Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Should procalcitonin be used to guide the initiation of antibiotic therapy in patients diagnosed with COVID-19?

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RECOMMENDATIONS

For initiating antibiotic therapy

We suggest against the use of procalcitonin alone as a basis for initiating antibiotic therapy among COVID-19 confirmed patients. *(Very low certainty of evidence; Weak recommendation)*

For discontinuing antibiotic therapy

If available, we recommend using a procalcitonin level of less than or equal to 0.25 ng/mL for discontinuing antibiotic therapy among COVID-19 confirmed patients. *(Very low certainty of evidence; Strong recommendation)*

Consensus Issues

Antibiotic misuse and abuse among COVID-19 patients is a common practice that needs to be addressed. Thus, the panel recognized that procalcitonin may have utility in guiding antibiotic use among COVID-19 patients. However, the panel was against the use of procalcitonin alone in initiating antibiotic therapy, citing that clinical evaluation and other laboratory parameters should be considered as well since procalcitonin levels can be elevated in certain conditions even in the absence of bacterial infection. Additionally, the evidence base included studies that investigated absolute cut-offs of procalcitonin rather than the comparative decrease or increase in its levels.

In contrast, the panel was unanimous in recommending the use of procalcitonin levels to discontinue antibiotic therapy among COVID-19 patients. This was to provide guidance to practitioners due to the common practice of continuing antibiotics indefinitely among critically ill patients.

Cited reasons for a weak recommendation on the use of procalcitonin for discontinuing antibiotic therapy include:

1) concerns on the cost and availability of procalcitonin;
2) very low certainty of evidence; and
3) use of indirect evidence to identify the cut-off level for discontinuation (i.e., the evidence base aimed to identify procalcitonin levels that differentiate the presence or absence of co-infection rather than the continuation or discontinuation of antibiotic therapy).

Cited reasons for a strong recommendation on the use of procalcitonin for discontinuing antibiotic therapy include:

1) the need to prevent antibiotic resistance, considering that multidrug resistance is a common cause of death among critically ill or severe COVID-19 patients; and
2) to prevent the higher costs associated with unnecessary antibiotic use (i.e., While procalcitonin is expensive, even an extra day of unnecessary antibiotic therapy would equate to higher costs for the patient).

Key Findings

- Four retrospective cohort studies were included in this review. Three provided data for calculation of diagnostic accuracy estimates, while one reported on the benefits and safety of using an antimicrobial therapy discontinuation protocol based on procalcitonin measurements. Studies used varying cut-off levels for procalcitonin and used it for guiding discontinuation of antibiotics.
- Sensitivity ranged from 0.40 to 0.87, while specificity ranged from 0.43 to 0.88. Across the three studies, a total of 42/816 (5.1%) had positive results on microbiological testing. No stratification as to whether patients with higher procalcitonin levels were associated with more severe or less severe COVID-19 cases.
- Using procalcitonin-based algorithms was found to be associated with lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs. 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] 0.70; 95% CI 0.6, 0.9) as well as mean DDD (ROM 0.70, 95% CI 0.6, 0.8). A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] 0.6, 95% CI 0.4, 1.1). Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope −0.07, 95% CI −0.11, −0.03) compared to those without procalcitonin measurements.
- Overall certainty of evidence was rated very low due to serious risk of bias, imprecision, and inconsistency.

Introduction

Procalcitonin is a protein prohormone of calcitonin produced by the C-cells of the thyroid gland. Its serum levels increase in systemic bacterial infection due to activation by cytokines and bacterial endotoxins.[1] Viral infections do not induce procalcitonin synthesis, thus the diagnostic marker can be used to distinguish between viral and bacterial infections.[2] In 2010, the PRORATA clinical trial designated a procalcitonin level of <0.25 ng/mL as a cut-off value to not initiate antibiotic use in the intensive care unit setting.[3] A diagnostic accuracy study by Self et al. in 2017 showed an association between increased probability of bacterial infection with high serum procalcitonin levels on admission; however, no threshold perfectly discriminated bacterial versus viral detection.[2]

COVID-19 patients generally have low procalcitonin levels but as disease severity becomes worse and systemic inflammation occurs, procalcitonin levels may rise.[4] Early stage COVID-19 and community-acquired pneumonia typically have similar initial presentation and the hyperinflammatory phase of COVID-19 makes it difficult to distinguish from secondary bacterial infection. Thus, starting an empiric antibiotic among COVID-19 patients is a common practice among clinicians.[5]

A review of evidence by Rawson et al. in 2020 showed low rates of bacterial/fungal co-infection among patients with COVID-19 in contrast to the high rates of antimicrobial prescribing among them.[6] Their study concluded that there should be evidence-based antimicrobial prescribing and stewardship strategies for COVID-19 patients to prevent the consequences of unintended antimicrobial use.

This evidence summary reviewed the utility of procalcitonin levels among COVID-19 confirmed patients in differentiating the presence or absence of community-acquired and nosocomial bacterial co-infections.

Review Methods

The PubMed for MEDLINE database, US NIH ClinicalTrials.gov, and WHO International Clinical Trials Registry were searched on 6 November 2021 using the search terms “SARSCoV2" or “COVID-19" and "procalcitonin" and "bacterial pneumonia" or "bacterial infections" or "sepsis". Observational studies or clinical trials that provided data to allow calculation of diagnostic accuracy measures were included. Eligible studies should use procalcitonin regardless of cut-off value for positivity, and microbiological testing as reference standard for detecting bacterial infection. Literature reviews, editorials, case reports, and case series were excluded.

Results

Characteristics of Included Studies

Diagnostic accuracy, relationship of procalcitonin with clinical outcomes

Three retrospective cohort studies among hospitalized COVID-19 confirmed patients (N=816) investigated the prevalence of bacterial co-infection and secondary bacterial infections through culture of blood, sputum, bronchoalveolar lavage washing, and urine specimens. Microbiologic testing results were then compared with serum procalcitonin levels. Based on culture results, patients were divided into two groups: (1) those with at least one additional pathogen isolated in any of the cultures and (2) those with no additional pathogen isolated. Different cut-off values were used for procalcitonin: 0.25 ng/mL, 0.25 pg/mL, and 0.1 ng/mL

For each group in Hughes et al. and Chen et al., the patients were further divided into two subgroups depending on whether procalcitonin levels were less than 0.25 ng/mL or more than or equal to 0.25 ng/mL. Cheng et al., described the prevalence of culture-positive bacterial infection among patients suspected with superimposed nosocomial bacterial infection at a designated cut-off of more than 0.1 ng/mL. Diagnostic accuracy for bacterial co-infection of procalcitonin for the three studies above was measured.

Of those with bacterial growth in culture specimens, one study (Chen et al.) further classified the patients into having co-infection (community-acquired infection) or superimposed bacterial infection (nosocomial infection). Of the 52 cases with growth, 25 (48%) had community-acquired infections, 25 (48%) had hospital-acquired infections, and 2 (4%) patients had both community and hospital-acquired infections.[7] In the other study by Hughes et al., all five cases with bacterial growth were community acquired.[8]

Benefits and safety of procalcitonin-guided protocols

One retrospective, cohort study in the UK (Calderon et al., 2021) assessed the effectiveness and safety of a procalcitonin-guided protocol on the use of empirical antimicrobials among suspected and confirmed COVID-19 pneumonia (n=259). Of the 117 patients with procalcitonin measurements, 73 (62.4%) had levels ≤0.25 ng/mL. No diagnostic accuracy measures were

reported in this study, although there were ten patients (8.5%) with positive blood culture and four (3.4%) with positive sputum cultures seen in the procalcitonin group.

A cut off level of ≤0.25 ng/mL was used to indicate stopping antimicrobial treatment, while higher levels either support or encourage continuing antimicrobials (0.25-0.4 ng/mL - supported; 0.5-1.9 ng/mL - encouraged; >2.0 - strongly encouraged). Procalcitonin results were interpreted along with other parameters (e.g., clinical suspicion of sepsis, CXR changes, infection other than respiratory illness). Outcomes included the following: (1) duration of antimicrobial exposure, (2) per-patient antimicrobial consumption (WHO Defined Daily Dose method), (3) safety (composite of death, admission to ICU >72 hours after starting antimicrobials, or readmission to hospital within 30 days).

Overall certainty of evidence

The overall certainty of evidence was rated very low for diagnostic accuracy. Studies had serious risk of bias issues related to timing of microbiologic testing in relation to procalcitonin measurements and representativeness of the sample population. Downgrading was also done due to imprecision in the estimates as well as inconsistent findings reported across the studies.

Summary of results of included studies

Diagnostic accuracy of procalcitonin

Varying diagnostic accuracy estimates were derived from three cohort studies. Sensitivity ranged from 0.40 to 0.87, while specificity ranged from 0.43 to 0.88. Across the three studies, a total of 42/816 (5.1%) had positive results on microbiological testing.

Using a cut-off value of **>0.1 ng/mL**, data from 212 COVID-19 patients with nosocomial infection in one study from China (Cheng et al. 2020) showed that the sensitivity of procalcitonin to detect culture-positive bacterial infection was 0.87 (95% CI 0.70, 0.96) while the specificity was at 0.43 (95% CI 0.35, 0.50). Of the 212 patients, 31 had positive culture isolates indicating a prevalence of 14.6%.

Using a cut-off value of **≥0.25 ng/mL**, another study from China (Chen et al., 2020) estimated a sensitivity of 0.50 (95% CI 0.12, 0.88) and specificity of 0.88 (95% CI 0.84, 0.91). A relatively similar sensitivity estimate of 0.40 (95% CI 0.05, 0.85) but significantly lower specificity estimate of 0.65 (95% CI 0.58, 0.72) was reported by a study in the UK. This study used a lower cut off level at **≥0.25 pg/mL**. Both studies documented very low prevalence (<3%) of bacterial growth in culture of specimens collected from COVID-19 confirmed patients.

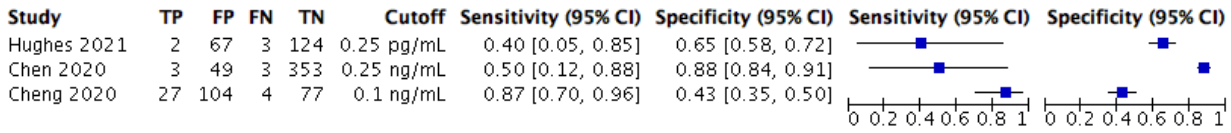

Figure 1. Accuracy of procalcitonin for detecting culture-positive bacterial infections in patients with COVID-19

Relationship of procalcitonin with disease severity

All studies did not specify whether the patients were admitted in the ward or intensive care unit (ICU). No stratification as to whether patients with higher procalcitonin levels were associated with a more severe or less severe COVID-19 case was done by both studies. However, Chen et al. showed that most culture-positive patients were those with mild to moderate COVID-19 (30 patients or 57.7%) severity, while seven (13.5%) had severe COVID, and 15 (28.8%) had critical

COVID-19 infection. However, this may be compounded by the baseline numbers showing a higher pool of patients with mild to moderate and less patients with severe or critical COVID.

Relationship of bacterial co-infection with mortality rate

Chen et al. demonstrated that COVID-19 patients with bacterial growth on culture specimens had a higher mortality rate (5.8%) versus COVID-19 patients without growth (0%), necessitating clinicians to ensure early identification of bacterial co-infection to initiate timely antibiotic treatment.[8] However, signs and symptoms of bacterial infection present similarly to COVID-19 infection. Hence, ancillary tests that allow clinicians to differentiate COVID-19 with or without bacterial infection are helpful to decrease hospital costs and improve adherence of clinicians to antimicrobial stewardship. Although bacterial culture is definitive in identifying the presence of bacterial pathogens, the turnaround time for its results are not as readily available as serum procalcitonin levels, leaving clinicians to rely on clinical data in decision-making.

Benefits and harms of procalcitonin-guided protocols

Based on the Calderon et al. 2021 study, patients with procalcitonin measurements had lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs. 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] 0.70, 95% CI 0.6-0.9) as well as mean DDD (ROM 0.70, 95% CI 0.6, 0.8).

In terms of safety, no significant differences were found between the groups. A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] 0.6, 95% CI 0.4, 1.1), although this was not statistically significant after adjusting for confounding variables such as age. Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope −0.07, 95% CI −0.11, −0.03), in contrast with the non-procalcitonin group (βslope −0.01, 95% CI −0.05, 0.02).

Other Considerations

Availability

Procalcitonin assay can be readily performed using available blood sample at the emergency department. This makes procalcitonin a potential test for aiding therapeutic dilemma of whether to start antibiotic therapy among COVID-19 patients. This, however, should be interpreted in conjunction with clinical examination and other laboratory parameters available as procalcitonin can be elevated in certain conditions such as chronic kidney disease and during a later severe course of COVID-19.[9]

Cost-Effectiveness

There is limited data on the cost-effectiveness of procalcitonin. Collins et al. reported decreased hospital costs with procalcitonin-guided antibiotic treatment in the ICU setting.[10] There are no studies on the availability of procalcitonin among hospitals in the Philippines as well as studies on equity, acceptability, and feasibility.

The standard price of procalcitonin at the Philippine General Hospital is Php 2,935. No published economic evaluation has been found investigating the cost-effectiveness of procalcitonin assays for this purpose.

Recommendations from Other Groups

The Philippine **Clinical Practice Guidelines for Sepsis and Septic Shock in Adults 2020** [11] recommended that when there is uncertainty, procalcitonin may be used as an adjunct to support the diagnosis of sepsis in adults (weak recommendation, low quality of evidence).

The **2021 Surviving Sepsis Campaign** [12] suggested using procalcitonin along with clinical evaluation to decide when to discontinue antimicrobials in adults with an initial diagnosis of sepsis or septic shock, if the optimal duration of therapy is unclear and if procalcitonin is available.

There are currently no recommendations on the use of procalcitonin to determine bacterial infection among COVID-19-confirmed patients from the WHO Living Clinical Practice Guidelines, [13] the NIH COVID-19 Treatment Guidelines, [14] and the Infectious Disease Society of America COVID-19 Guidelines.[15]

Research Gaps

Currently, there are no ongoing clinical trials on the use of procalcitonin levels to detect bacterial infection among COVID-19 confirmed patients. While culture of blood, respiratory tract specimens, urine, and other bodily fluids is the gold standard, bacterial culture has a relatively low yield and is affected by multiple factors such as adequate sampling, transport, specimen processing, and interpretation. Investigating the benefits of procalcitonin among clinically diagnosed bacterial pneumonia or sepsis in COVID-19 patients is also recommended for future research. In addition, the included studies did not specifically aim to determine the diagnostic accuracy of procalcitonin. Lastly, while a cut-off of more than or equal to 0.25 ng/mL was used in the two studies as recommended by the PRORATA trial [16] among non-COVID patients, no specific cut-off level has yet been proposed among COVID-19 patients.

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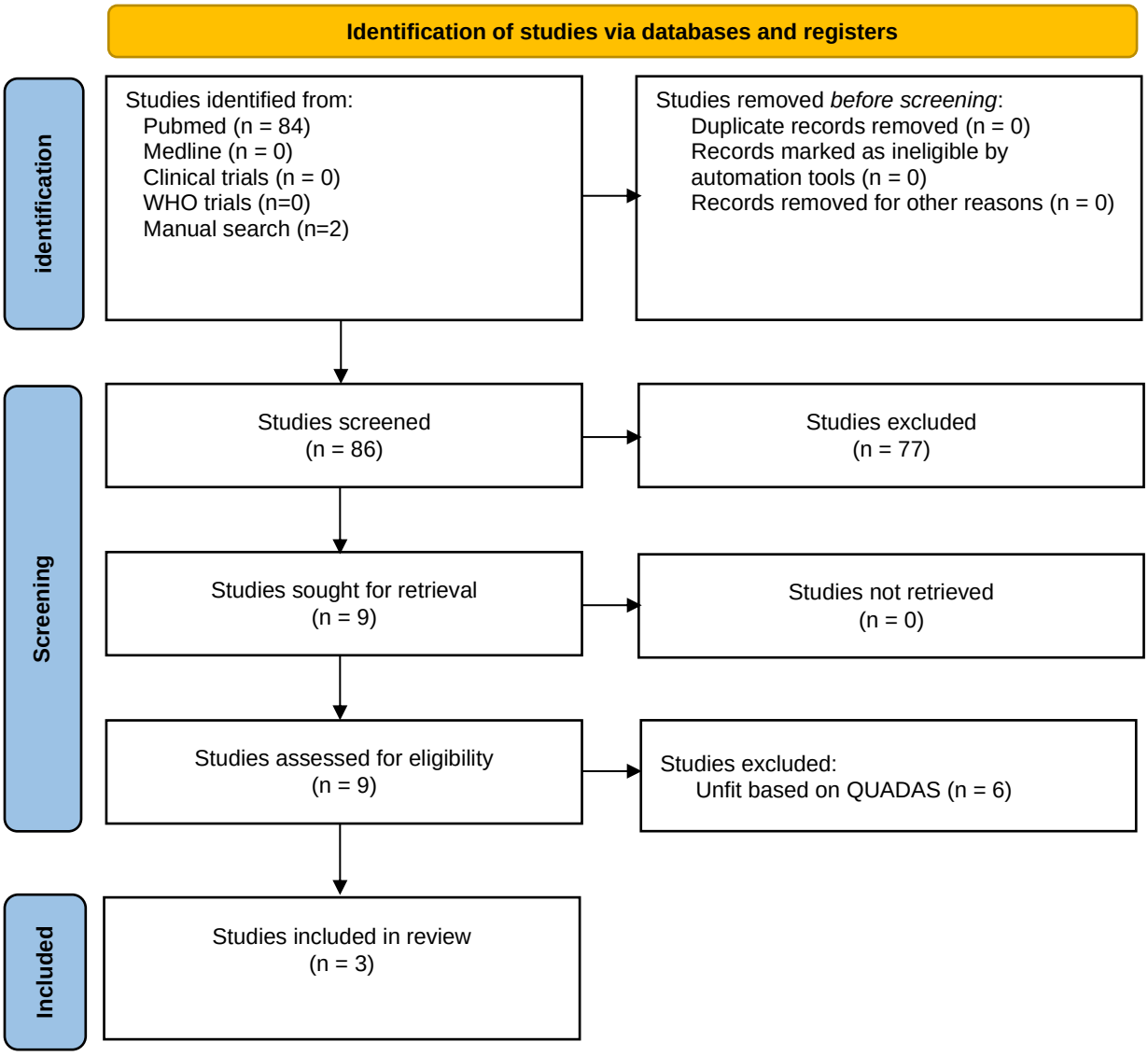
Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (8)				Diagnostic modalities that help determine the likelihood of bacterial infection on top of COVID-19 infection can help direct whether to initiate and/or continue antibiotic treatment.
Benefits	Large (1)	Moderate (6)	Small (1)	Uncertain		Using procalcitonin-based algorithms was found to be associated with lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] 0.70, 95% CI 0.6, 0.9) as well as mean DDD (ROM 0.70; 95% CI 0.6, 0.8). Potential to prevent unnecessary exposure and adverse reactions to antibiotics, prevent antibiotic resistance, prevent unnecessary prolonged hospital stay for IV antibiotic completion, and decrease overall hospital cost.
Harms	Large	Moderate (2)	Small (6)	Uncertain (1)		Based on available retrospective studies, there is no to minimal harm on performing serum procalcitonin determination among COVID-19 confirmed patients. A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] = 0.6, 95% CI 0.4, 1.1). Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope −0.07, 95% CI: −0.11, −0.03) compared to those without procalcitonin measurements.
Balance of Benefits and Harms	Favors the use of procalcitonin (2)	Probably favors the use of procalcitonin (6)	Does not favor the use of procalcitonin			

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Certainty of Evidence	High	Moderate (1)	Low (1)	Very low (6)			Overall certainty of evidence was rated very low due to serious risk of bias, imprecision, and inconsistency. Sensitivity ranged from 0.40 to 0.87, while specificity ranged from 0.43 to 0.88. Across the 3 studies, a total of 42/816 (5.1%) had positive results on microbiological testing.
Accuracy	Very Accurate	Accurate (1)	Inaccurate (6)	Very Inaccurate	Uncertain (1)		
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			No evidence
Resources Required	Uncertain	Large cost (4)	Moderate Cost (4)	Negligible cost or savings	Moderate savings	Large savings	While limited data is available in cost-effectiveness, Collins et al. reported decreased hospital costs with procalcitonin-guided antibiotic treatment in the ICU setting. The availability of the test (serum procalcitonin) may vary from institution to institution depending on available laboratory facilities. The standard price of Procalcitonin at the Philippine General Hospital is Php 2,935.
Certainty of evidence of required resources	No included studies (2)	Very low (3)	Low (2)	Moderate	High (1)		
Cost effectiveness	No included studies	Favors using procalcitonin (7)	Does not favor either using the procalcitonin or the comparator	Favors comparison (1)			No evidence
Equity	Uncertain (3)	Reduced (3)	Probably no impact (2)	Increased (1)			Based on available retrospective studies, there is no to minimal harm on performing serum procalcitonin determination among COVID-19 confirmed patients. Decreased hospital cost will also be favorable to patients and health facilities. Prevention of antibiotic-resistant organisms will also benefit the larger society.
Acceptability	Uncertain (3)	No	Yes (5)				Procalcitonin determination is already part of the routine tests done for COVID-19 confirmed patients, but cut-off values may vary from institution to institution.
Feasibility	Uncertain (1)	No	Yes (7)				

Appendix 2. Search Yield and Results



Appendix 3. Characteristics of Included Studies

Study ID Title Author	Study Design	Setting/ Country	N	Population	Intervention	Comparator/ Control	Outcomes
Clinical and etiological analysis of co-infections and secondary infections in COVID-19 patients: An observational study Chen et al 2021	Retrospective Cohort	Shenzhen Third People's Hospital, Shenzen, China	408	Hospitalized adult patients -COVID-19 confirmed via SARS-COV2 RT-PCR -mild, moderate and severe COVID-19 infections - with at least one microbiological test besides SARS-COV2 RT-PCR Exclusion: Patients with no microbiologic testing	Serum procalcitonin level	Blood samples and nasopharyngeal swabs and lower respiratory samples sent to the laboratory for molecular assay and/or conven-tional culture.	Clinical and etiological characteristics associated with co-infections and secondary infections of COVID-19 patients Identification of bacterial pathogens In-hospital Mortality rate Median hospital Stay
Hughes et al 2021 Procalcitonin to guide antibacterial prescribing in patients hospitalized with COVID-19 United Kingdom	Retrospective observational analysis	To analyze the correlation of PCT with antibacterial prescribing, confirmed bacterial infections, and determine if PCT aids with 48-72 hr review of antimicrobial therapy	624	> 18 years old Positive for COVID-19 RT PCR Exclusion: - COVID-19 suspect only 196 of which had serum procalcitonin determination 106 (54%) with antibiotics initiated on admission 85 (66%) continued antibiotics for > 72 hr	Procalcitonin serum assays (Alinity i B·R·A·H·M·S, Abbott, VA, USA); values of 0.25 pg/mL at 6–24 h post-COVID diagnosis Cutoff for positivity >= 0.25 pg/mL	Positive microbiological isolates (within 5 days of admission) that warranted targeted antibacterial treatment by the on-duty microbiology team	Clinical and etiological characteristics associated with co-infections and secondary infections of COVID-19 patients Idenfitication of bacterial pathogens In-hospital Mortality at 30 days Median Hospital Stay Prevalence of carbapenem and systemic antifungal treatment during admission
Cheng et al 2020 Analysis of the risk factors for nosocomial bacterial infection in patients with COVID-19 in a tertiary hospital Huangshi, China	Retrospective cohort	To explore exposure of risk factors and its impact on incidence of nosocomial bacterial	212	> 16 years old Positive for COVID-19 RT PCR 108 (50.9%) males 31 (14.6%) confirmed bacterial isolation (12 LRTI, 10 UTI, 7 blood, 1 URTI, 1 GIT) Exclusion:	Procalcitonin serum assays (cutoff for positivity > 0.1 ng/mL)	Positive microbiological isolates from urine, blood, lower respiratory tract specimens	Risk factors for the nosocomial bacterial infection of patients with COVID-19 Nosocomial bacterial infection rate among patients on mechanical ventilator,

Study ID Title Author	Study Design	Setting/ Country	N	Population	Intervention	Comparator/ Control	Outcomes
		infection in patients with suspected and confirmed COVID-19		COVID-19 suspect only Community-acquired bacterial infection			with indwelling urinary catheter, and arteriovenous catheterization
Calderon et al 2021 Evaluation of procalcitonin-guided antimicrobial stewardship in patients admitted to hospital with COVID-19 pneumonia United Kingdom	Retrospective cohort	To evaluate the effectiveness and safety of a procalcitonin-guided antimicrobial decision-aid in noncritically ill patients with COVID-19 pneumonia	259	Lab-confirmed or clinically-suspected COVID-19 Exclusion criteria: < 18 years old Admission to HDU or ICU within 72 hrs of admission Not receiving antimicrobials during their admission Indication for antimicrobial treatment other than respiratory tract infection Antimicrobials being stopped as part of treatment rationalization in end-of-life care	Procalcitonin (Cobas Elecsys BRAHMS; 22 serum for this assay was collected) cut off: 0.25 ng/mL		Duration of antimicrobial exposure (time from first to last dose plus dosing interval) Per-patient antimicrobial consumption (WHO Defined Daily Dose method) Safety (composite of death, admission to ICU > 72 hr after starting antimicrobials, or readmission to hospital within 30 days)

Appendix 4. GRADE Evidence Profile

Outcomes	No of studies (patient)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test Accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pre-test probability of 11.2%	Pre-test probability of 14%	Pre-test probability of 19%	
True positives	3 studies (42 patients)	case-control type accuracy study	Serious	not serious	serious	very serious[a]	All plausible residual confounding would reduce the demonstrated effect	60 (13 to 106)	21 (5 to 38)	102 (23 to 81)	⊕◯◯◯ Very Low
False negatives								52 (6 to 99)	19 (2 to 35)	88 (9 to 167)	
True negatives	3 studies (744 patients)	case-control type accuracy study	serious	not serious	serious	very serious[a]	All plausible residual confounding would reduce the demonstrated effect	662 (515 to 808)	715 (557 to 874)	603 (407 to 737)	⊕◯◯◯ Very Low
False positives								226 (80 to 373)	245 (86 to 403)	207 (73 to 340)	
Antimicrobial exposure	1 study	cohort	serious[b]	serious[c]	not serious	not serious	none	Patients with procalcitonin measurements had lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] = 0.70; 95% CI 0.6-0.9) as well as mean DDD (ROM = 0.70; 95% CI 0.6-0.8)			⊕⊕◯◯ Low

Safety (30-day mortality rate, antimicrobial consumption)	1 study	cohort	serious[b]	serious[c]	not serious	serious[d]	none	A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] = 0.6; 95% CI 0.4-1.1), although this was not statistically significant after adjusting for confounding variables such as age. Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope=−0.07, 95% CI: −0.11 to −0.03), in contrast with the non-procalcitonin group (βslope=−0.01, 95% CI: −0.05 to 0.02).	⊕◯◯◯ Very Low

CI: confidence interval

Explanations

a. There is no proven cut-off or threshold for serum procalcitonin levels among COVID

b. majority of the patient cohort were admitted prior to the routine use of dexamethasone (22 June 2020) and remdesivir (5 June 2020) for patients with COVID-19 in the UK, potentially impacting the extrapolation of the mortality and safety outcomes. Clinicians may have limited their use of the procalcitonin assay in patients in whom the presence of bacterial infection seemed less likely, such as those without clear clinical signs and symptoms suggestive of bacterial pneumonia

c. Discontinuation of antimicrobial therapy, not initiation d. Confidence intervals crossed 1.0

Appendix 5. Detailed Study Appraisal

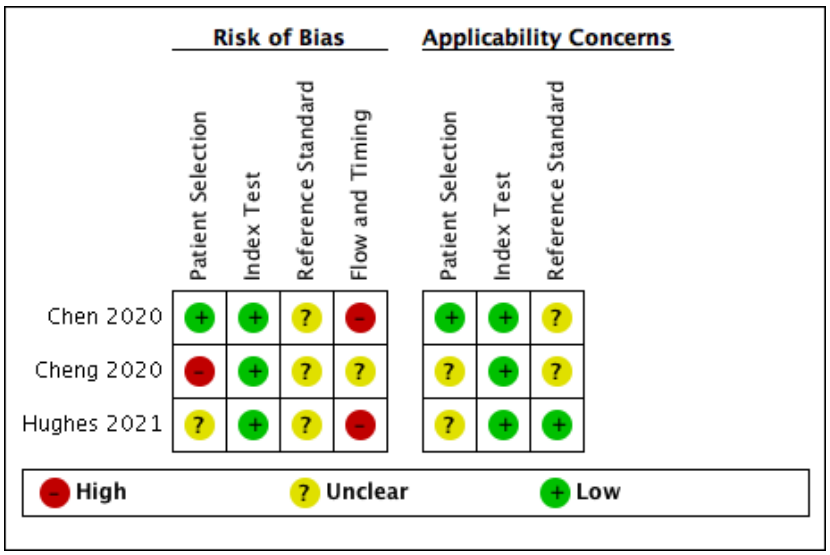


Figure 1. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study