THE PROS & CONS OF PROCALCITONIN

INITIATION, DE-ESCALATION & DISCONTINUATION OF ANTIMICROBIALS

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DISCLOSURES

- This program may contain the mention of drugs, brands or suppliers presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular drug, brand or supplier.

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.

LEARNING OBJECTIVES - PHARMACIST

At the end of this session, participants should be able to:

1. Explain why procalcitonin is hypothesized to be helpful for antimicrobial treatment decision-making
2. Discuss common misconceptions regarding the use of procalcitonin
3. Identify clinical scenarios where procalcitonin may be appropriate to use

LEARNING OBJECTIVES - TECHNICIAN

At the end of this session, participants should be able to:

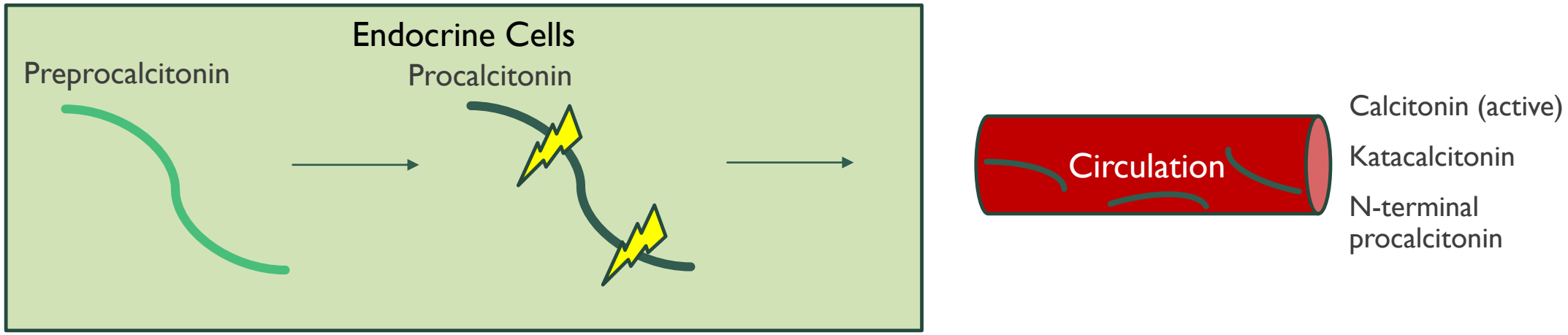
1. Restate why procalcitonin is helpful for antimicrobial treatment decision-making
2. List one indication where procalcitonin has shown efficacy in determining the need for antibiotic therapy
3. Identify possible future uses of procalcitonin

OVERVIEW

- Procalcitonin stimulation and relationship with infection
- Literature to support use for guiding antibiotic therapy
- Potential uses and algorithm examples

PROCALCITONIN … WHAT IS IT?

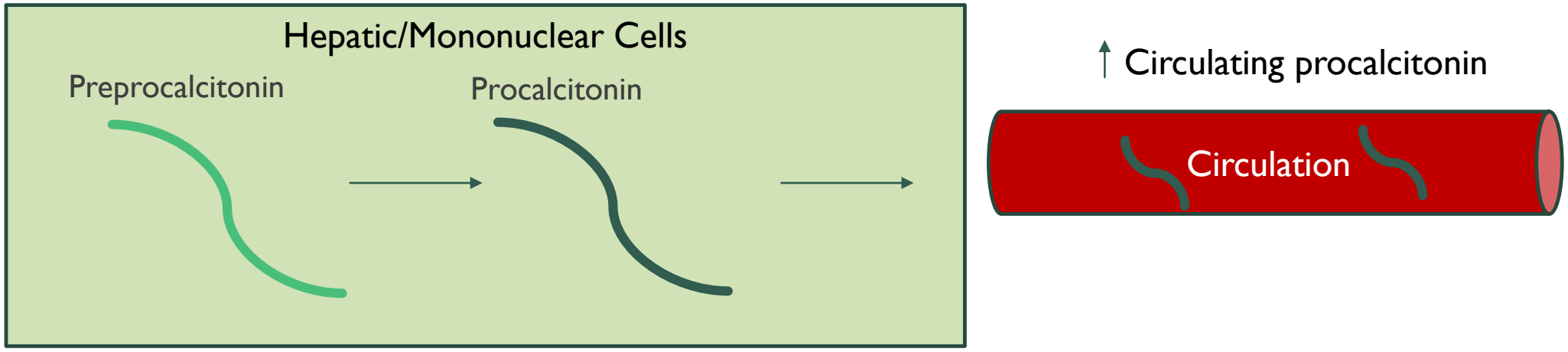
- 116 peptide hormone that is the precursor for calcitonin produced in thyroid tissue as a response to the CALC–1 gene
- Calcitonin is a hormone involved in calcium and phosphorus balance that is secreted due to elevated calcium, B–adrenergic stimulation, glucagon and gastrin stimulation
- Normal procalcitonin (PCT) will be low in healthy humans (≤ 0.05 ng/mL)



Source: Vijayan, AL et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. *J Intensive Care*. 2017 Aug 3;5:51

PCT INDUCTION DUE TO AN INFECTION

- PCT production is induced by different mechanisms
  - Direct induction by lipopolysaccharide or other toxins from bacteria
  - Indirect induction by inflammatory mediators such as IL-6 and TNF-α



Source: Vijayan, AL et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. *J Intensive Care*. 2017 Aug 3;5:51

PCT ASSOCIATION WITH INFECTION

- "Rediscovery" of an old laboratory test
  - High levels of preprocalcitonin noted in rats infected with gram negative bacteria
  - Sometimes referred to as a "hormokine" due to its similar behavior to a cytokine response in infections
- PCT thought to have high accuracy for diagnosis of infection, especially sepsis
  - Lag time associated with its onset in sepsis (2–4 hours)
  - Peak level at 24–48 hours after onset

Sources: Vijayan, AL et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. *J Intensive Care*. 2017 Aug 3;5:51
Meisner, M. Updated on procalcitonin measurements. *Ann Lab Med*. 2014 Jul;34(4):263-73.

ASSESSMENT Q1: Procalcitonin will be elevated in response to which stimuli?

A. Changes in calcium or phosphorus in the body
B. Systemic inflammation secondary to a bacterial infection
C. Viral envelope exposure during a viral infection
D. Immunosuppression due to steroids

RESPONSE Q1: Procalcitonin will be elevated in response to which stimuli?

A. Changes in calcium or phosphorus in the body

B. Systemic inflammation secondary to a bacterial infection

C. Viral envelope exposure during a viral infection

D. Immunosuppression due to steroids

TRADITIONAL BIOMARKERS VERSUS PCT

- C-reactive protein (CRP) has a low specificity for sepsis
  - Levels are known to elevate secondary to inflammation or trauma making sepsis determination difficult
- Lactate lacks specificity and does not increase in the acute period of sepsis
  - Does not clearly differentiate between different causes of sepsis
- Cytokine measurements are still novel markers of sepsis
  - Increase quickly in response to sepsis and septic shock
  - Lack specificity and may fluctuate due to unknown reasons

Source: Meisner, M. Updated on procalcitonin measurements. *Ann Lab Med*. 2014 Jul;34(4):263-73.

POTENTIAL LIMITATIONS OF PCT

- Many institutions are still working on making PCT available in their on-site laboratory
- Institutions that require PCT to be a "send out" will most likely not have provider buy-in for use
- May be falsely elevated in some scenarios or not elevated in certain bacterial infections

ADDITIONAL LIMITATIONS OF PCT

- May be falsely elevated with
  - Severe trauma
  - Autoimmune disorders
  - Prolonged cardiogenic shock
  - Medullary thyroid cancer
  - Heat stroke
  - Neonates (<48 hrs. of age)
- May be falsely negative with
  - Local bacterial infections
  - Endocarditis with no systemic inflammatory response
  - Bacteremia with no systemic inflammatory response

Source: Meisner, M. Updated on procalcitonin measurements. *Ann Lab Med*. 2014 Jul;34(4):263-73.

PCT EXPANDED USE APPROVAL

- Risk assessment of critically ill patients on their first day of ICU admission
  - Risk of progression to severe sepsis and septic shock
  - Change in PCT level to assess the cumulative 28–day risk of all-cause mortality in conjunction with other data

- February 2017: The U.S. Food and Drug Administration (FDA) cleared the expanded use of PCT to aid in the determination for antibiotic use for patients with lower respiratory tract infection, (LRTI) and sepsis
  - LRTI: initiation or discontinuation of antibiotics
  - Sepsis: discontinuation of antibiotics

Source: US Food and Drug Administration. FDA press release. 2017 Feb 23. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm543160.htm

POLL: At your institution, in which way is PCT available?

- A. It is a send out laboratory test that will result in 2+ days
- B. It is a test that is run through our on-site laboratory and with results in a few hours
- C. It is not available at our institution
- D. Unknown

LITERATURE REVIEW – APPROVED INDICATIONS FOR PROCALCITONIN

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- Suspected or confirmed sepsis for antibiotic initiation or discontinuation

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- Suspected or confirmed lower respiratory tract infections (LRTI) Community-acquired pneumonia (CAP), acute bronchitis and acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

STUDIES INVOLVING THE USE OF PCT IN SEPSIS

- A growing area of interest is with the use of PCT in the decision to initiate or discontinue antibiotics in septic patients focusing on limiting duration of antimicrobial exposure
- Most studies included patients that met SIRS criteria
  - SIRS = systemic inflammatory response syndrome
    - Tachycardia (heart rate > 90 beats/min)
    - Tachypnea (respiratory rate > 20 breaths/min)
    - Fever or hypothermia (temperature >38 or <36°C)
    - Leukocytosis, leukopenia, or bandemia (white blood cells >12,000/mm^3, <4000/mm^3, or bands $\geq$10%)
- YES & NO versus yes & no
  - ALL CAPS = strong recommendation

Source: Balk, RA. Systemic inflammatory response syndrome (SIRS): where did it come from and is it still relevant today? *Virulence*. 2014 Jan 1;5(1):20-6.

PCT TO GUIDE DURATION OF ANTIBIOTIC THERAPY IN INTENSIVE CARE PATIENTS

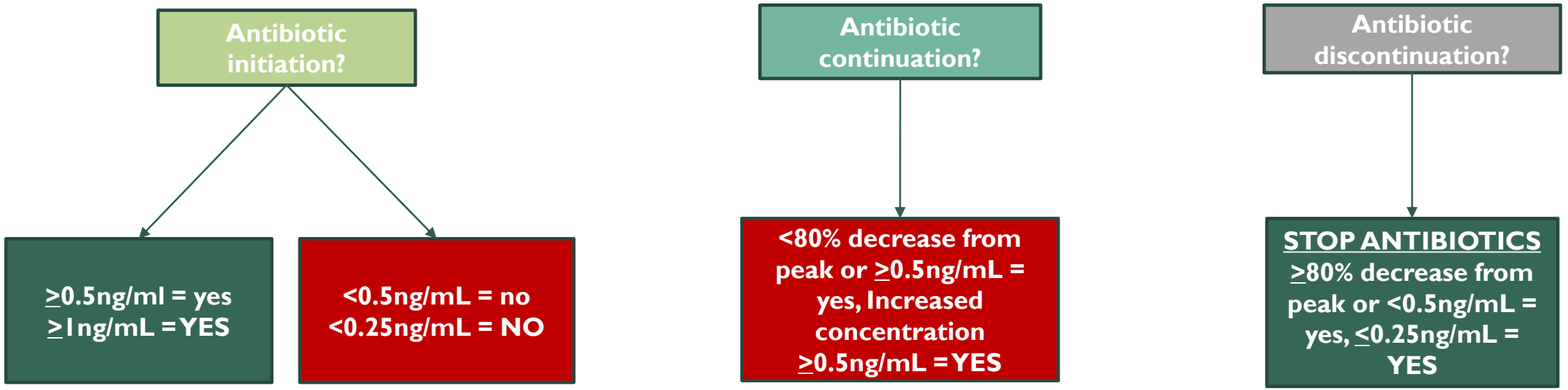
- Small study in Germany aimed to assess the usefulness of PCT for guiding antibiotic therapy versus standard of care
- Patients were included only if there was high suspicion for bacterial infection with 2+ systemic inflammatory response syndrome (SIRS) criteria
- Antibiotics were discontinued once signs and symptoms of infection improved and PCT< 0.1 ng/mL or if PCT dropped to 25–35% of peak PCT over 3 days

Endpoint	PCT (n=57)	Standard care (n=53)	P-value
Duration of therapy (days)	5.9 +/- 1.7	7.9 +/- 0.5	**< 0.001**
ICU days	15.5 +/- 12.5	17.7 +/- 10.1	**0.046**
Survival at discharge	42/57	39/53	>0.05

Source: Hochreiter, M., et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care*. 2009;13(3):R83

PRORATA TRIAL

- Small study aimed to assess the effectiveness of a PCT-based algorithm for reducing antibiotic exposure in the ICU in sepsis
- Patients were included if they had a suspected bacterial infection or sepsis during ICU stay
- Antibiotics were initiated or stopped depending on PCT (YES or NO = strong recommendation)



Source: Bouadma, L., et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *The Lancet*. 2010;375(9713):463-74.

PRORATA TRIAL (Continued)

Endpoint	PCT use	Standard of care	P-value
Mortality (28 days)	21.2%	20.4%	--
Mortality (60 days)	30%	26.1%	--
Days without antibiotics by day 28	14.3	11.6	**<0.0001**

- Large non-inferiority margin (10%) has lead some researchers to view this as a weaker study for PCT
- 53% of patients in PCT arm did not have therapy that followed the algorithm

Source: Bouadma, L et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicenter randomised controlled trial. *The Lancet*. 2010; 375(9713): 463-74.

SAPS TRIAL

- Large, multicenter trial in the Netherlands
- Objective: determine whether PCT-guided strategy can be found to be superior to standard of care for intensive care patients
- Primary endpoints
  - Efficacy: defined daily dosage (DDD) and total duration of antibiotic therapy (days)
  - Safety: overall mortality at 28 days and one year

Source: Assink-de Jong, et al. Stop antibiotics on guidance of procalcitonin study (SAPS): a randomised prospective multicenter investigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard of care approach can safely shorten antibiotic duration in the intensive care unit. *BMJ Infect Dis.* 2013;13:178-25.

SAPS TRIAL (Continued)

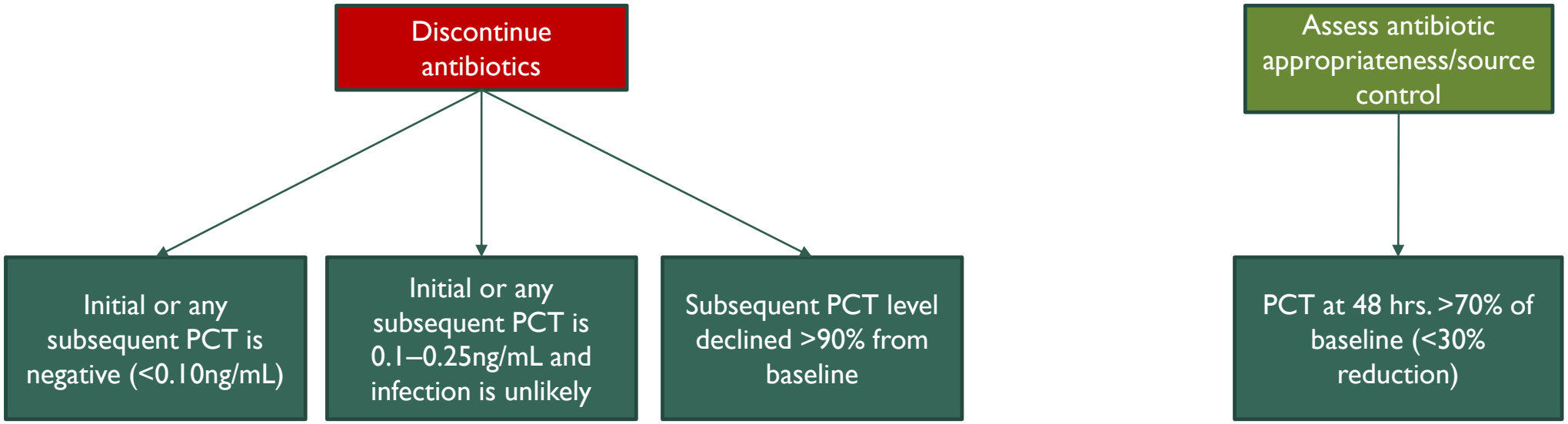
- Patients received daily PCT levels if randomized to the PCT arm
- Physicians received a recommendation to discontinue antibiotics if the PCT decreased to < 20% of its peak or reached a value < 0.5 ng/mL
- Findings: 71% of patients in PCT arm had antibiotics discontinued during their ICU stay

Endpoint	PCT use	Standard of care	P-value
DDD	7.5 (IQR 4–12.7)	9.3 (IRQ 5–16.6)	**<0.0001**
Median duration	5 (3-9)	7 (4–11)	**<0.0001**
Mortality (28 days) 107/538 (20%)	149/761 (20%)	196/785 (25%) 121/457 (27%)	**0.0154**
Mortality (1 year)	191/538 (36%)	196/457 (43%)	**0.0188**

Source: Assink-de Jong, et al. Stop antibiotics on guidance of procalcitonin study (SAPS): a randomised prospective multicenter investigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard of care approach can safely shorten antibiotic duration in the intensive care unit. *BMJ Infect Dis.* 2013;13:178-25.

PROGUARD TRIAL

- Multicenter trial to investigate whether a PCT algorithm with a low cut off of 0.1ng/mL can reduce antibiotic exposure in the critically ill population versus standard of care
  - Also evaluated predictive value of initial PCT level in determining site of infection and severity of sepsis and prognostic value of serial PCT levels



Source: Shehabi, Y., et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis: a randomized controlled trial. *Am J Resp Crit Care Med.* 2014 Oct;190(10)

PROGUARD TRIAL RESULTS

- Primary outcome: time to antibiotic cessation at 28 days, hospital discharge or death
  - Antibiotic-free days at day 28

Endpoint	PCT	Standard of care	P-value
Time to cessation	9 (6–20)	11 (6–22)	0.58
Antibiotic free days	20 (11–22)	17 (7–22)	0.18

- Baseline PCT was not predictive of mortality
- Decline in PCT over first 72 hour predictive of both hospital and 90-day, all-cause mortality
  - Survivors had greater declines in PCT

Source: Shehabi, Y., et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis: a randomized controlled trial. *Am J Resp Crit Care Med.* 2014 Oct;190(10)

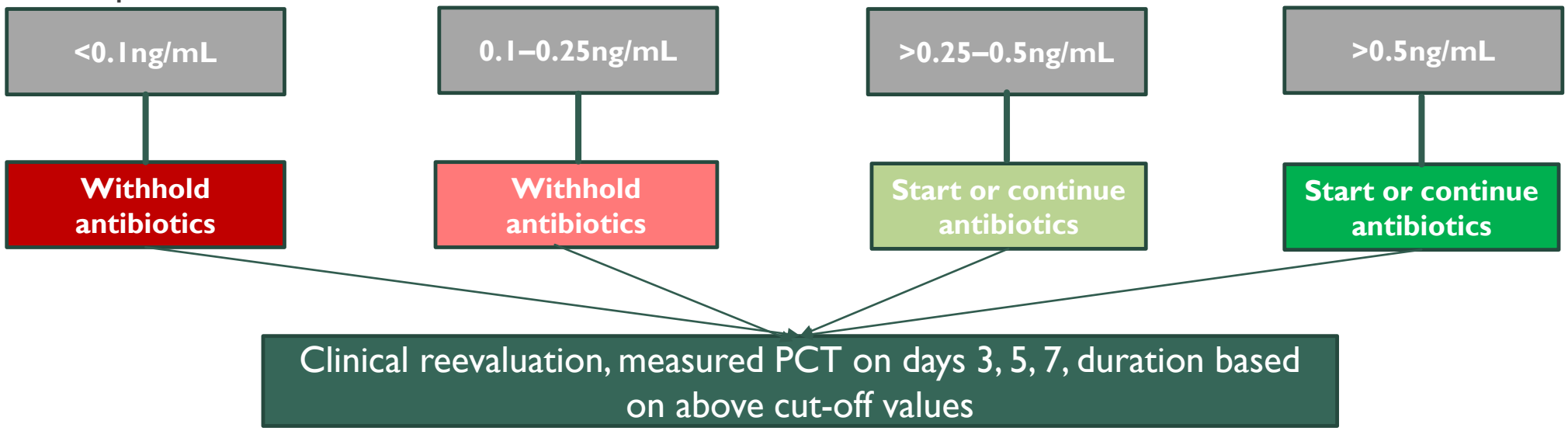
LOWER RESPIRATORY TRACT INFECTIONS

- Increasing amount of literature published to date
  - Usually in single centers with smaller patient sizes
  - Will highlight one of the initial large studies as well as the most recent meta-analysis that was conducted

- ALL CAPS = strong recommendation

PROHOSP STUDY

- Prospective, randomized, controlled trial to address limitations seen with the use of PCT for LRTIs
  - Multicenter
  - Strict use of guidelines and study protocol
  - Main objective: evaluate PCT-guided therapy decisions for LRTI effect on outcome, antibiotic use and length of hospitalization



Source: Schuetz, P., et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* Sep;302(10):1059-66.

PROHOSP RESULTS

- 1,359 patients were analyzed for outcomes
- Overall adverse outcomes (mortality or disease recurrence) were lower in both the per-protocol and intent-to-treat analyses for PCT versus standard therapy
  - This included CAP, AECOPD and bronchitis
  - Overall endpoint met non-inferiority criteria
- Antibiotic duration and prescriptions rates were also significantly reduced

Source: Schuetz, P., et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract injfections: the ProHOSP randomized controlled trial. *JAMA.* 2009 Sep;302(10):1059-66.

PCT TO INITIATE OR DISCONTINUE ANTIBIOTICS (META ANALYSIS)

- Schuetz, P., et al. conducted various meta-analyses over the past 10 years to continually evaluate the literature surrounding the use of PCT for acute respiratory tract infections
  - Clear evidence surrounded use of PCT to start or stop antibiotics
  - Unanswered question was its effect on clinical outcomes
- Primary outcome: all-cause mortality and treatment failure at 30 days
  - Also analyzed antibiotic use, side effects and length of hospital stay
- Included 26 trials with 6,708 patients
  - Evidence for mortality and antibiotic exposure was graded as high quality and moderate quality for treatment failure and side effects

Source: Schuetz, P., et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev.* 2017 Oct 12;10:CD007498.

META ANALYSIS CONCLUSION

- PCT guided therapy had significant effects on lowering overall antibiotic exposure and mortality
  - Results were similar between different clinical settings
    - Mortality was not estimated for outpatient studies but still shows low treatment failure

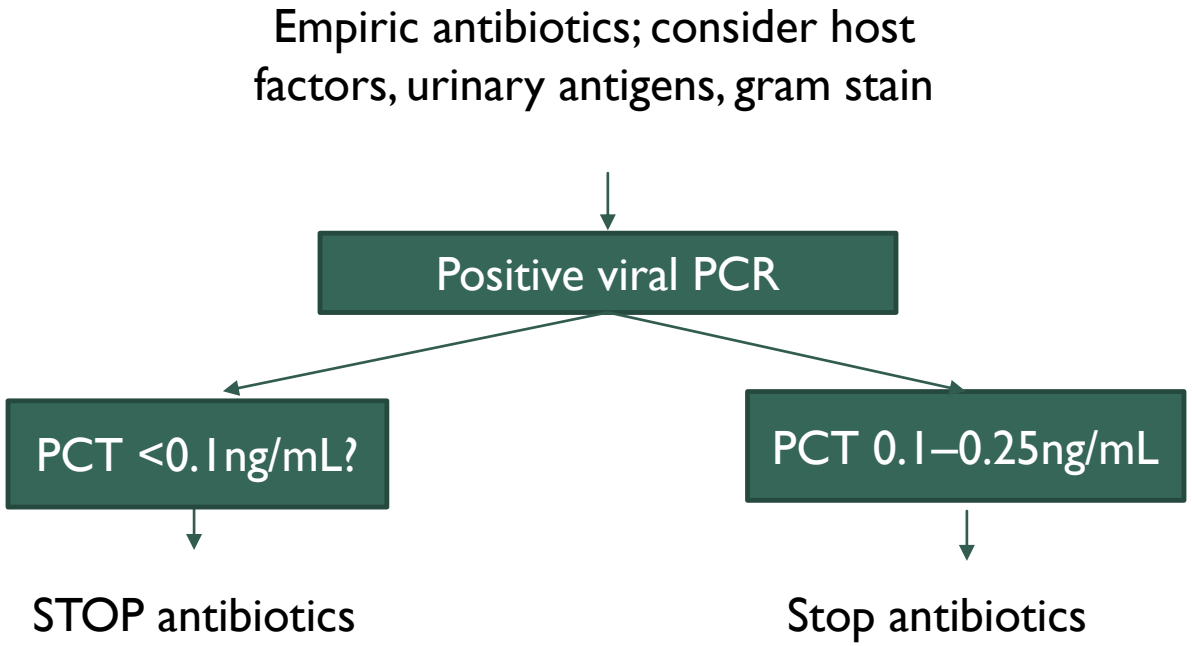
Endpoint	PCT (n=3336)	Standard (n=3372)	P-value
Death	8.6% [OR 0.83]	10%	**0.037**
Failure	23%	24.9%	0.068
Exposure	5.7 days	8.1 days	**<0.001**
Side effects	16.3% [OR 0.68]	22.1%	**<0.001**

Source: Schuetz, P., et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev.* 2017 Oct 12;10:CD007498.

SO SHOULD WE USE PCT TO GUIDE THERAPY?

- Bacterial resistance to our antimicrobials is a growing concern
  - Antibiotic use is high in sepsis and LRTIs
  - Antimicrobial stewardship may initially be hesitant to tackle antibiotic use in septic patients
- There is a growing amount of literature to support PCT guided antimicrobial decision-making
- Multiple institutions have implemented PCT algorithms to help practitioners with proper PCT use
- What does an algorithm look like?

ALGORITHM EXAMPLE #1 – COMMUNITY ACQUIRED PNEUMONIA

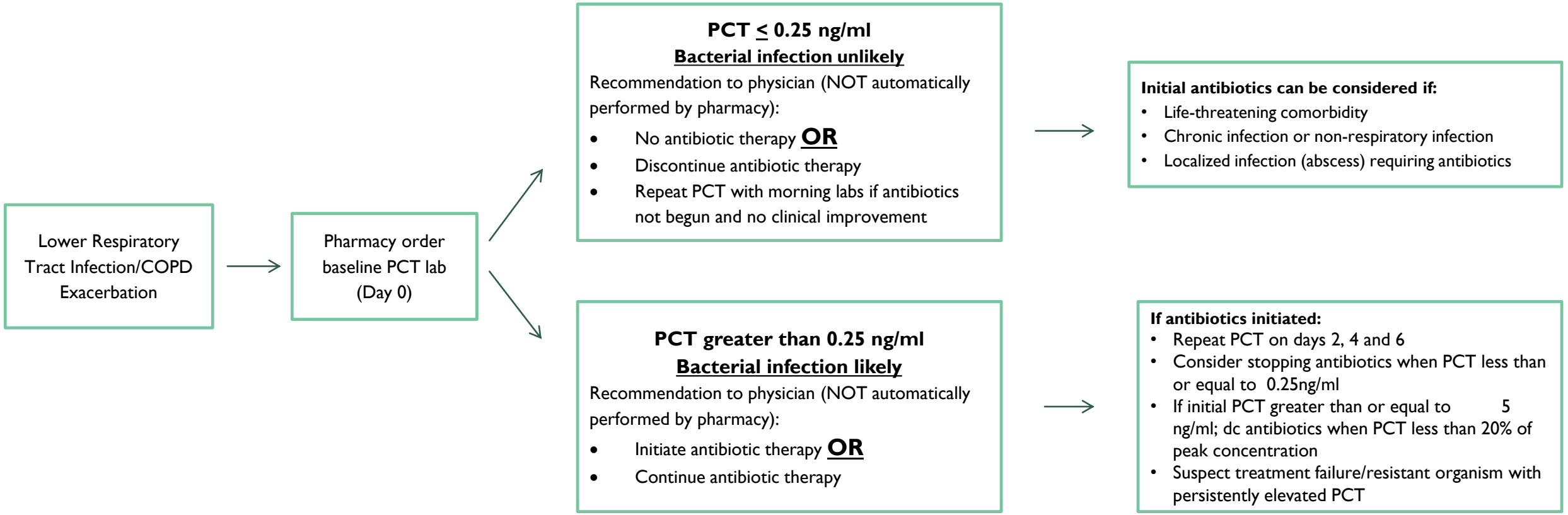


* Repeat PCT in 6–12 hours if antibiotics have not been started and no clinical improvement seen

* If patient clinically unstable, immunosuppressed, or high risk, consider overruling algorithm (PSI IV–V, CURB>2, GOLD III/IV)

Algorithm example courtesy of: Bronson Methodist Hospital, Kalamazoo, MI

ALGORITHM EXAMPLE #2



Algorithm example courtesy of: Presence St. Joseph Medical Center, Joliet IL

ALGORITHM EXAMPLE #2, continued

PCT less than or equal to 0.25 ng/ml

Bacterial infection unlikely

Recommendation to physician (NOT automatically performed by pharmacy):

- No antibiotic therapy **OR**
- Discontinue antibiotic therapy
- Repeat PCT with morning labs if antibiotics not begun and no clinical improvement

→

Initial antibiotics can be considered if:

- Life-threatening comorbidity
- Chronic infection or non-respiratory infection
- Localized infection (abscess) requiring antibiotics

Algorithm example courtesy of: Presence St. Joseph Medical Center, Joliet IL

ALGORITHM EXAMPLE #2

PCT greater than 0.25 ng/ml

Bacterial infection likely

Recommendation to physician (NOT automatically performed by pharmacy):

- Initiate antibiotic therapy **OR**
- Continue antibiotic therapy

If antibiotics initiated:

- Repeat PCT on days 2, 4 and 6
- Consider stopping antibiotics when PCT less than or equal to 0.25ng/ml
- If initial PCT greater than or equal to 5 ng/ml; dc antibiotics when PCT less than 20% of peak concentration
- Suspect treatment failure/resistant organism with persistently elevated PCT

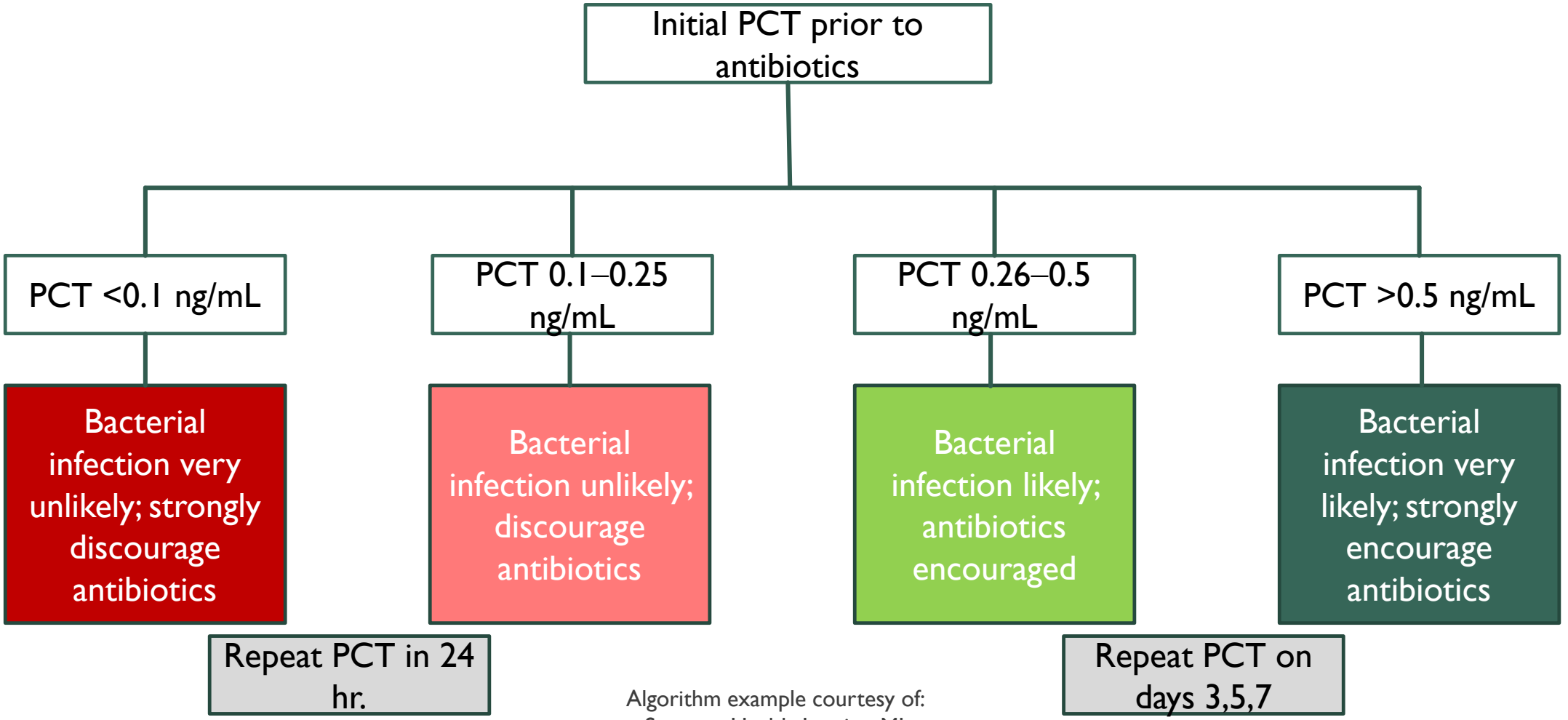
Algorithm example courtesy of: Presence St. Joseph Medical Center, Joliet IL

ALGORITHM EXAMPLE #3

- Provider criteria
  - Pharmacist must be ID-trained or trained in antimicrobial stewardship to order PCT and make recommendations
- Inclusion
  - Physician diagnosed LRTI (pneumonia, COPD exacerbation, bronchitis)
  - Adult patients (age 18 years or older)
- Exclusion
  - Patients requiring admission to critical care unit
  - Patient with ESRD/HD, pancreatitis, thyroid neoplasm, active small cell lung cancer
  - Post-surgical, trauma, or cardiac shock patients
  - Patient receiving IVIG
  - Concomitant local infections such as osteomyelitis, abscess, etc.

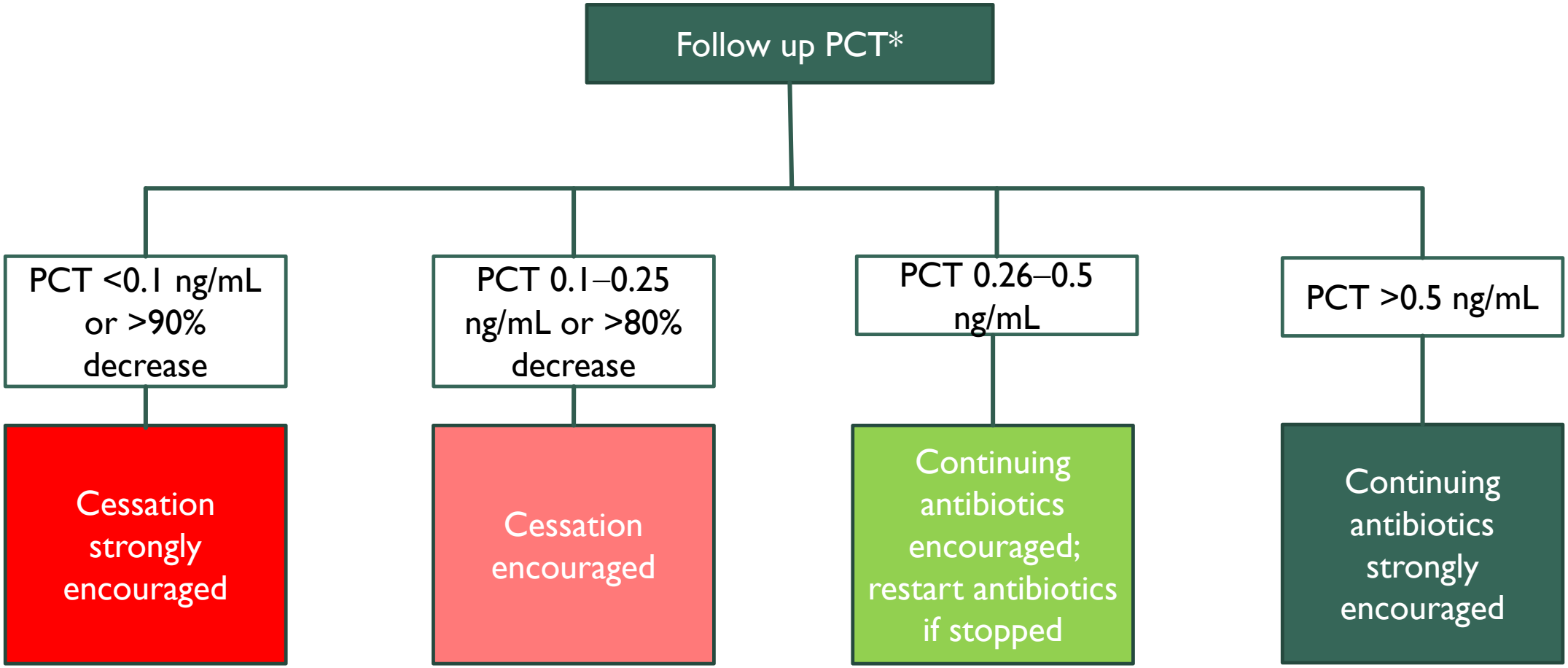
Algorithm example courtesy of: Sparrow Health, Lansing, MI

ALGORITHM #3 EXAMPLE INITIATION OF ANTIBIOTICS

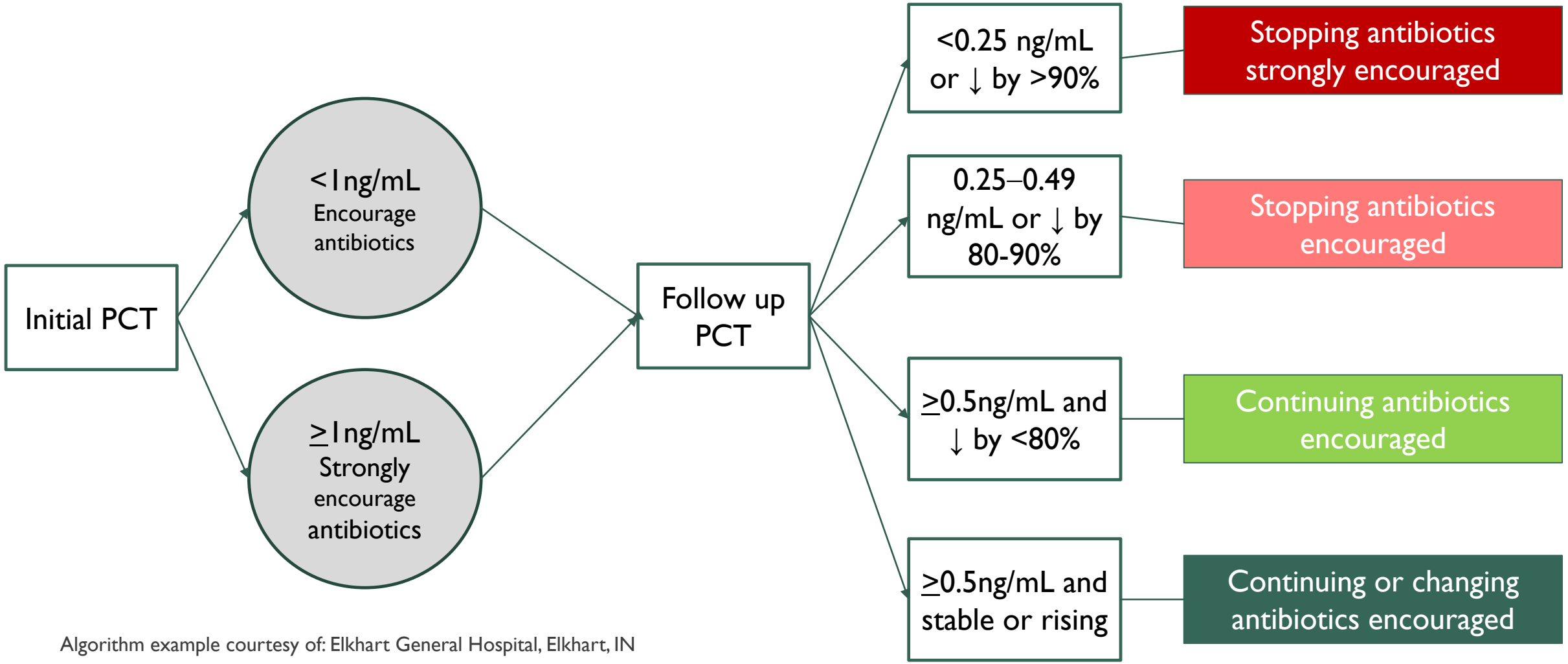


Algorithm example courtesy of:
Sparrow Health, Lansing, MI

ALGORITHM #3 EXAMPLE CESSATION OF ANTIBIOTICS



ALGORITHM EXAMPLE #4 – SEPSIS



Algorithm example courtesy of: Elkhart General Hospital, Elkhart, IN

FINAL THOUGHTS REGARDING PCT USE

- Some providers may use PCT to be the "tipping point" to decide whether or not to use antimicrobial therapy

  Ask yourself:

  - Are they using it for a local infection?
  - Could the PCT be elevated for another reason?
  - Are certain providers ordering PCT on every patient?
- Combined PCT use with rapid identification panels (RIDP)
  - Some providers may respond well if PCT is used as an addition to a RIDP that was positive for viral infection
- Inform your pharmacists about PCT use! Especially for critical access hospitals that are able to use PCT!
- Start small → implement an algorithm to guide in stopping antibiotics rather in preventing initiation

ASSESSMENT Q2: Procalcitonin should not be used in which of the following scenarios?

A. To determine if a patient is experiencing cellulitis or a deep venous thromboembolism of the leg
B. To determine if a patient may require antibiotics for a potential community acquired pneumonia
C. Routine laboratory monitoring to watch for hospital-acquired infections
D. In a septic patient to aid in the decision to administer broad spectrum antibiotics
E. Both A and C

RESPONSE Q2: Procalcitonin should not be used in which of the following scenarios?

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D. In a septic patient to aid in the decision to administer broad spectrum antibiotics

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ASSESSMENT Q3: For which indications could PCT-based algorithms be implemented to help manage antimicrobial use?

A. Urinary tract infection
B. Community acquired pneumonia
C. Sepsis/septic shock
D. Both B and C

RESPONSE Q3: For which indications could PCT-based algorithms be implemented to help manage antimicrobial use?

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