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ABOUT COVER

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MINIREVIEWS

Life after recovery from SARS, influenza, and Middle East respiratory syndrome: An insight into possible long-term consequences of COVID-19

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Abstract

Viral infectious diseases have become an increased public health issue in the past 20 years. The outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2002, influenza H1N1 in 2009, Middle East respiratory syndrome-CoV in 2012, and the current new coronavirus SARS-CoV-2 have shown that viral infectious diseases are a major concern in the 21st century. As the world lives under the pandemic of a new coronavirus (COVID-19), knowing the clinical characteristics from those past diseases and their long-term outcomes is important to understand the current coronavirus pandemic and its complications and consequences better and plan for possible future outbreaks. Several long-term complications have been described with these respiratory viral diseases, such as decreased pulmonary function, pulmonary fibrosis, chronic fatigue syndrome, avascular necrosis of bone, polyneuropathy, encephalitis, posttraumatic stress disorder, depression, and anxiety. This article summarizes several studies describing chronic complications and long-term outcomes of patients recovered from these viral syndromes.

Key Words: COVID-19; Long-term; Consequences; SARS; Middle East respiratory syndrome; Influenza

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Core Tip: As the world now lives more under the acute burden of this pandemic, very soon possible long term and late consequences of this disaster will appear and the globe will be challenged by those little known before and probably unknown complications. These late complications can potentially be due to the disease itself and/or the side effects of medications or medical interventions applied. Our task as health care professionals is to have a high suspicion upon approaching patients with history of this disease. We believe that by reviewing the recent outbreaks' long-term complications, we will have a better understanding of these potential complications.

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INTRODUCTION

The widespread infectious diseases became a significant public health issue globally in the past 20 years. There have been four major viral contagious outbreaks in the 21st century: The severe acute respiratory syndrome (SARS) in 2002, the H1N1 influenza pandemic in 2009, the Middle East respiratory syndrome (MERS) in 2012 and the current novel coronavirus (COVID-19) in 2019-2020. In between, every year, thousands of people die from complications of seasonal influenza around the world. Besides their high mortality rates, these viral infectious diseases proved to cause long-term outcomes for those who survive. Pulmonary lung dysfunction and residual parenchymal/imaging abnormalities can persist several years after hospital discharge. Many patients can develop avascular necrosis of bone due to the high doses of corticosteroids used in treatment. Several studies reported chronic fatigue syndrome with neuromuscular dysfunction as complications of these viral syndromes. The psychological and mental burden has also been proved in patients and health care workers involved in the treatment and coordination of these pandemics. Acute neurologic complications may cause long-term disability, which can have a significant impact on the health care system and the quality of life of those affected. This article aims to review studies describing long-term multi-system clinical outcomes in patients affected by SARS, MERS, and Influenza following the most recent outbreaks. A summary of main complications and long-term outcomes in patients affected by these outbreaks is shown in Table 1.

RESPIRATORY SYSTEM

SARS

The first cases of a new severe lower respiratory tract infection were reported in early 2003 in Guangdong, China, rapidly spreading throughout Asia and Canada in the following months. Later in that year, this infection became known to be caused by a new coronavirus, named SARS-CoV, that spread through 29 countries from January to September 2003, infecting a total of 8098 patients and causing 774 deaths, with a mortality rate of 9.5%[1]. SARS-CoV is a single-stranded positive RNA virus that belongs to the coronavirus genus and can be spread through the respiratory system, droplets, aerosol, and contaminated surfaces. Young adults between 20-50 years old were the most affected population. Most patients presented initially with fever, headache, joint pain, and dyspnea and could progress to pneumonia and spread to other systems with recovery or death.

Pulmonary involvement of SARS is described to occur in three distinct phases: From 1-7 d of infection (initial phase) mild unilateral ground-glass opacities predominates, from 7-14 d of infection (progression phase) there is an expansion of the ground-glass opacities that becomes multi-focal, bilateral and can progress to consolidations, finally after 2-3 wk of symptom onset the recovery phase begins, with the absorption of the lesions. Some patients may develop interstitial, lobular, and lobar thickening,

Table 1 General complications and long-term manifestations associated with SARS, Middle East respiratory syndrome, and influenza

System	Clinical and Image manifestation
Respiratory system	CT Ground-glass opacities and interstitial thickening
	Reduced lung function
	Low DLCO, VC and FVC
Musculoskeletal system	Chronic fatigue
	Myalgias
	Avascular necrosis of the hip
Neurologic system	Guillain-barré syndrome
	Miller fisher syndrome
	Gustatory and olfactory dysfunction
	Neurologic disease exacerbation
Mental disorders	PTSD
	Depression
	Anxiety
	Burnout

CT: Computed tomography; DLCO: Diffusion capacity of carbon monoxide; VC: Vital capacity; FVC: Functional vital capacity; PTSD: Post traumatic stress disorder.

honeycomb manifestations and traction bronchiectasis characterizing pulmonary fibrosis[1].

Chronic complications of SARS have been described in the following years of the outbreak. The respiratory system is the most affected, characterized by pulmonary fibrosis and decreased lung function. A recent systematic review and meta-analysis by Ahmed *et al*[2] showed that critically ill patients recovered from SARS presented with significant pulmonary function impairment and reduced exercise tolerance 3 to 6 mo post disease recovery[2]. These patients had also reduced diffuse capacity of the lung for Carbon monoxide (DLCO), vital capacity (VC), and forced vital capacity (FVC), which according to the authors, might have impacted aerobic capacity, general physical conditioning and exercise tolerance. The authors also describe that although many patients had improvement in lung function, the meta-analysis has shown that reduction in DLCO and lung fibrosis may persist for years in some patients[2].

Ng *et al*[3] studied the pulmonary function and persistent pulmonary CT abnormalities in patients recovered from SARS in Hong Kong, six months after hospital discharge. The investigators found that 43 out of 57 patients had some pulmonary function abnormality (with the mild obstructive defect as the most common finding), 20 patients had reductions in the carbon monoxide transfer factor (TLCO), 17 patients had abnormal total lung capacity, and four patients had abnormal FVC. Radiological abnormalities were also found in 43 patients out of 57: The median number of segments involved were three in the upper and lower lobes, and the use of corticosteroids was associated with the persistent findings[3].

The most common image findings in high-resolution pulmonary CT in the late stage of acute respiratory distress syndrome (ARDS) caused by SARS were ground-glass opacification, interstitial thickening, and consolidation, according to a study by Joynt *et al*[4]. Other findings were lung fibrosis, cysts, and even pneumothorax, which could be associated with mechanical ventilation, according to the authors. The use of mechanical ventilation or duration of treatment did not appear to have influenced imaging findings[4]. Wu *et al*[5] studied lung function and high-resolution CT image of the chest in 11 patients recovered from SARS at six and 84 mo after hospital discharge[5]. The investigators found that eight patients (72.7%) presented reticulation and interlobular thickening at 84 mo follow-up, two patients (18.2%) showed ground-glass opacification and only 1 had no lung abnormality. Traction bronchiectasis was found in six patients. As for the lung function, at 84 mo follow-up nine (81.8%) from the eleven patients had a low DLCO, eight (72.7%) had mild lung function damage, and 1 (9.1%) had moderate lung function damage[5].

SARS may show a clinical presentation similar to ARDS in the acute phase and shares with ARDS some imaging characteristics and long-term sequela represented by pulmonary interstitial thickening and ground-glass opacities[6].

Chan *et al*[7] described a series of patients treated from SARS in China in which 20% were found to have mild restrictive pulmonary defect six weeks after discharge[7]. The investigators also described other case series that showed reduced lung inspiratory and expiratory pressures, low DLCO, reduced FVC, and muscle fatigue that could partially explain restricted function lung defects in some patients[7].

Zhang *et al*[8] studied 71 health care workers that contracted and recovered from SARS during the outbreak in 2003 in China for 15 years, from August 2003 to March 2018[8]. Most of the patients had a diminished percentage of pulmonary lesions on CT scans (9.4% to 3.2%) from 2003 to 2004 that remained stable until 2018[8]. Image abnormalities most described were residual ground-glass opacities and interstitial thickening. Pulmonary function was the same between 2006 and 2018, and patients showed a mild decline in diffusion capacity from 2006 to 2018[8].

MERS

MERS is an ongoing coronavirus outbreak caused by the MERS-CoV which had the first case diagnosed in 2012 in Saudi Arabia. According to the most recent report from the World Health Organization, a total of 2494 cases of MERS, including 858 deaths (case-fatality rate: 34.4%), were reported globally in 27 countries. The clinical presentation is comprised of fever, chills, malaise, anorexia cough and dyspnea, nausea and vomiting that can progress to severe lower respiratory tract disease, ARDS, acute kidney injury and multi-organ failure, frequently requiring mechanical ventilation and intensive care hospital treatment[9]. The risk of transmission is increased with direct or indirect contact with dromedary camels and patients infected with MERS-CoV. People from 30 to 50 years are the most commonly affected, but higher mortality rates occur among patients 50-79 years, according to the WHO[10].

Batawi *et al*[11] studied the quality of life reported by survivors from MERS that required hospitalization in Saudi Arabia after one year of the diagnosis[11]. Average scores were low for physical functioning, general health, emotional role, and were worst among those patients that required intensive care unit (ICU) treatment compared with patients treated in the non-ICU environment.

Image findings in MERS are nonspecific, with ground-glass opacities and consolidation being the most commonly reported[12]. Lung fibrosis, ground-glass opacities, and pleural thickening are the most common chronic radiographic findings, with more abnormalities being associated with higher days of ICU treatment and older age upon diagnosis[13]. Some patients can develop traction bronchiectasis and fibrosis, along with subpleural bands and architectural distortion[14,15]. In one study with 14 critically ill patients diagnosed with MERS in 2014, nine patients died, and those who survived had good clinical outcomes after one year. However, the authors did not detail the pulmonary function status or image findings[16].

Influenza

Influenza viruses are negative-sense, segmented RNA viruses from the Orthomyxoviridae family that cause annual seasonal epidemics worldwide, and under some circumstances, can go through reassortment of its segmented genetic material, giving origin to different strains causing pandemics[17,18]. According to the centers for disease control and prevention (CDC), there were five influenza pandemics in the twentieth century (1918, 1930, 1957, and 1968) and one in the 21st century (2009 H1N1). The most recent one, caused by the H1N1pdm09 Flu Virus, caused 12469 deaths in the United States from April 2009 to April 2010 and has circulated seasonally throughout the country[19].

The most common acute and subacute respiratory and overall complications of seasonal and epidemic influenza are primary viral pneumonia, secondary bacterial pneumonia, pneumonia caused by opportunistic agents and exacerbation of chronic obstructive pulmonary disease, and asthma. However, during epidemics, infections tend to be more serious, usually requiring ICU treatment, presenting with a higher mortality rate than the seasonal disease[20,21].

Chen *et al*[22] reported chronic pulmonary complications from influenza A (H7N9) during two years after discharge from the hospital and showed interstitial abnormalities and fibrosis on lung image after six months, along with restrictive and obstructive lung function throughout the follow-up period[22].

Luyt *et al*[23] studied a total of 24 patients recovered from influenza A (H1N1) infection treated in ICUs with and without extracorporeal lung assist (ECLA) one year after hospital discharge and found that 50% of the patients in the group treated with

ECLA and 40% of them not treated with ECLA reported significant exertion dyspnea, and 75% and 64% of the patients in each group respectively had decreased diffusion lung capacity across the blood-gas barrier[23]. Both groups also had reduced exercise capacities and reported lower health-related quality of life compared with a group from the healthy population [23].

Li *et al*[24] showed in a study with children recovered from SARS that 34% had high-resolution CT residual abnormalities: Ground-glass opacities (31.2%), air trapping (8.5%), and combination of ground-glass and air trapping (18.8%). The investigators also found mild decreased pulmonary function in four out of 38 patients[24].

A summary of the main chronic clinical and imaging manifestations of SARS, MERS and Influenza is described on Table 2.

Musculoskeletal system

Avascular necrosis (AVN) of bone has been described as a significant complication of SARS, as critically ill patients frequently require high doses of corticosteroid treatment. Hong *et al*[25] described an incidence of 28 patients with AVN among 67 patients diagnosed with SARS, and that presented joint pain between March and May 2003[25]. The mean time from SARS diagnosis and development of AVN was 119 days, and all patients received a total dose of corticosteroid above 700 mg[25]. The most common affected sites were femoral head and knees. Magnetic resonance imaging (MRI) played an essential role in the diagnosis since no abnormalities were found on the radiographs. Later the investigators described in another study that Diffusion-weighted MRI could be used to reliably diagnose AVN in patients treated from SARS with corticosteroid[26].

Another study by Sun *et al*[27] investigated the possible role of anticardiolipin antibodies in the etiology of AVN in 62 patients diagnosed with post-SARS osteonecrosis and found that 33.9% of patients had at least one type of anticardiolipin antibodies (IgA, IgG, and IgM) compared to 7.7% in the control group. They concluded that these antibodies might play a role in the pathogenesis of post-SARS osteonecrosis[27].

The incidence of AVN after SARS varies among studies. Shen *et al*[28] described a 3% incidence in a group of 84 health care workers diagnosed with SARS and treated with different dosages of corticosteroids[28]. Li *et al*[29] found an incidence of 30% among a cohort of 40 patients diagnosed with SARS and treated with corticosteroids[29].

Lv *et al*[30] conducted a longitudinal study with 71 patients treated with corticosteroids for SARS over 36 mo after diagnosis. They showed that 29% of the patients developed AVN of the hips within 3-4 mo after treatment, two patients developed AVN after one year of the diagnosis and 11 patients after three years of observation outlining the long-term adverse effects[30].

Zhao *et al*[31] studied 190 hips from 117 patients that developed post-SARS AVN during seven years from diagnosis and found that 66 hips progressed in symptoms, 55 hips collapsed, and ten hips showed lesion regression[31]. According to the authors, the progression of symptoms and the bone collapse was associated with lesions with higher dimensions and lower viable lateral columns in the femoral heads. The mean time from the administration of corticosteroids and the development of AVN was 6.26 mo, and the mean time from the corticosteroid use and the development of symptoms was 18.39 mo[31]. In the 15-year follow-up study by Zhang *et al*[8], though, patients diagnosed with femoral head necrosis after treatment of SARS showed decreased AVN volume from 2005 to 2013 and plateaued until 2018[8].

Several patients that recovered from SARS were presented late with musculoskeletal pain, weakness, fatigue, shortness of breath, psychological distress, and significant sleep problems, known as the post-SARS syndrome. A retrospective study by Moldofsky *et al*[32] showed that chronic post-SARS syndrome was characterized by persistent fatigue, diffuse myalgia, weakness, depression, and nonrestorative sleep with associated REM-related apneas/hypopneas[32]. The authors suggested that this may be caused by the direct viral invasion of the central nervous system and peripheral tissues resulting in chronic post-inflammatory CNS pathology.

In a case-series by Stainsby *et al*[33], three patients diagnosed with SARS presented with a variety of neurological, muscular and joint findings that improved after conservative treatment, which according to the authors, could be caused by a viral myositis or from the use of corticosteroids in the treatment of the patients. The acute inflammatory condition with increased cytokines, platelet-activating factors, free radicals, and proteases was also raised as possible causes[33]. Table 3 summarizes the main chronic musculoskeletal findings in patients treated for SARS.

Table 2 Common respiratory system long-term manifestations associated with severe acute respiratory syndrome, Middle East respiratory syndrome, and influenza

Diagnosis	Clinical Manifestation
SARS	Interstitial thickening, traction bronchiectasis[1]
	Decreased exercise tolerance[2]
	Pulmonary ground-glass opacities, consolidations, pulmonary fibrosis[4,5]
MERS	Pulmonary ground-glass opacities, consolidation and pulmonary fibrosis[12,13]
Influenza	Lung interstitial abnormalities and fibrosis, restrictive and obstructive function patterns[21]
	Reduced exercise capacity[23]

MERS: Middle East respiratory syndrome; SARS: Severe acute respiratory syndrome.

Table 3 Common chronic musculoskeletal disorders associated with severe acute respiratory syndrome

Diagnosis	Clinical manifestation
SARS	Avascular necrosis of the hip and knee[25,28-31]
	Diffuse myalgia[32]
	Weakness
	Persistent fatigue[33]
	Non-restorative sleep

SARS: Severe acute respiratory syndrome.

Neurologic system

Coronaviruses can invade the nervous system by several routes, including transsynaptic transfer, direct invasion *via* the olfactory nerve, or migration across the blood-brain barrier, spreading to different central nervous system locations, including the brain, basal ganglia, midbrain, where neuronal death can occur[34], causing a wide range of neurological complications[35]. Immunologic process are also suggested as possible contributors to neurologic complications in these patients[36]. Patients with preexisting neurological disorders are at risk of developing complications from coronaviruses diseases in association with neurological disease exacerbation, especially those with previous diagnosis of dementia and Parkinson's disease[37]. Clinicians should be aware of this risk of exacerbation of neurologic disorders to take early preventive measures and long-term follow-up.

Most of the neurologic complications found in patients with viral infections like SARS, MERS, and Influenza are acute, with headache, anosmia, seizures, and encephalitis as the most common. Encephalitis and Guillain-Barre syndrome have been reported 2-3 wk after the acute symptoms of MERS and are diseases with the potential to cause long-term sequelae[38].

Recent case reports have linked SARS coronavirus to rapid-onset Guillain-Barré syndrome that evolved to tetraparesis or tetraplegia over a period of 36 h to 4 d and necessitated mechanical ventilation; and Miller-Fisher syndrome, presenting with ageusia, oculomotor palsy, ataxia, areflexia[39,40]. One patient presented with increased serum immunoglobulin antibodies and treatment with intra-venous immune globulin resulted in complete recovery.

It is important to mention the gustatory and olfactory dysfunction referred by patients after infection by COVID-19[41], that needs further long-term investigation and follow-up considering its potential to cause low quality of life.

Mental / psychiatric abnormalities

Psychiatric symptoms were common in patients affected by SARS and MERS and in health care workers involved in the frontlines of treatment. A study with 90 patients that survived the SARS outbreak showed 58.9% incidence of psychiatric disorders and 33.3% prevalence of any mental disorder after 30 mo[42]. Depression, anxiety, and

posttraumatic stress disorder (PTSD) were the most commonly diagnosed, and the symptoms were worst in health care workers affected by the disease[42].

In another study with patients recovered from SARS in Hong Kong, about 35% of the patients reported "moderate to severe" or "severe" anxiety and depressive symptoms, which were more prevalent in those who had family members killed by the disease or were health care workers[43]. PTSD symptoms have been found in 4% of patients one month after hospital discharge for SARS and 5% after three months of discharge in a cohort of 131 patients[44]. Park *et al*[45] evaluated survivors of MERS in a prospective cohort study at multiple centers throughout Korea, assessing PTSD and depression 12 mo after hospital discharge and found a 42.9% prevalence of PTSD symptoms and 27% prevalence of depression[45].

Another follow-up study from Lam *et al*[46] showed that even four years of hospital discharge patients affected by SARS had active psychiatric illnesses (40% prevalence) and chronic fatigue symptoms (40.3% prevalence)[46]. The quality of life of patients recovered from MERS and SARS has been assessed in a study by Batawi *et al*[11] one year after diagnosis showing similar results in both groups, but lower scores for those patients admitted to ICU during treatment[11].

Health care workers comprise a group especially sensitive to mental health problems during infectious disease outbreaks. The long-term impact 13 to 26 mo after the SARS outbreak in 769 health care workers has been assessed and showed significantly higher levels of burnout, psychological distress, and posttraumatic stress[47]. According to the investigators, personal variables that contributed to adverse outcomes were maladaptive coping by avoidance, hostile confrontation, self-blame contributed, and attachment anxiety[47].

An interesting topic that emerged during the COVID-19 pandemic is the widespread use of telemedicine, not only in clinical specialties but also in surgery specialties[48], which could be an option in the future to help underserved patients and reduce health care workers burden by consulting less-severe patients that should not go to a hospital through online counseling. Table 4 gives a summary of the main neurologic and mental chronic disorders associated with SARS, MERS and Influenza.

CONCLUSION

Viral infections and especially the recent SARS, MERS, and Influenza, can affect different systems with potential long-term clinical outcomes that may reduce the quality of life and impair the work capacity of the patients. A high prevalence of mental and psychiatric symptoms has been associated with SARS, and MERS recovered patients and health care workers involved in treatment. Chronic fatigue and neurologic sequelae were common complications among patients with SARS and influenza. Avascular necrosis of the hip and joint pain has also been described as a common complication from the high doses of corticosteroid treatment necessary in critically ill patients.

Table 4 Neurologic and mental chronic manifestations associated with severe acute respiratory syndrome, Middle East respiratory syndrome, and influenza

Diagnosis	Clinical manifestation
SARS/COVID-19	Gustatory and olfactory dysfunction[41]
	Miller-fisher syndrome
	Exacerbation of neurologic diseases
	Depression, anxiety, PTSD[42]
	Chronic fatigue[46]
	Burnout, psychological distress[47]
MERS	Encephalitis and guillain-barre syndrome[38]
Influenza	Encephalitis, seizures, headache

COVID-19: Coronavirus disease 2019; MERS: Middle East respiratory syndrome; PTSD: Post traumatic stress disorder; SARS: Severe acute respiratory syndrome.

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CASE REPORT

Stenotrophomonas maltophilia, an emerging pathogen in newborns: Three case reports and a review of the literature

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Abstract

BACKGROUND

Stenotrophomonas maltophilia (*S. maltophilia*) is a rare cause of neonatal sepsis with significant morbidity and mortality and has extensive resistance to several antibiotics leaving few options for antimicrobial therapy. Only a few cases have been reported in neonates from developing countries. We report three cases of critically ill, extramural babies with neonatal *S. maltophilia* sepsis. All three babies recovered and were discharged.

CASE SUMMARY

All three cases were term extramural babies, who were critically ill at the time of presentation at our neonatal intensive care unit. They had features of multiorgan dysfunction at admission. Blood culture was positive for *S. maltophilia* in two babies and one had a positive tracheal aspirate culture. The babies were treated according to the antibiogram available. They recovered and were subsequently discharged.

CONCLUSION

Although various authors have reported *S. maltophilia* in pediatric and adult populations, only a few cases have been reported in the newborn period and this infection is even rarer in developing countries. Although *S. maltophilia* infection has a grave outcome, our three babies were successfully treated and subsequently discharged.

Key Words: Ceftriaxone; Multidrug resistant; Neonatal sepsis; *Stenotrophomonas maltophilia*; Cotrimoxazole; Tigecycline

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Core Tip: *Stenotrophomonas maltophilia* is a rare cause of neonatal sepsis with significant morbidity and mortality and has extensive resistance to several antibiotics leaving few options for antimicrobial therapy. Although there have been reports in the adult population, only a few cases have been reported in neonates from developing countries. The majority of babies have succumbed to this deadly infection. We present three cases of out-born babies with neonatal sepsis, who were critically ill. All three babies recovered and were subsequently discharged.

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INTRODUCTION

Stenotrophomonas maltophilia (*S. maltophilia*) was previously known as *Pseudomonas maltophilia* or *Xanthomonas maltophilia*[1]. It is currently an important multi-drug resistant, gram-negative, oxidase-negative, and catalase-positive, non-fermenting nosocomial pathogen associated with significant mortality[1]. *S. maltophilia* is the only species of *Stenotrophomonas* known to infect humans. It ranks third amongst the four most common pathogenic non-fermenting *Gram negative bacilli* (*NFGNBs*), the others being *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Burkholderia cepacia* complex[2]. *S. maltophilia* may have varied manifestations such as bacteremia, pneumonia, urinary tract infection, meningitis, endocarditis *etc*[3]. It is found in water, sewage, soil, plants, animals and in hospital settings, and may also be isolated from washbasins, respirators, antiseptics, and medical devices leading to device-associated infections such as catheter-associated bloodstream infections, urinary tract infections, and ventilator-associated pneumonia[4,5]. The treatment of *S. maltophilia* infection is very difficult as it is intrinsically resistant to the majority of commonly used drugs, such as all Carbapenems, and Levofloxacin[6-9]. Strains are usually susceptible to Trimethoprim-Sulfamethoxazole, but this combination is not used in neonates due to adverse effects. Strains have variable susceptibility to Ceftazidime[6,7]. *S. maltophilia* has a contrasting antibiotic susceptibility pattern to other *NFGNBs* such as *A. baumannii*, *P. aeruginosa* and *Burkholderia cepacia*, and the correct identification of *S. maltophilia* is very important, as it has to be differentiated from these other organisms. However, it is very challenging for a routine laboratory to identify *S. maltophilia*, due to its inert biochemical profile and difficulty in the interpretation of phenotypic characteristics. Subsequently, its correct identification is essential as no single drug is effective against all *NFGNBs*, which hinders initiation of appropriate empirical treatment resulting in increased morbidity and mortality[10].

CASE PRESENTATION

Case 1

Chief complaints: An out-born baby, delivered to a primigravida mother at 38 wk, with a birth weight of 3000 g *via* a lower segment caesarean section (LSCS) due to fetal distress, cried immediately after birth, but developed severe respiratory distress in the form of retractions and grunting with pulse oxygen saturation of 84%.

History of present illness: The baby was started on oxygen by hood, and received intravenous fluids, Cefotaxime, Amikacin and Vitamin K. On day two of life, the baby's respiratory distress worsened with chest X-ray suggestive of right lung pneumothorax and was referred to our hospital.

Physical examination: On admission, the baby had severe respiratory distress with a Downes score of 6/10 and features of shock such as weak pulse, prolonged capillary refill time (CFT), heart rate (HR) of 190 bpm, blood pressure (BP) of 40/28 mmHg and peripheral oxygen saturation (SpO_2) of 82%. Right side air entry was decreased compared to the left side.

Laboratory examinations: A sepsis screen sent on admission was positive with procalcitonin (PCT) of 15.43 ng/mL, μESR of 12 mm, total leucocyte count (TLC) of 20300 and an IT ratio of 0.22. Blood culture sent on admission showed growth of *S. maltophilia* (multi-drug resistant) (Table 1). Lumbar puncture (LP) was negative for meningitis.

Imaging examinations: Imaging showed right lung pneumothorax with left side consolidation.

Case 2

Chief complaints: A term, 37 wk out-born baby, weighing 2600 g, delivered by LSCS due to previous LSCS, cried immediately after birth but developed respiratory distress soon after birth.

History of present illness: The baby was started on oxygen and *i.v*. antibiotics. On day three of life, the baby's respiratory distress worsened and the child was referred to our hospital.

Physical examination: On admission, the child had severe respiratory distress with a Downes score of 7/10 and had features of poor perfusion such as tachycardia (HR: 185/min), CFT of more than 3 s, extremely weak pulse and unrecordable BP and SpO_2.

Laboratory examinations: A sepsis screen sent on admission was positive with PCT of 25.3 ng/mL, μESR of 10 mm, TLC was 21200, platelet count was 44000 and IT ratio was 0.22. Prothrombin time (PT) was 22 s, INR was 1.8 and partial activated partial thromboplastin time (aPTT) was 64 s. Blood culture sent on admission grew *S. maltophilia*, and the sensitivity pattern is provided in Table 1. LP was negative for meningitis.

Imaging examinations: Chest X-ray on admission was suggestive of white out lungs.

Case 3

Chief complaints: A term 38 wk out-born baby boy was referred to our hospital with symptomatic hypoglycemia and respiratory failure.

History of present illness: A term 38 wk 2600 g, out-born male baby was delivered by LSCS due to non-progression of labor, to a 25-year-old primigravida mother who was leaking per vagina for 20 h. Antenatal history was uneventful. The child developed symptomatic hypoglycemia at 10 h of life with lethargy and one episode of seizures. A sepsis screen revealed C-reactive protein of 10.9 mg/L and the baby was started on Cefotaxime and Amikacin. He developed severe respiratory distress on day four of life and was intubated and then referred to our hospital on manual ventilation.

Physical examination: On admission, the baby was in shock with prolonged CFT, tachycardia (HR: 192/min, weak pulse, BP of 36/22 mmHg), posturing, and a SpO_2 of 95% on manual ventilation.

Laboratory examinations: A sepsis screen revealed PCT of 16 ng/mL, μESR was 12 mm and IT ratio was 0.20, platelet count was 23000 with a deranged coagulogram (PT: 29 s, INR: 2, aPTT: 78 s). Arterial blood gas revealed mild metabolic acidosis. Blood culture isolated *Staphylococcus epidermidis*; which was sensitive to Cotrimoxazole, Nitrofurantoin, Linezolid, Daptomycin, Teicoplanin and Vancomycin. Tracheal aspirate sent on admission grew *S. maltophilia* which was sensitive to Ceftriaxone and had intermediate sensitivity to Colistin, Aztreonam, Ceftazidime, Moxifloxacin and was resistant to Ampicillin, Amikacin, Gentamicin, Cefotaxime, Cefepime, Meropenem, Augmentin, Cefuroxime, Cefoxitin, Ciprofloxacin, Levofloxacin and Cotrimoxazole (Table 1).

Imaging examinations: Chest X-ray was suggestive of pneumonia. Cranial ultrasonography was suggestive of cerebral edema with chinked ventricles.

FINAL DIAGNOSIS

Case 1

Term/38 wk/AGA/*S. maltophilia* sepsis/septic shock/pneumonia/right side

Table 1 Antibiograms of the three cases included in this report

Case No.	Cefotaxime	Ceftriaxone	Cefepime	Ceftazidime	Cefu	Amik	Gent	Amp	Mero	Cipro	Levo	Moxi	Amox	S-T	Colis	Tigecy	Aztreo
1	R	R	R	R	R	R	R	R	R	R	S	R	R	R	S	T	R
2	R	R	R	S	R	R	R	R	R	S	S	S	R	S	R	S	NA
3	R	S	R	IS	R	R	R	R	R	R	R	IS	R	R	IS	NA	IS

Cefu: Cefuroxime; Amik: Amikacin; Gent: Gentamicin; Amp: Ampicillin; Mero: Meropenem; Cipro: Ciprofloxacin; Levo: Levofloxacin; Moxi: Moxifloxacin; Amox: Amoxicillin; S-T: Sulfamethoxazole-trimethoprim; Tigecy: Tigecycline; Aztreo: Aztreonam.

pneumothorax.

Case 2

Term/37 wk/AGA/*S. maltophilia* sepsis/septic shock/pneumonia/disseminated intravascular coagulation (DIC)/pulmonary arterial hypertension (PAH).

Case 3

Term/38 wk/AGA/*Staphylococcus epidermidis* and *S. maltophilia* sepsis/septic shock/pneumonia/meningitis/DIC.

TREATMENT

Case 1

On admission, the baby had severe respiratory distress with a Downes score of 6/10 and features of shock. The child was intubated and was started on synchronized intermittent mandatory ventilation (SIMV) mode with settings of 13/04/60/100% and a pneumothorax was drained using an intercostal drainage tube. A normal saline bolus was followed by ionotropic support with Dopamine and Adrenaline and *i.v.* antibiotics Vancomycin and Meropenem were started. Colistin was added on day three after admission, as there was no significant clinical improvement. On the fourth day of life, the chest tube was clamped and removed. The baby was extubated on day five of NIMV mode with settings of 16/05/40/21% and gradually changed to nasal continuous positive airway pressure (CPAP). Subsequently, the baby was weaned to nasal prongs and finally oxygen support was stopped on the eighth day of life. Vancomycin, Meropenem and Colistin were given for a total duration of 14 d. Ionotropes were slowly tapered and finally stopped on day five of life. The baby was started on measured tube feeding and then gradually to spoon feeding and breastfeeding by day ten of life.

Case 2

A term, 37 wk out-born baby, weighing 2600 g, delivered by LSCS due to previous LSCS, cried immediately after birth but developed respiratory distress soon after birth and was started on oxygen and *i.v.* antibiotics. On day three of life, respiratory distress worsened and the baby was referred to our hospital. On admission, the child had severe respiratory distress with a Downes score of 7/10 and was in shock, the child was intubated and started on conventional ventilation but was changed to high frequency ventilation with a maximum setting of mean airway pressure of 18, inspired oxygen fraction of 100%, DP of 60, frequency-10 and required maximum inotropic support of Dopamine 20, Dobutamine 20, Adrenaline 0.5, and Milrinone 0.2 μg/kg/min. A chest X-ray on admission was suggestive of white out lungs; therefore, the baby was given surfactant and within 24 h was changed to conventional ventilation (SIMV mode 18/5/50/50%). The baby also had PAH and was given Sildenafil by injection. Meropenem and Vancomycin were also administered. Colistin injection was added on day three after admission due to worsening clinical condition with shock and DIC. In addition to DIC, the baby also had thrombocytopenia, coagulopathy manifesting as orogastric and ET bleeding and received multiple platelet, fresh frozen plasma and packed red blood cell transfusions. The ventilator setting was gradually tapered and the baby was extubated to NIMV mode on the twelfth day after admission, and changed to nasal CPAP by day fifteen after admission and off oxygen by day seventeen. Blood culture sent on admission grew *S. maltophilia* with sensitivity to Tigecycline which was added and Colistin continued. The baby received Vancomycin for seven days plus Tigecycline and Colistin for fourteen days. Tube feeding was started on day six of life and gradually increased to full feeding by day eleven after admission. The baby was subsequently breastfed.

Case 3

The baby required ionotropic support with Dopamine, Adrenaline and intravenous fluids and was started on SIMV mode (18/6/45/50%). A sepsis screen was sent and the child was started on Meropenem, Vancomycin and Colistin. As the baby was critically ill and did not show an improvement in symptoms, Ceftriaxone was started and Meropenem was discontinued on day three after admission, as soon as the tracheal aspirate report was received. CSF analysis was performed after the platelet count had improved, which was suggestive of meningitis. The child received fresh frozen plasma and platelet transfusions for DIC. Ionotropic support was gradually tapered and then stopped by day seven after admission and tube feeding was started. The baby's sensorium and spontaneous efforts improved and he was extubated on the eleventh day after admission and changed to NIMV mode (16/6/50/30%). He was subsequently weaned off to CPAP by day fourteen. He was gradually weaned off CPAP by day sixteen and oxygen by day eighteen. Intravenous antibiotics were administered for 21 d, and he received full tube feeding by day twelve after admission and direct oral feeding by day sixteen.

OUTCOME AND FOLLOW-UP

Case 1

The baby was discharged from hospital on day fifteen of life, was being breastfed and had normal neurological status. At follow-up, the baby was being breastfed and was neurologically normal.

Case 2

The baby was discharged after eighteen days of hospitalization. At follow-up, the baby was being breastfed and was healthy.

Case 3

The baby was discharged after almost twenty two days of hospitalization on full feeds. At follow-up, the baby was neurologically normal, on mixed feeds and repeat cranial ultrasound was normal.

DISCUSSION

S. maltophilia is currently an emerging multi-drug resistant, opportunistic pathogen in both hospital and community settings. Studies have shown various risk factors for infection or colonization by *S. maltophilia*, including prior use of broad-spectrum antimicrobial agents such as Carbapenem, Ampicillin, Gentamicin, Vancomycin, Metronidazole, Piperacillin, Cefotaxime, Ceftazidime, Ciprofloxacin, Tobramycin, and Cefepime, and other drugs such as corticosteroids, cytotoxic chemotherapy, immunosuppressive therapy, H2 blockers, and parenteral nutrition[11-16]. Prolonged hospital stay, invasive procedures including mechanical ventilation, intubation, urinary catheterization, central venous catheterization, lower gestational age and low birth weight, neutropenia, underlying diseases such as hepatobiliary, chronic pulmonary, and cardiovascular diseases, organ transplantation, dialysis, intravenous drug use, and human immunodeficiency virus infection, malignancy, and exposure to patients with *S. maltophilia* wound infection were significantly associated with *S. maltophilia* infections[17-21]. In our patients we found that intensive care unit (ICU) stay, administration of broad spectrum antibiotics, and invasive procedures would have contributed to infection with this organism. Although according to the literature, premature and low birth weight babies are more prone to developing this infection, all our cases were term and with good birth weights[21].

According to Jia *et al*[7], maximum isolation of *S. maltophilia* was from respiratory specimens, whereas Abdel-Aziz *et al*[6], reported maximum isolation from urine samples followed by swabs and blood. In our cases, *S. maltophilia* was isolated from blood in the first two cases and from tracheal aspirate in the third case. The identification and antimicrobial susceptibility testing was carried out using VITEK and the results were confirmed with manual MIC calculations.

S. maltophilia has several resistance mechanisms to various antibiotic classes such as beta-lactams due to two inducible beta-lactamases, a zinc-containing penicillinase (L1) and a cephalosporinase (L2), an aminoglycoside acetyl-transferase that confers resistance to aminoglycoside antibiotics, and temperature-dependent changes in the outer membrane lipopolysaccharide structure confers added resistance to aminoglycoside antibiotics and possesses efflux pumps[22,23]. Although according to previous reports the organism is resistant to the majority of commonly used drugs such as all Carbapenems and Levofloxacin, and is susceptible to Trimethoprim-Sulfamethoxazole, with variable susceptibility to Ceftazidime[6-9], in our cases except for one, which was sensitive to Ceftazidime and the others were sensitive to Ceftriaxone, all were resistant to Aminoglycosides, Carbapenems, and Cephalosporins. Of the three cases, one was resistant, one was sensitive and one had intermediate sensitivity to Colistin. The first and second cases were sensitive to Tigecycline and in the third case sensitivity was not tested. Two cases were sensitive to Levofloxacin and one was resistant. One case was sensitive to Trimethoprim-Sulfamethoxazole and two were resistant. We administered Colistin and Tigecycline to our patients. In the third case we administered Ceftriaxone, as the organism had intermediate sensitivity to Colistin and Tigecycline sensitivity was not performed. The same baby was monitored for serum bilirubin levels and for other adverse effects. As shown in the literature, Ceftriaxone can be used in neonates and is contraindicated in babies at risk of developing unconjugated hyperbilirubinemia and concurrent administration with calcium[24-26]. In our third case, although tracheal aspirate was positive for *S. maltophilia*, the baby was treated according to the antibiogram, as clinical features were consistent with the infection. However, most clinicians are reluctant to treat this pathogen, when isolated from tracheal aspirate and often treat it as colonization rather than a pathogen[27]. Antibiograms of the three patients are shown in Table 1.

Most infections caused by *S. maltophilia* are associated with severe morbidity and long-term, extensive ICU treatment. According to previous reports, the mortality rates vary between 14%-62%[28,29]. Our three babies were discharged on full feeds with a hospital stay of 14 to 21 d.

CONCLUSION

Various case studies on *S. maltophilia* infections in India, such as *S. maltophilia* endophthalmitis[29], tropical pyomyositis[30], unilateral conjunctival ulcer[31], nonhealing leg ulcer[32] and meningitis[33], have been reported in pediatric and adult patients and the isolation rate of *S. maltophilia* was found to be 2.5% (5 isolates) out of 193 *NFGNBs*

in various clinical samples[34]. However, neonatal sepsis due to *S. maltophilia* has been reported only by Viswanathan *et al*[1] and Soren *et al*[35]. Here we report three cases of neonatal sepsis due to *S. maltophilia* along with their antibiograms Although *S. maltophilia* infection has a grave outcome our three out-born babies were successfully treated and discharged.

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CASE REPORT

Cutaneous leishmaniasis in Louisiana - one-year follow-up: A case report

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Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The corresponding author declares that he has no conflict of interest related to this case report.

CARE Checklist (2016) statement: The corresponding author has read

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Abstract

BACKGROUND

Reports of leishmaniasis are scarce in North America. It is considered to be one of the neglected tropical diseases. It is seen in immigrants from endemic areas to United States. Treatments are not readily available in the United States. Untreated or inadequately treated cutaneous leishmaniasis not only causes localized disfigurement but can advance to more permanent and devastating mucosal disfigurement and perforation, if caused by a species that can also cause mucocutaneous leishmaniasis.

CASE SUMMARY

A 42-year-old human immunodeficiency virus negative male immigrant from Honduras presented to the emergency department of our facility in Louisiana with a 2-mo history of a left lower extremity ulcer. It started as a painless blister that progressed in size and developed into other smaller lesions tracking up the thigh and became tender and erythematous. Clinically looked nontoxic and healthy. He was afebrile. Blood tests, except inflammatory markers, were within normal limits. The cellulitis of the leg was treated with 6 d of vancomycin that

the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016) for a case report.

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also relieved the pain. Skin biopsy was obtained, and histopathology was suspicious for leishmania. Polymerase chain reaction/deoxyribonucleic acid sequencing done by centers for disease control and prevention confirmed the diagnosis as *Leishmania panamensis*. There was no involvement of naso-oropharyngeal mucosa, confirmed by otolaryngology. The patient was treated with miltefosine for 28 d. Clinic follow-up after approximately 11 mo revealed a healed skin ulcer.

CONCLUSION
Cutaneous leishmaniasis should be in the differential diagnosis of skin ulcers of travelers from endemic areas. Awareness regarding diagnosis and treatment of leishmaniasis needs to be enhanced.

Key Words: Cutaneous leishmaniasis; Neglected diseases; Leishmania (Viannia) panamensis; Miltefosine; Leishmania; Case report

Core Tip: This case highlights the importance of prompt and accurate diagnosis, and appropriate treatment of cutaneous leishmaniasis to prevent further complications and advancement to mucosal form. It should be considered in the differential diagnosis of skin lesions with appropriate epidemiologic context. Oral therapy with miltefosine is available for use as in this case. It is important to evaluate for human immune-deficiency virus disease since presentation and complications in immunosuppressed individuals can be more severe.

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INTRODUCTION

Leishmaniasis is one of the neglected tropical diseases as per World Health Organization (WHO)[1]. Leishmaniasis is a vector-borne zoonotic disease which is caused by intracellular flagellated protozoans of the genus *Leishmania*. These are transmitted to the humans or other animals by the bite of infected female phlebotomine sand flies during blood feeding[2,3]. The disease is widespread in the tropical and subtropical areas. Per WHO, it is estimated that between 700000 to 1.0 million people are newly infected every year with leishmaniasis[4].

The disease has three main forms[4-6]. Cutaneous leishmaniasis (CL) is the most common form and can be localized or diffuse. Though it causes various types of skin lesions[7-9], it typically manifests as ulcers. The ulcers are usually well-defined, with raised edges and a reddish base (referred to as volcano-like or pizza-like ulcers), leading to permanent scarring and serious disability. Visceral leishmaniasis (Kala-azar), the most serious form, is fatal in more than 95% of cases if left untreated and includes irregular bouts of fever, bone marrow involvement and hepato-splenomegaly. Some species of CL if not treated can lead to mucocutaneous leishmaniasis (Espundia), which can cause devastating destruction of the nasopharyngeal mucous membranes. We present a case of CL with subgenus *Viannia* and species *panamensis* [*L. (V.) panamensis*].

CASE PRESENTATION

Chief complaints

"Skin lesion on left lower leg for last 2 mo, now with small "lumps and bumps"

tracking up my thigh with discomfort."

History of present illness

A 42-year-old male who immigrated from Honduras to the United States approximately 2 mo before presenting to our facility's emergency department in Louisiana. He reported 2 mo ago he was climbing mountains and cutting wood with his friends in Honduras when he felt a bite on his left lower leg. A few weeks later, he developed a blister at the site. Over the next 2 mo period, the lesion started to necrose and enlarge. Approximately 5-10 d prior to this presentation he started to see "lumps and bumps" on his leg tracking up from the wound to his thigh, with mild discomfort in his thigh. Prior to this presentation, the lesions were non-tender.

He denied any trauma, dog or cat bite, swimming in fresh or salt water, any thorn prick or gardening, fishing, seafood use. He denied any history of immunocompromise.

Review of systems: Positives: Skin: wound and tender nodules on leg; Negatives: (1): Constitutional: No fevers/chills, no weight loss; (2) Cardiac: No palpitations, no chest pain, no dyspnea, no edema; (3) Pulmonary: No shortness of breath, no cough, no hemoptysis; (4) Gastrointestinal: No nausea, vomiting or diarrhea; and (5) Genitourinary: No urinary symptoms.

History of past illness

Patient reported no known past medical or surgical history.

Personal and family history

Nonsmoker, no alcohol or illicit drug use history. No history of diabetes, and no history of immunosuppression in either the patient or in family members.

Physical examination

On presentation to the emergency department, patient was afebrile with temperature of 98 °F, heart rate 86 beats/min, respiratory rate 16 per min, blood pressure 127/79 mmHg and oxygen saturation of 98% on room air. His body mass index was 25 kg/m^2. He appeared clinically non-toxic and healthy. Nasal and oral examination was benign with no lesions or perforation noted. Abdominal examination did not reveal any tenderness or hepato-splenomegaly. There was an approximately 3 cm × 3 cm left lower extremity wound on the anterior tibial area, with some erythema in the surrounding area. There were tracking tender nodules from the wound up to his thigh, with indurated skin with mild tenderness on the thigh and on the nodules (Figure 1A).

Laboratory examinations

Blood counts were within normal limits with white blood cell count 9.7 (4.5 × 10^3/μL-11 × 10^3/μL), Hemoglobin 13.7 (13.5-17.5 g/dL), platelet count 254 (130 × 10^3/μL-400 × 10^3/μL). Chemistry revealed normal sodium, potassium, chloride and glucose levels with creatinine 0.82 (0.7-1.4 mg/dL), normal transaminases and lactic acid level. Inflammatory markers were elevated with C reactive protein of 2.5 (normal less than 0.9 mg/dL) and erythrocyte sedimentation rate 45 (normal 0-15 mm/h). Later in the hospital course, human immunodeficiency virus (HIV) was ruled out by a 4th generation HIV antibody/antigen test.

Imaging examinations

Plain X-rays of the ankle and tibia-fibula were normal. Venous doppler ultrasound of the lower extremity ruled out thrombosis. Computer tomography scan of the extremity with intravenous (IV) contrast revealed lymphadenopathy at left popliteal and left groin area. Small fluid collections or phlegmons at the nodules and ulceration sites were present (Figure 2).

Diagnostic assessment and interventions

Intravenous vancomycin was started for the leg cellulitis. Our suspicion was high for leishmaniasis because of his history of recently living in an endemic area, having a known insect bite, and friends with similar histories in Honduras being diagnosed with CL. He was evaluated by dermatology, who obtained a skin punch biopsy per Centers for Disease Control and Prevention (CDC) recommendations. Tissue was sent to our hospital laboratory and to the state public health laboratory where it was shipped to CDC. The results from our laboratory revealed negative bacterial, fungal and acid-fast bacilli cultures and stains. Histopathology was compatible with

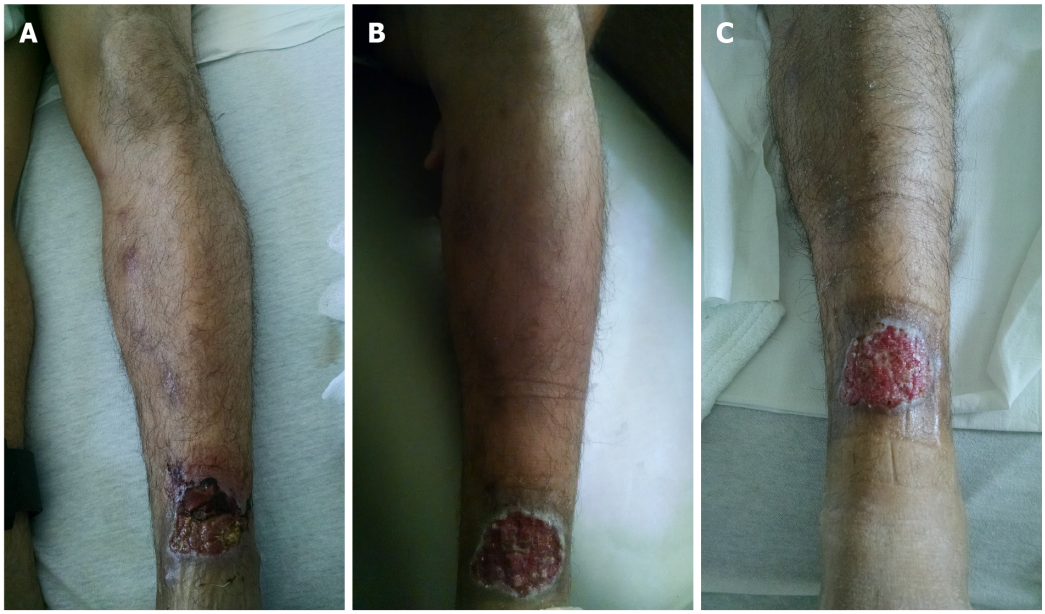


Figure 1 Physical examination. A: Skin ulcer with tracking nodules on admission; B and C: Skin ulcer after antibiotics for cellulitis.

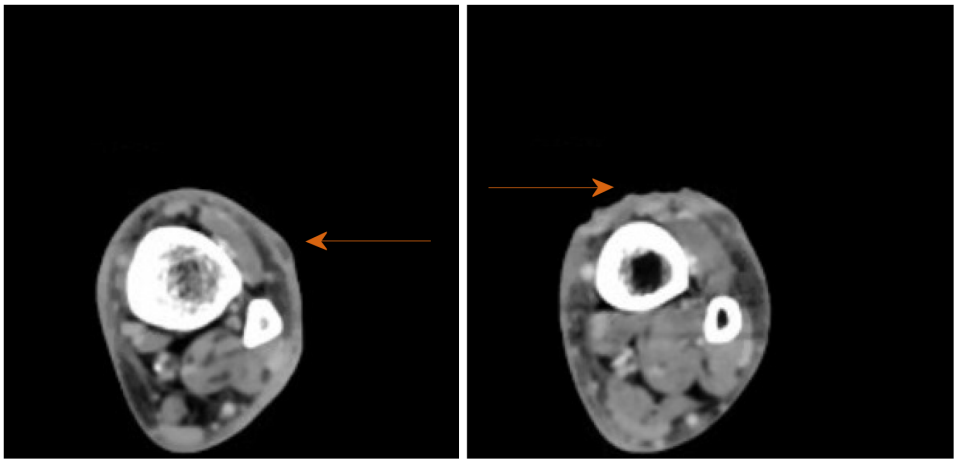


Figure 2 Computer tomography scan of left lower extremity, cross sectional view showing phlegmon and ulcerated skin (orange arrows).

leishmaniasis amastigotes (Figure 3).

Initial diagnosis

CL with sporotrichoid lymphangitis with cellulitis of the leg. After 6 d, IV vancomycin was stopped after resolution of the cellulitis and leg tenderness (Figure 1B and C). Final diagnosis was reported as *Leishmania panamensis* that was confirmed through polymerase chain reaction (PCR)/deoxyribonucleic acid (DNA) sequencing by CDC (Figure 4).

FINAL DIAGNOSIS

CL with *Leishmania (Viannia) panamensis.*

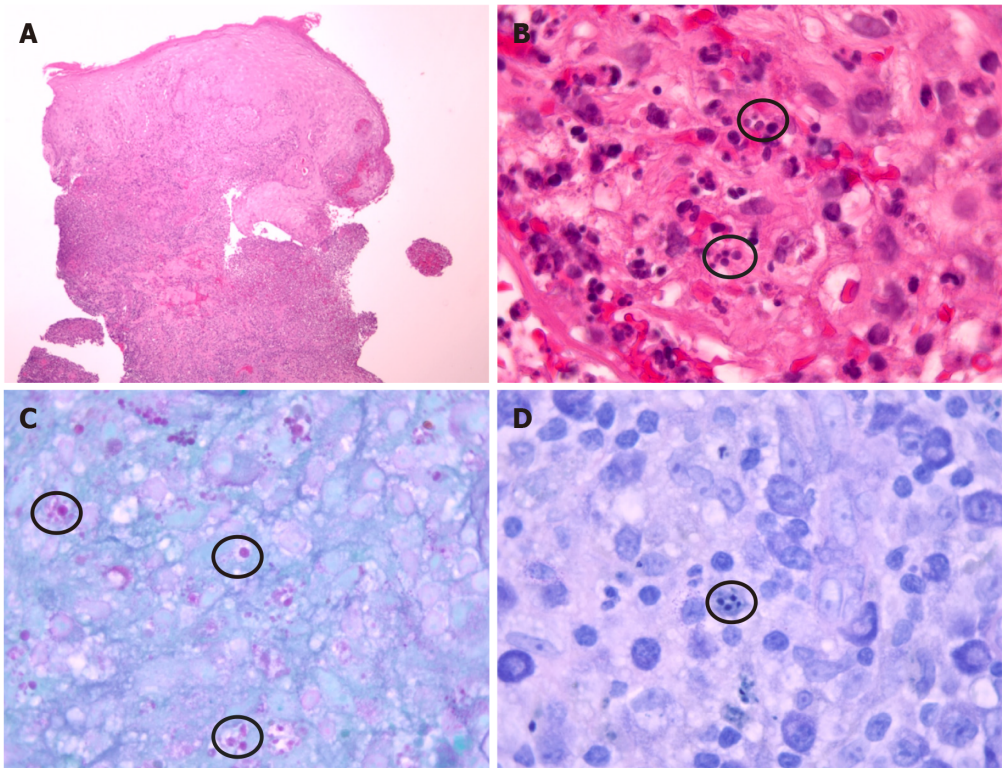
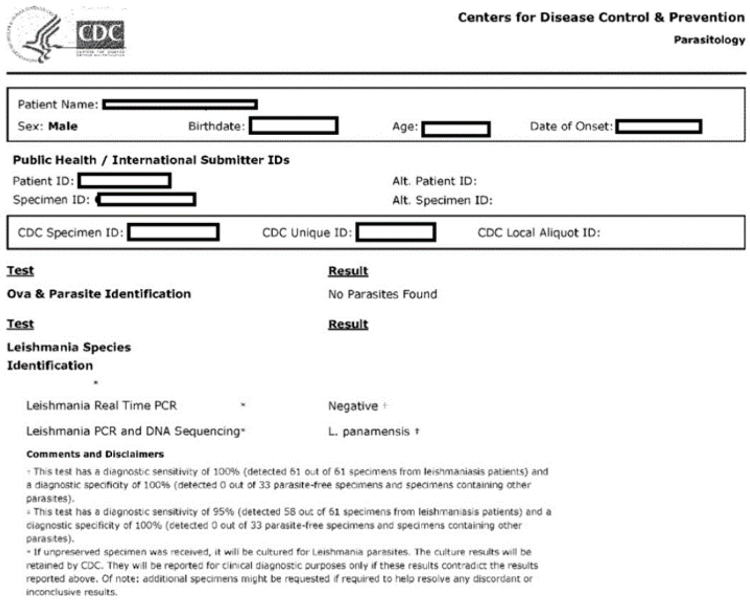


Figure 3 Histopathology was compatible with leishmaniasis amastigotes. A: Reactive squamous epithelium with mixed superficial and deep inflammatory infiltrate (hematoxylin-eosin staining, original magnification × 40); B: Organisms compatible with *Leishmania* amastigotes (hematoxylin-eosin staining, original magnification × 1000). Location within histiocytes is obscured by marked acute inflammatory infiltrate; C: Parasitized histiocytes with staining of *Leishmania* amastigotes (PAS, original magnification × 1000); and D: Parasitized histiocytes with staining of *Leishmania* amastigotes (Giemsa, original magnification × 1000).



Centers for Disease Control & Prevention
Parasitology

Patient Name: [redacted]
Sex: **Male** Birthdate: [redacted] Age: [redacted] Date of Onset: [redacted]

Public Health / International Submitter IDs
Patient ID: [redacted] Alt. Patient ID:
Specimen ID: [redacted] Alt. Specimen ID:

CDC Specimen ID: [redacted] CDC Unique ID: [redacted] CDC Local Aliquot ID:

Test	Result
Ova & Parasite Identification	No Parasites Found

Test	Result
Leishmania Species Identification	
Leishmania Real Time PCR *	Negative †
Leishmania PCR and DNA Sequencing*	L. panamensis †

Comments and Disclaimers

* This test has a diagnostic sensitivity of 100% (detected 61 out of 61 specimens from leishmaniasis patients) and a diagnostic specificity of 100% (detected 0 out of 33 parasite-free specimens and specimens containing other parasites).
† This test has a diagnostic sensitivity of 95% (detected 58 out of 61 specimens from leishmaniasis patients) and a diagnostic specificity of 100% (detected 0 out of 33 parasite-free specimens and specimens containing other parasites).
* If unpreserved specimen was received, it will be cultured for Leishmania parasites. The culture results will be retained by CDC. They will be reported for clinical diagnostic purposes only if these results contradict the results reported above. Of note: additional specimens might be requested if required to help resolve any discordant or inconclusive results.

Figure 4 Report from centers for disease control and prevention.

TREATMENT

As per CDC recommendations, otolaryngology consultants performed flexible fiberoptic laryngoscopy/nasopharyngoscopy and confirmed no mucosal involvement. The patient was treated with miltefosine 50 mg PO three times daily for 28 d.

OUTCOME AND FOLLOW-UP

Patient followed up with dermatology and infectious diseases clinic at several occasions, and then visited at approximately 11 mo with a healed ulcer (Figure 5).

DISCUSSION

About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia. According to WHO, in 2018, over 85% of new CL cases occurred in 10 countries: Afghanistan, Algeria, Bolivia, Brazil, Colombia, Iran, Iraq, Pakistan, the Syrian Arab Republic and Tunisia. It is estimated that between 600000 to 1 million new cases of CL occur worldwide annually[4]. Reports of leishmaniasis are scarce in North America. In the United States, it is seen in travelers from endemic areas. CL has also been reported in American military personnel returning home from assignments in Iraq and Afghanistan[10]. Usually CL skin lesions are painless. But if painful, there is generally an indication to treat it also as a bacterial superinfection. In our patient, the lesions were painful initially, but the pain subsided after treating the cellulitis. CL typically presents with skin lesions after an incubation period of 2 wk to 6-8 mo. There has been one reported case of CL with *Leishmania panamensis* with incubation period as long as 18 mo, that was successfully treated with IV amphotericin. This patient was also from Honduras and had atypical multiple lesions[9]. A sporotrichoid-like pattern of skin lesions is not typical of CL but has been seen in various other case reports in addition to our patient[11-13]. The case report published recently by Mann *et al*[13], discusses about a couple that traveled from Costa Rica. The husband had sporotrichoid like pattern of skin lesions.

In immunocompromised patients such as those with HIV, the disease course can be worse. Chances of reactivation is possible with decreased immunity[14].

Diagnosis

Diagnosis starts with obtaining a good history taking, including travel history, and a detailed physical examination. It is confirmed with biopsy of a skin lesion, ideally the active part of the lesion at the edge. Typical microscopic findings are mixed inflammatory infiltrate with many histiocytes and granuloma formation containing amastigotes[15]. But atypical microscopic findings such as tuberculoid granulomatous processes has also been identified without organisms seen in some reports[16]. Sensitivity of histopathologic examination in diagnosing CL is low, perhaps only 14%–18%[17]. The use of multiple diagnostic modalities including PCR and DNA sequencing helps confirm the diagnosis as well as provides speciation, useful to its management[18,19], like in our case also.

Treatment

Extensive guidelines regarding diagnosis and treatment have been created by professional medical societies[20]. The pentavalent antimonials have been considered the mainstay treatment for CL in most parts of the world except in North America, where they are not readily available[20]. Our patient's friends who had similar presentations in Honduras reportedly did respond to pentavalent antimonials, per his report. Topical paromomycin and parental amphotericin have also been used. Resistance against amphotericin and antimonials have been reported[21,22].

Miltefosine is thus far the only oral drug reported that can be used for all three types of leishmaniasis including in cases with HIV[23,24]. Miltefosine belongs to the class of alkyl phosphocholine drugs. It has shown antileishmanial activity, linking its activity mainly to apoptosis and disturbance of lipid-dependent cell signaling pathways[23]. Patients on treatment should be monitored for elevations in transaminases and serum creatinine. It should not be given to pregnant patients[23,24]. The recommended duration of therapy is 28 d, but longer duration of therapy has also been given as mentioned by Mann *et al*[13] where they offered 56 d therapy.

Like other reported cases[11,13,25], our case was also successfully treated with miltefosine (Figure 5). He was following with the corresponding author in the outpatient setting for approximately 11 mo as of the time of this submission. Our patient had no adverse events during treatment with miltefosine.

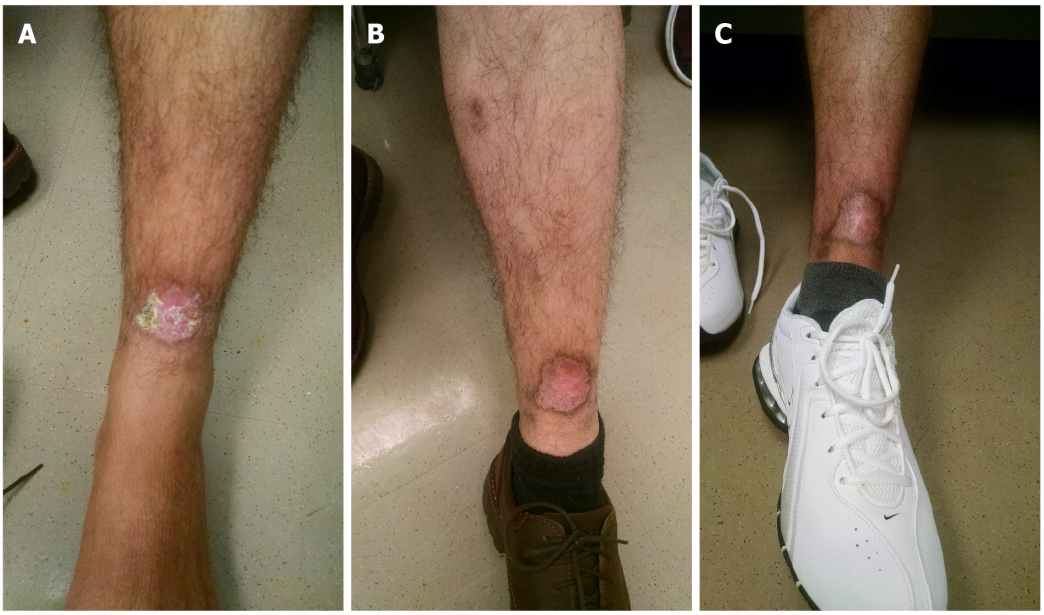


Figure 5 Patient followed up with dermatology and infectious diseases clinic at several occasions, and then visited at approximately 11 mo with a healed ulcer. A: Skin ulcer after 13 d of 28 d treatment with miltefosine; B: After 5 mo of treatment; and C: After 11 mo of treatment.

CONCLUSION

Though leishmaniasis is not common in North America, clinicians should be aware of it and include it in the differential diagnoses of skin lesions in patients who have traveled from endemic areas. Optimal therapy of CL is vital to prevent progression into mucosal form. As of today, there are no available preventive or therapeutic vaccines. The most effective way to prevent infection is avoiding sand fly bites by adopting controlled measures.

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CASE REPORT

Liver transplantation in patients with SARS-CoV-2: Two case reports

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Author contributions: Veras CM and de Assunção Ferreira NS contributed to data collection; Lima Paiva JHHG, Teles de Carvalho TM and Bastos Limeira CB contributed to the drafting of the manuscript and the creation of tables and figure; e Neves MSS, Mont`Alverne Pierre AM and Brasil IRC critically revised and approved the version to be published; all authors have read and approved the manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). This disease was declared a worldwide health problem with the characteristics of a pandemic. Most patients have mild symptoms and a good prognosis. Information on the evolution and prognosis of COVID-19 in solid organ recipients is scarce.

CASE SUMMARY

We describe two patients who underwent liver transplantation with a positive test result for detection of the viral sequence for COVID-19, using reverse-transcription polymerase chain reaction (RT-PCR), immediately before transplantation. The patients showed good evolution in the postoperative period, without signs of graft dysfunction. The immunosuppressive therapy was not modified. Both patients were discharged for subsequent outpatient follow-up.

CONCLUSION

In conclusion, it is expected that the experience at this center can be used as an example, aimed at the continuation of transplantations by other services and, thus, the morbidity and mortality of patients with liver disease on the transplantation waiting list can be reduced. Transplant centers must be able to readjust daily to the evolution of the COVID-19 pandemic.

Key Words: COVID-19; Liver transplantation; Coronavirus; Pneumonia; Immunosuppressed patients; Case report; Infection diseases

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Core Tip: Coronavirus disease 2019 (COVID-19), caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its consequences have resulted in high rates of morbidity and mortality worldwide in the first half of this year. This infection shows worse outcomes in certain at-risk populations, including those with cirrhosis of any etiology. Most patients with decompensated cirrhosis have poor quality of life and a high chance of progressing to death if they have high prognostic scores, such as the Model for End-Stage Liver Disease score. The definitive treatment for these patients is liver transplantation. Data related to the evolution and outcome of these patients when infected with SARS-CoV-2, including those undergoing transplantation, are scarce and contributions to the literature on this topic can help the adequate management of these patients, supporting the development of additional research and even guidelines. Thus, the publication of this report on two cirrhotic patients with COVID-19 who underwent liver transplantation is justified.

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INTRODUCTION

In December 2019, the first cases of viral pneumonia of unknown origin were documented in Wuhan, the capital of China's Hubei province. The virus was identified as a new coronavirus, called "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)". The infection was documented in hospital and community settings. Soon the virus spread throughout the Chinese territory and, subsequently, increasing numbers of cases were also observed in several continents[1]. Considering the severity of the situation, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) a public health emergency of international interest[2]. Liver transplantation programs were affected worldwide.

Most patients with COVID-19 have mild symptoms and a good prognosis. It is worth mentioning that asymptomatic cases have been described. However, patients with risk factors can develop severe SARS-CoV-2 disease, secondary to severe pneumonia, pulmonary edema, severe acute respiratory syndrome, acute kidney injury, coagulopathy or multiple-organ failure[3].

Based on data from other viruses, including SARS-CoV-2, immunosuppressed patients with COVID-19 were expected to have more severe clinical manifestations and a longer period of viral dispersal. However, the effects of immunosuppression on COVID-19 are not well established. Due to this fact, it remains controversial whether organ transplantation should be performed during the COVID-19 pandemic. Some recent guidelines suggested that transplantation can be performed as long as careful measures are taken[4].

A timely and accurate diagnosis, especially in cases with the potential to develop into the severe form of the disease, is extremely important to provide adequate clinical support to patients, and to limit the spread of the virus. Currently, detection of the viral sequence by reverse-transcription polymerase chain reaction (RT-PCR) is the test routinely used to confirm the diagnosis of SARS-CoV-2 infection[5].

This study aims to describe two patients with confirmed SARS-CoV-2 infection who successfully underwent liver transplantation.

CASE PRESENTATION

Chief complaints

Case 1: A 55-year-old male patient was admitted on March 9, 2020 to Hospital Geral de Fortaleza, state of Ceará, Brazil with a clinical picture of hepatic encephalopathy, abdominal pain, fever and upper gastrointestinal bleeding.

Case 2: A 40-year-old male patient, followed at the Liver Transplantation Service of Hospital Geral de Fortaleza was admitted on June 22, 2020 to undergo a liver transplantation with a Model for End-Stage Liver Disease-Sodium (MELD-Na) score of 24. The patient had no clinical complaints and was hemodynamically stable.

History of present illness

Case 1: The patient had a diagnosis of alcoholic-induced liver cirrhosis and a one-year withdrawal period.

Case 2: The patient was followed at the Liver Transplantation Service of Hospital Geral de Fortaleza due to liver cirrhosis caused by hepatitis B virus infection.

History of past illness

Case 1: The patient had no comorbidities, such as hypertension or diabetes. Moreover, he had no recent travel history.

Case 2: Previous complications in this patient included portal vein thrombosis. He had a history of peripheral vascular disease, with a healing venous ulcer in the left lower limb, with no signs of active infection. He had no other comorbidities and denied a travel history in recent months. He had a recent hospitalization history (20 d before) for intravenous antibiotic therapy due to erysipelas.

Personal and family history

Cases 1 and 2: No relevant family history.

Physical examination

Case 1: Physical examination revealed the presence of massive ascites. The other systems showed no changes. On admission, vital signs showed a respiratory rate of 22 breaths/min (brpm), heart rate of 97 beats/min (bpm), 96% oxygen saturation in ambient air and blood pressure of 140/80 mmHg.

Case 2: On clinical examination, only mild jaundice and an ulcer in the left lower limb without signs of infection were observed. The other systems showed no changes. On hospital admission, vital signs showed a respiratory rate of 18 brpm, heart rate of 89 bpm, oxygen saturation of 97% in ambient air and blood pressure of 110/70 mmHg.

Imaging examinations

Case 1: A computed tomography scan of the chest was performed, which showed lungs with reduced volume, left pleural effusion, atelectasis of the adjacent parenchyma and multiple diffuse ground-glass opacities (Figure 1A and B).

Case 2: A computed tomography scan of the chest showed evidence of discrete foci of ground glass attenuation affecting the bases of the lungs and discrete bilateral parenchymal bands (Figure 1C and D).

Further diagnostic work-up

Case 1: The patient's evolution required dialysis for acute kidney injury and his ascites were refractory to clinical measures, and required several relief paracenteses. Piperacillin/tazobactam therapy was started, due to bacterial peritonitis. An upper gastrointestinal endoscopy was performed, which did not show the presence of gastroesophageal varices, but demonstrated the presence of severe candidiasis and thus, antifungal therapy with fluconazole was started, which was later replaced by caspofungin. However, due to the lack of improvement in the patient's clinical status and laboratory tests, he was listed for liver transplantation according to the MELD-Na score of 35 and the Child-Pugh score of C. Despite the absence of respiratory symptoms, screening for SARS-CoV-2 infection was performed, with the collection of a nasopharyngeal swab for viral sequence detection by RT-PCR, but the result, which was positive, was only released after the transplant had been performed.

Liver transplantation was carried out on March 25, 2020, according to the standard surgical technique. During the procedure, the recipient developed cardiorespiratory arrest in asystole during the graft reperfusion period, which was effectively reversed with a cardiac massage cycle. The time of cold and hot ischemia was 6 h and 28 min and 32 min, respectively. The patient was extubated in the immediate postoperative period in the Intensive Care Unit and an O_2 saturation of 96% was maintained in ambient air, with an oxygenation index of 400.

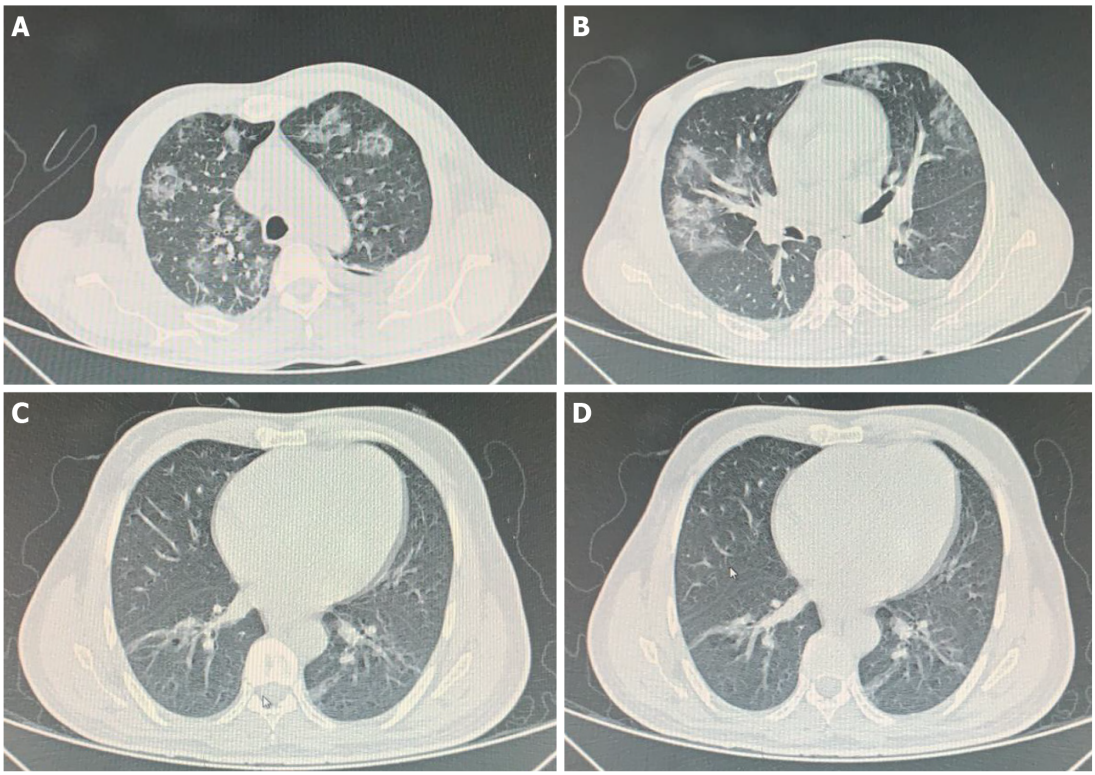

Figure 1 Chest computed tomography of transplanted patients with coronavirus disease 2019. A and B: Case 1, the lungs show reduced volume, left pleural effusion, atelectasis of the adjacent parenchyma and multiple diffuse ground-glass opacities; C and D: Case 2, discrete foci of ground glass attenuation affecting the bases of the lungs and discrete bilateral parenchymal bands.

The donor was a 56-year-old female patient with a previous history of diabetes mellitus. The patient developed a history of hypertensive peak and a decrease in the level of consciousness due to an intraparenchymal brain hematoma, with significant midline deviations. There was no screening for COVID-19, as the transplant occurred at the beginning of the pandemic and there was no defined protocol on the screening of donors at that time.

Case 2: According to the protocol of our service, screening for SARS-CoV-2 infection was performed using a nasopharyngeal swab (RT-PCR), as well as chest radiography. There were no alterations in the chest X-ray, and it was not possible to obtain the nasopharyngeal swab result before transplantation. Considering the patient's clinical condition of chronic liver failure at risk of worsening, the transplant team chose to proceed with the surgery.

The donor was a 42-year-old male patient who suffered a traumatic brain injury. He was receiving piperacillin-tazobactam due to a bacterial infection. He screened negative for COVID-19 following RT-PCR.

During the intraoperative period, the patient developed massive bleeding during the anastomoses, requiring vigorous volume replacement (3500 mL), 4 units of fresh frozen plasma and 2 units of packed red blood cells, in addition to blood recovery by cell-salvage. Moreover, an intraoperative thrombectomy was performed for portal vein thrombosis.

During the postoperative period, the patient was transferred to the Intensive Care Unit for patients with Coronavirus (ICU-COVID), and required invasive mechanical ventilation and vasopressors. Laboratory test results are shown in Table 1. The nasopharyngeal swab collected prior to surgery for viral sequence detection by RT-PCR was positive for SARS-CoV-2.

Table 1 Laboratory characteristics of the two transplanted patients with coronavirus disease 2019

	Case 1			Case 2		
	At hospital admission	Preoperative	At hospital discharge	At hospital admission	Preoperative	At hospital discharge
Fibrinogen	83	NA	NA	178	NA	NA
aPTT	1.97	1.6	1.2	1.4	0.96	0.88
Hemoglobin	8.7	6.0	11.1	11.8	8.9	6.4
Hematocrit	24.8	19.5	32.9	35.5	25.9	18
Leukocytes	22900	15100	9300	3100	16700	4300
Lymphocytes	711	615	2615	1092	754	492
Platelets	109000	100000	376000	42000	53000	20000
INR	2.72	2.78	1.02	1.84	1.28	1.32
Total bilirubin	7.44	23.25	0.74	2.87	2.07	1.46
Albumin	2.5	NA	NA	3.2	NA	NA
Urea	136	113	55	16	53	69
Creatinine	2.1	5.4	1.0	1.3	1.2	1.02
AST	105	NA	28	68	3005	1924
ALT	59	NA	39	35	1807	950
Sodium	125	127	NA	129	131	NA

Reference values: Urea (13-43 mg/dL); Creatinine (0.7-1.3 mg/dL); AST (< 32 mg/dL); ALT (< 31 mg/dL); TB (< 1 UI/L); PT (10-14 s); aPTT (22-28 s); Albumin (> 3.5 g/dL); Hemoglobin 11.3/15.2 g/dL); Leukocytes (3600-10000/mm^3); Platelets (150000-450000/mm^3); INR (1-1.3 s). AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; aPTT: Partial thromboplastin time; INR: International normalized ratio. NA: Not available.

FINAL DIAGNOSIS

Cases 1 and 2

SARS-CoV-2 infection and alcoholic-induced liver cirrhosis.

TREATMENT

Case 1

Following the release of the RT-PCR test result with a detectable SARS-CoV-2 viral load, the patient was transferred to the ICU-COVID; he was initially asymptomatic and therapy was started with azithromycin 500 mg/d for 5 d, ivermectin 12 mg/d for 2 d and oseltamivir 150 mg/d for 5 d. Additionally, an immunosuppression protocol was prescribed, with methylprednisolone 250 mg/d with dose tapering on subsequent days, associated with tacrolimus 1 mg/kg/d with a goal serum level of 4-7 ng/mL and everolimus 2 mg/d.

Case 2

Prophylactic intravenous fluconazole for candidemia (risk due to several transfusions) and immunosuppression protocol with methylprednisolone 250 mg/d with dose tapering on subsequent days, associated with tacrolimus 1 mg/kg/d with a goal serum level of 4-7 ng/mL were initiated, plus everolimus 1 mg/d. Additionally, due to the history of hepatitis B, hyperimmune immunoglobulin and entecavir were prescribed. The patient developed a pulmonary infection, and piperacillin-tazobactam, azithromycin 500 mg/d for 5 d and ivermectin 12 mg/d for 2 d were started.

OUTCOME AND FOLLOW-UP

Case 1

On the third postoperative day, he had a fever peak of 38.5ºC associated with desaturation (91% oxygen saturation), and antibiotics were replaced by polymyxin B and meropenem, as the blood culture showed the growth of *Escherichia coli* sensitive to such drugs. Oxygen was supplied through a nasal catheter, with a flow rate of 3 L/min, with the patient remaining comfortable and with an oxygen saturation > 94%. Table 1 shows the laboratory test results. The patient continued to receive acetylsalicylic acid and sulfamethoxazole with prophylactic trimethoprim, according to the liver transplantation protocol of the service. Over the next few days, the patient showed an improvement curve and no new clinical complications. He was discharged to outpatient follow-up after 38 d of hospitalization.

Case 2

The patient's evolution showed clinical improvement and he was extubated on the second postoperative day, with an initial need for 5 L/min of oxygen through a nasal catheter to maintain adequate oxygen saturation and an oxygenation index of 420. Over the next few days, complete weaning from oxygen support was attained.

He showed clinical and laboratory improvement and was discharged from the ICU after 1 wk, and discharged from the hospital after 12 d. He was then referred to outpatient follow-up. During the follow-up period, a new nasopharyngeal swab was collected to screen for SARS-CoV-2 infection, 16 days after the first test and a detectable result has remained to date.

DISCUSSION

The liver is the second most commonly transplanted solid organ worldwide, second only to the kidney. The transplanted population is exposed to several emerging diseases and may even develop symptomatic and, sometimes, severe infections[6,7]. The SARS-CoV-2 pandemic presents a challenging scenario to the reality of transplantations, considering that due to immunosuppression, newly transplanted patients are subject to a high risk of developing complications from infections[8].

The most frequently reported symptoms of SARS-CoV-2 infection in the general population comprise fever, dry cough, myalgia and headache. A Swiss study described the results of a series of 21 patients submitted to solid-organ transplantations who contracted COVID-19, in whom the clinical presentation did not significantly differ from the symptoms described in the general population[9]. In the reported cases, the patients did not have flu-like symptoms during hospitalization.

However, case 1 had a fever peak and showed oxygen desaturation on the third postoperative day, which can be attributed to symptoms of infection by SARS-CoV-2 or by another bacterial infectious process. The evolution of case 2 showed a slower weaning from oxygen support in the postoperative period. A North American study reported a worse prognosis in solid organ recipients with COVID-19[10]. Preliminary data indicate that late transplant recipients have more severe disease than recent transplant recipients, suggesting that immunosuppression itself is not a criterion for severity, and a metabolic component, such as arterial hypertension, diabetes and obesity, which are typically present in late recipients is responsible for the worse prognosis in this population[11].

A study reported on four transplant recipients who were diagnosed with SARS-CoV-2 between 7 and 10 d after the transplant. Three had a good evolution and one died due to a cause unrelated to COVID-19[12]. In our center, only these two patients were transplanted with SARS CoV-2 infection detected by RT-PCR during surgery and both showed a good evolution. To date, there has been no description in the world literature of other recipients with SARS-CoV-2 infection detected by RT-PCR immediately before transplantation. Despite our small sample, our data confirmed the recent literature indicating that immunosuppression alone is not a factor of poor prognosis in the presence of COVID-19. As recommended by the transplant societies, our patients were screened for COVID-19 prior to the procedure, in order to predict possible adverse developments in the postoperative period and allow more adequate multidisciplinary patient care. However, the difficulty in obtaining the results and the fact that the patients did not have respiratory symptoms were essential in the decision by the medical team to proceed with the transplant, even without the COVID-19 test results. Another important fact was the patients' disease severity, as both patients had

an important risk of worsening liver disease, given their high MELD score.

There are reports in the literature of several pathogens that can be transmitted through grafting. In the case of heart and lung transplantation, the International Society of Heart and Lung Transplantation recommends considering the exclusion of suspected or confirmed donors with SARS-CoV-2 infection, as the microorganism is predominantly found in respiratory secretions[13]. With regard to liver transplantation and COVID-19 infection, recent recommendations suggest that the procedure can be performed during the pandemic[14]. However, transmission *via* the liver graft cannot be excluded, since the virus has been found in blood in up to 15% of cases. A study described the autopsy results of 27 patients and showed that SARS-CoV-2 can be detected in multiple organs, including the lungs, pharynx, heart, liver, brain and kidneys[15]. It is noteworthy that liver damage may be caused by direct liver injury due to COVID-19, medication-induced hepatotoxicity and immune-mediated inflammation.

In our center, we chose to continue to perform transplants during the pandemic, limiting the procedure to candidates with greater need for transplantation, as in the described cases. The use of personal protective equipment to reduce the transmission chain as much as possible is mandatory among health professionals, and any professional who is symptomatic or has positive results for COVID-19 is removed from the procedure.

The current proposal in our center is to screen all possible donors for SARS-CoV-2 infection using RT-PCR. If the donor is positive, they are immediately excluded.

With regard to the recipient, the current proposal of this transplantation center is that during the outbreak of certain diseases, as in the case of COVID-19, an initial screening is carried out by telephone, to determine flu-like symptoms and contact with suspected or confirmed cases of SARS-CoV-2 infection. It is also advised that the patient should remain in social isolation for at least 14 d before the transplant, to avoid possible infectious contamination.

A clinical history of flu-like symptoms is again performed upon hospital admission. Additionally, chest X-rays and nasopharyngeal swab screenings are performed to minimize the risk of transmission. Computed tomography of the chest is reserved for patients with significant alterations shown on chest X-rays. If the patient is suspected of having COVID-19, the transplant is postponed and should be performed in a timely manner. However, it is important to emphasize that the clinical condition is taken into account, in order to define whether the patient has the possibility of an adverse evolution if the transplant is postponed, especially in patients without respiratory complaints.

As relevant data are scarce, it is important to identify a population of recipients that can safely undergo solid organ transplant even with RT-PCR detected SARS-CoV-2 infection, in whom the risk of not undergoing the transplantation is higher than that of the infection.

To date, there is no proven therapy for the treatment of symptomatic coronavirus cases. Recent studies have shown clinical improvement after the use of corticosteroid therapy in cases of severe acute respiratory syndrome associated with COVID-19[16].

Hydroxychloroquine, lopinavir/ritonavir and remdesivir were not used in the present study and immunosuppressive therapy after liver transplantation was not altered, as the patients showed progressive clinical improvement and they were easily weaned from mechanical ventilation in the postoperative period.

CONCLUSION

Two cases of successful liver transplant are described in patients with a positive test for COVID-19 immediately after transplantation, with minimal symptoms and no graft dysfunction after the procedure. In this new post-COVID-19 era, the experience in this center can be used as an example, in order that other services can continue to perform transplants and, thus, reduce the morbidity and mortality of this population on the waiting list. Transplant centers must be able to readjust daily to evolution of the COVID-19 pandemic and care during the pandemic must be intensified, requiring a donor and recipient screening process to detect COVID-19. If the disease is detected, transplantation should be carefully considered. It is worth mentioning that the care and use of personal protective equipment by the multidisciplinary team is crucially important to prevent the viral propagation cycle.

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