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Infections and spinal cord injury: Covid-19 and beyond

Raquel Madroñero-Mariscal^{a,b}, Ángel Arévalo-Martín^c, Francisco Gutiérrez-Henares^d, Miguel Rodríguez-Cola^e, Melchor Alvarez de Mon^{f,g}, and Elisa López-Dolado^{h,i}

^aRehabilitation Department, Fundación del Lesionado Medular and Hospital Universitario Infanta Leonor, Madrid, Spain; ^bLaboratory of Interfaces for Neural Repair, Hospital Nacional de Paraplégicos, Toledo, Spain; ^cLaboratory of Neuroinflammation, Hospital Nacional de Paraplégicos, Toledo, Spain; ^dRehabilitation Department, Hospital Nacional de Paraplégicos, Toledo, Spain; ^eInternal Medicine Department, Hospital Nacional de Paraplégicos, Toledo, Spain; ^fHospital Universitario Príncipe de Asturias, Madrid, Spain; ^gSchool of Department of Medicine and Medical Specialties, School of Medicine, Universidad de Alcalá (UAH), Alcalá de Henares, Spain; ^hRehabilitation Department, Laboratory of Interfaces for Neural Repair (LINER), Hospital Nacional de Paraplégicos, Toledo, Spain; ⁱDepartment of Medicine and Medical Specialties, School of Medicine, Universidad de Alcalá (UAH), Alcalá de Henares, Spain

List of abbreviations

ARDS	acute respiratory distress syndrome
bdMARDs	biological disease-modifying anti-rheumatic drugs
CT	computerized tomography
Covid-19	coronavirus disease 2019
GCs	glucocorticoids
HPA	hypothalamic-pituitary-adrenal
IUC	indwelling urethral catheter
ICU	intensive care unit
ISNCSCI	International Standards for Neurological Classification of the Spinal Cord Injury
JAKi	Janus kinase inhibitors
MRI	magnetic resonance imaging
NICE	National Institute for Clinical Excellence
NE	norepinephrine
PI	pulmonary infections
PEP	positive expiratory pressure
PPE	personal protective equipment
ISC	self-catheterization
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SPC	suprapubic catheter
SCI	spinal cord injury
SCIP	spinal cord-injured patients
SNS	sympathetic nervous system
SPNs	sympathetic preganglionic neurons
UTI	urinary tract infections
WHO	World Health Organization

Introduction

An epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan in December 2019 and quickly spread across the world. The 2019 coronavirus disease (Covid-19) was declared a pandemic on March 11, 2020, by the World Health Organization (WHO). On February 7th, 2021, 105,962,538 cases were confirmed worldwide with 2,313,136 deaths ([Johns Hopkins Coronavirus Resource Center, 2020](https://www.jhu.edu/2020/02/07/coronavirus-cases-worldwide/)). This new SARS-CoV-2 has brought higher levels

of illness, deaths, and fear to our planet than any other virus in current history. In this context, it is mandatory to determine the effect in people with spinal cord injury (SCI).

SCI induces numerous chronic disorders that put these individuals at a high risk of severe Covid-19 prognosis. Specifically, the SCI population presents higher rates of hypertension, SCI-induced immunosuppression, and, if the metamer level is T8 or above, respiratory failure with continuous or episodic hypoxemia due to respiratory muscle weakness. Sympathetic denervation following SCI compromises body temperature regulation, as a result of dysautonomia, which not only complicates the early diagnosis of Covid-19 which places them at risk of a poor prognosis, but also makes it difficult to control infection transmission to other patients and/or healthcare staff.

In general population, clinical symptoms appear after an incubation period of around 5 days (Zhu et al., 2020), presented in order of frequency as: fever (87.9%), dry cough (67.7%), asthenia (38.1%), dyspnea (18.6%), pharyngeal pain and odynophagia (13.9%), headache (13.6%), arthromyalgia (14.8%), chills (11.4%), nausea or vomiting (5%), nasal congestion (4.8%), and anosmia and diarrhea (3.7%). Approximately 80% of patients present as asymptomatic or with few symptoms including dry cough and fever or low-grade fever (Guan et al., 2020), but the remaining 20% of cases develop around the 7th day after the onset, severe hypoxemic respiratory failure that progresses to Acute Respiratory Distress Syndrome (ARDS) (15% of the total) and even to multi-organ failure (5% of the total), requiring mechanical ventilation and admission to an Intensive Care Unit (ICU) (Huang et al., 2020). Up to 18% of patients who request consultation for Covid-19 compatible symptoms do not present radiological alterations. When these appear, the most frequent clinical sign is unilateral or bilateral ground glass opacification with an interstitial pneumonia pattern or bilateral patched consolidation, evident on plain radiography and on chest computerized tomography (CT) examination (56.4%) (Hosseiny et al., 2020; Zu et al., 2020). At diagnosis, more than 80% of patients present lymphopenia (Guan et al., 2020), which is more severe and accompanied by neutrophilia in patients requiring ICU admission (Huang et al., 2020). The main cause of death after Covid-19 infection is respiratory failure and fulminant myocarditis, (Ruan et al., 2020). In these patients, a highly exaggerated inflammatory response has been described known as hyperinflammatory syndrome, with a massive release of cytokines into the bloodstream (Mehta et al., 2020; Ritchie & Singanayagam, 2020) similar to that observed in hemophagocytic syndromes caused by other viruses (Ramos-Casals et al., 2014). A series of clinical factors have been described, associated with symptoms of greater morbidity and mortality: male gender, age above 60 years—especially above 80 years old, where the fatality rate is close to 16%—and the presence of previous comorbidities such as: hypertension, ischemic heart disease, diabetes mellitus, lung disease, and various disease entities that lead to immunosuppression, such as autoimmune diseases or cancer (Zhou et al., 2020). Analytical markers associated with a higher risk of mortality are sustained lymphopenia and elevation of D-dimer, IL-6, ferritin, LDH, and troponin (Zhou et al., 2020).

The aim of this chapter is to analyze the clinical presentation of Covid-19 in spinal cord-injured patients (SCIP). The authors pretend to make pause to understand if this emergent disease, which is deadly hitting our general population, behaves in the same or different way as in these especial patients, in order to understand if the SCI condition is acting as a risk factor for morbidity or not, and why. For this purpose, we believe the immune system plays a significant role in infection, especially from our knowledge of other infections.

Immunosuppression due to spinal cord injury

Among non-specialist the most evident consequences of SCI is loss of mobility and sensibility. However, in spite of their dramatic effect on patient quality of life, this is only the tip of an iceberg compared to the other lifelong neurological and non-neurological sequelae. These patients have an immunodepressed state characterized by changes in the number and function of immune cells that render them highly susceptible to infections (Bracchi-Ricard et al., 2016; Brommer et al., 2016; Kopp et al., 2017). Indeed, these are the leading cause of morbidity and mortality after SCI (Thietje et al., 2011). In this chapter, we review why immunodepression occurs after SCI and how this affects the ability of patients to cope with the current Covid-19 pandemic and other infectious diseases.

Pathophysiology of spinal cord injury-induced immunodepression

The physiological responses to physical or psychological stress are mediated by the coordinated response of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Both systems mediate the so-called fly-or-fight responses by setting the whole organism to cope with stressful stimuli at the expenses of arresting functions that are not indispensable for immediate survival. This physiological and evolutionary adapted response may, however, turn into a maladaptive chronic situation. Spinal cord injuries are a source of tremendous physical and psychological stress that unfortunately exemplifies the effect on the immune system of maladaptive SNS and HPA responses.

Dysregulation of the sympathetic nervous system

The main mechanism driving immunodepression after SCI is the dysregulation of the autonomic sympathetic nervous system. The cell bodies of the sympathetic preganglionic neurons (SPNs) are localized in the lateral horn of the spinal cord, in the intermedio-lateral nucleus. Classically, it has been considered as sympathetic the neurons located from T1 to the first lumbar segments (L2–3), although recently, the parasympathetic neurons located in the lateral horn of the sacral segments have been shown to have phenotypical and ontogenetic characteristics of SPNs (Espinosa-Medina et al., 2016). In any case, SPNs synapse in sympathetic ganglia majorly with post-ganglionic noradrenergic neurons, which in turn release norepinephrine (NE) in the target organs, though a minority of post-ganglionic sympathetic neurons are cholinergic, as those innervating sweat glands (Dale & Feldberg, 1934). The timing and intensity of SPNs activation is controlled by nuclei located in the brainstem, pons and hypothalamus that project inhibitory descendants into the spinal cord (Dénes et al., 2005). After a severe SCI, these supraspinal projections are interrupted and, thus, SPNs loss their inhibitory inputs. Consequently, when these neurons are activated, it may give raise to an exaggerated or more durable sympathetic response and, thus, to an excessive release of NA in the target organs. In addition, the sublesional spinal circuitry involved in the control of preganglionic neurons undergoes a remodeling process that favors the connectivity between activating interneurons and SPNs (Ueno et al., 2016). Overall, the resultant sympathetic overactivation below the lesion level underlies a plethora of autonomic dysfunctions after SCI, including the suppression of the immune system.

The sympathetic nervous system innervates both the primary and the secondary lymphoid organs, and modulates all the immune processes, from hematopoiesis to immune responses (Jung et al., 2017; Noble, Brennan, & Popovich, 2018). Immune cells sense NE majorly through beta-2-adrenergic receptors, although monocytes/macrophages also express lower levels of alpha-1- and alpha-2-adrenergic receptors (Kavelaars, 2002). The overall effect of adrenergic receptor activation on physiological conditions over innate immune cells is anti-inflammatory (Meltzer et al., 2004; Nance & MacNeil, 2001). On B cells, NE participates in T-cell mediated IgG production (Alaniz et al., 1999; Kohm & Sanders, 2001), while the effects of NE over T lymphocytes is more complex and varies according to the cellular stage of maturation and timing of exposure. Depending on the stage of maturation of T CD8⁺ cells, exposure to NE may either promote or decrease their cytolytic activity (Nance & Sanders, 2007). Similarly, exposing Th1 cells to NE before their activation decreases the synthesis of IL-2 and IFN-gamma, while exposing them to NE after activation increases the synthesis of IFN-gamma (Nance & Sanders, 2007). In any case, the overall effect of NE over adaptive immune responses is also considered to be anti-inflammatory, inhibiting Th1 cell differentiation and promoting Treg-suppressive activity (Elenkov, Wilder, Chrousos, & Vizi, 2000; Guereschi et al., 2013).

After SCI, immune cells may be subjected to persistent or more intense exposure to NE, which results in immunosuppression (Prass et al., 2003). A factor that may dramatically affect the sympathetic dysregulation-induced immunodepression is the lesion level, being lesions at T5 or above associated to a greater impairment of the immune system both in patients and in experimental animal models (Brommer et al., 2016; Lucin et al., 2007; Lucin et al., 2009). This observation coincides with the fact that most of the sympathetic innervation of immune organs arise from preganglionic neurons located below T5. The innervation of lymph nodes is not resolved, but it is considered to originate from spinal segments close to their location in the body (Nance & Sanders, 2007). Thymus receives most of its innervation from above T5, specifically between T1 and T7 (Trotter et al., 2007). In any case, the sympathetic dysregulation induced by SCI suppresses immune cells in the decentralized lymphoid organs. This statement is supported by direct experimental evidence showing that immune suppression effects depend on beta-2-adrenergic stimulation and may be reverted by receptor antagonists (Table 1). Indirect evidence is further provided by the observation of a relationship between lesion level and extent of immunodepression (Table 2).

TABLE 1 Effects of SCI over immune cells with experimental evidence of dependence on beta-2-adrenergic receptor stimulation.

Cell type	Effect	References
B cells	(1) Impaired primary humoral responses (2) Apoptosis	(1) Lucin et al. (2007), Oropallo et al. (2012) (2) Lucin et al. (2009)
T cells	Apoptosis	Lucin et al. (2009)
CD8 ⁺ T cells	T cell exhaustion	Zha et al. (2014)

Experimental evidence shows that SCI-induced immune suppression effects depend on beta-2-adrenergic stimulation and may be reverted by receptor antagonist. *SCI: spinal cord injury.*

TABLE 2 Effects of SCI over immune cells dependent on lesion level.

Cell type	Effect	References
B cells	Decreased number	Lucin et al. (2007), Held, Steward, Blanc, and Lane (2010), Zhang et al. (2013)
T cells	Decreased number	Lucin et al. (2009)
CD4 ⁺ T cells	Decreased number	Zhang et al. (2013)
NK cells	Decreased number	Herman et al. (2018)
Dendritic cells	Decreased number	Iversen et al. (2000)

The observation of a relationship between the injury level and severity and the extent of immunodepression highlights the effects of SCI over immune cells. *SCI: spinal cord injury.*

There is evidence of the contribution of sympathetic overactivation to immune depression after SCI results from autonomic dysreflexia crises, potentially triggered by any sustained sensory stimuli entering the spinal cord below the lesion level. This occurs mainly in patients with severe lesions above T5 because these injuries render without inhibitory supraspinal inputs the SPNs that control abdominal circulation (Weaver et al., 2002). As a consequence, SPNs overactivation occurs and results in vasoconstriction and hypertension. As a counteractive measure it is triggered a vagal response that induces vasodilatation (only successful above the lesion level) and bradycardia, which may be life-threatening if derives into a cardiac arrest. It has been experimentally proved that in these crises, the overactive sympathetic response further aggravates immunodepression in animals with high thoracic (T3) SCI (Zhang et al., 2013), which may help to explain why infections result in morbidity and mortality among patients with tetraplegia compared to patients with paraplegia.

Another potential symptom of immunodepression driven by the autonomous nervous system is the “inflammatory reflex” (Pavlov & Tracey, 2017). When the vague nerve is stimulated, spleen macrophages are polarized into an anti-inflammatory profile. Evidence shows that the spleen does not receive parasympathetic innervation. However, the vagus nerve synapses with sympathetic post-ganglionic neurons in the celiac ganglion, eliciting the release of NE in the spleen. In response, T lymphocytes produce acetylcholine, which acting on alpha-7-nicotinic receptors expressed by macrophages inhibits the production of TNF-alpha, IL-1 beta and IL-18 by these cells. The contribution of the inflammatory reflex to SCI-induced immunodepression is not elucidated, but it seems reasonable to believe that it could be triggered by the vague nerve reflex that takes place during autonomic dysreflexia crises.

Dysregulation of the hypothalamic-pituitary-adrenal axis

The activation of the HPA axis after SCI is well documented by the increase of blood serum glucocorticoids (GCs) in patients and in experimental animals. Besides the direct immunosuppressive actions of GCs on immune cells, glucocorticoids (GCs) and NE synergize to modulate immune cell function. GCs increase the affinity and persistence in the cell membrane of beta-2-adrenergic receptors (Davies & Lefkowitz, 1981; Mak et al., 1995) while NE potentiates GCs signaling (Rangarajan, Umesono, & Evans, 1992). As such, when cortisol and the NE analog terbutaline are added together, they synergize to induce apoptosis of B and T cells in vitro (Lucin et al., 2009). Notably, the spleen atrophy and the decrease in the number of splenocytes induced by an experimental SCI in T3 is partially reverted by the joint administration of antagonists of beta-2-adrenergic and GC-receptors (Lucin et al., 2009). In addition, it should also be considered that adrenal glands are innervated by the SNS, which induces the release of GCs.

Leading infection diseases in spinal cord-injured patients

Infection is one of the leading complications of inpatients, especially severe for SCIP due to the risk of death when it occurs a progression to a bloodstream infection. These patients have a greater predisposition to suffer infectious diseases because of their required use of medical devices such as intravenous and urinary catheters or ventilators. Special conditions suffered by these patients such as lack of mobility or bladder and respiratory dysfunctions contribute to a higher level of infection (Esclarín de Ruz et al., 2009).

There are two main features that make diagnosis of infection particularly challenging in SCIP. First, their loss of feeling can mask standard symptoms which make its diagnosis more difficult to diagnosis. Second, there are also some other

described conditions that can simulate an infection, but they are really the manifestation of another disease with no infection as it occurs in hyperthermia, abdominal retention, and pulmonary embolism or collapsed lung (Esclarín de Ruz et al., 2009).

In general terms for treatment, it is strongly recommended to use narrow-spectrum and less toxic antibiotics to avoid eliminating patient’s native bacterial flora. It is also important to choose an appropriate directed antibiotic therapy to avoid the appearance of resistant bacteria.

The major infections that suffer SCIP are explained below (Table 3).

Urinary tract infections (UTI)

UTI are the most frequent cause of infections (95%) in SCIP. They increase the risk of morbidity and mortality because of interruptions of rehabilitation treatment, required visits to the emergency room, and progression to a sepsis. The latter can make SCIP more likely to develop an immunodeficiency syndrome that facilitates the appearance of recurrent UTI (Craven et al., 2019; Esclarín de Ruz et al., 2009). *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* are the most frequently involved pathogens causing an UTI (Skelton-Dudley et al., 2019).

Physiopathology and etiology

Neurogenic bladder presents overdistension and high pressure due to the interruption of its voiding process. This produces an ischemia of the bladder’s wall, which causes bacteria to invade its submucosal layer, and starts the UTI. If this process repeatedly occurs, collagen forms a scarred tissue that replaces muscle fibers from the bladder’s wall, which decreases bladder’s wall compliance. This leads to increase ischemia of the bladder’s wall and bladder’s overdistension (Fig. 1) (Linsenmeyer, 2018).

To avoid high intravesical pressure and overdistension of the bladder’s wall, more than a 60% of SCIP need a medical device to facilitate their bladder voiding such as an intermittent self-catheterization (ISC), an indwelling urethral catheter (IUC) or a suprapubic catheter (SPC). ISC is the gold standard method because it allows a cyclic emptying and filling of the bladder, comparable to the physiological bladder’s functioning. Some studies as Kinnear et al., 2020, suggest that ISC is associated with lower rates of UTI when comparing with other medical devices. Despite that, SCIP who use ISC are likely to suffer UTI when they drink plenty of fluids or they do not practice the voiding method regularly, because of an overdistension of the bladder’s wall. It becomes worse when patients have an overactive bladder and/or a decreased bladder function (Kinnear et al., 2020).

TABLE 3 Principle infection features in SCIP.

	UTI	PI	Covid-19
Frequency	It is the most frequent cause of infection (95%) in SCIP	<ul style="list-style-type: none"> The 50% of SCIP who suffer acute tetraplegia develop pneumonia during acute hospitalization PI and respiratory failure are the major causes of death in this population 	Unknown but lower than expected
Pathogens	<ul style="list-style-type: none"> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i> 	<ul style="list-style-type: none"> Pneumococcus, Pseudomonas (outpatients) No data (inpatients) 	SARS-CoV-2
Etiology	<ul style="list-style-type: none"> Changes due to neurogenic bladder produce an overdistension of the bladder, high intravesical pressure and bladder compliance decrease that can lead to an UTI Medical devices that are used for facilitating bladder voiding can lead to an UTI as well 	<ul style="list-style-type: none"> The dysfunction of inspiratory and expiratory muscles, the increased risk of dysphagia disorders and the changes inside lung that produces a neurogenic pulmonary edema can lead to a PI Medical devices to assist with breathing can lead to a PI as well 	<ul style="list-style-type: none"> Immunosuppression induced by SCI Neuromuscular respiratory failure due to respiratory muscles weakness and clearance secretions’ decrease in SCI levels of injury above T6–T8

Continued

TABLE 3 Principle infection features in SCIP—cont'd

	UTI	PI	Covid-19
Diagnosis	<ul style="list-style-type: none"> It is necessary to differentiate between: <ul style="list-style-type: none"> Asymptomatic bacteriuria/bladder colonization: <ul style="list-style-type: none"> $\geq 10^2$ cfu/mL bacteriuria at sediment or any bacteria detected at sediment when using IUC no symptoms ^aUTI: <ul style="list-style-type: none"> bacteriuria (with one primary organism detected at culture) one bladder symptom at least: <ul style="list-style-type: none"> hematuria new/increased incontinence change in urine odor/clarity pyuria one general symptom at least: <ul style="list-style-type: none"> fever acute autonomic dysreflexia acutely increased spasticity sepsis persistent fatigue vomiting When symptoms appear, urine and blood cultures are required When symptoms persist, it may be necessary to carry out additional test as ultrasounds, cystoscopy or kidney scan, to rule out complications (hydronephrosis, vesicoureteral reflux, urinary lithiasis or kidney abscesses) Blood biomarkers (procalcitonin and interleukin-6) has shown poor evidence in ITU detection 	<ul style="list-style-type: none"> Clinical symptoms: fever, dyspnea, secretions Chest X-ray that shows infiltrates within lungs Alterations in blood gas analysis Leukocytosis Culture and sputum Gram stain: <ul style="list-style-type: none"> when NOT wearing an artificial airway: Sputum culture (>25 polymorphonuclear leukocytes and < 10 epithelial cells per field) when wearing an artificial airway: <ul style="list-style-type: none"> bronchoalveolar lavage sample: $>10^4$ cfu/mL tracheal aspiration sample: $>10^6$ cfu/mL 	<ul style="list-style-type: none"> Mild symptoms of onset: hypoxia, secretion clearance impairment could be the only symptoms of onset; but SCIP can also present fever, dyspnea, fatigue, anosmia, ageusia, arthromyalgias, and headache Close observation to neurofunctional outcomes, especially with the help of the International Standards for Neurological Classification of the Spinal Cord Injury (ISNCSCI) Worksheet, is needed to know if this infection produces sensory and motor deficits in these patients Whenever those symptoms are suspected, it is needed to make a RT-PCR SARS-CoV-2 from nasopharyngeal or bronchial aspiration test to confirm the infected condition Other paraclinical tests: Chest X-ray (to explore infiltrates at lungs), gas blood analysis (to explore ventilation perfusion state), and a blood analysis (to rule out lymphopenia, increase of d-dimer, ferritin and IL-6) After 7–14 days from the onset of the symptoms, if patient presents a favorable clinical evolution, a serological SARS-CoV-2 should be done to look for IgM and IgG levels
Treatment	<ul style="list-style-type: none"> The choice of the most appropriate antibiotic treatment depends on culture results Long-term antibiotic treatment (from 7 to 14 days) is recommended 	<ul style="list-style-type: none"> Prompt empirical antibiotic treatment is needed <ul style="list-style-type: none"> ^bCommunity acquired pneumonia <ul style="list-style-type: none"> empiric anti-pseudomonal coverage is recommended optimize secretion mobilization: <ul style="list-style-type: none"> Multi-modal treatment Quad coughing Mechanical insufflator-exsufflator ^bEarly hospital-acquired pneumonia <ul style="list-style-type: none"> empiric antibiotic treatment depends on most common pathogens for each hospital, ICU and anti-microbial susceptibility patterns of each community It is recommended to use agents from a different antibiotic class than the patient has recently received 	<ul style="list-style-type: none"> The same as general population In these patients, respiratory rehabilitation is especially important due to their condition of respiratory muscle weakness (secretions' clearance therapies, lower and upper active-assisted or passive kinesiotherapy, and relaxation exercises, and a positive expiratory pressure exercises with a Threshold PEP device to optimize the alveolar recruitment) It is mandatory that Physiotherapists use PPE for self-protection

TABLE 3 Principle infection features in SCIP—cont'd

	UTI	PI	Covid-19
Prevention	<ul style="list-style-type: none"> • Minimize urinary retention: anti-cholinergic medications or onabotulinum toxin A (Botox) injections for overactive bladders • Change bacterial flora of the bladder: <ul style="list-style-type: none"> - urine acidification (methenamine hippurate) - bacterial interference • Strengthen the host: <ul style="list-style-type: none"> - probiotics - proanthocyanidins (cranberry extracts) - immune biotherapy • Reduce biofilm formation: <ul style="list-style-type: none"> - D-mannose - nanoparticles - to cover the catheter with hydrophilic material - bacteriophages 	<ul style="list-style-type: none"> • ^bOutpatients: <ul style="list-style-type: none"> - annual Influenza and Pneumococcal polysaccharide vaccines - aggressive mobilization of secretions • ^bInpatients: <ul style="list-style-type: none"> - standard precautions <ul style="list-style-type: none"> - hand washing - gloving and gowning - to perform tracheal and nasopharyngeal respiratory techniques and cares under aseptic conditions - to consider non-invasive positive-pressure ventilation instead of invasive ventilation - to perform orotracheal rather than nasotracheal intubation whenever possible - to clear secretions - to avoid saliva or respiratory secretions microaspiration by raising the head of the bed from 30 to 45 degrees - to perform pre-operative breathing exercises and post-operative incentive spirometry - to remove patients out of bed as soon as possible - to prevent hospital-acquired, ventilator associated, and healthcare-associated pneumonia 	<ul style="list-style-type: none"> • Isolation and hygienic measures, the same as in general population. • Caregivers and health workers need to use PPE for self-protection.

Pathogens, frequency, etiology, diagnosis, treatment, and prevention strategies of the main infections that affect SCIP. *Covid-19*: coronavirus disease 2019; *ICU*: intensive care unit; *PEP*: positive expiratory pressure.; *PI*: pulmonary infections; *PPE*: personal protective equipment; *SARS-CoV-2*: severe acute respiratory syndrome coronavirus 2; *SCIP*: spinal cord-injured patients; *UTI*: urinary tract infections.

^aModified from: Craven, B. C., et al. (2019). *Conception and development of urinary tract infection indicators to advance the quality of spinal cord injury rehabilitation: SCI-high project*. *Journal of Spinal Cord Medicine*, 42(sup1), 205–214.

^bModified from: Burns, S. P. (2007). *Acute respiratory infections in persons with spinal cord injury*. *Physical Medicine and Rehabilitation Clinics of North America*, 18(2), 203–16.

Diagnosis

First, it is important to provide an early UTI detection. For this purpose, it is necessary to differentiate between asymptomatic bacteriuria and symptomatic UTI. The first one appears when there is a count of 10² cfu/mL or higher at the urine sediment, and when any bacteria are detected with the use of IUC. In this situation, the patient shows no symptoms, and it is considered a colonization of the bladder. This situation is different from an UTI because colonization does not need to be treated as it may play a protective role to the bladder flora (Kirshblum et al., 2011; Linsenmeyer, 2018). To make the diagnosis of UTI, the Experts in Urohealth and/or UTI recognition and management and the SCI-High Project Team at Craven et al. (2019), propose the following criteria: bacteriuria should be confirmed with at least one germ in the urine culture, at least one bladder symptom (hematuria, change in urine odor and clarity, new or increased incontinence, pyuria) and at least one general symptom (fever, sepsis, acute autonomic dysreflexia, persistent fatigue, acutely increased spasticity, vomiting, etc.).

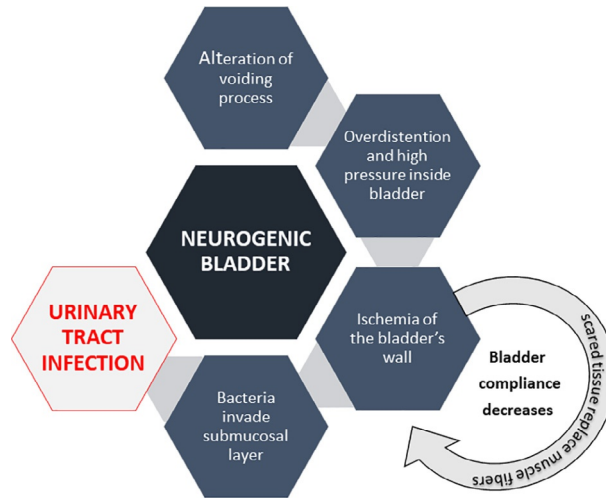


FIG. 1 Physiopathology of urinary tract infections. Step-by-step summary of the sequence of events leading to urinary tract infections (UTI) in SCI neurogenic bladder.

When those symptoms appear, it is necessary to take a urine and a blood culture in order to prescribe an appropriate antibiotic treatment to reduce antibiotic resistance and other associated complications in these patients.

It may be useful to practice a urine sediment because the majority of patients wearing a IUC present leukocyturia (50 leukocytes or more per field). The absence of leukocyturia excludes the diagnosis of UTI. This test has a high negative predictive value. Pyuria is only significant when there is also leukocyturia (Esclarín de Ruz et al., 2009).

If, in spite of an appropriate antibiotic treatment, symptoms persist, it may be necessary to carry out some additional tests such as ultrasound examination, cystoscopy, or kidney scan, to look for a structural cause or a complication being the leading cause of the persistent UTI (hydronephrosis, vesicoureteral reflux, urinary lithiasis, or kidney abscesses).

Blood biomarkers have shown poor evidence in the detection of UTI. Procalcitonin has been described as a biomarker in the diagnosis of UTI and pyelonephritis in pediatric population, but not in adults. IL-6 could help to differentiate between UTI and pyelonephritis, but further validation is needed yet (Skelton-Dudley et al., 2019).

Treatment and prevention

SCIP develop complicated UTI because of the urinary tract dysfunction. Because of this reason, it is necessary to follow a long-term antibiotic treatment from 7 to 14 days. To avoid the increased likelihood of anti-microbial resistance and to reduce the administration of wide spectrum antibiotics, it is necessary to perform a urine culture to select the most appropriate antibiotic treatment (Esclarín de Ruz et al., 2020).

Though some studies advise using prophylactic antibiotics as nitrofurantoin to prevent catheter associated UTI (Chew et al., 2019); the truth is that more consistent evidence is required to make this recommendation in a safe way to compensate the risk of resistances appearance derived from the use of these antibiotics (Skelton-Dudley et al., 2019), because there are some other studies like Morton et al. (2002), which show that using prophylactic antibiotics is worthless as it does not decrease the number of UTI, and even may be harmful, as it reduces asymptomatic bacteriuria while increasing antibiotic resistance.

To prevent recurrent UTI in SCIP it is desirable to improve patients' conditions minimizing urinary retention and optimizing urinary voiding, using anti-cholinergic medications or onabotulinum toxin A (Botox) when they have an overactive bladder. Also, it is important to correct anatomical problems like urethral stricture or bladder calculi (Linsenmeyer, 2018).

There are other prevention strategies for SCIP with recurrent UTI. The most commonly used are: (1) changing the bacterial flora of the bladder with urine acidification; or (2) strengthening the host by administering probiotics, proanthocyanidins such as cranberry extracts or D-mannose (to reduce biofilm formation on the bladder and catheter wall). In the foreseeable future, clinicians will also have nanoparticles capable of inhibiting biofilm formation by *E. coli* and *Staphylococcus aureus*, but this promising strategy is currently in the pre-clinical phase. To cover the catheter with hydrophilic material before its introduction to the bladder delays and decreases the number of UTI in acute SCI (Cardenas et al., 2011) by blocking the biofilm catheter formation. The use of bacteriophages that are responsible for producing a depolymerase

enzyme that breaks the extracellular polysaccharide matrix of the biofilms on urinary catheter, are also useful when the patient has developed antibiotic resistance because, when antibiotic-resistant bacteria become resistant to the phage, in some cases, the bacterial sensitivity to antibiotics is restored. Also, immune biotherapy uses the administration of antigenic components to be recognized as “danger signals” which contribute to activate the innate immune system as a prophylactic method (Linsenmeyer, 2018).

Pulmonary infections (PI)

The 50% of SCIP who suffer acute tetraplegia develop pneumonia during acute hospitalization and rehabilitation (Schilero et al., 2005). PI and respiratory failure are major causes of death in this population (Yong et al., 2012). Review study by Burns (2007) has identified Pneumococcus as the first leading pathogen causing pneumonia in outpatients with SCI, while Pseudomonas is the second one. Conversely, there are no published data on etiologic pathogens that cause pneumonia during acute hospitalization and rehabilitation for these patients. It is assumed that the etiology of a nosocomial pneumonia depends on the type of hospital, ICU, and anti-microbial susceptibility patterns of each community (Díaz, Martín-Loeches, & Vallés, 2013).

Review study by Burns (2007) also shows that in ventilator-dependent patients, more than 90% of patients suffering from pneumonias and requiring hospitalizations have previously developed upper respiratory tract infections.

Physiopathology and etiology

Depending on the level and severity of the SCI, there are different mechanisms that are thought to be involved in causing pneumonia. In complete lesions above C3, the respiratory muscles are paralyzed. In C3–C5 lesions, despite varying degrees of phrenic nerve injury, respiratory neuromuscular activation is preserved but dysfunctional. Lesions below C5 retain some degree of ventilatory function due to intercostal and abdominal muscles, but above all, both diaphragms are preserved. These three situations involve inspiratory and expiratory hypofunction, which leads to dyspnea, decreased vital capacity, ineffective cough and problems with mucociliary clearance (Yong et al., 2012), and also they are more likely to suffer dysphagia disorders, especially due to tracheostomy, rigid fixation and high complete lesions due to the delay of mechanical ventilation weaning (Abel, Ruf, & Spahn, 2004). Apart from that, patients with low thoracic SCI, who retain good muscular respiratory function, may develop neurogenic pulmonary edema due to pulmonary vein constriction, increased pulmonary capillary hydrostatic pressure, alveolar damage and increased capillary permeability due to transient sympathetic discharge, which is underdiagnosed and provides the right environment for developing PI (Yong et al., 2012) (Fig. 2).

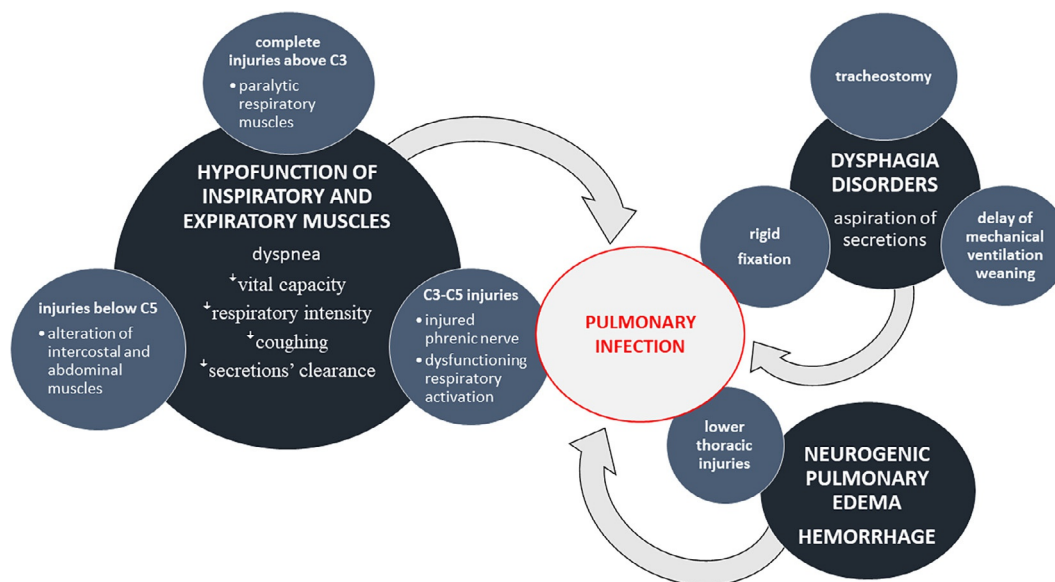


FIG. 2 Physiopathology of pulmonary infections. SCI-induced inspiratory and expiratory muscles hypofunction, dysphagia disorders, and neurogenic pulmonary edema can lead to develop a pulmonary infection in spinal cord-injured patients.

Diagnosis

Fever, respiratory symptoms as dyspnea or secretions, chest X-rays with infiltrates within lungs and alterations in blood gas analysis, and leukocytosis determine a diagnosis of pneumonia. To administrate an appropriate antibiotic treatment, it is necessary to make a culture and a sputum Gram stain.

In cases where a patient is not wearing an artificial airway, it is sufficient to make a sputum culture. A sample of >25 polymorphonuclear leukocytes and <10 epithelial cells per field is considered representative of the lower respiratory tract. In cases where patients are wearing an artificial airway, it is necessary to take a sample by bronchoalveolar lavage or a tracheal aspiration. An infection is diagnosed when there are $>10^4$ cfu/mL in bronchoalveolar lavage sample or $>10^6$ cfu/mL in tracheal aspiration sample (Esclarín de Ruz et al., 2020).

Treatment and prevention

While obtaining a culture, and before administrating a specific antibiotic treatment it is necessary to use a prompt empirical antibiotic treatment for avoiding respiratory infection progression. The choice of empiric antibiotic coverage depends on the most common pathogens for each hospital, ICU and anti-microbial susceptibility patterns of each community.

Burns (2007) recommends the management of community acquired pneumonia to consider empiric anti-pseudomonal coverage. It is also recommended to optimize secretion mobilization by multi-modal treatment, quad coughing or mechanical insufflator-exsufflator. To choose the empiric antibiotic coverage for SCIP with an early hospital-acquired pneumonia, it is recommended to use the same medications used for hospital-acquired pneumonia in patients without SCI, as the etiologic organisms for pneumonia that develop during acute care in SCIP are still undescribed. It is recommended to include agents from a different antibiotic class than the patient has received recently.

To prevent respiratory infections in outpatients with spinal cord injury, Burns (2007) recommends annual Influenza and Pneumococcal polysaccharide vaccines, and aggressive mobilization of secretions. In the case of SCI inpatients, the same author also recommends using the standard precautions (hand washing, use of gloves and gowns), performing the various tracheal and nasopharyngeal respiratory techniques and cares under aseptic conditions, as well as considering non-invasive positive pressure ventilation instead of invasive ventilation, opting for orotracheal instead of nasotracheal intubation whenever possible, clear secretions, avoid saliva or respiratory secretions microaspiration by raising the head of the bed from 30 to 45 degrees, perform pre-operative breathing exercises and post-operative incentive spirometry, and remove patients out of bed as soon as possible, to prevent hospital-acquired, ventilator-associated and healthcare-associated pneumonia.

There are other less frequent but also important infections that can affect SCIP such as pressure ulcer infections, surgery wound infections, intra-abdominal abscesses causing acute abdomen, sepsis... that are not explained here but expert SCI physicians need to know deeply to provide the acutest diagnosis and the best care and treatment to these patients. The latter review of the most frequent infections of SCIP (UTI) and the more severe ones (PI), pretend to help to achieve the greater understanding of the new Covid-19 infection in these patients.

COVID-19 disease: A new infectious normality in spinal cord-injured patients?

As it is well established, SCIP can be quite fragile. When Covid-19 pandemic started, we feared that they would have to face poor evolution and harsh prognosis, because of the presence of immunosuppression and induced autoimmunity, but above all, because of the respiratory muscles' weakness in all those cases with injury levels above T6–T8 (López-Dolado & Gil-Agudo, 2020). In addition, the mortality rate from influenza pneumonia was known to be higher than that of the general population (Soden et al., 2000). However, this grim prognosis does not seem to be confirmed. In fact, it has been reported that SCIP with concomitant Covid-19 infection show mild initial symptoms and better outcomes, even being aged over 60 and/or presenting clinically severe phenotypes (D'Andrea et al., 2020; Rodríguez-Cola et al., 2020), (Table 3). This apparently "indifferent" behavior toward Covid-19 infection has also been described in some autoimmune osteoarthropathies such as rheumatoid arthritis, also in those patients treated with biological disease-modifying anti-rheumatic drugs (bDMARDs) or Janus kinase inhibitors (JAKi) (Stradner et al., 2020). Data regarding Covid-19 and SCI are sparse, and further studies are needed to investigate the course of Covid-19 in SCIP, whether or not they have comorbidities and whether they are acute or chronic, but two simple although important points must be taken into account. First of all, the typical immune response involved in viral infections is sensibly different than in bacterial ones. Viruses are intracellular pathogens while bacteria are extracellular, so the role of CD8s and NK is quite different in both cases (see above). Second, as important as the pathogen in clearing up any infection is the immune system that fights against it, so in this regard, the SCIP cannot be considered as a homogeneous population. Factors such as advanced age, the presence of

comorbidities or long-term SCI chronic stages would negatively influence the immune response and could conditionate different risk levels (Monroe et al., 2019). Finally, with the available data to date, it is not possible to support or reject that Covid-19 infection is less symptomatic or severe in SCIP, since the use of drugs that dampen the local pulmonary inflammatory response is common in this population and the available data mostly come from case reports or at most from case series, valuable work for sure, but with restricted levels of evidence.

Another interesting aspect is the thrombogenic nature of Covid-19 shared by SCI. Using proteomic analysis to look for diagnostic biomarkers of Covid-19 infection in a cohort of SCIP, a specific role of heparin response to Covid-19 infection was found, supported by a significant correlation with proteins implied in coagulation/platelet activation. In this study, SCIP with Covid-19 receive from the moment of diagnosis prophylactic heparin, a common practice with these persons when bedridden is needed to avoid typical thrombotic and embolic complications (Calvo et al., 2020). Interestingly, heparin has demonstrated therapeutic potential against SARS-CoV-2 infection as a competitive inhibitor in general population Covid-19 patients.

It is well established that close to half of the hospitalized Covid-19 patients exhibit neurologic manifestations at the onset of the infection. To the author's knowledge, no study has been found that specifically analyzes this aspect in SCIP, although myalgias, headache, anosmia, and ageusia have frequently been found (Liotta et al., 2020). Sensory and motor deficits, barely been reported in the general population, have not been detected at all in SCIP, which does not mean that they have not appeared, but that we have not been able to detect them. Close observation to the neurofunctional outcome of the Covid-19 SCIP in the near and further future will permit to address this aspect.

The prevalence of Covid-19 infection among acute or chronic SCIP is unknown, but judging by the number of published cases, it seems lower than that of the general population (D'Andrea et al., 2020; López-Dolado & Gil-Agudo, 2020; Rodríguez-Cola et al., 2020). Part of the explanation could lie in the lower number of social contacts experienced by individuals who have reduced mobility and disability, in addition to the hygienic measures usually and constantly taken by their caregivers, which are similar to the measures that protect general population from Covid-19. The risk of transmission for the caregivers is nevertheless, another matter. Because being paucisymptomatic, Covid-19 infection could go unnoticed, turning the SCIP into a reservoir that would substantially increase the risk of contagion their caregivers. Therefore, caregivers and health providers must have access to adequate personal protective equipment (PPE) (Cossarizza et al., 2020). On top of that, both patients and their caregivers have experienced this pandemic, anxiety, loneliness and sadness, emotions that, if not addressed, will have negative impact on the health of all those groups (Taylor et al., 2020). The current pandemic has severely restricted SCIPs' access to health services, either for clinical control and follow-up, or to receive rehabilitative interventions. It is our vocation and obligation to use all the tools at our disposal, like the telemedicine platforms to maintain a safe, economical method of patient care.

Despite the burden of this worldwide disease there is no specific drug available to combat Covid-19. Vaccine efficacy depends largely upon the vaccine target and platform. Generally, the clinical development of a new vaccine requires many years of efforts in this area. However, having the results of previous efforts related to SARS-CoV and MERS vaccine research available, this time it has been possible to develop several vaccines, yet almost ready for their massive use in general population. There are no data to support the preferential vaccination of SCIP if the expressiveness and severity of the Covid-19 infection is taken into account. However, the fact that they can become virus reservoirs, and therefore, a source of transmission, is a compelling reason to recommend its extensive vaccination. Former experiences during previous pandemics, such as HIV1 or influenza, highlighted the need to make every effort not just to get the vaccine but to inform the target population to achieve sufficient vaccination rates. All possible efforts to ensure that accurate and clear information reaches the target SCIP must be done, since it is known that the better the information available on the disease and the vaccine, the higher the vaccination rate (LaVela et al., 2012). The medical community serving SCIP constitutes an exceptional group for quality information on Covid-19 vaccination to permeate (Locatelli et al., 2013). Thus, the current pandemic has shown us that from now on we should include in our health education programs all necessary information to protect SCIP against emerging pathogens and, among them, a better knowledge of available vaccines.

Applications to other areas of neuroscience

In this chapter we have reviewed the implication of the alteration of immune system in spinal cord-injured patients, and how this process leads the different infections that can suffer these patients. We also interlink the role of this immunosuppressed induced condition, with the current SARS-Cov-2 pandemic.

A better understanding about the interaction between the nervous system and the immune system could be reached by comprehending how SARS-Cov-2 virus affects patients with central nervous system diseases, such as in the spinal cord-injured patients, as Covid-19 influences the nervous system functioning and the immunity status as well. Due to its

neurotrophic feature, the deep knowledge of its structure, function, infection mechanism and characteristics, may help to improve the design of the current viral vectors applied at Neuroscience.

It should be an increasingly common requirement at the educational and clinical practice to include the study of the effects on our immune system in order to achieve the acutest and better understanding of every oldest known and new diseases. These diseases develop in a shared territory between neuroscience and immunology, so the deep knowledge of this space “in between” is a challenge, not only for physicians and immunologists, but also for neuroscientists, the spearhead of a successful knowledge in the research of central nervous system diseases and disabilities.

Mini-dictionary of terms

Respiratory syndrome coronavirus 2: Infection disease caused by Coronavirus that originates a severe damage to the lungs that involves a respiratory insufficiency, even in some cases, a breathing failure, requiring artificial ventilation supply.

Immunodepression: State of weakness of the immune system that delays and makes difficult to develop a prompt and active defense response against pathogens that invade human body. It has been demonstrated that spinal cord injury is a systemic disease which precipitates systemic changes that affect the immune system in this way.

Sympathetic nervous system: Part of the autonomic nervous system made up of neurons located from the first thoracic to the first lumbar segments which are presumed to carry out within its multiple functions, to innervate the primary and secondary lymphoid organs and modulate all the immune processes. Any process affecting this sympathetic nervous system, as spinal cord injury, could result in an alteration of the immune response of a patient.

Hypothalamic-pituitary-adrenal axis: Complex hormonal communicating system between the brain and different body glands that participate in different body responses, as the stress responses, energy metabolism, or the modulation of immune responses, as sympathetic nervous system does as well. In addition, adrenal glands, which are part of this axis, are innervated by the sympathetic nervous system. If a patient suffers a spinal cord injury, it will result in an alteration of all those responses by damaging the sympathetic nervous system and by altering this axis as well.

Bloodstream infection: Presence of pathogen organisms in the blood, having come directly from outside or being the spreading of a previously local infection. This is a severe infectious disease that can threaten patient’s life.

Native bacterial flora: Specific species of bacterial organisms that normally dwell different parts of human body without causing a disease. In fact, the loss of these bacterial organisms could imply the invasion from other pathogens that can lead an infection, so this native bacterial flora usually plays a protective role.

Neurogenic bladder: Dysfunction of the bladder due to a neurological damage that implies an overdistension of the bladder’s wall and an increased high pressure inside due to the alteration of its voiding process. Therefore, patient suffers incontinence and urine retention that may need medications and/or medical devices to facilitate and normalize their bladder’s voiding.

Recurrent urinary tract infection: Repeated infection of the urinary tract that does not disappear despite adequate anti biotic treatment. In spinal cord-injured patients, it should make consider the presence of a urinary complication as hydronephrosis, vesicoureteral reflux, urinary lithiasis, or kidney abscesses. First, it will be necessary to rule out these disorders to treat the infection successfully, later on.

Biofilm: Adherence of pathogens to the wall of artificial products that are in direct contact to body tissues, such as medical devices, that are able to produce a protective layer that make them resistant to standard antibiotic treatments. When it appears in a catheter and it remains unnoticed, the catheter biofilm becomes a leading cause of recurrent urinary tract infection and appearance of resistant bacterial pathogens.

Dysphagia disorders: Alteration of the deglutition process that implies the risk of passing food through airway by the larynx. It is a leading cause of pneumonia, which is considered to be the severest infection in spinal cord-injured patients because it can threaten their life.

Neurogenic pulmonary edema: Fluid invasion of the alveolar spaces from the lungs due to an inflammatory cascade which is thought to be the result of the immune system’s damage suffered in severe neurological injured patients. The resulting pulmonary edema could behave as an adequate environment for developing a pulmonary infection in these patients.

Telemedicine and telerehabilitation: Way of supplying a medical attention, or medical, and/or rehabilitation treatment that replace the classic patient’s physical attendance at the place of the doctor visit, by a telephone or video consultation, which avoids patients’ movements from home or familiar environment. It provides an effective source of access to medical healthcare to chronically affected patients as spinal cord-injured patients, who may find impairments to achieve transportations, especially during pandemic restriction period.

Key facts of “infections and spinal cord injury: Covid-19 and beyond”

Key facts of “immunosuppression due to spinal cord injury”

- Spinal cord injury is a systemic disease.
- Spinal cord injury induces an alteration of the immune system.
- This alteration of the immune system leads patients to suffer from infections.
- The better understanding of the modifications produced by the alteration of the immune system enables physicians and scientists to be able to appreciate the clinical presentations of these diseases, and patient’s responses to treatments, as well.

Key facts of “Leading infection diseases in spinal cord-injured patients”

- Infection is one of the leading complications of spinal cord-injured patients because this disease can threaten their life.
- Urinary tract infections are the most frequent cause of infection in these patients because they present a neurogenic bladder and they usually need to use medical devices to facilitate their bladder’s voiding.
- Its acute diagnosis will be of great importance to establish a long-term and appropriate antibiotic treatment to avoid antimicrobial resistances and further complications.
- Pulmonary infections are the most severe cause of infection in these patients because they can lead to a respiratory insufficiency and breathing failure that can strongly threaten patients’ life.
- While waiting for etiologic organisms’ results and before starting an adequate antibiotic treatment guided by those results, with the only clinical suspicion, physicians need to start an empirical antibiotic treatment, to avoid the progression of the infection.

Key facts of “Covid-19 disease”

- Most of the published studies show a tendency of milder initial symptoms and a less severe evolution of the Covid-19 disease in spinal cord-injured patients, but currently further validation is needed to support or reject that Covid-19 infection is less symptomatic or severe in this population.
- Covid-19 disease has shown a thrombogenic nature in spinal cord-injured patients that must be treated with heparins.
- In spite of coronavirus’ neurotropism, it has not been detected a sensory or motor deterioration in spinal cord-injured patients due to Covid-19 disease yet; but close observation to the neurofunctional outcomes should be done to ensure this affirmation.
- As Covid-19 disease could go unnoticed, turning the spinal cord-injured patients into a reservoir that could increase the contagion of their caregivers, medical community serving these patients should do every possible effort to provide appropriate healthcare educational programs with all the information needed to protect them from emerging pathogens that include the better knowledge of the available vaccines.
- Telemedicine has demonstrated to be a useful and effective tool to provide access to medical healthcare to chronically affected patients as spinal cord-injured patients, especially during this pandemic restriction period.

Summary points

- Spinal cord injury induces not only a loss of mobility and sensibility, but also numerous chronic disorders.
- Spinal cord-injured patients suffer a dysregulation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, which causes an alteration of all their immune processes.
- The combination of this situation with other locally impaired conditions provides a suitable environment for developing an infection.
- Urinary tract infections are the most frequent infections in these patients, because of the presence of a neurogenic bladder and the use of catheters to facilitate its voiding.
- Pulmonary infections are the severest ones, because of the respiratory muscle weakness, dysphagia disorders, pulmonary edema, and the use of ventilators to assist with breathing.
- The deep understanding of the physiopathology of these infections should help us to understand its appropriate diagnosis, treatment, and methods of prevention.

- The pandemic Covid-19, which is deadly hitting our general population, seems to show a tendency of milder initial symptoms and a less severe evolution in spinal cord-injured patients, but currently further validation is needed to support or reject it.
- The altered immune response could play a critical role in the clinical presentation of these patients.
- Telemedicine has demonstrated to be a useful and effective tool to provide access to medical healthcare to these chronically affected patients, especially during this pandemic restriction period.

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