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This lesson is a knowledge-based CPE activity and is targeted to pharmacists and technicians in all practice settings.

Learning Objectives

At the completion of this activity, the participant will be able to:

1. State two positive changes you can make to your practice following participation in this series.
2. Summarize three practice updates or changes you acquired while participating in this series.

Disclosure

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Genetic Mutations in Cancer: *BRCA1* and *BRCA2*

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Cancer is a genetic disease that results from an accumulation of mutations in genes that normally control cellular growth. This accumulation of mutations can arise from either somatic or germinal tissue. While the majority of mutations are somatic and result from environmental exposures, lifestyle, the aging process, or simply chance, germline mutations are inherited. These inherited mutations in specific tumor suppressor genes and DNA mismatch genes predispose individuals to various hereditary cancer syndromes.[1]

Of the tumor suppressor genes associated with inherited cancer syndromes, *BRCA1* and *BRCA2* play an important role in the repair of damaged DNA and the stability of genetic material within cells. However, when these genes are mutated or altered, the DNA repair process may not function properly, which causes cells to be more prone to developing additional genetic alterations that can lead to cancer. When an individual carries a mutated *BRCA1* or *BRCA2* gene, their offspring have a 50% chance of inheriting the mutation. Although offspring may possess a normal second copy of the gene, the effects of mutations in *BRCA1* and *BRCA2* remain visible.[2]

In general, *BRCA1* and *BRCA2* gene mutations are the leading genetic factors for breast and ovarian cancers.[2] Most notably, these genes are the strongest susceptibility genes for breast cancer, as they are responsible for 90% of hereditary breast cancer cases. In addition, *BRCA1* and *BRCA2* are accountable for majority of hereditary ovarian cancer.[3] When inherited, individuals tend to develop breast and ovarian cancer at younger ages than those who do not possess these mutations.[2]
Across the general population, 12% of women will develop breast cancer and 1.3% will develop ovarian

cancer during their lifetime.[4] In contrast, a recent study aimed to estimate age-specific risks of breast, ovarian, and contralateral breast cancer for mutation carriers to evaluate risk modification by family cancer history and mutation location. The resulting cohort of over 9,000 mutation carriers demonstrated that about 72% of women who inherit a harmful *BRCA1* mutation and about 69% of women who inherit a harmful *BRCA2* mutation will develop breast cancer by the age of 80, while the cumulative ovarian cancer risk was 44% for *BRCA1* and 17% for *BRCA2* carriers.[5] Apart from breast and ovarian cancers, *BRCA1* and *BRCA2* mutations have been associated with fallopian tube and peritoneal cancers. Likewise, men with *BRCA2* mutations, and to a lesser extent *BRCA1* mutations, are at an increased risk of breast and prostate cancers, while both men and women are at an elevated risk of pancreatic cancer.[2]

Table 1: Cancer Risk in General Population Compared to *BRCA1/2* Carriers

Cancer	General Population Risk[4]	*BRCA1* Carrier Risk[4]	*BRCA2* Carrier Risk[4]
Breast	12%	46-87%	38-84%
Ovarian	1-2%	39-63%	16.5-27%

In order to determine an individual's *BRCA1* and *BRCA2* status, multigene (panel) testing is used to conduct next-generation sequencing to detect harmful mutations. However, the expert consensus argues for testing individuals who do not have cancer only when the individual's personal or family history suggests the probable incidence of a harmful mutation due to the fairly infrequent incidence of harmful *BRCA1* and *BRCA2* gene mutations in the general population. In particular, the United States Preventive Services Task Force recommends that women who have family members with breast, ovarian, fallopian tube, or peritoneal cancer be evaluated to determine if they have a family history that is suggestive of an increased risk of a harmful mutation in *BRCA1* or *BRCA2*.[2]

When an individual's family history is indicative of *BRCA1* or *BRCA2* mutations, it is recommended to first test the family member with cancer if possible. If this individual is shown to have a harmful *BRCA1* or *BRCA2* mutation, other family members should then consider genetic counseling to determine potential risks and the need for genetic testing. If genetic testing is performed, a positive test indicates that the individual has inherited a known harmful mutation in *BRCA1* or *BRCA2*; thus, an increased risk of developing certain cancers is present. However, a positive result does not determine whether or not the individual will ultimately develop cancer, as some individuals who inherit these mutations never develop cancer. On the other hand, a negative result can be more difficult to interpret, as it is dependent on an individual's family history of cancer and whether a *BRCA1* or *BRCA2* mutation has been discovered in a blood relative.[2]

Once an individual's risk is determined, this risk is managed through a number of methods. First, enhanced screening, such as starting breast cancer screenings at a younger age or more frequently is an option. Therefore, experts typically recommend that *BRCA1* or *BRCA2* mutation carriers begin clinical breast examinations starting at age 25 to 35 years old, along with a mammogram every year. If detected at an early stage, breast cancer may have a better probability of being treated successfully. In contrast, ovarian cancer does not have an established early screening method.[2]

Additionally, risk-reducing prophylactic surgery is available to remove at-risk tissue, such as a bilateral prophylactic mastectomy to reduce the risk of breast cancer development. In regards to reducing ovarian cancer risk, a woman's ovaries and fallopian tubes can be removed.[2]

Lastly, chemoprevention medications can be utilized to reduce the risk of cancer. For example, tamoxifen or raloxifene are FDA-approved to reduce the risk of breast cancer in women at high risk of development. Similarly, oral contraceptives are thought to reduce the risk of ovarian cancer by around 50% in both the general population and women with harmful *BRCA1* and *BRCA2* mutations.[2]

Overall, *BRCA1* and *BRCA2* mutations stand at the forefront of genetic mutations leading to breast and ovarian cancers. Therefore, knowledge of family history and personal risk are significant factors necessary for proper risk management. When risk is properly assessed, risk management can result in early detection and a higher probability of successful treatment.

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Antiemesis Treatment for Chemotherapy-Induced Nausea and Vomiting

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Pharmacists in all roles and positions support patients with knowledge and expertise. Here we discuss medications that are recommended to prevent and/or treat emesis in adult cancer patients, according to the National Comprehensive Cancer Network (NCCN)[1] and American Society of Clinical Oncology (ASCO) guidelines[2].

Patients with cancer present in all healthcare settings; therefore, pharmacists knowledgeable of the agents used to manage different types of chemotherapy-induced nausea and vomiting (CINV) are better able to provide patient care. Acute CINV is defined as occurring within 24 hours of chemotherapy. Delayed CINV occurs more than 24 hours after chemotherapy. Breakthrough CINV occurs despite optimal antiemetic prophylaxis. Anticipatory nausea and vomiting (ANV) occurs before chemotherapy as a conditioned response, developed after significant nausea and vomiting during previous chemotherapy treatments.[1]

Acute and Delayed CINV
For management of acute and delayed emesis, chemotherapy agents are classified into emetic risk categories. Antiemetic regimens are selected based on the highest emetic risk medication in the treatment plan. Below is a review of the antiemetic medications used to treat acute and delayed CINV.

Agents used in Acute and Delayed CINV prevention

Medication	
Substance P/Neurokinin 1 Receptor Antagonists (NK1 RA)	Aprepitant
	Aprepitant injectable emulsion
	Fosaprepitant
	Netupitant*
	Fosnetupitant*
	Rolapitant
5-HT3 Receptor Antagonists (5-HT3 RA)	Dolasetron
	Granisetron
	Ondansetron
	Palonosetron
Corticosteroid	Dexamethasone
Atypical Antipsychotic	Olanzapine
Typical Antipsychotic, Phenothiazine Derivative	Prochlorperazine
5-HT4 Receptor Agonist	Metoclopramide

*available in fixed combination with palonosetron only

Breakthrough Emesis Treatment
Breakthrough and anticipatory nausea can present when the patient is not actively receiving chemotherapy. Prevention of nausea and vomiting is ideal. If emesis does occur, this can lead to anticipatory nausea and vomiting in the future and/or discontinuation of chemotherapy. [3] If patients experience emesis despite optimal therapy, it is recommended to try an agent from a different class than was used previously and subsequent antiemetic regimens should be adjusted accordingly.

Cornerstones of acute CINV management, 5-HT3 RAs, NK1 RAs, dexamethasone, and olanzapine, are usually utilized first. Dexamethasone and 5-HT3 RAs are included in most antiemesis regimens so their use in breakthrough CINV is limited. Olanzapine is becoming more widely utilized as evidence emerges supporting its safety and efficacy in CINV.[4] It is often the last of the four most-utilized antiemetics for acute and delayed CINV prophylaxis, so it can usually be added as breakthrough emesis treatment and to subsequent emesis prevention plans. Concomitant use of olanzapine and dopamine blocking agents such as metoclopramide and haloperidol can increase the risk of extrapyramidal symptoms (EPS).[1] Benzodiazepines benefit patients who experience anxiety before, during, or after chemotherapy. Scopolamine has been shown to be effective in CINV and dizziness associated with body movement.[5] Prochlorperazine is often preferred to promethazine, because it has less histamine blocking properties and so is less sedating.[1] Cannabinoids have shown some evidence of effectiveness but not more effective than first line therapies, so it's recommended use is limited to second or third line for CINV.[1,6] Haloperidol and metoclopramide use is limited to after other therapies have failed because of their drug-drug interactions and adverse effect profiles.

Agents used in breakthrough emesis treatment
Select a medication from a class not already utilized in the antiemetic regimen

Atypical Antipsychotic	Olanzapine
Benzodiazepine	Lorazepam
Cannabinoids	Dronabinol
Nabilone	Nabilone
Phenothiazines	Prochlorperazine
Promethazine	Promethazine
5-HT3 Receptor Antagonists (5-HT3 RA)	Dolasetron
Granisetron	Granisetron
Ondansetron	Ondansetron
Corticosteroid	Dexamethasone
Other	Haloperidol
	Metoclopramide
	Scopolamine

Anticipatory Emesis Management
Since ANV is a conditioned response to severe CINV during or after previous chemotherapy, preventing severe CINV is optimal. There is evidence the incidence of ANV is decreasing compared to the 1980s, which is suspected to be due to more effective antiemetic medications becoming available.[7] However, ANV remains a challenge to treat as it can be resistant to many pharmacological treatments.[7] Evidence shows behavioral therapies are more effective than pharmacologic treatments likely due to ANV being a conditioned response. [7] Most studies have focused on three general behavioral therapy strategies: systemic desensitization (SD), progressive muscle relaxation training (PMRT), and hypnosis.[8] SD involves counter-conditioning of a developed response and was first utilized in the treatment of learned fears and phobias. [7] PMRT, often used with relaxation techniques, has been shown to decrease the duration of CINV. [9] PMRT is performed when the patient arrives at the clinic or sees the chemotherapy nurse, as these are experiences which are often associated with ANV. [10] These strategies and relaxation training have shown to improve some patients' anxiety and quality of life when ANV is controlled.[11] Pharmacological treatments of ANV are generally limited to a benzodiazepine, such as lorazepam.

When assessing antiemetic therapy for patients, pharmacists and other providers can improve patient outcomes when cognizant of possible CINV and familiar with effective therapies for the various types of nausea and vomiting associated with chemotherapy.

Resources:

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Understanding Biosimilars

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Biologics are large, complex molecules that are composed of live cells. They consist of thousands of atoms to create highly specific molecules that are used to treat more complex diseases/conditions. The first biologic manufactured is referred to as the originator or reference product. A biosimilar has no clinically meaningful differences in safety, purity, and potency from the reference product.[1]

Biosimilars differ mostly by the manufacturing process. Once the patent on a biologic reference product expires, the manufacturer does not have to release how they formulated the original product. It then becomes a backward twirl for others to try and "copy" the reference product. While they are not identical to the reference product, they are highly *similar*, hence the term biosimilar. There are more patents on the manufacturing process than the product itself.

The process involved in development initially entails identifying the gene of interest to modify. Once identified, manufacturers use a particular host cell for the desired gene. The next measure is to increase the protein expression after finding a way to replicate the cell line. This is where biologics can vary as they are grown in living systems that have their own unique cell line.[2,3] Final steps involve harvesting the protein cells and purifying the protein selected.[4]

Similar to the Food and Drug Administration (FDA) 351(a) biologic approval pathway, the FDA sets regulations specific for the approval process for biosimilar products, known as the 351(k) biosimilar pathway. It is important to recognize the two differ. The biosimilar pathway to approval is an entirely separate and much shorter process than the biologic pathway. Compared to a biologic reference product, once approved, it goes through an extensive clinical studies phase, strongly relying on clinical data for the requirement of full reports on safety and efficacy in investigations. A biosimilar relies on the existing analytical data from the biologic reference product, in addition to new data demonstrating its comparison to the novel biologic. Biosimilars are provided a blanket indication for the same indications as the reference product once they can provide sufficient clinical evidence there is no difference in efficacy.[5]

Both biologics and biosimilars that have gained FDA approval can be found in the Purple Book. Much like the Orange Book, which demonstrates which products are therapeutically equivalent, the Purple Book displays the biologics approved as well as the biosimilars that were derived from the reference product.[7]

When making clinical decisions that can impact a patient's life and the cost for the pharmacy, it is crucial to understand how biologic reference products and biosimilars differ and what commonality they share. Together they will share the exact same primary structure. Both bioequivalences are comparative in clinical trials. They both receive the same approval for purity, safety, and potency from the FDA. As far as their biologic activity goes, there is no clinically meaningful difference. Both products will have the same mechanism of action as well as indications.[4,6]

While the primary amino acid structure is the same, biosimilars are produced from different cell lines and have a different composition process. Biosimilars can vary from reference product due to **minor structural variations causing a different formulation that can include varying inactive ingredients.** Due to this, the stability of the product, storage requirements, and expiration can vary from the biologic reference product. Another factor is the price difference may vary substantially.

Overall, biosimilars are highly comparable to their original biologic reference product. With the expedited FDA approval process, it allows for potentially more affordable medications to be accessible with the same safety, purity, and potency standards of all other FDA approved medications.

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Procalcitonin Utilization

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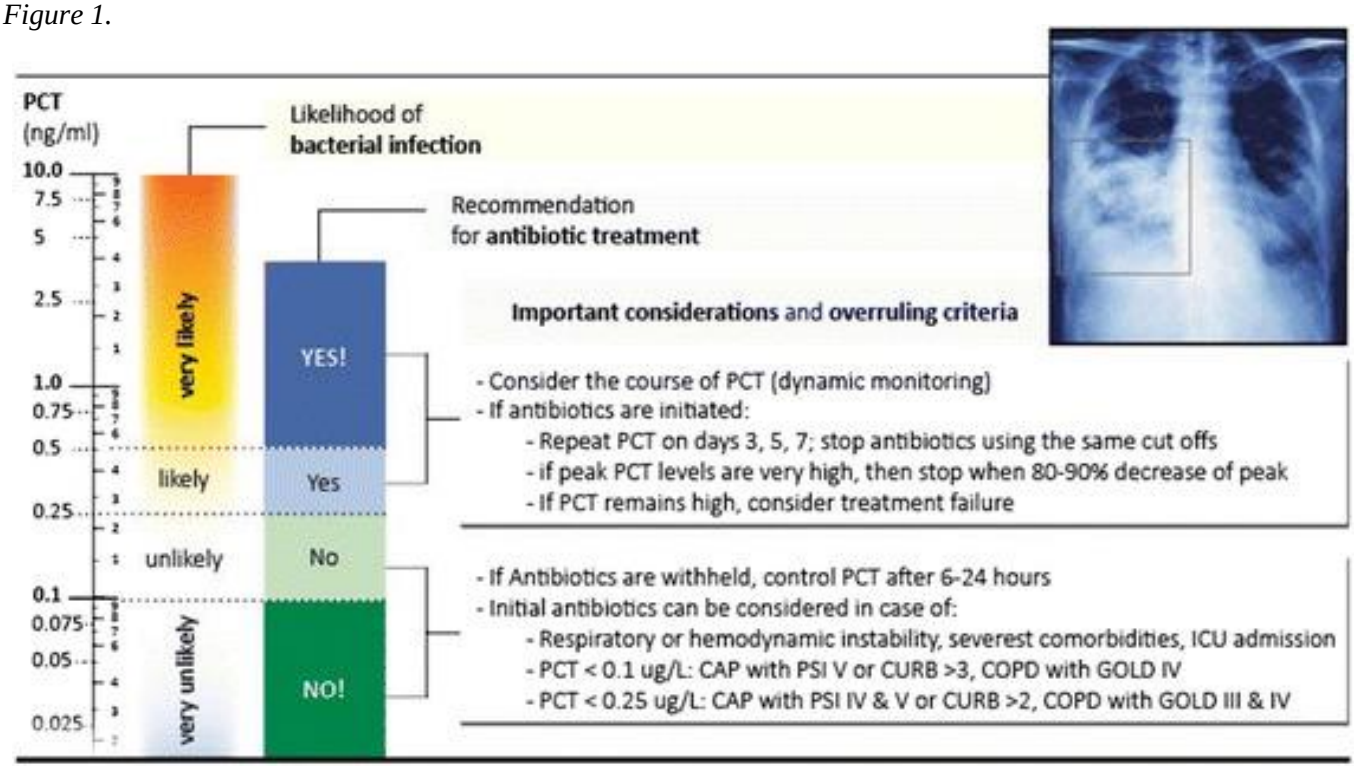
Background:[1,2]

The Infectious Diseases Society of America (IDSA) estimates that roughly 50% of inpatient antibiotic utilization is inappropriate. One clinical scenario included in this estimate is the inappropriate administration of antibiotics to patients without bacterial illness. For instance, approximately 90% of cases of acute bronchitis are caused by viruses; however, roughly two-thirds of all patients presenting with this illness in the United States will receive antibiotics. Given this trend, an increasing national interest has been taken in diagnostic aids which may increase accuracy in the diagnosis of acute bacterial illnesses in order to reduce the unnecessary utilization of antibiotics and, thus, minimize unintended consequences associated with their use (i.e. adverse drug reactions, development of *C. difficile* infection, development of resistance, etc.). This review will describe how serum procalcitonin (PCT) levels can be used in community healthcare to prevent inappropriate use of antimicrobial agents.

What is procalcitonin?[3-11]

PCT is a precursor of calcitonin contained in many tissues throughout the body. Normal physiologic PCT levels are low at less than 0.1 mcg/L, but during periods of severe infection PCT is released in large quantities, providing a specific and sensitive identifier of bacterial infections when serum levels rise above 0.25 mcg/L. Advantages of obtaining serum PCT compared to lab cultures and other biomarkers in infection diagnosis include a strong correlation between the start of infection and the elevation of PCT, the rapidity of turnaround time for the results (obtainable within several hours of exam), and it acts as a strong indicator of either bacterial or viral infection. Serum PCT levels rise 2-4 hours after onset of bacterial infections, with levels peaking 8-24 hours after onset of infection. This is opposed to viral infections, where PCT serum levels remain consistent with the pre-infection levels. Studies suggest that the presence of endotoxins and lipopolysaccharides upregulate the production of PCT in bacterial infections. Contrary to bacterial infections, the release of cytokines during the host immune response to viral infections is known to downregulate PCT synthesis through TNF-alpha inhibition.

Figure 1.



Procalcitonin (PCT) algorithm in patients with respiratory tract infections in the emergency department. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the emergency department encourages (>0.5 ng/ml or >0.25 ng/ml) or discourages (<0.1 ng/ml or <0.25 ng/ml) initiation or continuation of antibiotic therapy more or less based on specific PCT cut-off ranges

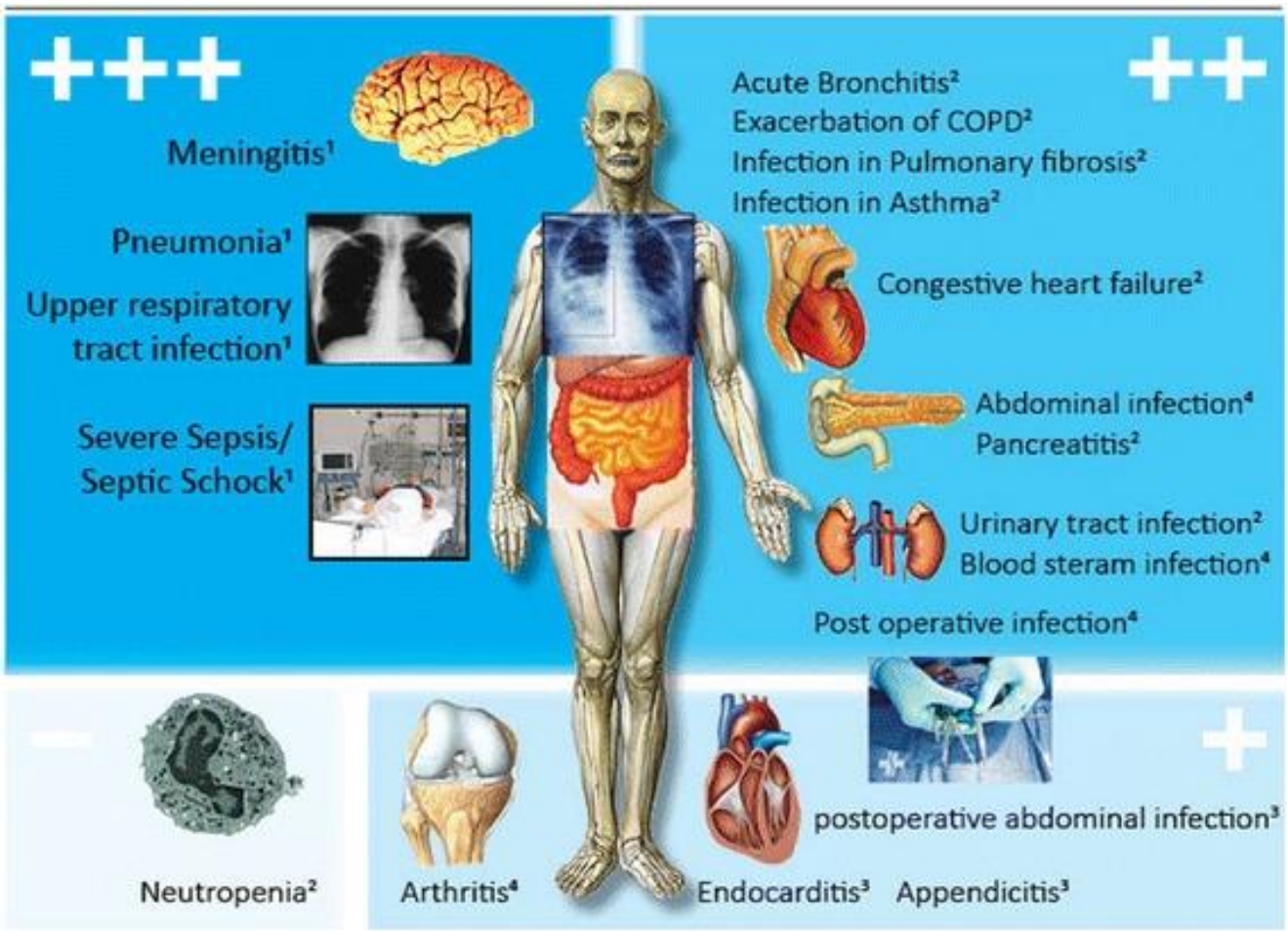
Additional Considerations

Certain subsets of patients should not undergo PCT analysis. This includes but is not limited to patients who are under the age of 18, pregnant or breastfeeding, with poor kidney function, severe immunosuppression, trauma, or who have other serious health conditions. In addition, PCT can be elevated in situations other than bacterial causes. False-positive elevated PCT readings can be contributed to massive stress (severe trauma), cytokine stimulating treatment, conditions allowing translocation of bacteria, malaria and some fungal infections, or prolonged cardiogenic shock. There are also situations when PCT levels may be low when a true bacterial infection exists. A false-negative can occur early in the course of infection, when the infection is localized, or with infections of *Mycoplasma pneumoniae* or *Chlamydiophila pneumoniae*. When using PCT levels, it is important to consider all of the patient's clinical data when diagnosing infection type and treating with antibiotics.

How is procalcitonin used in clinical practice?[12-14]

Procalcitonin (PCT) is used as a biomarker for early detection of systemic bacterial infections. Other inflammatory biomarker, such as C-reactive protein, lack specificity in determining bacterial vs non-bacterial infections. With a specificity of 79%, PCT is an additional tool that clinicians can use to reduce the overuse of antimicrobials and has proven to be a helpful diagnostic tool in patients with lower respiratory tract infections (LRTI). Furthermore, PCT can also be used in the management of antimicrobial therapy in patients with sepsis of unknown origin. While PCT should not be used in the diagnostic criteria for sepsis, it can be used to decrease the duration of antimicrobial therapy. *Figure 2* contains a summary of evidence regarding procalcitonin use in clinical practice.

Figure 2.



Summary of evidence regarding procalcitonin (PCT) for diagnosis and antibiotic stewardship in organ-related infections. While for some infections, intervention studies have investigated benefit and harm of using PCT for diagnosis and antibiotic stewardship (left side), for other infections only results from diagnostic (observation) studies are available (right side). +: moderate evidence in favor of PCT; ++: good evidence in favor of PCT; +++: strong evidence in favor of PCT; – no evidence in favor of PCT.

Procalcitonin Use in LRTIs[12-14]

Multiple randomized controlled trials have yielded sufficient data to recommend the use of PCT in the management of patients with LRTIs such as pneumonia, chronic bronchitis, and other assorted lower respiratory tract infections such as acute exacerbations of chronic obstructive pulmonary disease (COPD). LRTIs are considered one of the most important drivers for the over-use of antibiotics, contributing to the rise of multi-drug resistant pathogens. A 2012 Cochrane meta-analysis found a strong reduction in the use of antibiotics when treatment duration was guided by biomarkers such as procalcitonin. According to this meta-analysis, PCT monitoring resulted in a reduction in treatment time and exposure to antibiotics. However, this is only based on community-acquired disease, and evidence suggests PCT levels should only be used in patients with suspected community-acquired LRTIs. See the below *Table 1* for recommended treatment and interpretation of procalcitonin levels.

Table 1: Procalcitonin Utilization in LRTI.

	INITIAL PROCALCITONIN LEVEL (DRAWN ON ADMISSION):			
PCT Result:	**≤0.1 ng/mL**	**0.1 - 0.25 ng/mL**	**>0.25 – 0.5 ng/mL**	**>0.5 ng/mL**
Antimicrobial Recommendation:	Strongly Discouraged	Discouraged	Encouraged	Strongly Encouraged
Overruling the Algorithm:	**Consider Alternative Diagnosis** Consider overruling algorithm and initiating antimicrobials if patient is clinically unstable (hemodynamic or respiratory instability) or at high risk for adverse outcomes (PSI class IV-V, CURB-65 >3, or GOLD III-IV)		N/A	N/A
Follow-up/Other Comments:	Reassess patient's status and repeat PCT in 6-24 hours if warranted.*		Recheck PCT level every 2-3 days to consider early cessation of antibiotics using the above breakpoints or, if initial values >5-10 ng/mL, when a 90% reduction is seen from peak values. If procalcitonin is rising or unchanged at repeat, consider possibility of treatment failure and workup need for expanded antimicrobial coverage and/or further diagnostic evaluation.	

PCT = Procalcitonin ** Repeat procalcitonin levels should be considered in patients NOT started on antibiotics where no clinical improvement is observed at 6-24 hours and in patients in whom the algorithm is overruled (i.e. initially with low procalcitonin levels who are started on antimicrobials due to clinical instability or risk for adverse outcomes).*

Procalcitonin Use in Sepsis[12-14]

Procalcitonin levels can also be used in the management of sepsis. It is **NOT RECOMMENDED** to be used in the diagnosis of sepsis, due to the high mortality associated with delaying antimicrobial therapy. Procalcitonin levels should be utilized by trending values in combination with patient specific clinical data to assess and guide clinical therapy. *Table 2* below shows recommended utilization of antibiotics in patients with "sepsis of unknown origin". Patients with sepsis of known origin, however, are still recommended to follow treatment guideline duration of therapy.

Table 2: Utilization of FOLLOW-UP Procalcitonin Levels in Sepsis.

PCT Result:	**<0.25 ng/mL**	**0.25 – 0.49 ng/mL -OR- ≥80% reduction from peak value**	**≥0.5 ng/mL -AND- <80% reduction from peak value**	**≥0.5 ng/mL -AND- Rising or stable when compared with previous value**
Antimicrobial Recommendation:	Antimicrobial cessation strongly encouraged	Antimicrobial cessation encouraged	Antimicrobial cessation discouraged	Antimicrobial cessation strongly discouraged
Overruling the Algorithm:	Consider antimicrobial continuation if patient clinically unstable.		N/A	N/A
Other Comments/Considerations:	A PCT value which is rising or not declining is a poor prognostic indicator and suggests infection is not controlled. Consider further diagnostic evaluation.			

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