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UNDERSTANDING THE DISEASE

Bacterial and fungal superinfections in critically ill patients with COVID-19

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Are critically ill patients with coronavirus disease 2019 (COVID-19) at high risk of bacterial and fungal superinfections developing on the top of the viral infection in the lung or in other body sites? And from which organisms? Answering these apparently simple questions could be far more difficult than expected, for at least three important reasons.

The first one is that the timing of development of superinfection (early or late) with respect to the intensive care unit (ICU) admission may have relevant clinical implications. Indeed, borrowing from experiences in other ICU populations it cannot be excluded a priori that early and late superinfections may be profoundly different in terms of risk [1, 2]. However, early and late superinfections have been frequently lumped together in the currently available literature on COVID-19 patients, making it difficult to firmly grasp their separate risks [3, 4]. The second reason is that the high case fatality of the viral disease per se may be an important competing risk for the development of late superinfection, which may lead to an unintended underestimation of the risk of superinfection at the bedside of alive patients. The third reason specifically involves invasive aspergillosis, for which the current absence of a standardized definition for non-proven disease in non-neutropenic critically ill patients may preclude a reliable risk assessment also in COVID-19 patients [5]. In the next few paragraphs, we briefly discuss each of these three intertwined, important issues.

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Early and late superinfections

The prevalence of laboratory-confirmed bacterial superinfection in critically ill COVID-19 patients in ICU could be around 14% (95% confidence interval 5–26%) according to a recent meta-analysis [3]. However, in most included studies there was no distinction between early and late infections. Although on the surface this may appear mere semantics, in reality such a distinction has important implications for antimicrobial prescribing in real life. Indeed, should it be proven that most superinfections in critically ill COVID-19 patients develop late and not early during the ICU stay (or during exposure to the hospital environment), the widespread attitude toward universally prescribing empirical antibacterials in critically ill COVID-19 patients since ICU/hospital admission could no longer be supported [4]. This is in line with a recent observational cohort of 78 critically ill COVID-19 patients, in whom the cumulative risk of developing a bloodstream infection (BSI) after at least 48 h from ICU admission was estimated to be of almost 25% at 15 days after ICU admission [6]. Compared with the meta-analytic results reported above and notwithstanding the important limitation of the small sample size, such results seem to suggest that most were late superinfections, which is in line with the low prevalence of superinfection at hospital admission registered in other experiences in COVID-19 patients [7].

Superinfection-free COVID-19 case fatality as a competing risk

The basic, intuitive rule is the following: if a critically ill COVID-19 patient dies early during ICU stay without superinfection, he/she can no longer develop a late superinfection. Although this is obvious, it should be noted that the very same patient usually remains in the denominator for estimating the prevalence of superinfection in the entire population of critically ill COVID-19

patients [3, 4]. In turn, if the calculated prevalence is inadvertently perceived as the risk of late superinfection in the subgroup of patients still alive after the first days of ICU stay, this could lead to an underestimation of the risk of late superinfection at their bedside. Given the high case fatality of COVID-19 in critically ill patients (> 25%) [8], it cannot be excluded that the magnitude of this potential underestimation could be remarkable.

COVID-19-associated pulmonary aspergillosis

More than 30 cases of COVID-19-associated pulmonary aspergillosis (CAPA) have been published to date [9]. Overall, the possible development of invasive pulmonary aspergillosis in some critically ill COVID-19 patients is somewhat expected, considering the following, likely cumulative risk factors: (1) the epithelial lung damage caused by either the virus or the dysregulated host response; (2) the frequent use of corticosteroids [10]; (3) a possible similarity with influenza-associated invasive aspergillosis (IAPA) [11]. However, some clinically relevant differences between IAPA and CAPA have been described. For example, it has been hypothesized that the different distribution in the airways of the host cells receptors used by SARS-CoV-2 and influenza viruses may imply a different risk of invasive *Aspergillus* tracheobronchitis (i.e., lower for COVID-19 than influenza patients). In addition, different effects of the two different viruses on the host immune response could possibly explain a usually worse disease progression in IAPA than in CAPA. Finally, the diagnostic performance of fungal

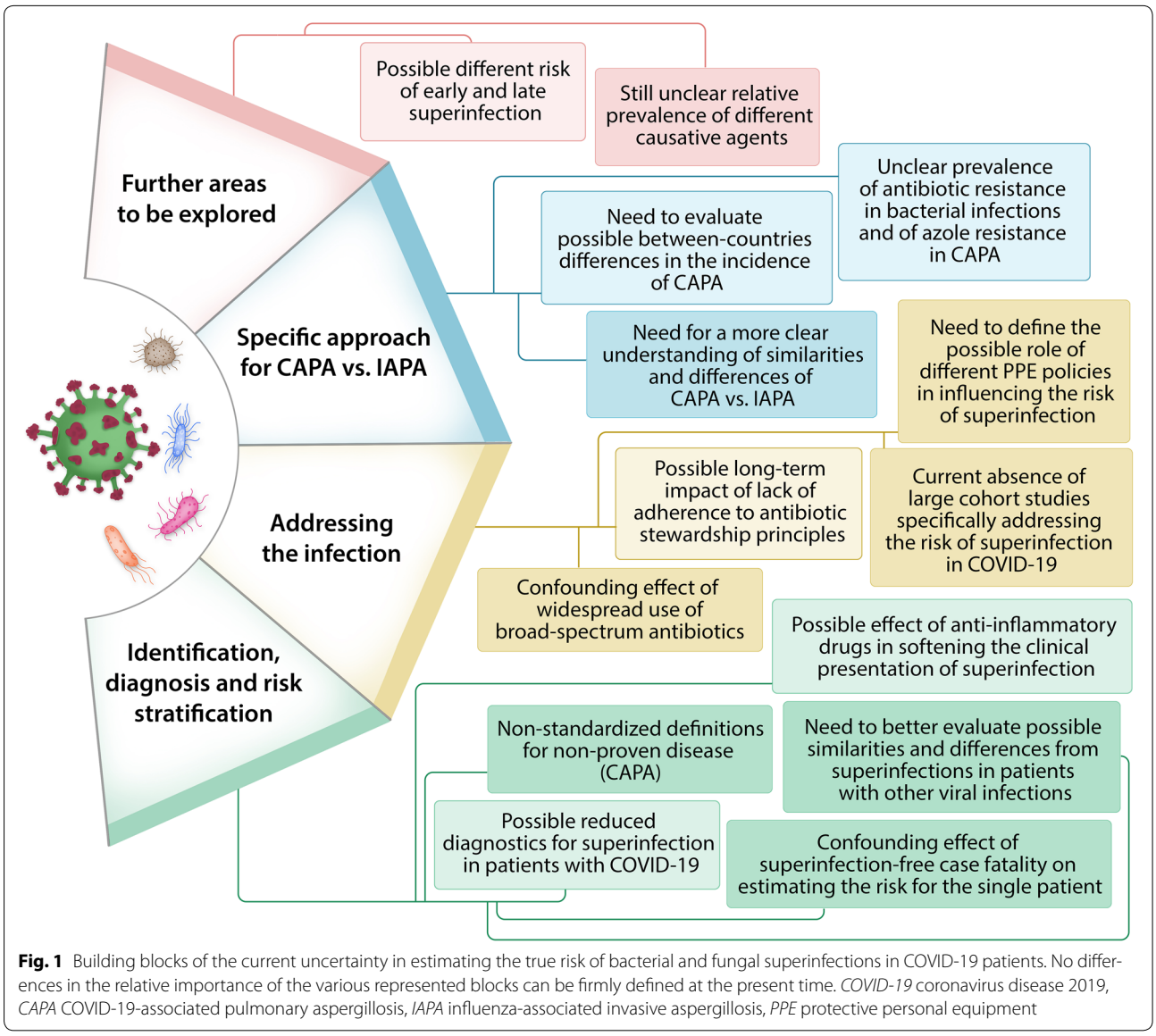

Fig. 1 Building blocks of the current uncertainty in estimating the true risk of bacterial and fungal superinfections in COVID-19 patients. No differences in the relative importance of the various represented blocks can be firmly defined at the present time. *COVID-19* coronavirus disease 2019, *CAPA* COVID-19-associated pulmonary aspergillosis, *IAPA* influenza-associated invasive aspergillosis, *PPE* protective personal equipment

antigens tests could be different (e.g., lower sensitivity of serum galactomannan in CAPA than in IAPA) [11, 12]. Very importantly, all of this also stands against the backdrop of a lack of a standardization in the definition of non-proven invasive aspergillosis in non-neutropenic critically ill patients, which itself contribute in further fueling the uncertainty regarding the true prevalence of CAPA. While waiting for the results of ongoing projects to improve the definition of invasive aspergillosis in ICU patients [5, 13], the most reliable definition for non-proven CAPA remains that of putative invasive pulmonary aspergillosis according to the AspICU algorithm [14]. However, although of important help, it is of note that this algorithm requires a positive airways culture for *Aspergillus*, and respiratory cultures were shown to have low sensitivity when tested against a reliable reference standard (histology/autopsy) [15].

In conclusion, the true prevalence of bacterial and fungal superinfections in critically ill COVID-19 patients still remains elusive. In our opinion, a possible underestimation of the risk of late superinfection may occur at the bedside of ICU patients with COVID-19, for the reasons summarized in Fig. 1. Notably, all these confounding factors also hamper a clear identification of the most frequent bacteria associated with superinfection, with either Gram-negative or Gram-positive organisms having alternatively deemed as the major culprit [3, 4]. Further dedicated investigation is necessary to better understand the true risk and the disease spectrum of superinfection in critically ill patients with COVID-19, with the ultimate aim of improving their management and outcomes.

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