Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Coronavirus disease 2019 (COVID-19) associated bacterial coinfection: Incidence, diagnosis and treatment

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Abstracts Coronavirus disease 2019 (COVID-19) emerged as a pandemic that spread rapidly around the world, causing nearly 500 billion infections and more than 6 million deaths to date. During the first wave of the pandemic, empirical antibiotics was prescribed in over 70% of hospitalized COVID-19 patients. However, research now shows a low incidence rate of bacterial coinfection in hospitalized COVID-19 patients, between 2.5% and 5.1%. The rate of secondary infections was 3.7% in overall, but can be as high as 41.9% in the intensive care units. Overprescription of antibiotics to treat COVID-19 patients fueled the ongoing antimicrobial resistance globally. Diagnosis of bacterial coinfection is challenging due to indistinguishable clinical presentations with overlapping lower respiratory tract symptoms such as fever, cough and dyspnea. Other diagnostic methods include conventional culture, diagnostic syndromic testing, serology test and biomarkers. COVID-19 patients with bacterial coinfection or secondary

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infection have a higher in-hospital mortality and longer length of stay, timely and appropriate antibiotic use aided by accurate diagnosis is crucial to improve patient outcome and prevent antimicrobial resistance.

Introduction

In December 2019, a novel coronavirus, SARS-CoV-2, emerged to cause a pandemic that rapidly spread to cause nearly 500 billion infections and more than 6 million deaths, by the end of March, 2022. The World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) outbreak as a Public Health Emergency of International Concern (PHEIC) on Jan 30, 2020. In severe cases of COVID-19, viral pneumonia occurs and a hyper-inflammatory syndrome or "cytokine storm" resembling bacterial sepsis, with multiorgan failure and elevated inflammatory biomarkers may develop.[1,2] Bacterial coinfections and superinfections may further increase mortality, leading to empiric and frequently inappropriate antimicrobial use and increased antimicrobial resistance.

Coinfections with bacteria occurs during other viral infections, such as influenza, respiratory syncytial virus (RSV), severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The incidence rate of bacterial coinfections in patients with influenza ranged from 2% to 65%, with *Streptococcus pneumoniae* and *Staphylococcus aureus* accounting for 35% and 28% respectively.[3] Bacterial/fungal coinfection rates in SARS ranged from 1% to 43%, with *S. pneumoniae* and *Staphylococcus* spp. being most commonly reported at admission.[4] However, rates of bacterial coinfection in critically ill patients with MERS varied from 1% (5/349) to 19%.[4–6] During the first wave of COVID-19 pandemic, empiric antibacterial agents were prescribed in 56—90% of patients due to previous experience of bacterial coinfections occurring in other respiratory viral pneumonia, uncertainty concerning the novel coronavirus, severity in critically ill patients and difficulty in establishing or excluding a diagnosis of bacterial coinfection clinically. The objective of this study was to review current literature on the incidence, pathogenesis, symptoms, diagnostic measures, treatment and outcome of COVID-19 associated bacterial infections.

Incidence of bacterial coinfections

COVID-19 patients with coinfections or secondary infections have poor outcomes, and are associated with a higher in-hospital mortality rate, higher rate of ventilation use and longer hospital stay.[7–10] The definition of COVID-19 associated bacterial coinfections and secondary infections varied across different studies. Most studies defined a bacterial coinfection to occur within 48 h of admission and infections after 48 h of admission as secondary infections,[10–12] while other studies used a cut-off of 72 h after admission.[13,14] The incidence rate is influenced by the different diagnostic procedures and specimen types used in the studies, as well as a seasonal factor. Common sites of infection and pathogens were listed in Table 1. The studies included were mostly from the COVID-19 pandemics of alpha- and delta-variants. As the omicron-variant was only first identified in November, 2021, currently, none of the studies specifically focused on the epidemiology of COVID-19 associated bacterial coinfection in omicron-variants.

Community-acquired bacterial infection

Incidence rate of community-acquired bacterial coinfections among hospitalized COVID-19 patients, defined as occurring within 48 h of admission with positive microbiology results, is very low; ranging from 2.5% to 5.1%.[10,11,14–17] Bacterial coinfection rates reported in outpatient populations are as low as 1%. However, the incidence rate can be underestimated when the diagnosis is based on positive microbiology results. Most of the studies were retrospective and not all patients within the study had

Table 1 Common sites of infection and associated pathogens in COVID-19 associated bacterial infections (CABI).

Site of infection	Common pathogens
Community-acquired bacterial infections	
Urinary tract infection[15,19]	*E. coli*, *K. pneumoniae*
Respiratory tract infection[15]	*S. pneumoniae*, *H. influenzae*, *S. aureus*
Skin and soft tissue infection[13,15]	
Secondary bacterial infections	
Bloodstream infection[25,28]	Coagulase-negative *Staphylococcus* spp., *Enterococcus* spp.
Ventilator associated pneumonia[28,30,31]	*Pseudomonas aeruginosa*, MRSA, *Enterobacter* spp. and *Klebsiella* spp.

specimens collected for conventional cultures. In addition, empirical antibiotics were often used before specimen collection which may further lower the yield rates of microbiological cultures. One retrospective cohort study including 64,691 patients reported a bacterial coinfection rate of 18.5% when the diagnosis was made by clinical judgement.[18]

The most common clinical syndromes of bacterial coinfections were genitourinary tract infections, which accounted for 57%–70% of all infection sites,[15,19] followed by 19% respiratory tract infections[15]; skin and soft tissue infection and bacteremia in 1%.[13,15] *Klebsiella* spp., *Escherichia coli*, *Haemophilus influenzae*, *S. pneumoniae* and *S. aureus* were the most commonly isolated pathogens in patients with community-acquired bacterial coinfections.[7,10]

Risk factors for bacterial coinfections in COVID-19 patients included older age of greater than 72 years old, chronic kidney disease and admission from a skilled nursing facility. Older age with a median of 72.6 years old in confirmed CABI group versus 64.5 years old in those without CABI was found in one study (rate ratio 1.3, 95% CI 1.08–1.57, P = 0.06).[14] A skilled nursing facility was defined as one which provided high level of medical care by or under the direct supervision of licensed health professionals.[14,20] Severe and critically ill patients had a 4.42-fold (95% CI: 1.63–11.9) higher risk for bacterial coinfection at admission.[21] A higher proportion of patients with bacterial infections received treatment with systemic steroids (AOR 4.60; 95% CI: 1.24–17.05) compared to those without bacterial infections.

The diagnosis of atypical pneumonia in patients with COVID-19 is difficult due to similar clinical manifestations, and diagnosis require serology testing for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and/or *Legionella pneumoniae*. One retrospective study in Europe including 443 COVID-19 patients found that at admission, 26% of the patients tested positive for *Mycoplasma* IgM, 18% of the patients positive for *Chlamydia* IgM, but none had positive results for *Legionella* urinary antigen test.[20] Patients who had positive antibody tests were associated with more severe clinical features, higher white blood cell counts, lower lymphocyte counts and a higher oxygen demand. A wide variation in positivity rate of *Mycoplasma* IgM, ranging from 0% to 56.4%, were reported in COVID-19 patients.[10,20,22–24] However, the results should be interpreted carefully, as to whether the high incidence rate of positive *Mycoplasma* IgM serology is the consequence of true coinfection or due to cross-reactivity of antibodies during SARS-CoV-2 infection.

Secondary bacterial infection

Secondary infections appear to be more common than community acquired infections in COVID-19 patients with an incidence rate of 3.7% in all hospitalized patients, and up to 41.9% in patients admitted to the intensive care units (ICU).[7,9,17,25–30] Risk factors included age greater than 60 years old, receiving mechanical ventilation, urinary catheterization, arteriovenous catheterization, having a higher APACHE II score (15 points vs 13 points in those with and without nosocomial infections in the ICU, respectively, p = 0.02),[28] diabetes mellitus, and use of corticosteroid or tocilizumab.[8,9,18,28,29] According to a retrospective study in the United States including 64,691 patients, early steroid and tocilizumab use were associated with an increased risk of bacterial secondary infection with incidence rates of 5.7% and 9.9% respectively.[18]

Bacteremia, ventilator-associated pneumonia (VAP), hospital-acquired pneumonia/tracheobronchitis were the most common clinical syndromes of superinfection and pathogens were similar to those found in patients without COVID-19. Median time to the first secondary infection from hospital admission was 12 days (IQR 8.5–16.5 days) and median time to the first secondary lower respiratory tract infection after hospital admission was 16 days (IQR 10–29 days).[25]

The most common pathogens found in bloodstream infections were Coagulase-negative *Staphylococcus* spp., *Enterococcus faecium* and *Enterococcus faecalis*.[25,28] Coagulase-negative *staphylococci* are common skin colonizers, and was defined as true infections only if two or more positive cultures along with clinical signs suggesting bloodstream infection. *Pseudomonas aeruginosa* (38%), methicillin-resistance *S. aureus* (MRSA) (24%), *Enterobacter* spp. (18.8%) and *Klebsiella* spp. were the most frequently isolated pathogens from respiratory tract specimens in patients with VAP.[28,30,31]

One review article including 621 patients from 75 studies focusing on postmortem autopsy found that 32% had potential lung superinfections. Pneumonia accounted for 95% of the cases while 3.5% were lung abscesses or empyema and 1.5% had septic emboli. The most frequent pathogens were *Acinetobacter baumannii*, *S. aureus*, *P. aeruginosa* and *Klebsiella pneumoniae*.[32]

Pathogenesis

SARS-CoV-2 infect humans through binding to the ACE2 receptors. The exact mechanism of how SARS-CoV-2 virus contribute to the pathogenesis of bacterial secondary infection is unknown. SARS-CoV-2 has demonstrated rapid evolution with emergence of variants of concern that differ in pathogenesis, transmissibility and severity. The current dominant variant worldwide, the omicron-variant, has shown to have high transmissibility but low severity, and milder pathological changes in the upper and lower respiratory tract of omicron infected hamsters compared to those caused by previous variants.[33] These features may potentially affect the pathogenesis of bacterial coinfection. The area of pathogenesis of bacterial coinfection in COVID-19 in different variants of concern requires further research. However, how other respiratory viruses such as influenza, parainfluenza and RSV may cause secondary bacterial infections is well studied and may provide a clue to the possible co-pathogenesis in SARS-CoV-2 infections.

During acute infection, respiratory viruses damage the human's respiratory tract, and not only breakdown its integrity but also affect its physiological function. Virus can facilitate bacterial adhesion to respiratory epithelial cells which may increase bacterial colonization and contribute to secondary infections. The disease severity varies between different viruses and bacteria.[34,35] Studies using an

influenza murine model showed that both viral and bacterial titers were increased in the lungs during coinfections compared with single infections, through a synergistic type I interferon response. This response also results in increased susceptibility to invasive infections causing high mortality.[35]

Viral infections impair both the innate and adaptive immune response. An animal study on the pathogenesis of how influenza infection facilitates bacterial superinfection revealed significant impairment of the early alveolar macrophage mediated bacterial clearance in influenza-infected mice.[35] Cytokines and chemokines released by alveolar macrophages, which is required for recruitment and activation of neutrophils, were also decreased during influenza infection.[36] It has been demonstrated that SARS-CoV, which causes SARS, regulate immune function-related gene expression in human monocytes and also suppress type I interferon (IFN) production by impeding the formation of functional TRAF3-containing complex resulting in secondary bacterial infection.[37] Further research on the molecular pathogenesis of COVID-19 associated secondary bacterial coinfection is essential for the development of future diagnostic and therapeutic strategies.

Clinical manifestations

The symptoms of COVID-19 associated bacterial coinfections and secondary infections are very similar to those in patients without COVID-19 infection. For example, besides fever, patients with urinary tract infection often present with urgency, frequency, dysuria and flank pain. Patients with lower respiratory tract coinfections and secondary infections had symptoms including fever, cough with or without sputum production and dyspnea.[32] Differentiating between respiratory symptoms caused by COVID-19 with and without bacterial coinfection is a challenge. This resulted in over-prescription of empirical antibiotics in patients presented with only respiratory manifestations. However, bacterial coinfections in sites other than the lungs accounts for the majority of the patients upon admission. A thorough history taking to include extrapulmonary symptoms, and focused physical examination along with laboratory tests, can be a guide for physician to suggest a diagnosis of bacterial coinfection and use antibiotic appropriately.

Diagnosis

COVID-19 associated bacterial infections can be difficult to diagnose owing to similar clinical presentations to patients without coinfection and lack of microbiologic testing in COVID-19 patients. Reduced microbiologic testing may be due to concerns with transmission of SARS-CoV-2 during procedures to obtain respiratory tract specimens and the acute service pressure during the pandemic.[21] As a consequence, syndromic diagnostic testing and biomarkers were widely used, in addition to conventional cultures, for the diagnosis of bacterial coinfections during the COVID-19 pandemic. Comparison of different diagnostic methods are listed in Table 2.

Conventional cultures

Conventional cultures remain the diagnostic gold standard not only for identifying the causative pathogen but also for antibiotic susceptibility testing. However, bacterial coinfections can be underestimated if conventional culture is the only measure for diagnosis. Only 40.8%—73% of hospitalized COVID-19 patients had blood cultures collected[10,25,38] and about 15—20% had respiratory tract specimens obtained. Sputum and tracheal aspirates were the most common respiratory specimens sent for culture in non-ventilated and ventilated patient, respectively, followed by bronchoalveolar lavage.[10]

Another concern is the difficulty in differentiating a true infection from colonization, which may lead to over-diagnosis of bacterial infections. An increased prevalence of fungal and *P. aeruginosa* colonization in severe COVID-19 patients compared to non-COVID-19 cases were reported.[39]

Table 2 Comparison of different diagnostic methods used in COVID-19 associated bacterial infections (CABI).

Methods	Advantage	Disadvantage
Conventional cultures	- Able to identify causative pathogen and determine antibiotic susceptibility	- Need to differentiate colonization from infection
Syndromic diagnostic testing	- Short turnaround time - Can identify some fastidious micro-organisms and common resistance target genes	- Need to differentiate colonization from infection - High cost
Procalcitonin	- Can be used to guide discontinuation of antibiotics under adequate infection source control	- Low specificity in COVID-19 patients
Serology testing	- Can be used to aid diagnosis of atypical bacterial pneumonia with compatible clinical presentation - Pneumococcal and *Legionella* urinary Ag for rapid diagnosis	- Cross-reactivity of antibodies during SARS-CoV-2 infection should be considered

Thus, when making a diagnosis, clinical symptoms, underlying diseases, risk factors and disease severity should also be taken into consideration.

Syndromic diagnostic testing

Syndromic diagnostic testing is an alternative method for detection of coinfection and can reduce approximately 1 day in turnaround time compared with conventional cultures. The panel can also detect some fastidious microorganisms and common resistance target genes within one day. There are several studies[40–42] on the accuracy of multiplex PCR compared with conventional cultures in critically ill COVID-19 patients using lower respiratory tract specimens. The results showed a sensitivity rate ranging from 89.3% to 100% and the specificity rate from 88.4% to 100% depending on the pathogen[40]; and a positive predictive value (PPV) of about 60% and negative predictive value exceeding 99%.[41,42]

Another prospective cohort study including 200 COVID-19 patients conducted in Germany and Switzerland found that 43% of the patients with a positive result of community-acquired bacterial pathogens (CABP) were detected at admission.[43] The specimens were collected via the nasopharyngeal swab and the most frequently isolated pathogens were *S. aureus* (27%) and *H. influenzae* (13.5%). A positive CABP was not correlated with ICU admission, mortality and inflammatory markers.

In conclusion, based on the excellent sensitivity, syndromic diagnostic testing may be useful to rule out bacterial coinfections and to avoid antibiotic overprescription, but routine screening with nasopharyngeal specimen at admission may result in a high detection rate of bacteria that represent colonization only and is not recommended.

Role on biomarkers

Procalcitonin (PCT) and C-reactive protein (CRP) are two biomarkers frequently tested in patients with infectious diseases. PCT is a peptide precursor of calcitonin which is released in response to pro-inflammatory stimuli, especially bacterial infections, and has been useful as a diagnostic indicator to discriminate between bacterial and viral infections. According to the recommendation of 2021 Surviving Sepsis Campaign, PCT has limited role in initiation of antimicrobials but can be used to guide antibiotic discontinuation under adequate infection source control.[44] CRP is an acute phase reactant produced during an inflammation process but according to previous research, it is nonspecific in diagnosing bacterial infection.

COVID-19 patients without bacterial coinfections can present with high CRP levels and a low to moderate PCT levels initially.[45,46] In a study including 5700 COVID-19 hospitalized patients in New York, the average PCT level was 0.2 ng/mL at admission.[47] However, a rise in PCT level is associated with disease severity in COVID-19 patients, and may also indicate bacterial coinfection. One meta-analysis showed that increased PCT values with a cutoff $>$ 0.5 ng/mL was associated with a nearly 5-fold higher risk of severe SARS-CoV-2 infection.[48]

In hospitalized patients, PCT had a sensitivity of 91% and a specificity of 81% for the detection of secondary bacterial infections with a cut-off value of 0.55 ng/mL. Meanwhile, CRP has a lower sensitivity and specificity of 81% and 76% respectively.[49] In patients admitted to ICU, a PCT level above 1 ng/mL ruled in secondary bacterial infection with a PPV of 93%, whereas PCT level below 0.25 ng/mL ruled out secondary bacterial infection with a NPV of 81%.[45] As CRP often rises in the initial stage of COVID-19, it does not have a predictive value for the diagnosis of bacterial coinfection at admission and during ICU stay, serial PCT may have a role to rule out nosocomial bacterial infections and to guide antimicrobial stewardship.[45]

Serology testing

Serology testing has been widely used to diagnose atypical bacterial pneumonia, including *Mycoplasma* IgG, IgM, *Chlamydia* IgG, IgM and *Legionella* urinary antigen. The sensitivity of serologic tests depends on the time point of the serum sample and on the availability of paired serum collected 2-4 weeks later. Pneumonia caused by *S. pneumoniae* can also diagnosed with urine pneumococcal antigen, sensitivity and specificity were 60% and 99.7% respectively.[50] *Mycoplasma* IgM positive rates in hospitalized COVID-19 patients ranged from 0% up to 56.4% and most studies report *M. pneumoniae* coinfection rate in the range of 1.5%—3.5%.[10,24] The incidence of *Mycoplasma* pneumonia may be overestimated when based on serology testing only, since these studies were retrospectively reviewed and *Mycoplasma* IgM was tested only one time.

Treatment

During the first wave of COVID-19, most of the hospitalized patients were prescribed at least one antibiotic, despite a low incidence rate of community-acquired bacterial coinfections. One systemic review including 24 studies and 3506 patients demonstrated that 71.8% (95%CI: 56.1%—87.7%) of the patients received an antibiotic at some time during admission while only 3.5% of the patient were diagnosed with community-acquired bacterial infection and 14.3% had hospital-acquired bacterial infection.[16] Quinolones and the 3rd generation cephalosporins were the most commonly prescribed, comprising of up to 74% of antibiotics used.[16] The pooled prevalence of co-infection with resistant bacteria was 24% (95% CI 8—40%; n = 25 studies: I^2 = 99%). Among multi-drug resistant organisms, methicillin-resistant *S. aureus*, carbapenem-resistant *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* were most commonly reported.[51] The COVID-19 pandemic has fueled the antimicrobial resistance (AMR) global crisis due to the increase in the empiric use of antibiotics, disruptions to infection prevention and control practices in overwhelmed health systems, and diversion of human and financial resources away from antibiotic stewardship and AMR programs. Studies evaluating the impact of COVID-19 pandemic on antimicrobial resistance showed that the rate of *A. baumannii* and *K. pneumoniae* resistance to carbapenems significantly increased in 2020 compared with isolates in the pre-COVID-19 era; in addition, a significant increase in

resistance to polymyxin B, particularly for *K. pneumoniae* isolates, with a rate increase from 5% to 50%, was observed.[52,53] Antimicrobial resistance kills an estimated 700,000 people every year, in view of this, both the WHO guidelines and 2021 NICE guideline recommend not to give antibiotic therapy or prophylaxis for patients with mild or moderate COVID-19, unless signs and symptoms of a bacterial infection exist.

Genitourinary tract infection accounts for 57%—70% of community-acquired bacterial infections in hospitalized COVID-19 patients[15,19] and the most common pathogen is *E. coli* and *Klebsiella* spp. Empiric antibiotics should target *E. coli* and *Klebsiella* spp. and tailored to the local resistance patterns when bacterial coinfections of genitourinary tract is highly suspected. Bacterial pneumonia is the second most common community-acquired coinfection in COVID-19 patients, most frequently caused by *H. influenzae*, *S. pneumoniae* or *S. aureus*, and often treated with either a third-generation cephalosporin, such as ceftriaxone, or fluoroquinolones. Rationale for the choice of antibiotics includes: first, ceftriaxone and fluoroquinolones are active against most community-acquired pathogens, and fluoroquinolones against pathogens of atypical pneumonia. Second, once daily dosing is more convenient and can reduce the frequency of patient contact with healthcare personnel. Fluoroquinolones are associated with QTc prolongation and should be used with caution.

Empirical antibiotic for secondary bacterial infections should target common pathogens caused by the most frequent clinical syndromes associated with COVID-19, including bacteremia, ventilator-associated pneumonia (VAP), and hospital-acquired pneumonia/tracheobronchitis. Choice of antibiotic should be tailored to the local resistance patterns. Coagulase-negative *Staphylococcus* spp. and *E. faecium* were the most frequently isolated organism from bloodstream infections while *P. aeruginosa* and MRSA were major pathogens of VAP. Obtaining cultures of the blood, urine, sputum and a urinary antigen serological test prior to initiating antibiotics is important if bacterial coinfection or secondary infection is suspected to allow de-escalation and specific antimicrobial treatment, to reduce AMR. The necessity of antibiotic use should be assessed daily.

Outcome

Bacterial coinfections or secondary infections in COVID-19 patients are associated with a poor prognosis. Overall mortality in patients hospitalized for more than 48 h was 9.8% in a cohort of 989 patients with either coinfection or secondary infection.[11] A study including 1,565 patients, with 3.7% having at least one episode of hospital-acquired infection, demonstrated a significantly higher in-hospital mortality rate in patients with secondary infections compared with those without (40.7% and 11.8%, $p < 0.001$).[9] Another retrospective, observational study of 254 critically ill patients also demonstrated that those with coinfections have a higher ICU mortality rate (crude OR 1.78, 95%CI 1.03—3.08, $p = 0.04$) and a longer length of hospital stay (subhazard ratio = 0.53, 95%CI 0.39—0.71, $p < 0.001$).[7] Thus, identifying patient with coinfection or secondary infection and timely initiation of appropriate antibiotics is crucial to improve survival.

Conclusions

COVID-19 associated bacterial coinfections are rare during the pandemic, and most of the published guidelines recommend against routine antibiotic use. The most common sites of bacterial coinfections at admission include the genitourinary tract, followed by the lower respiratory tract. Bloodstream infection and ventilator-associated pneumonia comprise the majority of secondary infections. Studies included were mostly from during the COVID-19 pandemics with the alpha- and delta-variants. The omicron-variant was first identified in November, 2021. To date, none of the studies specifically addressed the epidemiology of COVID-19 associated bacterial coinfection in omicron-variants, and further research is required.

Conventional culture remains the most important diagnostic measure but syndromic testing and biomarkers can be a useful tool for antibiotic stewardship to guide de-escalation and discontinuation of unnecessary antibiotics. Syndromic diagnostic testing has a high sensitivity for diagnosing bacterial coinfections, and can be used to exclude bacterial coinfection; nevertheless, routine screening for "nasopharyngeal" specimens is not recommended as it may only lead to detection of colonized pathogens. Serology testing is important for identifying the presence of atypical pneumonia; however, results vary widely across studies, and the true incidence of atypical pneumonia among COVID-19 patients requires further study.

Higher in-hospital mortality rates are seen in COVID-19 patients with bacterial coinfection and secondary infection. However, due to the low incidence of coinfection, empiric antibiotic with a 3rd generation cephalosporin or fluoroquinolones to cover commonly encountered community-acquired pathogens is recommended only if a bacterial coinfection is highly suspected. Antibiotics treatment for secondary infections should be tailored to local epidemiology and resistance patterns. Continuing antimicrobial stewardship during the COVID-19 pandemic is crucial to prevent antimicrobial resistance.

Declaration of competing interest

All authors report no conflicts of interest.

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