we demand better adherence in studies?
  - Ethical implications
  - Appropriate study population

LRTI Patient-Level Data Subgroup Analysis	Standard Therapy	PCT-guided Therapy	Adjusted OR or Difference (95% CI)
CAP	1028	999	
Initiation of Antibiotics (n)	1019 (99%)	898 (90%)	0.07 (0.03, 0.14)
Duration of Antibiotics in days median (IQR)	10 (8, 14)	7 (5, 10)	-3.34 (-3.79, -2.88)
Mortality	111 (10.8%)	92 (9.2%)	0.92 (0.74, 1.15)
Bronchitis	282	249	
Initiation of Antibiotics (n)	185 (66%)	61 (25%)	0.15 (0.10, 0.23)
Duration of Antibiotics in days median (IQR)	7 (5, 8)	7 (4, 9)	-0.38 (-1.21, 0.46)
Mortality	0 (0%)	2 (0.8%)	N/A
AECOPD	296	288	
Initiation of Antibiotics (n)	216 (73%)	137 (48%)	0.32 (0.23, 0.46)
Duration of Antibiotics in days median (IQR)	8 (6, 10)	6 (3, 9)	-1.58 (-2.33, -0.82)
Mortality	8 (2.7%)	9 (3.1%)	1.15 (0.46, 2.89)
Outpatients	467	430	
Initiation of Antibiotics (n)	381 (81.6%)	215 (50%)	0.13 (0.09, 0. 19)
Duration of Antibiotics in days median (IQR)	7 (6, 10)	6 (4, 8)	-1.75 (-2.28, -1.21)
Mortality	3 (0.6%)	2 (0.5%)	1.11 (0.28, 4.45)

Modified table from Table 15, Figures 11 and 12 in the bioMérieux executive summary and Section 26.3

Has the safety of PCT-guided management been established for:

- For all subpopulations (i.e., CAP, COPD, bronchitis)?
- For outpatients in these subpopulations?
- For antibiotic initiation?
- For antibiotic discontinuation?

Are additional limitations for certain patients needed?

What are Potential Risk Mitigations?

- Aid in the diagnosis of sepsis/LRTI
- To be used in association with imaging and other laboratory tests
  - Healthcare facilities with moderate to high complexity laboratories
  - Clinical Judgment
- User education
  - Antimicrobial stewardship programs to develop internal policies and procedures

The ProACT Trial

- 5 year, multicenter study to study the effect of procalcitonin on antibiotic use and adverse outcomes in adult ED patients with acute LRTI
- **Primary Outcome:** Total antibiotic exposure, defined as the total number of antibiotic-days by Day 30.
- **Secondary Outcome:** Rate of antibiotic initiation by the initial ED clinician

The ProACT Trial

Other: Procalcitonin level

A procalcitonin (PCT) will be drawn level within one hour after randomization in the ED, and if hospitalized, 6-24 hours after the initial ED blood draw, and on Days 3, 5, and 7. Days 3, 5, and 7 blood draws for procalcitonin will only occur in hospitalized patients on antibiotics and/or at the treating physician's discretion.

Other Name: PCT level

Other: Results of procalcitonin (PCT) level to treating clinician

In the ED, we will quickly (<1 hour goal) provide clinicians the procalcitonin result.

Other: Provide procalcitonin guideline to treating clinician

Procalcitonin antibiotic guideline --

Procalcitonin level (ug/L) -- Bacterial etiology -- Recommendation

< 0.1 -- Very unlikely -- Antibiotics strongly discouraged(1)

0.1 - 0.25 -- Unlikely -- Antibiotics discouraged(1)

> 0.25 - 0.5 -- Likely -- Antibiotics recommended(2)

> 0.5 -- Very likely -- Antibiotics strongly recommended(2)

1. Initial antibiotics can be considered for critical illness, Legionella pneumophilia. Procalcitonin should be evaluated in context with all findings and the total clinical status; clinical judgment always necessary.
2. For outpatients, antibiotic duration based on level (> 0.25-0.5 ug/L:3 days; > 0.5-1.0 ug/L:5 days; >1.0 ug/L:7 days). Physician follow-up is recommended.

Other: Telephone Visit

We will collect the number of antibiotic days during telephone visits occurring on or around Day 15 and Day 30

Summary

- PCT correlates with bacterial infection in sepsis/LRTI.
  - The diagnostic accuracy of PCT is difficult to assess precisely due to the imperfect comparator.
- Use of antibiotics is reduced when PCT is utilized as proposed by bioMérieux.
- No significant differences in adverse outcomes were observed.
  - Algorithm adherence and aspects of clinical trial design complicate safety analysis
  - Subpopulation analysis was performed on smaller patient subsets.

Conclusions

- FDA generally concurs that PCT-guided therapy reduces antibiotic use with the proposed diagnostic algorithm.
  - The submission reflects an accurate description of the current data available.
  - Limitations from current data are well-recognized.
  - Results from prospective studies (e.g., ProACT, TRAP-LRTI) may not be available for several years.
- Significant concerns exist regarding safety and conditions of use.

Question to the Panel

Please discuss the potential advantages and disadvantages of using this test as proposed in the IFU. In your discussion, please note whether the current submission addresses any potential new risks from the modified IFU, if so please describe those risks. Please address each aspect of the modified Indications for Use independently including:

a) As an aid in antibiotic decision making for inpatients or outpatients, with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

b) As an aid in decision making for antibiotic discontinuation for patients with suspected or confirmed sepsis

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