COVID-19 and renal disease in elderly patients

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Abstract

The pandemic blast of COVID-19 uncovered well known weakness of financial chain and put our economic organizations facing off dramatic consequences if new strategies will not be developed to adapt health-care on detailed sub-groups of patients. The exponential number of older and frail subjects aged >65 years represents a challenge for public health. Patients affected by renal disease are an aged population that showed a particular attitude to contract infection and a higher mortality rate respect to general population. In this brief article, we would point out the focus on the management of issues related to renal patients facing off with coronavirus infection, in particular in a geriatric population particularly exposed to contagion like hemodialysis patients and precautions decided to slow the spread of contamination.

Introduction

The exponential number of older and frail subjects aged >65 years represents a challenge for public health. The pandemic blast of COVID-19 uncovered well known weakness of financial chain and put our economic organizations facing off dramatic consequences if new strategies will not be developed to adapt health-care on detailed sub-groups of patients.[1] In few months an avalanche overwhelmed in an unexpected way our existences even if the warning growl for a possible pandemic occurrence recently arrived in 2003 with severe acute respiratory syndrome (SARS). It represented the first global threat of the 21st century and spontaneously disappearing in June 2003. The novel coronavirus instead was identified in December 2019 as the agent responsible for some cases of pneumonia in Wuhan, Hubei Province, China.[2] On February 2020, the World Health Organization (WHO) named the disease caused by the new coronavirus COVID-19 (Coronavirus Disease 2019).[3] The number of infections has increased dramatically first in China and then in other countries around the world, so much so that in March 2020 the WHO declared a pandemic. The peak of contagion in China was reached between the end of January 2020 and the beginning of February 2020 with more than 80,000 cases.[4] Immediately after China, South Korea, Italy, Iran and Japan and, at a later time, also Spain, France, Germany, the United Kingdom and the United States also presented an increase in the number of infections. Mortality is estimated at 2-3% in critical cases.[5-7] In Italy at the date of April 13, 2020, the overall case-fatality rate was 7-fold higher than in other counties but it is probably due to a highly underestimated number of infections. Recent data from the Italian *Istituto Superiore di Sanità* showed that COVID-19 is more lethal in older subjects: the 96.4% of died patients had more than 60 years. When data were stratified by age groups, individuals aged 70 years or older represent 35.5% of cases while subjects aged ≥80 years were 52.3%.[8]

Patients affected by renal disease are an aged population that showed a particular attitude to contract infection and a higher mortality rate respect to general population. In this brief article, we would point out the focus on the management of issues related to renal patients facing off with coronavirus infection, in particular in a geriatric population particularly exposed to contagion like hemodialysis patients and precautions decided to slow the spread of contamination.

Chronic kidney disease patients and COVID-19

Since most chronic renal patients are elderly as consequence of physiologic decline of renal function and higher susceptibility to renal diseases,[9] the COVID-19 is a relevant problem in chronic renal patients for its increased risk of complications and mortality. Furthermore, the use of some antiviral and immunosuppressive therapies to fight COVID-19 infection is complicated by kidney damage with acute kidney injury. The age and the chronic renal pathology together are probably a risk factor for COVID-19 for the immunosuppressive status. Immunosenescence is known in elderly and it is characterized by an impaired function of both, adaptive and innate immunity.[10,11] Many are the alterations like: thymic involution, a decline of number naïve T-cells[12] and of progenitor B-cells,[13,14] a reduced expression of MHC class II on macrophages.[15] An important immunosuppressive status was also identified in chronic renal disease patients: i) decreased granulocyte and monocyte/macrophage phagocytic function;[16] ii) defective antigen presenting capacity of antigen presenting cells;[17] iii) depletion of the antigen presenting dendritic cells;[18] iv) reduced numbers and antibody producing capacity of B lymphocyte;[19] v) depletion of naïve and central memory $CD4^+$ and $CD8^+$ T lymphocyte;[20] vi) impaired cell-mediated immunity.[21,22] For all these reasons, old patients with chronic renal disease have to strictly respect indications from Ministry of Health and from Nephrological Scientific Societies for the prevention of COVID-19. Two host receptors have been proposed for COVID-19 attack to pneumocyte: CD26, also known as dipeptidyl-peptidase IV (DPP4) and ACE-2 (angiotensin-converting enzyme 2).[23,24] For this reason, drug targeting these two receptors: DPP-4 inhibitors and angiotensin-receptor blockers (ARBs) were involved in recent discussions. Most patients affected by chronic renal disease are treated with ACE inhibitors (ACE-I) and angiotensin-receptor blockers (ARBs). Several studies have shown that ARBs and

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ACE-I increase ACE2 expression in the kidney and the heart.[25-27] It is probably but not demonstrated that these classes of antihypertensive drugs can increase ACE2, that is the receptor for COVID-19, also in alveolar cells. It had been speculated that the use of these drugs could predispose patients to increased infection and more severe illness but really some studies suggest that ACE2 is protective in lung injury during coronavirus infection.[26,28] The nephrology community interrogated whether or not discontinuing ARBs and ACE-I in COVID-19 patients as long as the official statements by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) has recommend that treatment should be as conservative as possible in patients at risk for COVID-19 or in those already diagnosed with COVID-19.[29,30] Additionally, ARBs also associated with decreased mortality in patients with pneumonia.[31] In this context, there is another very important, recent observation that ACE2 receptor abundance decreases in the elderly in all tissues. Prospective studies will be required to evaluate whether ARBs may have a therapeutic potential also in COVID-19 patients.[32]

Dialysis patients and COVID-19

Dialysis patients are an aged population burdened with considerable comorbidities and with a high prevalence of frailty detected with geriatric tools of 3 times respect to individuals with normal renal function. They are often affected by heart failure, coronary artery disease, valvopathy, hypertension, diabetes Mellitus, respiratory problems (*i.e.* chronic obstructive pulmonary disease) which exposes them to a high risk of mortality if they contract acute lung disease.[33-36] The dialysis patient infected with COVID-19 is of complex management by the healthcare provider. Fever is often absent due to uremic immunodepression and each patient is at high risk for other patients and health care staff. Transmissibility is made possible by the fact that they are dialyzed in a single environment, with difficulty in sanitizing between one shift and another. In addition, the pervasive prevalence of cognitive dysfunction[37] in uremic population make difficult social distancing provisions. According to a report from the Hemodialysis Centre of the University Hospital of Wuhan,[38] in the period from January 14, 2020, date of the first confirmed case, to February 17, date of extinction of the epidemic in the centre, have occurred: 37 cases out of 230 patients on hemodialysis (16%); 4 cases out of 33 operators (12%) diagnosed with COVID-19. The presumed causes of death of seven patients were not directly related to pneumonia, but due to cardiovascular and cerebrovascular diseases. The two clear measures effective in limiting the internal epidemic until its extinction were: i) increase of prevention and protection measures for patients and staff of the centre; ii) universal screening of patients and staff at the centre for the rapid isolation and redistribution of patients.[39]

On February 27, 2020, the Italian Society of Nephrology, illustrated a protocol for the management of dialysis patients according to the cases,[40] although all patients must thoroughly wash their hands and arm of the artero-venous fistula and disinfect the attachment points before the attack: i) in absence of disease manifestations, they must wear the surgical mask from when they arrive to when they leave; ii) patient arriving on dialysis with fever or infectious airway manifestations, must be evaluated by the specialist infectivologist to establish swabbing indications. Pending the outcome of the nose-pharyngeal swab, the patient should be hospitalized and dialyzed in a room suitable for contumacy with safety devices for health personnel (FFP2 mask, hair cap, water-repellent gown with long sleeves, eye protection, gloves). If the result of the swab is positive, the use of headgear, disposable gown in waterproof TNT, goggles, visor, FFP3 mask, over-shoes, gloves is available for healthcare personnel; iii) In case of respiratory failure and fever, the patient will be brought to the attention of resuscitators; iv) patients on peritoneal dialysis should be managed at home as far as possible.

Transplanted renal patients and COVID-19

The age of kidney transplant patients has increased over the past 20 to 25 years.[41] The number of transplants performed annually among patients aged ≥65 years has more than tripled between 1998 and 2016.[42] These patients are at major risk of COVID-19 infection and complications because of the intake of immuno-suppressed drugs that make the immune system ineffective even more. For this reason, it is advisable to reduce hospital access to a minimum agreeing with the referral center, if possible, online visits.

Acute renal injury and COVID-19

Kidney was not identified as a direct target of coronavirus infection but some findings reported possible subsequent effects also on renal parenchyma with acute kidney injury evolution. Acute kidney injury caused by coronavirus infection is not rare. In literature, in previous reports of SARS and Middle East respiratory syndrome coronavirus infections, acute kidney injury (AKI) developed in 5% to 15% cases and carried a high (60%-90%) mortality rate. Recently reports suggested a lower incidence (3%-9%) of AKI in those with COVID-19 infection.[43] Lately, Guan *et al.* described that the incidence of AKI was 0.5% in 1099 patients with novel coronavirus pneumonia, and in 173 critically ill patients, AKI arose in 5 patients (2.9%).[44] Cheng *et al.* displayed an incidence of AKI in 710 consecutive COVID-19 patients in a single-centre of 3.2%. The exact incidence of AKI remains to be confirmed with larger sample size in the future.[45] The acute kidney injury due to Coronavirus infection is mainly manifested as acute tubular necrosis, but the precise responsible mechanism is still not known. It may be due to a cytopathic direct effect of virus, or indirectly to sepsis and massive activation of the immune system with extreme release of cytokines, the so called *cytokine storm syndrome*, hypoxemia, rhabdomyolysis and renal hypoperfusion.[22,43]

Dipeptidyl peptidase and angiotensin converting enzyme represents bindings sites for SARS-CoV-2 and are also located on renal cells.[43] Urinary abnormalities (albuminuria and proteinuria) are found with a relative high incidence up to percentages of 34-63%. On renal imaging with CT it was showed a reduced density characteristic of phlogistic evolutions.[46]

Extracorporeal therapies such as hemoperfusion or hemofiltration could be used to support different organs in a multiple organ dysfunction condition. Heart, lungs, kidneys, and liver can be partially replaced or at least sustained. The concept of ECOS (extracorporeal organ support) includes different types of circuits, different types of devices and filters which allow the extraction and the purification of blood. It was demonstrated that blood purification removes cytokines and improves hemodynamic and oxygenation. For this reason it could be used in patients with AKI and inflammatory storm.[47] In patients in Intensive Care Units (ICUs) with complicated COVID-19 syndromes a significant improvement has been achieved with the use of hemoperfusion with cartridges containing highly biocompatible sorbents and microporous resins.[48] Adsorption can be applied both alone and in combination with other blood purification techniques.[49] These therapies improve the extreme release of cytokines and have a benefit in terms of organ function and hemodynamic support. Cartridges are divided in selective (*e.g.* polymyxin B hemoperfusion PMX HP) and

non-selective types (Cytosorb® and HA330-HA resin Jafron HA). The HA330-HA adsorbent inside the cartridges adsorbs excessive inflammatory factors and oxidative metabolites in the blood. It down-regulates the intensity of inflammatory response (in particular IL-6 amount) and restore the body's immunity. Moreover, it improves hemodynamic and respiratory parameters, reduce intensive care unit length of stay and ICU mortality. Another device is the Cytosorb® that is an equally non selective extracorporeal cytokine absorber. All these cartridges could be used alone or associated with a conventional continuous veno-venous hemofiltration/hemodiafiltration circuit.[50]

Renal implications of pharmacotherapy and COVID-19

Drugs more used to fight COVID-19 infection were remdesivir, chloroquine /hydroxychloroquine, lopinavir/ritonavir, darunavir/ritonavir, darunavir/cobicistat, tocilizumab. Most drugs demonstrated a good renal tolerability while others need dose adjustments.

Remdesivir

Remdesivir is a nucleotide analogue that seems to have activity against COVID-19, as well as against SARS and MERS. It is incorporated in the nascent viral RNA chain, resulting in its premature termination. The impact remains unknown even if it proves to be active in reducing viral load and lung function. Two trials are currently underway in China on the use of remdesivir in COVID-19. No renal function adjustment is required.[7,51-54]

Chloroquine/hydroxychloroquine

Chloroquine/hydroxychloroquine belong to the quinolone family both seem to inhibit the viral activity of the coronavirus *in vitro*, with higher potency for hydroxychloroquine. They seem to be able to exert their effect by increasing the endosomal pH necessary for virus-host cell fusion. Chloroquine appears to interfere with the glycosylation of SARS cell receptors. The use of these drugs in COVID-19 is associated with improved patient outcome. The administration of 500 mg chloroquine BID for 10 days, or hydroxychloroquine 200 mg BID for 10 days is recommended. Hydroxychloroquine needs adjustment for renal function: 200 mg x 2/day if eGFR>30 mL/min; 200 mg/day if 15<eGFR<30 mL/min; 200 mg every other day if <15 mL/min (or in 3-weekly or bi-weekly dialysis). Chloroquine is partially excreted renal and therefore a reduction of the dosage in renal failure should be made but there are no precise determinations. It is contraindicated if eGFR <10 mL/min.[55-62]

Lopinavir/ritonavir

Lopinavir/ritonavir is known second-generation antiretroviral that inhibits HIV protease, is effective in vitro against SARS and in animal studies against MERS. The use has been described in several cases, reducing the coronavirus-19 charge rapidly in association with ribavirin. No adjustment for renal function is necessary.[63-65]

Darunavir/ritonavir and darunavir/cobicistat

Daruravir is a third generation antiretroviral that inhibits HIV viral protease. It demonstrates potency in viral suppression and increased tolerance in lopinavir/ritonavir, although the evidence in COVID-19 is limited. However, if lopinavir/ritonavir is not available, its use is recommended at darunavir/ritonavir 800 +100 mg/day or darunavir/cobicistat 800+150 mg/day. No adjustment is required for renal function.[66]

Tocilizumab

Tocilizumab has been included for a few days in the more severe treatments of COVID-19 as an IL-6 inhibitor. It is indicated in the BCRSS (Brescia-COVID Respiratory Severity Scale (BCRSS)/Algorithm) score >=3, in the presence of high levels of IL-6 (>40 pg%) or alternatively high levels of D-dimer and/or PCR and/or ferritin and/or fibrinogen, progressively increasing. It is contraindicated in age <18 years; if ALT/AST have values 5 times higher than normal levels; neutrophils <500 cell/mmc; PLT<50.000 cell/mmc; sepsis from other non-COVID-19 pathogens; complicated diverticulitis or intestinal perforation; ongoing skin infection; anti-rejection immunosuppressive therapy. A scheme with a maximum of 3 infusions is proposed at a dosage of 8 mg/kg of body weight (maximum dosage for infusion 800 mg), with second infusion at a distance of 8-12 h from the first and third infusion at a distance of 16-24 h (if the clinical response is partial or incomplete). Tocilizumab should be combined with steroid and/or antiviral treatment. Dose adjustment for renal function is not necessary.[67]

Conclusions

COVID-19 is the new emergency in public health. It represents a big risk for elderly patients and in particular for those with long-lasting renal disease. Since little is known about optimal therapy and we are a long way from a possible vaccine, the most effective strategy for controlling this infection is still the prevention. It is necessary that all the Nephrology Units and Dialysis in strict collaboration with geriatricians have a precise protocol of action for the management of patients. It should be preferable when possible an online visit and for patients that have to go to hospital, it is necessary ensuring pre-triage and triage with temperature measurement. When there is a suspected COVID-19 case should be immediately isolated and subjected to a nasopharyngeal research for SARS-CoV-2. In this way, it will be possible limiting the diffusion of the virus to other patients and to the medical staff that can be a dangerous carrier.

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