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Using risk factors and markers to predict bacterial respiratory co-/superinfections in COVID-19 patients: is the antibiotic steward's toolbox full or empty?

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Using risk factors and markers to predict bacterial respiratory co-/superinfections in COVID-19 patients: is the antibiotic steward's toolbox full or empty?

Abstract

Background:

Adequate diagnosis of bacterial respiratory tract co-/superinfection (bRTI) in COVID-19 patients is challenging, as there is insufficient knowledge about the role of risk factors and (para)clinical parameters in the identification of bacterial co-/superinfection in the COVID-19 setting. Empirical antibiotic therapy is mainly based on COVID-19 severity and expert opinion, rather than on scientific evidence generated since the start of the pandemic.

Purpose:

Reporting the best available evidence regarding the predictive value of risk factors and (para)clinical markers in the diagnosis of bRTI in COVID-19 patients.

Methods:

A multidisciplinary team identified different potential risk factors and (para)clinical predictors of bRTI in COVID-19 and formulated one or two research questions per topic. After a thorough literature search, research gaps were identified and suggestions concerning further research were formulated. The quality of this narrative review was ensured by following the Scale for the Assessment of Narrative Review Articles (SANRA).

Results:

Taking into account the scarcity of scientific evidence for markers and risk factors of bRTI in COVID-19 patients, to date, COVID-19 severity is the only parameter which can be associated with higher risk of developing bRTI.

Conclusions:

Evidence on the usefulness of risk factors and (para)clinical factors as predictors of bRTI in COVID-19 patients is scarce. Robust studies are needed to optimise antibiotic prescribing and stewardship activities in the context of COVID-19.

Keywords: Bacterial respiratory tract infection; COVID-19; Co-infection; Superinfection; Antimicrobial stewardship

Introduction

Antimicrobial resistance (AMR) has become a major threat. Although leading to more than 1.2 million attributable deaths per year worldwide [1], projections predict AMR to become the first cause of death in 2050 [2-3]. The COVID-19 pandemic might have an additional impact on AMR as the pandemic resulted in increased antibiotic use, disruption of antimicrobial stewardship programs and decreased effectiveness of infection prevention strategies [4-7].

Bacterial co-infections in COVID-19 patients are referred to as 'community acquired' infections diagnosed during the first 24-48 hours of hospitalization, whereas superinfections (or 'secondary infections') are referred to as nosocomial infections (Supplementary Material). Although the incidence of bacterial co-infections and superinfection (bCS) in COVID-19 patients seems respectively low (3.5%) and intermediate (14.5%) (or higher in ventilated patients), reported antibiotic prescription rates are disproportionally high, especially in the intensive care setting, ranging from 68 to 80% [8]. Higher bacterial respiratory tract co-/superinfections have been described for influenza patients, involving more than 10% of hospitalized non-ICU patients and more than 30% of critically ill patients. This could be due to underreporting in the COVID-19 setting and to different innate and adaptive immune response mechanisms depending on the viral pathogen [9-10].

Various reports have highlighted the difficulty to reliably diagnose bCS in COVID-19 patients, due to the low specificity of frequently used markers of bacterial pneumonia in this particular setting [11-13]. Moreover, definitions of bCS in COVID-19 patients used in literature vary widely and are often solely based on microbiological results or on clinical diagnostic criteria instead of a combination of both [14-16]. For example, the World Health Organization recommends that antibiotics should not be prescribed for patients with confirmed moderate COVID-19, unless there is clinical suspicion of a bacterial infection. However, no details are provided on when and how to suspect bCS [17]. National guidelines suggest that exceptions can be made for patients with proven or a high likelihood of COVID-19 who present with radiological findings and/or inflammatory markers compatible with bCS. Other exceptions for restrictive antibiotic use are patients who are severely ill or immunocompromised. The authors labelled this recommendation as a 'good practice statement' with weak strength of evidence [18]. The absence of evidence based (inter)national guidelines concerning antibiotic use in COVID-19 patients mirrors the lack of knowledge on the role of predictive and diagnostic factors, such as radiological and inflammatory markers as well as risk factors such as immune suppression.

This narrative review investigates the potential of different markers and risk factors to predict the presence of bacterial respiratory tract co-/superinfection (bRTI) in COVID-19 patients. A narrative review was chosen above a systematic review as an explorative study to evaluate the (in)homogeneity of the existing literature and the used definitions, as significant heterogeneity wouldn't justify a systematic review.

Methods

Based on existing literature and personal experience, a multidisciplinary team, composed of two infectious disease experts, one trainee in infectious diseases, one microbiologist and one hospital pharmacist, selected the following potential risk factors and markers of bRTI in COVID-19 patients: inflammatory markers (including C-reactive protein (CRP) and procalcitonin (PCT) levels), COVID-19 severity, microbiological markers (presence of positive microbiological results for respiratory samples, blood cultures, pneumococcal antigen and *Mycoplasma spp/Legionella spp/Chlamydia spp* detection methods), the presence of comorbidities, the presence of immunosuppressive treatment and radiological markers (presence of dense consolidations or organizing pneumonia). Each risk factor and marker was appointed to one expert. One or two questions with clinical relevance were formulated per topic. Research gaps were identified and suggestions concerning further research were formulated (Table 1). Definitions of bacterial co-infection and superinfection can be found in the Supplementary Material. However the timing of occurrence and physiopathological mechanism of bacterial co-infection and superinfection are different, we decided to dedicate this narrative review to both entities, as rational antibiotic guidance is of great importance in COVID-19 patients, independently of the used terminology.

Search strategy and selection criteria

A literature search was conducted, using a search strategy as listed in Supplementary Material (table S1). Search strategies were applied in the PubMed database. The following papers were excluded: case reports, case series including less than 20 patients, letters to the editor or comments, duplicates, papers which were unrelated to the research question, papers reporting on tuberculosis, viral or fungal co-/superinfections, papers reporting on a pediatric population, papers written in another language than English, papers comparing community acquired pneumonia with a COVID-19 population without including COVID-19 bRTI events and publications where the used methodology was not in line with the

best available scientific practice (for example, no correction for multiple statistical testing). Eligible papers found in citing references were included (Supplementary Material, table S2). Articles of interest were reviewed by the designated authors separately, followed by a revision by all team members.

Quality assessment

Implementation of the Scale for the Assessment of Narrative Review Articles (SANRA) ensured quality assessment of the narrative review [19]. The six items included in this scale are: explanation of the importance (1), the aims of the review (2), literature search (3), referencing and presentation (4) of evidence level (5) and relevant endpoint data (6). We aimed to attain the highest level for each of those points.

Results

1. Inflammatory markers

***Question**: What are the performances of the inflammatory biomarkers procalcitonin (PCT) and C-reactive protein (CRP) to predict bRTI in hospitalized patients with COVID-19? (Table 2)*

1.1 Procalcitonin

Before the pandemic, evidence indicated that, especially in severe lower respiratory tract infections, PCT kinetics could contribute to shorter duration of antibiotic treatment [20]. While for lower respiratory tract infection, the absolute value of PCT is still controversial in the guiding of antibiotic initiation, the use of serial decreasing PCT levels has proven to be safe to interrupt antibiotic treatment [21-22].

Many studies assessed the role of PCT to predict bCS in COVID-19 patients. All were retrospective and many included small numbers of patients due to a monocentric design. Moreover, patients included were highly heterogeneous: some studies included COVID-19 patients of any severity while others were restricted to critically ill patients in the intensive care unit (ICU). Regardless of COVID-19 severity at time of PCT measurement, high PCT levels were associated with more important COVID-19 COVID-19 severity, progression of disease and

mortality [12, 23-26]. However, one should be cautious when interpreting PCT levels in patients receiving dexamethasone or tocilizumab, as these can influence the PCT kinetics [27].

Regarding the role of PCT to predict bacterial superinfection, various studies have found higher PCT levels in patients with documented bacterial infection. The main bacterial infections were bacteremia, lower respiratory tract infection (LRTI) and urinary tract infections. A PCT level > 0.5 ng/mL is generally considered predictive of bacterial infection in the setting of a respiratory focus. In COVID-19 patients, however, a PCT level > 0.5 ng/mL was a poor predictor of document bacterial infection. In contrast, a PCT lever < 0,5 ng/ml had a high negative predictive value in different studies [11,23,25]. Some studies have assessed different thresholds of PCT and found similar findings [11,26,28]. In a retrospective study performed in one institution in the United Kingdom (UK), patients with low levels of PCT (<0.25 ng/mL) had lower prescription rate of antibiotics. The authors suggested PCT guided antibiotics prescription as an effective strategy to reduce antibiotic consumption. However, high PCT levels were associated with higher risk of antibiotic prescriptions, including carbapenems. It was not reported if antibiotic prescriptions were appropriate or not, highlighting the risk of overprescription when relying on PCT levels to guide prescription [29].

1.2 C-reactive protein

CRP guided antibiotic prescription may contribute to more appropriate antibiotic prescribing in suspected LRTI. CRP is routinely used in clinical setting to guide antibiotic prescription, albeit the evidence is low [30-31]. As for PCT, elevated CRP value in COVID-19 patients accurately predicts severe disease and clinical deterioration [32].

In a large retrospective study in two London Hospitals, CRP levels at time of admission were not different between COVID-19 patients with and without bacterial co-infection. In a comparison with non-COVID-19 bacterial CAP, the absence of elevated WBC and antibiotic-related decrease in CRP was shown to exclude bacterial co-infection in 46% patients admitted with COVID-19 [33].

Of note, both dexamethasone and tocilizumab have shown to impact the CRP kinetics in critically ill patients, limiting its use in the prediction of bCS [27].

Conclusion:

In summary, both CRP and PCT levels correlate with COVID-19 severity in admitted COVID-19 patients but poorly predict bCS. Low PCT levels has high negative predictive value for bCS. However, evidence to support routine use of PCT is limited.

More accurate prediction of bCS could be provided by blood transcriptional signatures. A recent study identified host transcriptomic signatures (not including PCT nor CRP) able to discriminate between COVID-19 patients and patients with documented bacterial infections (in the absence of COVID-19) [34]; more research is required in order to evaluate if such transcriptomic signature could discriminate COVID-19 patients with and without bCS.

2. COVID-19 severity

Question: *Does the severity of COVID-19 influence the risk of bRTI? (Table 2)*

COVID-19 patients may develop severe illness and rapid clinical deterioration with the development of ARDS, sepsis and/or multiple organ failure [35].
In previous viral pandemics, bRTI in critically ill patients were reported in up to 30% during the Influenza A pandemic (2009) [36], but they were rarely present in SARS-CoV-1 (2002) [37] and the Middle East respiratory syndrome coronavirus (2012) [38]. In critically ill COVID-19 patients, the reported incidence of bRTI seems to be intermediate, ranging from 8.1 to 16%, with higher rates of superinfections (27-54%) compared to co-infections (15.4%) [14, 39-45]. The higher rates of bacterial superinfections in patients with severe COVID-19 admitted to the ICU are probably due to the long stay and the well-known ICU related complications. However, the broad heterogeneity between the studies, the lack of uniform diagnostic criteria for bRTI and a high frequency of prior antibiotic use makes it difficult to estimate its true incidence.Moreover, bRTI diagnosis is challenging in the context of COVID-associated ARDS since both presentations overlap, which makes it difficult to differentiate bRTI from colonization [42].
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Bacterial co-infection rates seem to be associated with increased COVID-19 severity (e.g. mechanical ventilation, ICU admission) [14].
Various studies also demonstrated that superinfection rates are independently related to COVID-19 severity, mechanical ventilation and duration of mechanical ventilation, as well as

ICU admission and mortality [14, 43-45]. While on the one hand, invasive mechanical ventilation is an independent risk factor for the development of bacterial superinfection [14], on the other hand bacterial superinfection may also contribute to a prolonged duration of MV duration [45].

Although the incidence of especially bacterial superinfections in severe and critically ill COVID-19 patients is high, there is currently insufficient evidence to support empirical use of antibiotics based on COVID-19 severity alone.

3. Microbiological markers

Question: *What are the performances of microbiological markers such as Mycoplasma or Chlamydia pneumoniae identification, urinary pneumococcal and Legionella pneumophila antigen, blood cultures and respiratory sample cultures to predict bRTI in hospitalized patients with COVID-19? (Table 2)*

3.1 Mycoplasma and Chlamydia pneumoniae

Co-/superinfection with SARS-CoV-2 and bacteria causing atypical pneumoniae such as *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* has been described in a few articles [37,46-49].

Despite the fact that serological testing is not recommended anymore to diagnose respiratory atypical infections, various studies still use (the evolution of) serology as diagnostic tool, instead of using exclusively molecular tools.

A study performed early in the pandemic found high rates of presumed *Mycoplasma pneumoniae* (9%) and *Chlamydia pneumoniae* (30%) co-infections using serological assays. However, seropositivity was also associated with more severe disease, likely reflecting aspecific immune activation or cross-reactivity. Moreover, no further study confirmed such elevated co-infection rates [50-51]. A global study including more than 630.000 *Mycoplasma* tests (of which 62% direct tests), revealed significantly reduced detection rates compared to the pre-COVID-19 era. This can be explained by decreased transmission due to the implementation of non-pharmaceutical interventions against COVID-19 [51].

Currently, there is insufficient evidence to recommend systemic testing for *Mycoplasma* and *Chlamydia pneumoniae* since IgG positivity can mirror passed infections and IgM positivity can

be aspecific. If infection with bacteria causing atypical pneumonia is expected, one should test with molecular techniques such as PCR.

3.2 Legionella species

Since Legionnaire's disease is associated with a high mortality rate, several studies focused on the usefulness of *Legionella pneumophila* testing in COVID-19 patients. So far, the evidence is that *Legionella* co-infection in COVID-19 patients is rare and should therefore not be routinely tested [52-55]. One should however notice that most studies relied on urinary antigen tests, which do not detect other serotypes and species than *Legionella pneumophila* serotype 1. Moreover, testing for nosocomial Legionella should follow local guidelines.

3.3 Pneumococcal antigen

Streptococcus pneumoniae is one of the most common pathogens associated with respiratory co-infection in COVID-19 patients, representing up to 57% of co-infections [56]. Although S. *pneumoniae* infection can be detected in respiratory and blood specimens, time to positive culture takes at least 24 hours. *S. pneumoniae* immunochromatographic urinary antigen tests have the advantage of being non-invasive and rapid [57]. The usefulness of routine *S. pneumonia* urinary antigen testing in COVID-19 patients admitted through the emergency department was analyzed in one Italian retrospective study comprising 575 patients. S. *pneumoniae* urinary antigen testing did not significantly affect the overall mortality nor the length of admission and is therefore currently not recommended. However, since S. *pneumoniae* urinary antigen testing has previously shown to be reliable and cost-effective and since the authors observed a trend toward statistical significance, future prospective randomized trials might be useful [58].

3.4 Blood cultures

Over the last two years, several, mostly retrospective studies, evaluated the usefulness of blood cultures to predict bCS in COVID-19 patients. Despite their heterogeneity, most findings indicate that bacteremia is rather rare in COVID-19 patients, ranging from 0.2 to 1.6% when possible contamination is excluded, and mainly of nosocomial origin [58-63]. Other studies describe higher rates of blood stream infections, reaching 25% of included patients at day 15 of hospitalization and further increasing with longer hospitalization duration. However, those studies were exclusively performed in the ICU setting and a significant rate of contaminated blood cultures were possibly included [64-65]. Blood cultures are useful if systemic

superinfection is suspected and/or in case of clinical deterioration and/or if hospital acquired infections are suspected. Compared to non-COVID-19 patients, higher rates of contaminated blood cultures were reported in COVID-19 patients. Therefore, results of positive blood cultures should be interpreted with care in order to prevent overestimation of bacteremia rates [61-63-,65].

3.5 Respiratory samples

The presence of bacteria in respiratory samples of patients admitted with COVID-19 was mostly investigated in retrospective studies; most of them being heterogeneous with some only focusing on non-ICU wards, others on the ICU alone and some of them evaluating both. Rates of bRTI differ strongly among studies [14,66-68]. The meta-analysis by Lansbury *et al.* (2020), including 30 studies and almost 4000 patients, showed that 7% of hospitalized COVID-19 patients had a bacterial co-/superinfection, increasing to 14% in the ICU setting. The large representation of gram-negative organisms causing superinfections is consistent with the types of pathogens frequently associated with hospital–acquired pneumonia. As this is a known complication of ICU care, this does not necessarily suggest a specific predilection for gram-negative co-infections in the COVID-19 setting [39]. Similar incidences of ventilator-associated pneumonia in COVID-19 and non-COVID-19 patients were reported [69-70]. In a retrospective, observational cohort study including 1195 COVID-19 ICU patients, the same authors found a median lag time of 15 days before identification of the first positive significant respiratory sample [69]. Using molecular methods, high rates of co-/superinfection with diverse microorganisms were observed. However, the presence of these micro-organisms was not associated with unfavorable outcomes. This suggests that the use of empirical antibiotic treatment is not justified in patients admitted for COVID-19, also taking into account the limitations of molecular methods regarding the discrimination between colonization and true infection [71]. Although most reviews exclusively use the presence of positive microbiological samples as diagnostic criterium of bRTI, probably leading to an overestimation of bRTI rates, underdetection could also be the rule due to concerns for aerosolization of SARS-CoV-2. In addition, although the presence of productive cough seems to be associated with higher odds for antibiotic prescribing in hospitalized COVID-19 patients, there is currently insufficient evidence concerning a potential association between the presence of productive cough and bRTI [74].

In conclusion, there is insufficient evidence that routine use of microbiological markers can help to predict bRTI in patients admitted with COVID-19. Microbiological tests/assays should only be performed if co/super-infection is suspected. Although negative results could stimulate clinicians to stop antibiotic treatment, frequent colonization could also promote inadequate antibiotic prescription.

4. Comorbidities

Question: *Are certain comorbidities associated with higher risk of bRTI in hospitalized COVID-19 patients? (Table 2)*

Different studies pointed out that antibiotic prescribing for suspected bRTI is more liberal in hospitalized COVID-19 patients with certain comorbidities, including cerebrovascular disease, (history of) pulmonary disease and ongoing immunosuppressive treatments [72-74]. Although certain COVID-19 guidelines suggest a lower threshold for antibiotic prescribing in COVID-19 patients with comorbidities, there are conflicting results concerning comorbidities as a risk factor for bRTI in COVID-19 patients [18,75]. The systematic review and meta-analysis of Langford *et al.* did not identify any association between the presence of chronic lung disease, diabetes mellitus or cardiovascular disease and bCS. This meta-analysis includes very heterogenous studies. Moreover, diagnoses of bCS were exclusively made on microbiological grounds, limiting the interpretability [14]. Various studies identified comorbidities such as arterial hypertension, chronic kidney disease, asthma and immunological diseases as possible risk factors for bRTI in COVID-19 patients. However, a correction for multiple statistical testing was often missing [76-77].

In summary, even though antibiotic prescribing for suspicion of bRTI seems to be higher for COVID-19 patients with certain comorbidities, robust prospective studies are needed to evaluate the role of comorbidities as a specific risk factor for bRTI in COVID-19.

5. Immunosuppressive therapy used in the context of COVID-19

Question: *Do immunosuppressive COVID-19 therapies influence the incidence of bRTI? (Table 2)*

Question: *Should we lower the threshold to initiate antibiotics in patients receiving immunosuppressive COVID-19 therapies? (Table 2)*

Best practices of COVID-19 treatment have varied along the pandemic. Drugs that have shown to significantly reduce mortality are immunosuppressive or immunomodulating agents such as corticosteroids, anti-interleukin (IL)-6 monoclonal antibodies and the Janus kinase (JAK) inhibitor baricitinib [78-81]. While the rationale to use these agents is based on the prevention of the hyperinflammatory status in severely ill COVID-19 patients, the treatment might increase the risk of bCS, and especially bacterial superinfection. For the purpose of this review, only studies reporting on immunosuppressive drugs with a proven benefit were included.

Although adverse drug event registration is a prerequisite in good clinical practice [82], reports of bCS caused by immunosuppressive drugs are very limited in published literature. The safety profile of the immunosuppressive drugs investigated in the context of COVID-19 was reported in 26 studies. Eighteen studies did not specifically mention the type of adverse event or the source of the secondary infection, leading to exclusion. This resulted in the inclusion of ten studies (Table 3). Six studies evaluating the use of the anti-IL-6 monoclonal antibodies tocilizumab (n=4) and sarilumab (n= 2), three studies focusing on corticosteroids. No studies on baricitinib reported sufficiently detailed information of bacterial infection occurrence so far. Nevertheless, general safety data on baricitinib appear to be reassuring [83-85].

In all evaluated studies on immunosuppressive therapy, the statistical analyses of the outcome measure were limited. As the incidence of bCS in COVID-19 patients is low, randomized trials require a large sample size in order to detect a statistically significant difference of bacterial infection rates in active versus control arm. Unfortunately, the standard of care treatment was not specified in all studies, which complicated the interpretation of the data. In the MetCOVID study, for example, administration of antibiotics could have significantly influenced the bRTI rate [86]. After the publication of the RECOVERY results on dexamethasone, corticosteroids also became an important part of COVID-19 treatment [87]. This could have led to additional bias because corticosteroids were frequently used since then in standard care. Unfortunately, their use was not systematically reported, leading to increased interpretation difficulties. Besides a comprehensive study design, a thorough definition of standard of care therapy is required to determine the potential impact of an individual immunosuppressive agent on the occurrence of bRTI in COVID-19 patients. While serious infections were reported in most safety data, it is also important that researchers describe the infection type and putative organism in a detailed manner to better understand bCS rates related to immunosuppressive therapy used in the context of COVID-19.

For now, we can conclude that there is insufficient evidence to start empirical antibiotic treatment in patients receiving immunosuppressive COVID-19 therapies.

6. Radiological markers

Question: *Are radiological findings useful to predict bRTI in hospitalized COVID-19 patients? (Table 2)*

Since the start of the pandemic, different authors have addressed radiological markers as driver of antibiotic prescribing in COVID-19 patients [16,74,88]. For example, in a retrospective cohort study, including 429 patients with COVID-19, 51% of the 171 antibiotic prescriptions were initiated due to presence of 'radiological consolidation' on chest computed tomography [75]. It is known that a significant part of hospitalized COVID-19 patients develop organizing pneumonia, which is due to microvascular injuries, secondary oedema and the filling of alveoli with granulation tissue, without evidence of bacterial co-/superinfection [89].

Many studies were conducted to compare radiological findings of COVID-19 pneumonia with other types of bacterial or viral pneumonia, often with the purpose to validate deep learning programs to detect COVID-19 pneumonia [90-92]. Radiological findings such as the presence of dense consolidations and air bronchogram seem to be frequently used in the diagnostic process of bRTI in COVID-19 patients, assuming that the pre-COVID-19 bacterial pneumonia guidelines would still apply in the COVID-19 setting. Nevertheless, to date, there is insufficient data to predict bRTI in COVID-19 patients, exclusively based on radiological features.

Conclusion

Although suspicion of bRTI in COVID-19 patients is common, evidence supports very low conclusive diagnoses of bRTI in this population, especially outside the ICU setting. Systematic meta-analyses investigating the incidence of bRTI in COVID-19 are based on microbiological diagnosis instead of a combination of microbiological and clinical criteria. This is probably due to the lack of sensitivity and/or specificity of clinical markers of bRTI in the COVID-19 setting, which is confirmed in this literature review. Despite the fact that the presence of certain radiological signs, such as dense consolidations, are often used as criteria to initiate antibiotic treatment, it is unclear if these radiological markers are associated with a higher risk of bRTI. Routine respiratory sampling for microbiological diagnosis, as well as *Mycoplasma pneumoniae* and *Legionella pneumophila* testing seem to have limited utility in detecting the presence of bRTI in COVID-19, unless strong suspicion of bRTI. Negative results could however convince clinicians to withhold from antibiotic therapy. COVID-19 severity seems to be associated with higher rates of bRTI in COVID-19 patients. Thus, in patients

with severe COVID-19 the threshold for initiation of antibiotic therapy in case of bRTI suspicion should be lower, especially in mechanically ventilated patients in the ICU setting. However, there is currently insufficient evidence to justify empirical use of antibiotics in critically ill patients based on COVID-19 severity alone. It is unclear if the presence of certain comorbidities is associated with a higher risk of contracting bRTI. Both PCT and CRP have low performance to predict bacterial superinfection. However, a low PCT value has high negative predictive value for bRTI in the COVID-19 setting. The main practical message of this review is that, although most (potential) markers of bRTI have low potential to predict bacterial infection, antibiotic treatment should be discouraged in the absence of those markers. A combination of different markers (microbiological, radiological, inflammatory markers,…) can however lower the threshold to empirically initiate antibiotic treatment, especially in severely ill patients. Transcriptomic signature distinguishing viral and bacterial infections have been identified and should be validated in cohorts of COVID-19 patients with and without bCS [34]. Finally, the available data suggest that therapeutic immunosuppressive drugs are safe in light of bacterial infection risk, although no definite conclusion can be made.

This review is limited by the heterogeneity in currently available literature. Some articles exclusively cover bRTI, while others focus on bCS in general. Settings differ from one study to another, and bacterial co-infection or superinfection are not always defined clearly. Despite the somewhat artificial differentiation between bacterial co- and superinfections, the role of predictors and risk factors in predicting bacterial co- or superinfection could be different for both entities. The risk of experiencing bacterial nosocomial infection during hospitalization increases progressively after admission and is very dependent of the setting (ICU admission, intubation,…). This makes a binary categorization of co-infection or superinfection, using a cut-off of 24-48 hours, less ideal for daily practice, even if it is true that bacterial infections in recently hospitalized patients are rare, in contrast to patients with a prolonged stay. It might perhaps be more useful to compare ventilated patients with non-ventilated patients, as mechanical ventilation seems to be a significant risk factor for bRTI. Moreover, few reports on risk factors of bacterial co-/superinfection differentiate between co-infection and superinfection. This is why a systematic differentiation between bacterial co- and superinfection for every discussed marker/risk factor was not possible in this review. The potential association of every marker or risk factor with bRTI occurrence was evaluated independently. However, prediction as well as bRTI diagnosis and treatment should probably depend on an overall assessment of the patient's clinical status, including the reported markers and risk factors. One should take into account that most papers included in this review did not include any patients with the less pathogenic newer Delta and Omicron variants. Due to the lower hospitalization and mortality rates of these newer variants, lower absolute counts of bacterial co-/superinfection could be expected. However, it is unknown whether bRTI rates

of patients hospitalized due to the newer COVID-19 variants are similar to the previously reported rates.

In conclusion, the findings of this review emphasize the need for large, robust studies, investigating the impact of the discussed markers and risk factors in the prediction of bRTI in the COVID-19 setting. We plead for a more standardised research approach using explicit definitions and patient selection, while differentiating between bacterial co-infection and superinfection. Standardisation is the only way to move forward in the identification of risk factors and paraclinical markers of bRTI. The conduction of a systematic meta-analysis will only then come to its full meaning. A better understanding of the role of predictive factors for bRTI is crucial to facilitate antimicrobial stewardship activities and to counter antibiotic overuse and thus antimicrobial resistance.

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Statements and declarations:

Competing interests: J. Van Laethem, J. Pierreux, S.C.M. Wuyts, D. De Geyter, SD. Allard, Nicolas Dauby declare having no conflicts of interest.

Transparency declaration:

N. Dauby is a post-doctorate clinical master specialist of the Belgian F.R.S-FNRS and reports personal fees from Roche and Boehringer-Ingelheim, and non-financial support from Pfizer, Janssen, and Merck Sharp & Dohme, all outside the submitted work. All other authors: none to declare.

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Consent to participate/to publish: not applicable.

Table 1

Research gaps in the field of markers and risk factors of bacterial respiratory co-/superinfection in COVID-19 patients from the literature review

Research gap(s)	Relevance for daily practice	Proposition of study methodology
Clinical impact of PCT-based antibiotic stewardship	Appropriate antibiotic prescribing	Randomized control trial comparing PCT versus no PCT use to guide antibiotic prescribing in hospitalized COVID-19 patients
Identification and validation of host-derived transcriptomic or gene signature	POCT testing in the emergency department to discriminate patients with and without bacterial infection	Comparison of COVID-19 patients with culture proven bCS and uninfected ones. Matched for severity of diseases, age and comorbidities
Insufficient evidence on the impact of microbiological markers on the outcomes of COVID-19 patients The role of productive cough as potential predictor of bRTI in the COVID-19 setting	Incorporation of microbiological markers and/or the presence of productive cough in the decision process concerning antibiotic treatment guidelines in the COVID-19 setting.	Setting up large, prospective multicentre studies to evaluate the impact of microbiological markers on the outcome of COVID-19 patients, separately for the ICU and non-ICU wards. The impact on the antibiotic consumption should be further studied.
Lack of evidence regarding to markers/scores for COVID-19 severity related to the development of bRTI in COVID-19 patients.	Incorporation of these markers/scores in the decision process to guide appropriate antibiotic use in COVID-19 patients	Identification of markers/scores for COVID-19 severity by large, prospective studies

Impact of the presence of certain comorbidities on the occurrence of bRTI	Lower antibiotic prescribing threshold for certain patient risk groups	Robust prospective studies investigating the incidence of bRTI in patient groups with certain comorbidities versus absence of comorbidities
Bacterial infection rate caused by immunosuppressive COVID-19 therapy is unknown.	Preliminary data are reassuring as they suggest a low risk of bacterial co-/superinfections related to immunosuppressive COVID-19 treatment.	Large scale randomized controlled trials are necessary with a clear definition of the proposed therapy for patients receiving usual care. Authors should provide sufficient details on infection type and putative micro-organisms to fully assess the safety profile of the investigational immunosuppressive drug.
Role of radiology in the identification of bacterial co-/superinfection in the COVID-19 setting. Exact role of radiological findings such as -the presence of dense (lobar) infiltrates -the presence of air bronchogram -the presence of signs of bronchiolitis (e.g. tree-in-bud)	Incorporation of radiological findings in the decision process concerning antibiotic treatment guidelines in the COVID-19 setting. Timely identification as well as delabeling of presumed bacterial co-/superinfection in COVID-19 patients.	Compare radiological findings between cohorts with probable or definite bRTI versus cohorts with excluded bRTI; separately for the ICU setting and the ward setting.

Abbreviations: PCT: procalcitonin; POCT: point of care testing; bCS: bacterial co-/superinfection; bRTI: bacterial respiratory tract co-/superinfection; ICU: intensive care unit

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786 **Table 2**

787 Research questions and main conclusions per topic in the field of markers and risk factors of bacterial
788 respiratory co-/superinfection in COVID-19 patients

Marker/risk factor of bacterial respiratory co-/superinfection	**Research questions**	**Main conclusions**
Inflammatory markers	What are the performances of inflammatory biomarkers PCT and CRP to predict bRTI in hospitalized patients with COVID-19? Does PCT contribute to antibiotic stewardship ?	Both PCT and CRP have low performance to predict bacterial superinfection. Low PCT value has high negative predictive value. There is insufficient evidence that PCT-guided prescription contributes to decreased antibiotic prescribing in the COVID-19 setting.
Microbiological markers	What are the performances of microbiological markers such as Mycoplasma or Chlamydia pneumoniae identification, urinary pneumococcal and Legionella pneumophila antigen, blood cultures and respiratory sample cultures to predict bRTI in hospitalized patients with COVID-19? Do those parameters contribute to antibiotic stewardship ?	There is insufficient evidence that routine testing of Mycoplasma *and Chlamydia pneumoniae* can be useful to guide clinicians to use targeted therapies. *Legionella pneumophila* testing should not be performed systematically since the occurrence is very rare in COVID-19 patients. Pneumococcal antigen testing was only described in one study and conclusions cannot be drawn. Bacteremia seems to be rare in COVID-19 patients and

		predominantly nosocomial. Blood cultures should only be performed when systemic superinfection is expected. The occurrence of bRTI do not differ between COVID-19 and non COVID-19 patients. Respiratory samples should not be taken systematically and only when co/super-infection is suspected. Empirical antibiotic treatment should not be given since the occurrence of bRTI is rare and mostly nosocomial.
COVID-19 severity	Does COVID-19 related COVID-19 severity influence the occurrence of bRTI? Can we use scores for COVID-19 severity to predict bRTI in hospitalized COVID-19 patients? Does mechanical ventilation and the duration of mechanical ventilation has an influence on the incidence of bRTI ?	In critically ill patients with COVID-19, the reported incidence of bacterial co-infection seems to be relatively low (8.1-16%). Nonetheless, those patients seem to be at a higher risk to develop bacterial superinfections (27-54%). Studies emphasize the worse outcome and higher mortality associated with bCS and the association between COVID-19 severity (ICU setting, mechanical ventilation, APACHE-II score) and the development of bacterial superinfection. However, there is currently insufficient evidence to support empirical use of antibiotics in severe or critical covid-related disease based on COVID-19 severity alone.
Comorbidities	Are certain comorbidities associated with higher risk of bRTI in hospitalized COVID-19 patients?	There are conflicting findings concerning the presence of certain comorbidities as risk factor for bRTI. There is a large heterogeneity between studies.
Immune suppression	Should we lower the threshold to start antibiotics in patients receiving immunosuppressive COVID-19 therapies? Do immunosuppressive COVID-19 therapies influence the rate of bRTI?	Anti-IL-6 monoclonal antibodies and corticosteroids have proven their efficacy in COVID-19 treatment. However, several limitations were identified among the included studies, which complicates the interpretation of the safety profile of the individual drugs. The available data suggest that the use of these immunosuppressive drugs is safe, although no definite conclusion can be made.

Radiological markers	Are radiological findings useful to predict bRTI in hospitalized COVID-19 patients?	It is unclear if certain radiological markers, like the presence of dense consolidations, are predictive for bRTI

PCT: procalcitonin; CRP: C-reactive protein; WBC: white blood cell; bRTI: bacterial respiratory tract co-/superinfection; bCS: bacterial co-/superinfection; APACHE: Acute Physiology and Chronic Health Evaluation

Table 3: Included studies reporting on bCS rates in patients receiving immunosuppressive drugs with a proven clear benefit in the treatment of COVID-19.

Author	Study design	Country	Number of patients	Patient profile	Investigational drug	Standard of care (SOC)	Conclusion	Reference
IL-6 ANTAGONISTS								
Branch-Elliman 2022	RCT	USA	50 patients (20 sarilumab, 200 SOC)	Hospitalized patients with moderate COVID-19 disease, without ventilation or ICU admission	SOC	Corticosteroids were allowed	No difference in bacterial infection rate: - sarilumab: 15% - SOC: 16.7%	10.1371/journal.pone.0263591
Gordon 2021 (REMAP-CAP)	RCT	Six countries	895 patients (353 TCZ, 48 sarilumab, 402 SOC)	ICU patients	TCZ and sarilumab	Corticosteroids were allowed	- TCZ: 9 ADEs: 1 secondary bacterial infection - Sarilumab: 0 ADEs - Control: 11 ADEs, 0 secondary bacterial infection	10.1056/NEJMoa2100433
Hermine 2020 (CORIMUNO)	RCT	France	131 patients (64 TCZ, 67 SOC)	Hospitalized patients with oxygen need (≥3 L/min oxygen), without ventilation or ICU admission	TCZ	Antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants	Decreased incidence of serious bacterial infections: - TCZ: 2/64 - Control: 11/67	10.1001/jamainternmed.2020.6820

Ip 2020	Retrospective study	USA	611 patients (198 TCZ, 413 SOC)	ICU patients	TCZ	75% corticosteroids	Secondary bacteremia: - TCZ: 18/134 (13%) of patients - Control: 44/413 (11%) of patients	10.1371/journal.pone.0237693
Mehta 2021	Retrospective propensity score matched case-control study	USA	107 patients (33 TCZ, 74 SOC)	Intubated patients	TCZ	No corticosteroids	Similar bacterial infection rates in the TCZ group compared to controls (OR 0.37; 95% CI, 0.09-1.53; p=0.168)	10.1371/journal.pone.0249349
RECOVERY Collaborative Group 2021	RCT	UK	4116 patients (2022 TCZ, 2094 SOC)	Hospitalized patients with oxygen need (oxygen saturation <92% or requiring oxygen therapy) and evidence of systemic inflammation (CRP≥75 mg/L)	TCZ	77% corticosteroids	- TCZ: 3 ADE reports: 1 otitis externa, 1 *Staphylococcus aureus* bacteremia, 1 lung abscess - Control: not mentioned	10.1016/S0140-6736(21)00676-0
CORTICOSTEROIDS								
Dequin 2020	RCT	French	149 patients (76	ICU patients	Hydrocortisone	According to ARDS guidelines	Bacteremia:	10.1001/jama.2020.16761

(CAPE COD)			hydrocortisone, 73 control)				- treatment: 6.6% - control: 11.0% Cumulative incidence of infection: HR 0.81 (95% CI, 0.49-1.35); p=0.42	
Jeronimo 2021 (MetCOVID)	RCT	Brazil	416 patients (209 methyl-prednisolone, 207 control)	Hospitalized patients with ARDS	Methylprednisolone	Ceftriaxone plus a macrolide	No difference in sepsis occurrence.	10.1093/cid/ciaa1177
Liu 2020	Retrospective propensity score matched case-control study	China	774 patients (409 corticosteroids; 365 control)	Hospitalized patients with ARDS	Different corticosteroids (methylprednisolone; prednisolone; dexamethasone; hydrocortisone)	Not specified	Bacterial lower RTI: - treatment: 5.8% - control: 3.4% No significant difference (p=0.336)	10.1172/JCI140617

Abbreviations: ADE=Adverse Drug Event; ARDS=Acute Respiratory Distress Syndrome; CI=Confidence Interval; CRP=C-Reactive Protein; HR=Hazard Ratio; ICU=Intensive Care Unit; OR=Odds Ratio; RCT=Randomized Controlled Trial; RTI=respiratory tract infection; TCZ=Tocilizumab; UK=United Kingdom; USA=United States of America