Enterococcus and COVID-19

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Based on the uncontrolled use of antibiotics and the lack of worldwide-accepted healthcare policies, the COVID-19 pandemic has provided the best premises for the emergence of life-threatening infections. Based on changes described in the intestinal microbiome, showing an increased number of *Enterococcus* bacteria and increased intestinal permeability due to viral infection, infections with *Enterococcus* have taken the spotlight in the healthcare setting. The COVID-19 pandemic has launched the best premises for the development of highly resistant bacterial strains due to unregulated antimicrobial use and the lack of proper worldwide-accepted protocols. *Enterococcus* genus represents one of the most common findings in human infections. It is no surprise that during the pandemic, a high number of this type of infection was anticipated.

Enterococcus VRE COVID-19 long COVID SARS-CoV-2

1. Enterococcus and Bloodstream Infections

Most of the articles in this brief entry described *Enterococci* solely in the context of BSI. In order to better understand the relationship between COVID-19 and BSIs with *Enterococcus,* the researchers further classified them into articles that compared their findings with a control group (such as patients with influenza, COVID-19-negative patients or a different time period) and articles that simply described the incidence of *Enterococcus* infections among COVID-19 patients that developed a BSI [1][2][3][4][5][6][7][8][9].

In the first group, one study compared the number of *Enterococcus* cases within a COVID-19-positive group with the number of cases within an influenza-positive group [1]; another one used two control groups, one consisting of influenza patients and one consisting of just COVID-19-negatives [2]; a third one made a comparison between the incidence of *Enterococcus* BSI during similar periods, 1 year apart, before and after the start of the pandemic (2019 and 2020) [3]; and the fourth study compared the proportions of BSIs caused by *Enterococcus* during three different years [8].

No *Enterococcus* isolates were found from either group of influenza patients from the two studies that analyzed them, so no statistical analysis comparing them to COVID-19 groups could be made. The incidence of *Enterococcus* BSI among COVID-19-positive patients varied between 0.47% and 2.6% [1][2].

All the BSI studies that used control groups other than influenza found a solid association between *Enterococcus* BSI and COVID-19. De Voe at al. describe that *Enterococcus* spp. BSI occurred in 2.6% of COVID-19 patients

(8/314 cases—6 *E. faecalis* and 2 *E. faecium*), compared to the 0.33% of the COVID-19-negative group (48/14,332 cases), the adjusted odds ratio being 3.75 (95% CI: 1.49–9.41) [2]. Cuntrò et al. compared the incidence of *E. faecalis* and *E. faecium* BSIs in an ICU before the pandemic (Feb 22nd to May 21st, 2019) with their incidence during the pandemic (Feb 22nd to May 21st, 2020). What they determined was that there was a substantial increase in the number of *E. faecalis* cases—28 in 2019 vs. 74 in 2020 ($p < 0.001$, Fisher's test), but no significant increase for *E. faecium*—27 in 2019 vs. 32 in 2020 ($p = 0.41$, Fisher's test) [3]. Bonazzetti et al. compared the proportions of BSIs caused by *Enterococcus* between 2020, 2019 and 2018. The rate was significantly higher in 2020 (71.7% vs. 33.3% and 20%; $p = 0.016$) [8].

The rest of the studies included in this brief entry, involving BSI with *Enterococcus,* mainly provide an incidence of this infection that varies between 17.2% and 37.5% [4][5][7][9]. Giacobbe et al. and Posteraro et al. went one step further, and described the incidence of the most common species, *E. faecium* and *E. faecalis* [4][7]. In those studies, the incidence of *E. faecium* varied between 3.5% and 8.88%, while *E. faecalis* remained somehow constant at around 17%. Therefore, the researchers can notice that there could be a tendency for a greater occurrence of *E. faecalis* cases in COVID-19 patients, rather than *E. faecium*, which would be consistent with the other earlier findings described by Bonazzetti et al. [8].

Vancomycin-resistant *Enterococci* were also present within these studies. Most of them report the frequency between 2.38% and 18.1% of all *Enterococci* [4][5][6]. However, Signorini et al. reported a much higher incidence of VRE − 33.3% [9].

Palanisamy et al. described that 81.8% of *Enterococci* was MDR: resistance to erythromycin was reported in 90.9% of isolates, to ampicillin and ciprofloxacin in 81.8%, to tetracycline in 54.5% and to teicoplanin in 18.1%. In addition, another relevant observation from this research was the high mortality [5].

2. Enterococcus from Various Samples from COVID-19 Patients

Six of the studies included in this entry analyzed secondary infections in patients diagnosed with COVID-19. It was observed that a wide range of bacterial infections occurred in these patients, notably: *Streptococcus pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterococcus faecium, Enterococcus faecalis, Acinetobacter baumannii* or *Haemophilus influenzae*.

Two of the articles emphasized finding *Enterococcus* not only in samples recovered from patients, but in environmental samples too. In one of them, after detecting five cases of COVID-19 with VRE infections, some tests from environmental sites were made. Eleven cases of VRE were determined from those samples. *E. faecium* was the bacteria isolated, and further analysis described two clusters of closely related strains. Interestingly, one of these clusters corresponded to COVID-19-positive patients. The other study revealed that in the USA, *E. faecalis* and *E. faecium* have emerged as further common nosocomial infections after MRSA, being responsible for 7.4%

and 3.7% of all HAIs. The researchers detected isolates of VRE in environmental samples, highlighting what an important role contaminated surfaces have in VRE transmission to COVID-19 patients [10][11].

Serano et al. outlined the descending order of the specimen types depending on the number of positive cultures in secondary infection: blood, endotracheal aspirate, urine, sputum wound swab or bronchoalveolar lavage. Regarding *E. faecalis* and *E. faecium*, these were in the first half of frequency scale from positive cultures [12].

Furthermore, Saeed N et al. have shown that these two bacteria occurred in 44 cases of 261 patients with secondary co-infections. The pathological products that were used to find the microorganisms were blood culture, sputum culture, stool culture, endotracheal aspirate and bronchoalveolar lavage culture [13].

Enterococcus has been isolated from a wide variety of pathological products from patients with COVID-19 and, thus, implies an eminent threat for human health. It also raises awareness of the importance of microbiologic diagnosis in order to provide long-term proper healthcare.

3. Enterococcus and Gut Microbiota of COVID-19 Patients

Two of the articles focused on the gut microbiota (GM) changes that occurred in patients diagnosed with COVID-19 from Italy and China. Gaibani et al. analyzed stool samples from patients with COVID-19 from three different hospitals in Bologna (Italy), where the results from the next-generation sequencing method were compared with the publicly available sequences from matching sex and age in healthy Italians and critically ill non-COVID-19 patients [14]. Zhou et al. analyzed samples from Wuhan Union Hospital, where the GM of two groups of moderate COVID-19 patients were compared, one of the groups presenting fever (≥37.3 °C) and the other one without fever. Compared to the data prior to the pandemic, an increased number of secondary infections was reported, which led to monitoring the GM of COVID-19 patients. It was decided that it has an important effect on mediating the inflammatory response, favoring the production of pro-inflammatory cytokines, such as IL-6, thus causing fever in virus-infected patients [15].

In both articles, following examination of samples from COVID-19 patients, a disruption to the microbiota homeostasis was observed. Particular to this infection was the reduced diversity of the microbiota (alpha diversity) in comparison to the healthy controls (p value = 0.0008, Wilcoxon test) [14)], with reduced health-associated microorganisms from the *Ruminococcaceae, Bacteroidaceae* and *Lachnospiraceae* families, responsible for producing short-chain fatty acids (SCFA), important in human immunological and metabolic homeostasis, featured by an increasing growth of potential pathogens, especially *Enterococcus*, in addition to *Staphylococcus*, *Lactobacillus* and *Serratia* (p value ≤ 0.02) [14]. There seems to be a causal relationship between *Enterococcus* spp. and bloodstream infections (BSIs) developed in COVID-19 patients. Two of the dominant species responsible were *E. faecalis* (1.8%) and *E. faecium* (8.4%) [14].

An interesting observation was made when analyzing the GM profiles of COVID-19 patients. Those who entered the ICU and developed BSI presented a loss of alpha diversity (p value ≤ 0.004) accompanied by an abundance of

Enterococcus (*p* value ≤ 0.001), compared to the opposite profiles, who did not enter the ICU and did not develop BSI [14]. A similar depletion in alpha diversity was observed in patients presenting fever, in contrast to those without fever. Moreover, fever could be associated with a decreased relative abundance of *Bacteroidetes*, as well as a significant enrichment of *Enterococcus faecalis, Saccharomyces cerevisiae and Haemophilus parainfuenzae*, whereas the GM of non-fever patients indicated the growth of *Anaerostipes*, a butyrate-producing bacteria which suppresses the inflammatory cytokine production. The latter has been observed to be lacking in those with fever [15]. Furthermore, the GM of critically ill patients who tested negative for COVID-19 showed the presence of *Enterobacteriaceae* (*Klebsiella* spp.) (*p* value ≤ 0.001), which mainly distinguished the samples from patients who tested positive for the infection [14].

Due to the ability of SARS-CoV-2 to enter the cells of the digestive tract, therefore leading to enteric manifestations through virus-induced immune-mediated damage, the GM of the infected patients developed an accumulation of opportunistic pathogens or pathobionts, potentially antibiotic-resistant [14]. Consequently, the crossing of the bacteria to the circulation through the damaged intestinal epithelium was facilitated, which is very clinically relevant. Finally, studies have found that GM plays a major role in the pathogenesis of inflammation and the evolution of infection with SARS-CoV-2, controlling the immune responses.

4. Enterococcus and COVID-19—Case Reports

There were reported cases of COVID-19 patients presenting a secondary bacterial infection in four of the articles, which is not atypical in the context of infection with SARS-CoV-2.

In one case, a patient presented with the following symptoms: fever, dyspnea and cough. He was later diagnosed with nosocomial pneumonia caused by *Enterococcus faecalis* and tested positive for COVID-19. It is yet unknown if the pulmonary affection was determined by the bacterial co-infection or by the virus alone [16].

One article outlined a higher incidence of hospital-acquired infected endocarditis (HAIE) between March and April 2020, compared to the correspondent months 5 years prior to the pandemic (*p* = 0.033). Four cases of HAIE were reported in this period, the pathogenesis of two of them being *Enterococcus faecalis*, and for the others, *Staphylococcus aureus* and *Candida albicans*. The diagnosis was made after analyzing blood or valve culture. All four patients with HAIE underwent central venous and urinary catheterization when admitted to the hospital, which appeared to be the source of infection [17]. Co-infections with bacteria and fungi are a common complication in COVID-19 cases [18]. Another article discussed the case of a patient diagnosed with both COVID-19 and infected endocarditis (IE), who presented nonproductive cough, shortness of breath and fatigue. After a blood culture analysis, the etiology of IE was *Enterococcus faecalis*. After a persistent bacteremia following antibiotic therapy with vancomycin and gentamicin and an insertion of a new catheter, the patient suffered an aortic valve surgery, which identified a vegetation >10 mm of *Enterococcus faecalis*. The treatment changed to ampicillin and ceftriaxone [19].

The last case-report article presents a patient who underwent a simultaneous heart-kidney transplant (SHKT) previous to the first cases of SARS-CoV-2 in the respective area. In the weeks following the intervention, he was admitted to the hospital for respiratory failure, open non-healing wounds and multiple secondary infections due to opportunistic bacteria. A perinephric collection showed vancomycin-resistant *Enterococcus* (VRE) and his blood samples grew out MRSA bacteremia. He was also tested positive for SARS-CoV-2, in spite of being asymptomatic. The patient was immunosuppressed following the procedure, which led to complications [12].

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