Original Research Article

Procalcitonin as a biomarker and risk stratification tool in COVID-19 patients.

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ABSTRACT

COVID19 is a systemic disease with a highly variable clinical course, ranging from being asymptomatic to manifestations like bilateral interstitial pneumonia, and multi-organ failure**.**

***Aims & Objectives*:** To evaluate whether Procalcitonin can act as a biomarker for risk stratification and identify patients at risk for clinical deterioration-critical disease.

Study design: This was a prospective cohort study.

Place and Duration of Study: Medical High Care & Intensive Care Unit at University Hospital Ayr, UK between January 2021 and March 2021.

Methodology: The patients were classified into two groups, low PCT group (<0.5 µg/L) and high PCT group (>0.5 µg/L) at 48 hrs of admission to the unit. Primary outcomes compared were requirement of invasive ventilation, multi-organ failure, antibiotic consumption, and mortality. Continuous variables were analysed using two-sample unpaired t test while categorical variables were compared using Fisher's exact test. A p- value of <0.05 was considered statistically significant.

Results: A total of 40 COVID 19 patients were included in the study, with 23 patients in the low PCT group and 17 patients were included in the high PCT group. The mean PCT at 48 hrs in the low PCT group was 0.327$\pm$0.098 µg/L, whereas in the high PCT group, it was 2.862$\pm$1.409 µg/L, the differences being statistically significant ($p<0.0001$). 56.52% patients(n=13) had multi-organ failure & mortality remained 26.09% in the Low PCT group whereas 94.12% of the patients (n=16) developed multi-organ failure & the mortality was 70.59% in the high PCT group, differences being statistically significant. Also, significant differences were noted in the usage of antibiotics between the two groups.

Conclusion: We concluded that Procalcitonin levels could be used reliably for risk stratification and raised PCT values would help identify a subgroup of COVID-19 patients with increased likelihood of critical disease and poor outcome.

Keywords: [Procalcitonin (PCT); COVID-19 disease; Risk stratification; Mortality; Multi-organ failure (MOF)]

1. INTRODUCTION

Coronavirus disease (COVID 19) is a systemic disease affecting a wide variety of cells. Patients infected with it demonstrate a highly variable clinical course of the disease, ranging from being asymptomatic to multi-organ failure [1]. COVID-19 disease is classified into four categories, mild, moderate, severe, and critical pneumonia [2]. Mild pneumonia is reserved

for asymptomatic infection or patients having mild clinical symptoms without abnormal radiology. Moderate pneumonia is for symptomatic disease with abnormal radiological findings. Severe pneumonia is defined when there is disease progression to meet any of the following criteria: (i) markedly increased respiratory rate of ≥30 breaths/min; (ii) SPO2 ≤93% in resting state; or (iii) PaO2 /FiO2 (partial pressure of oxygen/fraction of inspired oxygen) ≤300 mmHg (1 mmHg = 0.133 kPa). And lastly, Critical pneumonia is said to occur when there is rapid progression of the disease with any of the following conditions: (i) respiratory failure requiring mechanical ventilation; (ii) shock; or (iii) any other organ failure requiring intensive care unit admission for management [3]. Secondary bacterial infections leading to sepsis and septic shock are also very common complications in the COVID 19 patients especially those admitted in the Intensive care unit [4]. Procalcitonin (PCT) though a marker of bacterial infection, could play a vital role in the management algorithms for all lower respiratory tract infections [5]. In addition, PCT would be useful in the identification of critical patients who are at a heightened risk of multi-organ injury [6].

Secondary bacterial infections are a leading cause of morbidity and death following respiratory viral infections [7]. The increase in antibiotic resistance presents a global public health concern. The issue has also been highlighted by WHO as the cause of concern especially in context of COVID 19 which in the first wave showed prolific usage of antibiotics [8]. Subsequent guidelines have limited use of empiric antibiotics in COVID 19 patients in absence of bacterial co-infection. Extensive usage of antibiotics around the world has been linked to increased morbidity and mortality secondary to complex drug-resistant infections, such as severe diarrheal diseases such as Clostridium difficile colitis etc [9]. Additional strain on an overwhelmingly overburdened healthcare system is put by the cost of prolonged hospital stays and expensive drugs which highlights the role of antibiotic stewardship [10]. Although with more experience in dealing with COVID 19 patients over the last one year had precluded the routine use of antibiotics yet these patients would develop secondary bacterial and fungal infections which needed close monitoring. More recent data is suggestive of a link between the disease severity in patients infected with COVID-19 and the serum PCT levels [11]. Based on the initial reports, PCT was incorporated in the laboratory work-up in patients diagnosed with COVID-19 [12] and we were interested in ascertaining the prognostic value of Procalcitonin to determine the severity of COVID19 infection.

AIMS & OBJECTIVES: To evaluate whether Procalcitonin can act as a biomarker for risk stratification and identify patients at risk for clinical deterioration-critical disease. The other main objectives were to compare between the two groups:

1) Incidence of multi-organ failure and mortality as per the PCT values

2) Incidence of requirement of invasive and sole non-invasive ventilation

3) The antibiotic usage in COVID-19 patients based on the PCT values.

2. MATERIAL AND METHODS

This prospective, single-centered, cohort study was undertaken at University Hospital Ayr, UK for a pragmatic assessment of Procalcitonin in COVID-19 patients admitted in the Medical High Care and Intensive Care Unit. Our study conformed to the STROBE guidelines. Eligible criteria included patients aged ≥ 18 to <70 years, admitted in MHC and ICU with a positive SARSCoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) result diagnosed as having Severe pneumonia who were deemed for full escalation as per the signed treatment escalation plan. Exclusion criteria included: (1) Age<18 yrs or >70 yrs. (2) pregnancy, (3) post-surgery (4) insufficient data provided (5) Patients with known highly

elevated bilirubin levels (40 mg/dL) or triglycerides (1000 mg/dL) shall not be eligible (interference with procalcitonin measurements).

The study conformed to the ethical standards of the latest version of the Declaration of Helsinki. Diagnostic algorithm (Appendix) was drafted and after Internal Review Board approval, it was circulated amongst the relevant staff working in Medical High Care and Intensive Care Unit. Written informed consent was obtained from all patients included in the study. Procalcitonin-guided therapeutic and diagnostic interventions were utilized as an indication to start or escalate antimicrobial therapy according to the proposed hypothesis. All patients undertook PCT testing upon their admission/first 24 hrs (baseline PCT) to the unit followed by serial Procalcitonin measurements done routinely on alternate days- 48 hrs, etc or when the patient clinically deteriorated and had increased suspicion of bacterial co-infection. PCT cut-off levels had been adapted from the Pro-HOSP randomised controlled trial (RCT) investigating the effect of PCT guided antibiotic prescribing in lower respiratory tract infections. 13 PCT cut-offs in the majority of RCTs had been consistent at 0.25µg/L and 0.5 µg/L in ward and ITU patients respectively. A lower cut-off level of 0.5 µg/L was chosen for this study in clinically stable patients and 0.25 µg/L if increased likelihood of bacterial co-infection, clinically unstable upon admission/ in first 24 hrs of unit admission. Also, Culture samples from blood, urine, airways, and other suspected sites were performed according to the standard of care whenever bacterial infections were suspected or when there was increase in PCT values as per the algorithm.

The patients were classified into two groups, low PCT group (<0.5 µg/L) and high PCT group (>0.5 µg/L) at 48 hrs of admission to the unit. Primary outcomes compared between the groups included requirement of invasive ventilation, multi-organ failure, antibiotic consumption and mortality. The day of each PCT result was correlated with the start of any antibiotic courses. The total no of antibiotic regimens prescribed were noted alongside day of escalation. Also at 48 hrs, escalation, continuation, or de-escalation of antibiotics as per PCT values were documented. Antibiotic related side effects within the 28 days were recorded including: Clostridium difficile infection, Methicillin-resistant Staphylococcus aureus (MRSA) acquisition and isolation of an extended-spectrum beta-lactamase (ESBL) from a clinical sample, etc. The maximum PCT level recorded and worsening infection needing escalation of antibiotics was also documented.

Statistical analysis

Microsoft Excel worksheets was used to tabulate the data. Data was analyzed by means of descriptive statistics viz, frequency, mean, standard deviation and percentage. Odd's ratio and z statistics were utilized to determine the strength of association of risk factors. The two-sample unpaired t test was used for comparison of continuous data and Fischer exact test was used to analyze categorical data. The value of $p < 0.05$ was considered statistically significant.

2.1 Subheading: PCT as biomarker for severity in COVID patients

3. RESULTS

A total of 40 COVID 19 patients were included in the study. According to PCT value at 48 hrs, the low PCT group included 23 patients whereas 17 patients were included in the high PCT group. The mean age in Low PCT group was 54.565 ± 10.676 years with 52.17% males(n=12) and 47.83% females(n=11). On the other hand, mean age in the high PCT group was 57.411 ± 7.754 years with 52.94% males(n=9) and 47.06% females(n=8).

In the low PCT group, mean PCT at 48 hrs was 0.327± 0.098 µg/L. Only 17.39% of patients had antibiotics started in first 24 hours(n=4) and 13.04% of patients had antibiotics stopped in 48 hrs(n=3). None of the patients had antibiotics escalated at 48 hrs in the low PCT group. In the high PCT group, mean PCT at 48 hrs was 2.862±1.409 µg/L. 17.64% of the patients(n=3) in the high PCT group had antibiotics started in the first 24 hrs and all patients (100%) had antibiotics escalated or commenced at 48 hrs.

The various observations and results are summarized in Tables 1 and 2.

TABLE 1: Comparison of Procalcitonin (PCT) values at various time intervals

PCT LEVELS (ng/ml)	**LOW PCT GROUP**(MEAN±SD)	**HIGH PCT GROUP**(MEAN±SD)	**p-value**	**95% confidence interval**
PCT IN FIRST 24 HRS	0.302± 0.156	0.575±0.435	0.0268	-0.503 to -0.042
PCT IN 48 HRS	0.327± 0.098	2.862±1.409	<0.0001	-3.249 to -1.820
PCT LEVEL AT THE TIME OF START OF ANTIBIOTICS	1.722±1.564	2.578±1.391	0.1362	-1.834 to 0.1228
MAXIMUM PCT LEVELS RECORDED	4.640±4.584	11.398±3.854	<0.0001	-9.546 to -3.969

TABLE 2: Comparison of study parameters amongst the groups

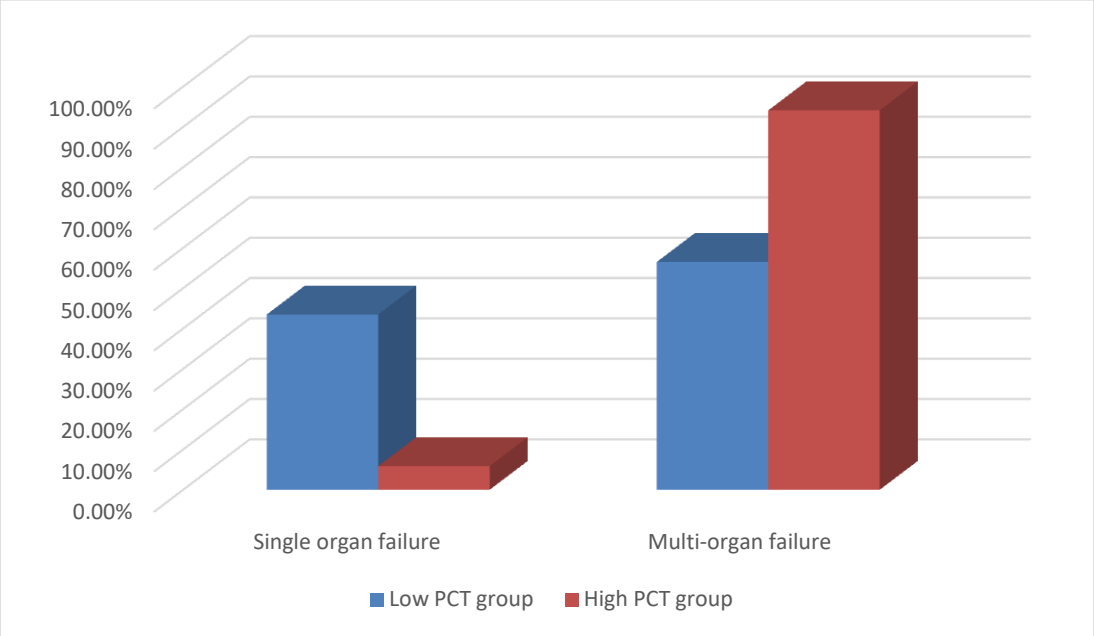
	Low PCT group	**High PCT group**
Average day of start of antibiotics	3.782±3.437 days	1.882±0.332 days
Escalation of antibiotics	47.82% (n=11)	100% (n=17)
Invasive ventilation requirements	52.17% (n=12)	100%(n=17)
Multi-organ failure	56.52% (n=13)	94.12% (n=16)
Mortality	26.09% (n=6)	70.59% (n=12)

In the low PCT group, 52.17% patients(n=12) required invasive ventilation and 47.83%(n=11) were managed solely on Non-invasive ventilation. Also, 56.52% patients(n=13) had multi-organ failure. And the mortality was found to be 26.09%(n=6) in the Low PCT group and 73.91%(n=17) survived. Moreover, it was found that 13.04%(n=3) of the patients required more than two antibiotic regimens whereas 34.78% (n=8) needed two antibiotic regimens. And 26.08%(n=6) of the patients in the low PCT group needed either no antibiotic or just one antibiotic regimen. Only 13.04% patients (n=3, 2 in subset of >2 & 1 in subset of <2 antibiotic regimens) had drug related adverse effects like MRSA, EBL, etc. In the high PCT group, 94.12% of the patients(n=16) had multi-organ failure. All the patients (100%) required invasive ventilation, and none sufficed only on Non-Invasive ventilation in the high PCT group. Mortality was found to be 70.59% of the patients in the high PCT

group(n=12) and 29.41% of the patients(n=5) survived. 88.24% of the patients(n=15) required more than two antibiotic regimens and 11.76% of the patients(n=2) needed two antibiotic regimens. Drug related adverse effects were noted in 35.29% of the patients (n=6, 5 in subset of >2 & 1 in subset of <2 antibiotic regimens).

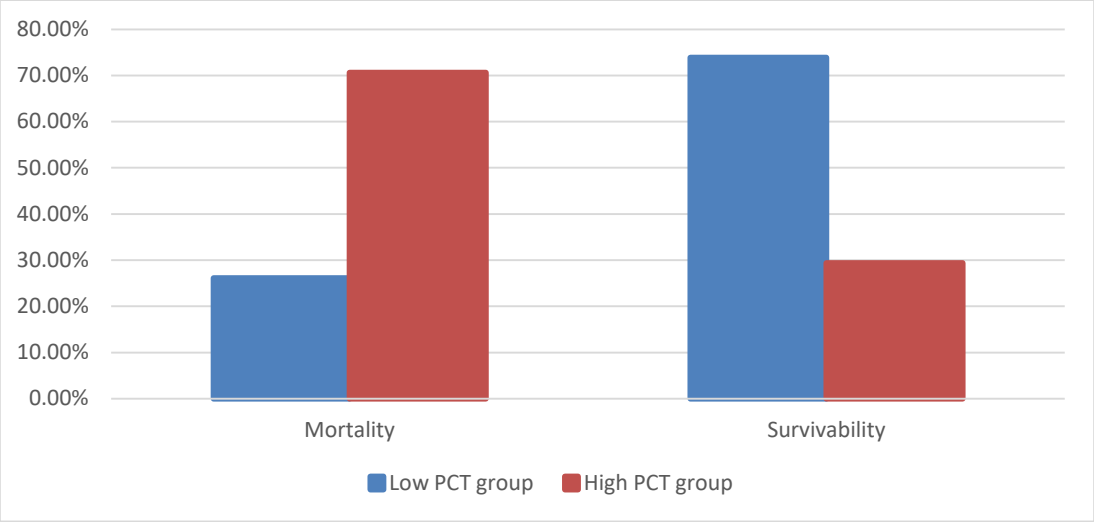
The comparison between the groups is clearly illustrated in Figures 1-3.

FIGURE 1: Comparison of Single organ vs multi-organ failure amongst the groups



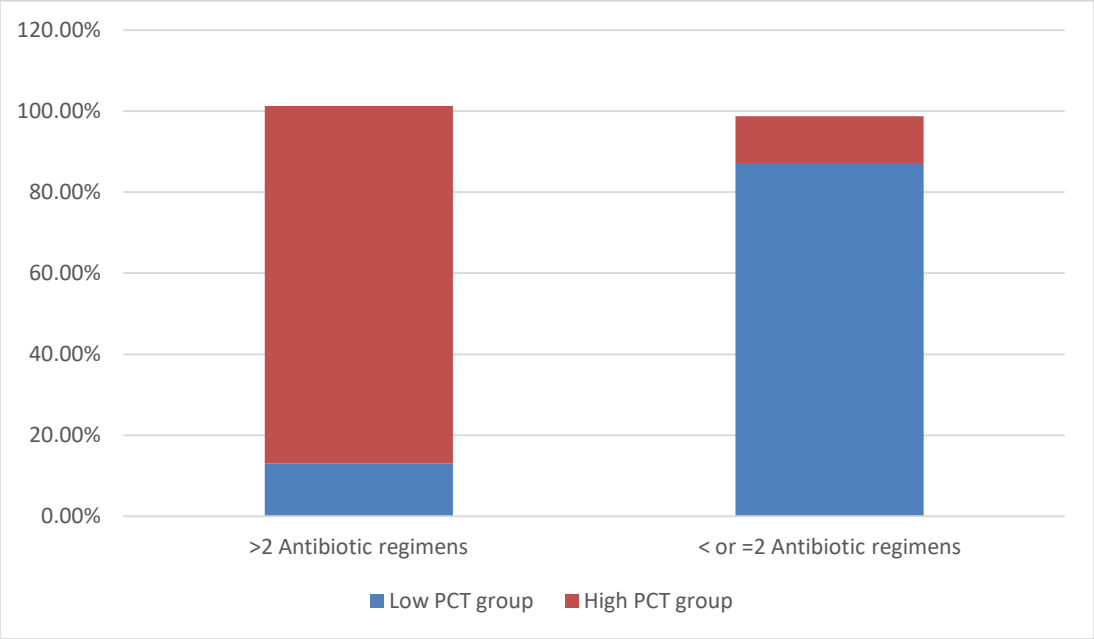
*p=0.0119

FIGURE 2: Comparison of Mortality vs Survivability amongst the groups



*p=0.0095

FIGURE 3: Comparison of antibiotic usage amongst the groups



*p<0.0001

DISCUSSION

As demonstrated in Table 1, the differences in the PCT levels recorded between the two groups were statistically significant. This is in concordance with the study conducted by Hu et al [3], who recorded the serum PCT values within three days as 0.23 ± 0.26 µg/L in the severe group (n = 21) and 0.44 ± 0.55 µg/L in the critical group (n=12). In our study, notable differences were noted in the incidence of critical disease and multi-organ failure between the two groups. This is in agreement with the study done by Hu et al who recorded statistically significant increase in total serum values of PCT as the disease worsened [3]. Also, Heesom et al [13] demonstrated invasive ventilation in 60% of the patients in low PCT

group vs 77.8% in the high PCT group. As shown in Figure 2, significant differences were noted between mortality vs survivability amongst the groups in our study (p=0.0095). This in agreement with other studies in the past which correlated elevated PCT positively with increased severity of COVID-19 [14]. A five-fold increased risk of severe COVID 19 was demonstrated by the meta-analysis conducted by Lippi and Plebani [15]. Another meta-analysis conducted by Vazzana et al [16] reviewed the prognostic value of PCT for severe disease and adverse outcome in COVID-19 patients and concluded that raised PCT levels could identify a group of COVID-19 patients at increased severity risk. Also, they found in various pooled studies that most of the infections occurred in patients with severe course and/or fatal outcome (105 of 117, 89.7%). And the risk of severe course and/or fatal outcomes was significantly increased in patients with evidence of bacterial infection (OR, 20.8; 95% CI, 11.6 to 37.4). This in agreement with our study in which we calculated two tailed p-value of usage of >2 antibiotic regimens vs <2 antibiotic regimens amongst the two groups as <0.0001, which is extremely statistically significant (Figure 3).

In contrast to other inflammatory biomarkers like ESR and C Reactive Protein, PCT values remain low in the non-bacterial causes of inflammation and infection [17]. A large-scale meta-analysis has previously proposed the use of PCT as a useful guide for the safe reduction of antibiotic prescription rates in COPD patients [18]. PCT can be used to reduce unnecessary antibiotic prescriptions in patients with symptoms of COVID-19 as demonstrated in the study conducted by Peters et al [10] in which they showed that antibiotics were either never started or were stopped within 48 hrs in 72% of all COVID-confirmed cases with PCT <0.25 µg/L. They demonstrated that PCT use helped reduce antibiotic prescriptions in all COVID- suspected or confirmed cases by 44%. This is partly in agreement with our study in which we found that in the low PCT group, 82.60% patients(n=19) didn't have antibiotics started in first 24 hrs and none of the patients had antibiotics escalated at 48 hrs whereas in the high PCT group, it was noted that 17.64% of the patients(n=3) had antibiotics started in the first 24 hrs and all patients (100%) had antibiotics commenced or escalated at 48 hrs. The two-sample unpaired t-test demonstrates statistically significant differences in the average day of start of antibiotics between the two groups (p=0.0168) and in the corresponding PCT values between the two groups (p=0.1362). The Odd's ratio for adverse drug side effects in all patients requiring > 2 antibiotics vs those needing < 2 antibiotics in both groups is 7.000. 95% CI is 1.2222 to 40.0907, z statistic is 2.185 and p- value is 0.0289, which depicts statistically significant positive association. Schuetz et al [19] conducted a patient level meta-analysis to assess the effect of PCT guided antibiotic treatment on mortality in acute respiratory infections and concluded that the use of procalcitonin to guide antibiotic treatment in patients with acute respiratory infections reduces antibiotic exposure and side-effects and improves survival.

We used PCT levels at 48 hrs because we had observed that although the COVID infections like other viral infections could have low PCT levels at presentation, it is their progress in the first 48 hrs that mostly determined their clinical course in Severe pneumonia. And we were able to demonstrate that PCT levels at 48 hrs being extremely statistically significant could be used reliably for risk stratification and prognostication as it could indicate increased propensity of critical disease.

4. CONCLUSION

We demonstrated that patients in the high PCT group were more likely to require invasive ventilation and develop multi-organ failure as compared to the patients in the low PCT group. Also, the antibiotic usage was notably greater in the high PCT group as compared to the low

PCT group. Furthermore, we found that the mortality in the high PCT group was significantly more than the low PCT group. Hence, we conclude that Procalcitonin levels could be used reliably for risk stratification and raised PCT values would help identify a group of COVID-19 patients at heightened risk of critical disease and poor outcome.

LIMITATIONS OF STUDY: This study was undertaken in one hospital in UK and hence results can't be generalized. Also, the size of sample studied was small. We would like more studies to happen across hospitals in the UK and worldwide with greater sample size so as to present a much clearer picture. Also, staff was made aware of the study right from the start which may account for bias in the study.

CONSENT

All authors declare that 'written informed consent was obtained from all patients (or other approved parties) involved in the study for publication of this research article.

ETHICAL APPROVAL

We certify that the surveys were conducted in compliance with relevant laws and institutional guidelines and that the appropriate institutional committee has approved them. Pro-calcitonin is routinely used in our hospital since past 10 years. The management algorithm was approved by the internal review board, University Hospital Ayr, UK and written informed consent was obtained from all patients included in our study. Our work conforms to the ethical standards of the latest version of the declaration of Helsinki.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

Procalcitonin: PCT
Coronavirus disease: COVID-19 disease
Multi-organ failure: MOF
Medical High Care: MHC
Intensive Care Unit: ICU
University Hospital Ayr: UHA

APPENDIX:

Patients with suspected or confirmed COVID-19

Does my patient need antibiotics?

Most patients do not require antibiotics

• CRP can be raised in COVID-19 infection and does not necessarily indicate a bacterial infection
• Many patients have a prolonged fever with COVID-19
• If in doubt ask a senior team member for advice

Factors that reduce the likelihood of secondary bacterial infection:

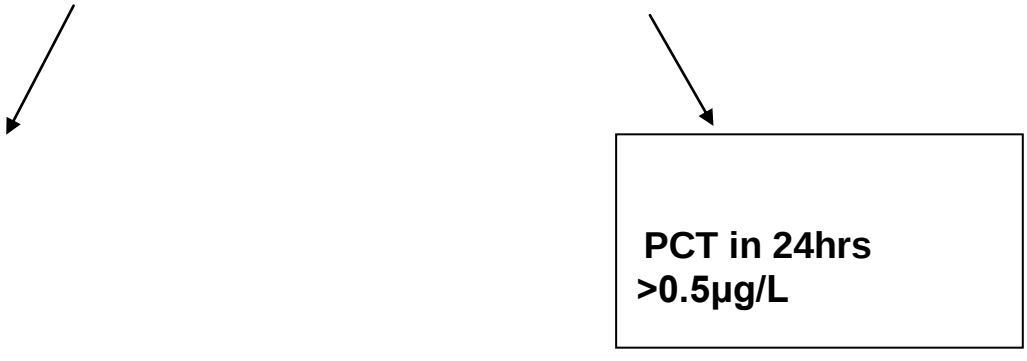
• CXR - bilateral symmetrical consolidation/ground glass change
• Bloods - lymphopenia without neutrophilia
• Symptoms - dry cough, clear sputum

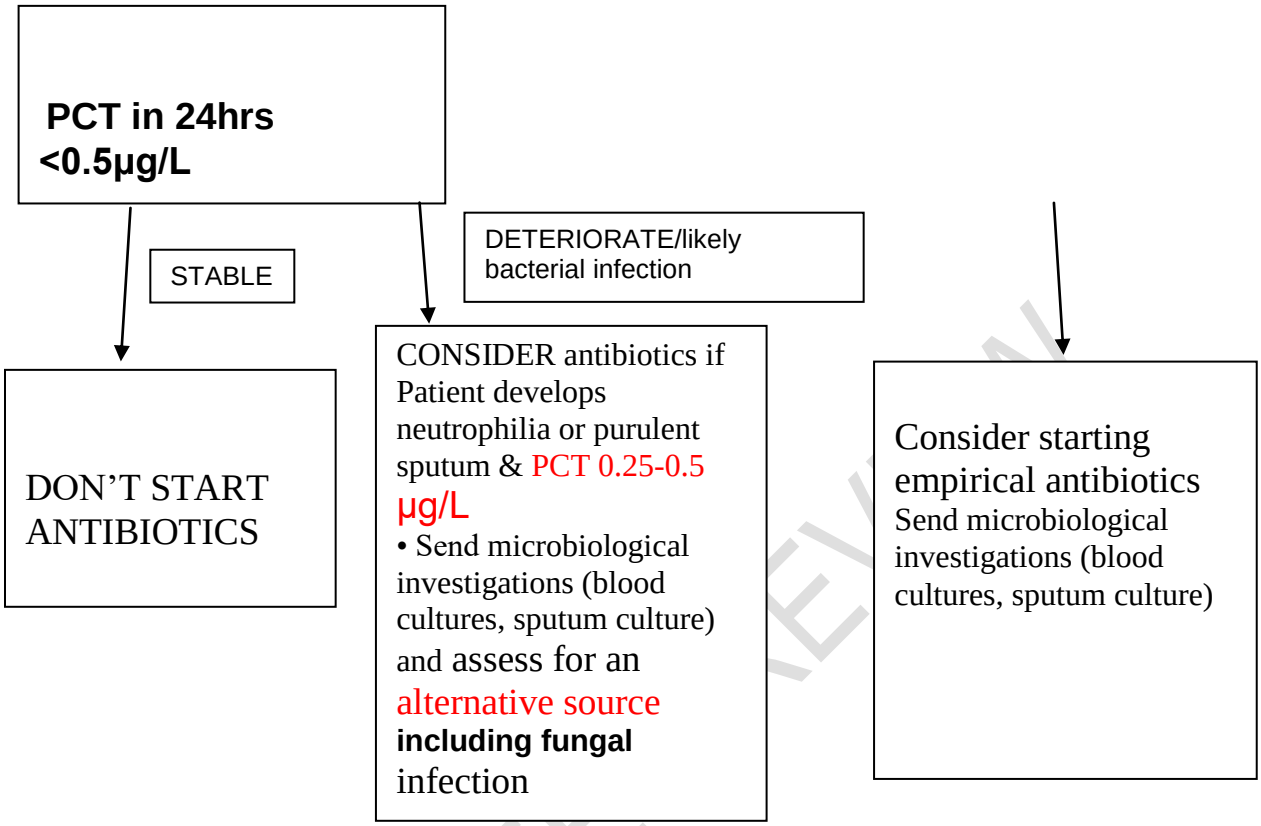
Factors that increase the likelihood of secondary bacterial infection:

• CXR – unilateral / asymmetrical consolidation
• Bloods - neutrophilia or increase in WCC
• Symptoms - purulent sputum

GUIDELINES FOR STARTING ANTIBIOTICS

DO BASELINE PCT IN ALL PATIENTS IN FIRST 24 HRS





GUIDELINES FOR ESCALATION & STOPPING ANTIBIOTICS

REPEAT PCT AT 48 HOURS/ALTERNATE DAYS IN ALL PATIENTS