# Acute Kidney Injury in COVID19

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# Incidence

**Patients with suspected or confirmed COVID-19 may present with acute kidney injury (AKI) as part of their overall illness.**

**In a meta-analysis of approximately13,000 mostly hospitalized patients, the incidence of AKI was 17 %, although the range of AKI incidence in the included studies was broad (range 0.5 to 80 percent).**

**Approximately 5 percent of patients required kidney replacement therapy(KRT)**

# Recommendations:

1. Timing of AKI with symptom onset, hospitalization, confirmation of infection, disease severity and level of care should be characterized for appropriate clinical management (not graded).

2. We recommend use of the Kidney Disease: Improving Global Outcomes (KDIGO) consensus definition for AKI, including serum creatinine (SCr) level and urine output, in clinical practice (evidence level: 1A).

3. We suggest using kidney- specific tests along with measures of kidney function to characterize clinical presentations, course and outcomes of AKI (evidence level: 2B).

diagnosis

**TABLE**

# Defining Acute Kidney Injury

*Criteria: Patients must have one of the following*

- Increase in SCr ≥ 0.3 mg/dL within 48 h
- Increase in SCr ≥ 1.5 × baseline that is known or presumed to have occurred within the past 7 d
- Urine volume < 0.5 mL/kg/h for 6 h

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*Severity*

**Stage 1** 1.5-1.9 × baseline SCr or ≥ 0.3-mg/dL increase in baseline SCr

**Stage 2** 2.0-2.9 × baseline SCr

**Stage 3** 3.0 × baseline SCr or increase in SCr to ≥ 4.0 or renal replacement therapy (eg, dialysis)

Abbreviation: SCr, serum creatinine.

Source: KDIGO. *Kidney Int.* 2012.[1]

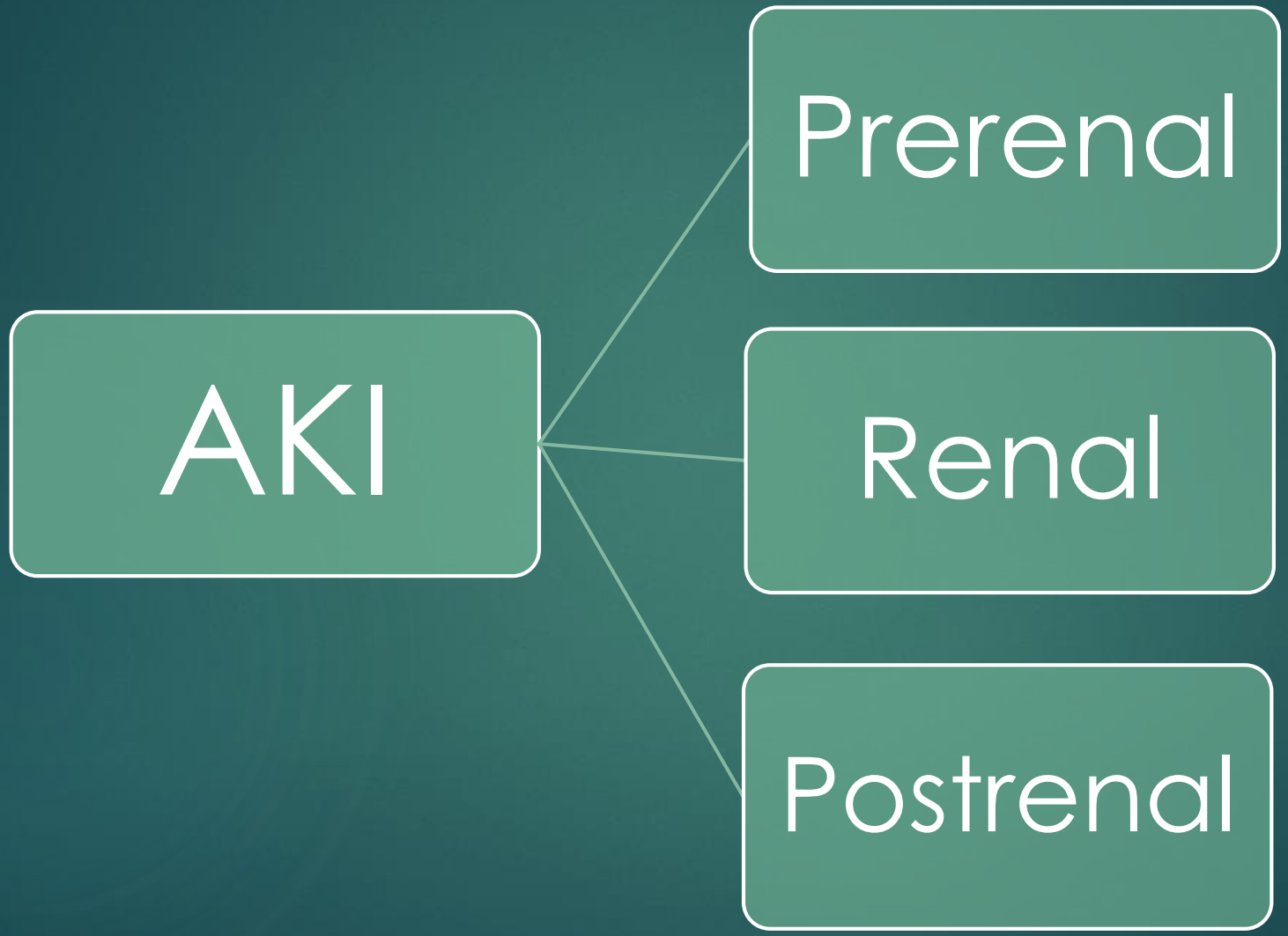
# Estimation of GFR

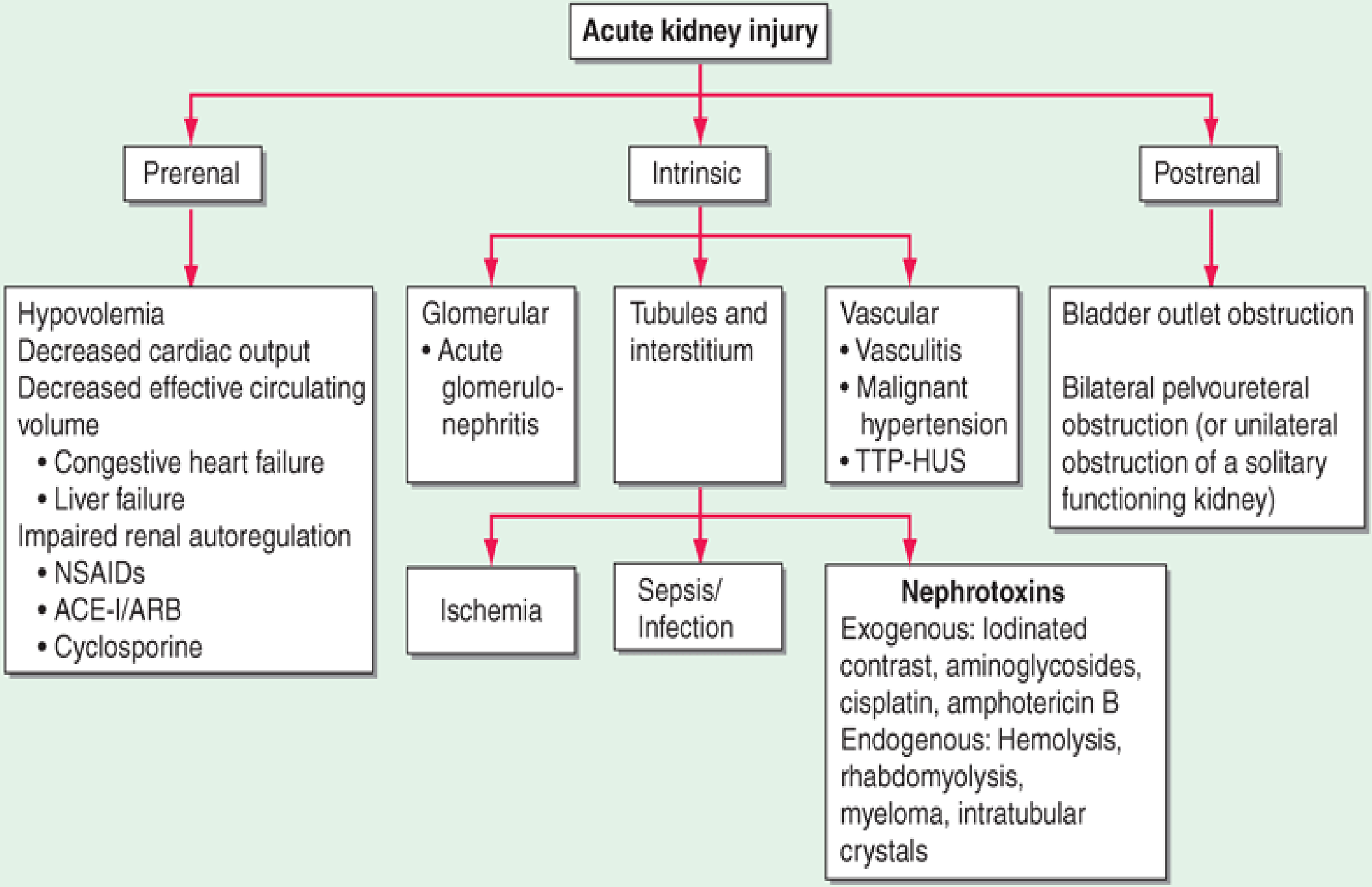
- Cockcroft- Gault Formula

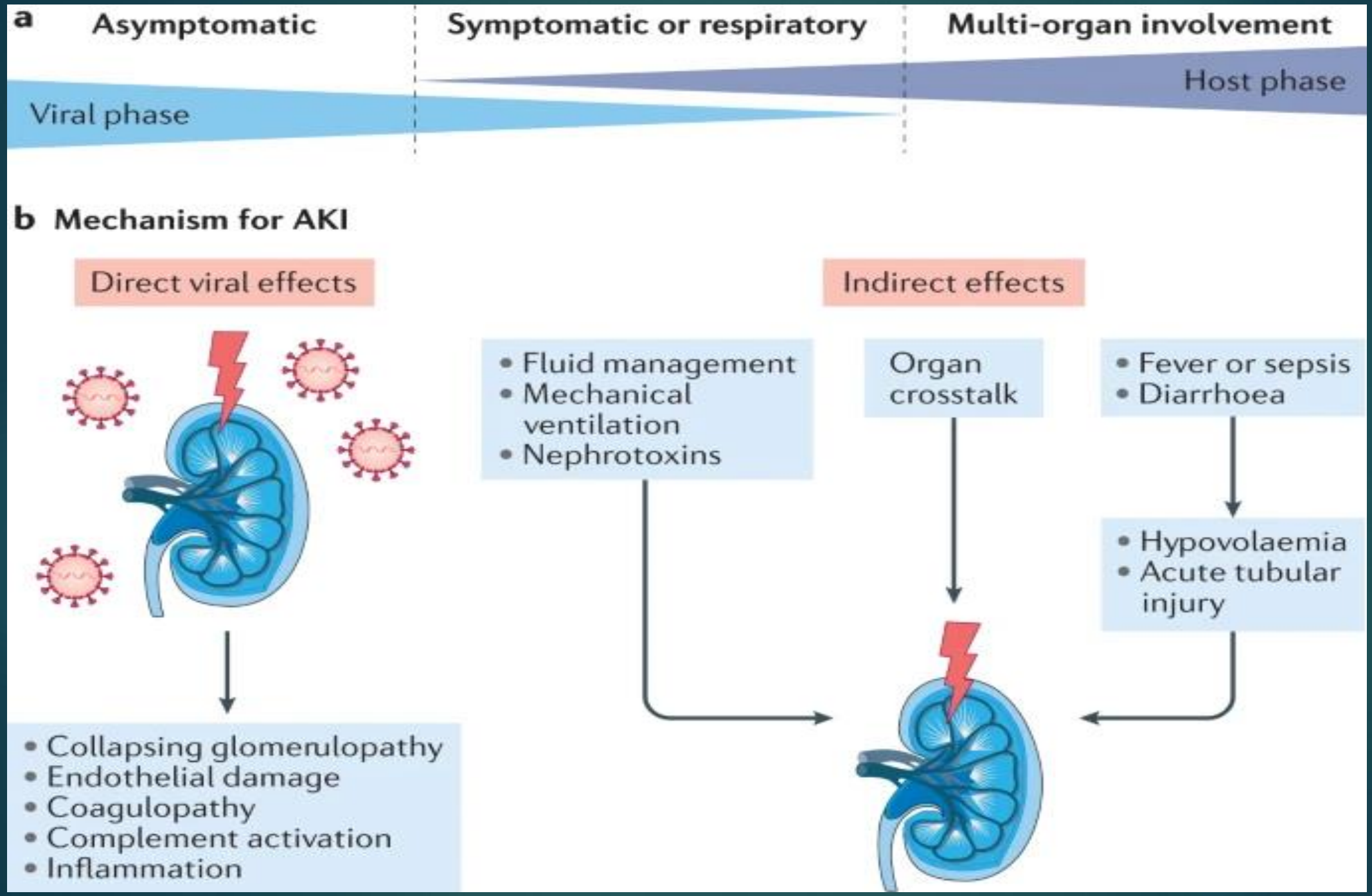
$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{Weight in Kg}}{72 \times \text{Serum Creat (mg/dl)}} \times (0.85 \text{ if female})$$

- MDRD Study Equation

$$\text{GFR (mil/min/1.73 m}^2) = 186 \times (S_{Cr})^{-1.154} \times (\text{age})^{-.203} \times (0.724 \text{ if female}) \times (1.210 \text{ if African American})$$

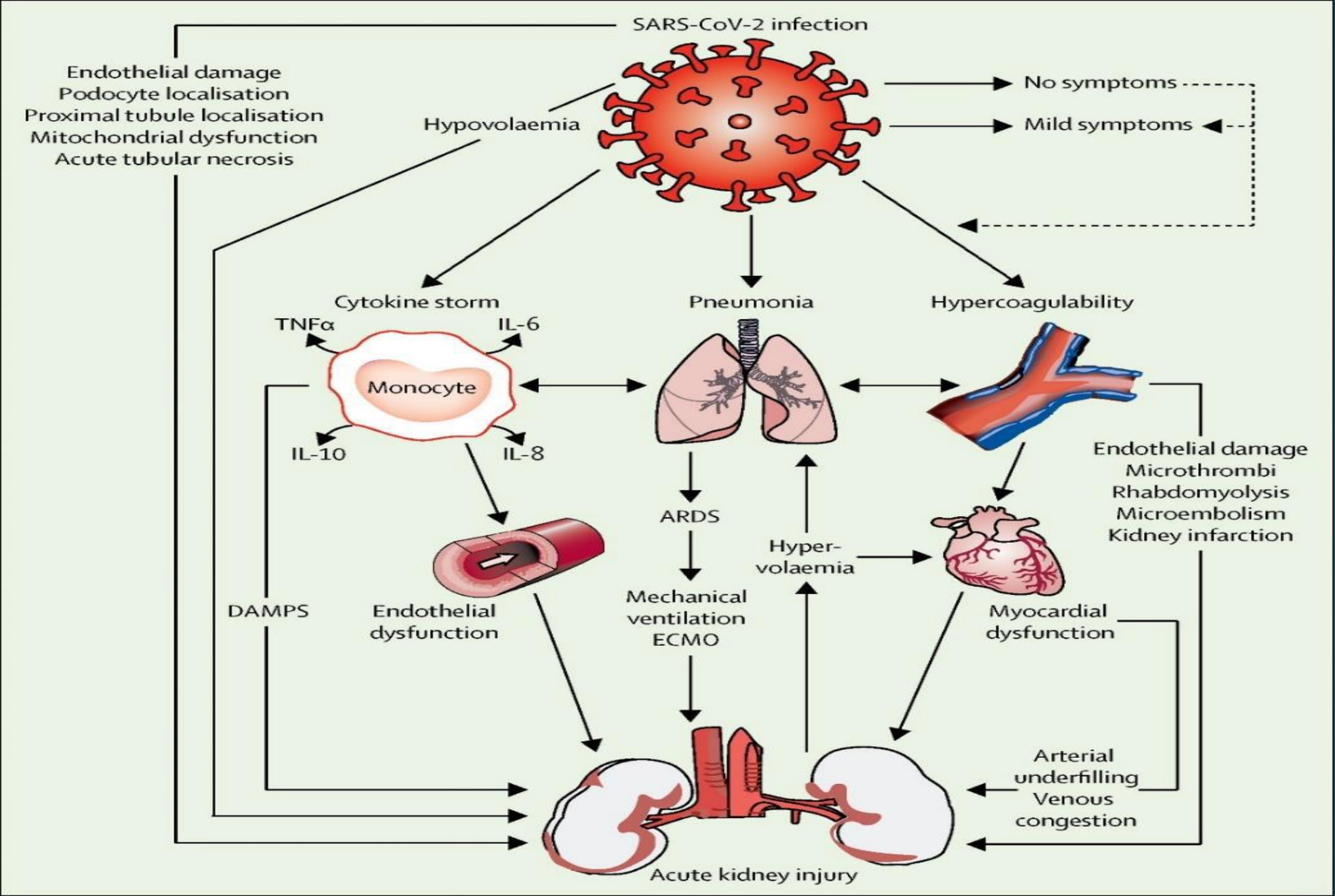

AKI
Prerenal
Renal
Postrenal


Acute kidney injury
Prerenal
Intrinsic
Postrenal
Hypovolemia
Decreased cardiac output
Decreased effective circulating volume
• Congestive heart failure
• Liver failure
Impaired renal autoregulation
• NSAIDs
• ACE-I/ARB
• Cyclosporine
Glomerular
• Acute glomerulo-nephritis
Tubules and interstitium
Vascular
• Vasculitis
• Malignant hypertension
• TTP-HUS
Bladder outlet obstruction
Bilateral pelvoureteral obstruction (or unilateral obstruction of a solitary functioning kidney)
Ischemia
Sepsis/ Infection
Nephrotoxins
Exogenous: Iodinated contrast, aminoglycosides, cisplatin, amphotericin B
Endogenous: Hemolysis, rhabdomyolysis, myeloma, intratubular crystals

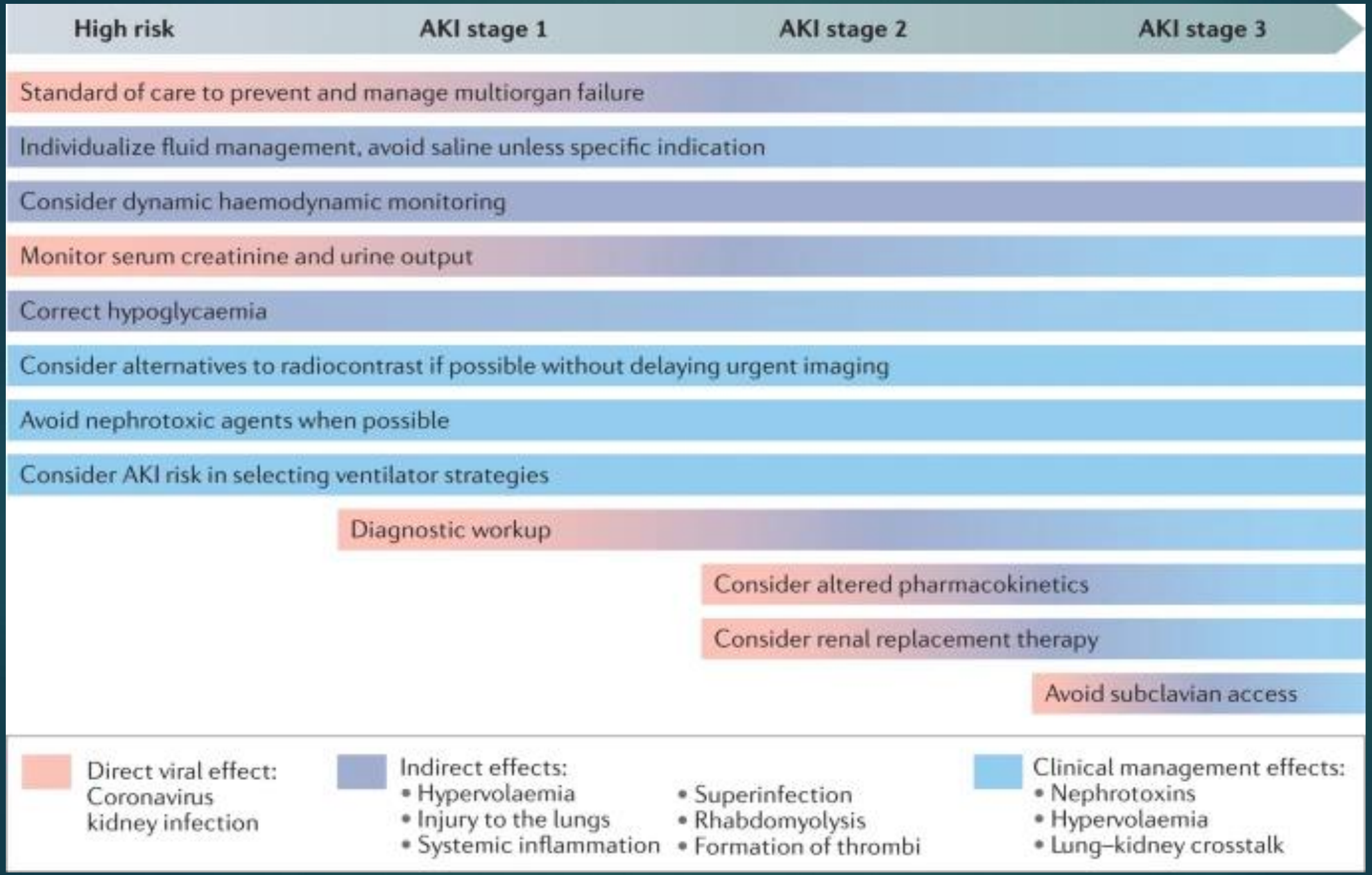


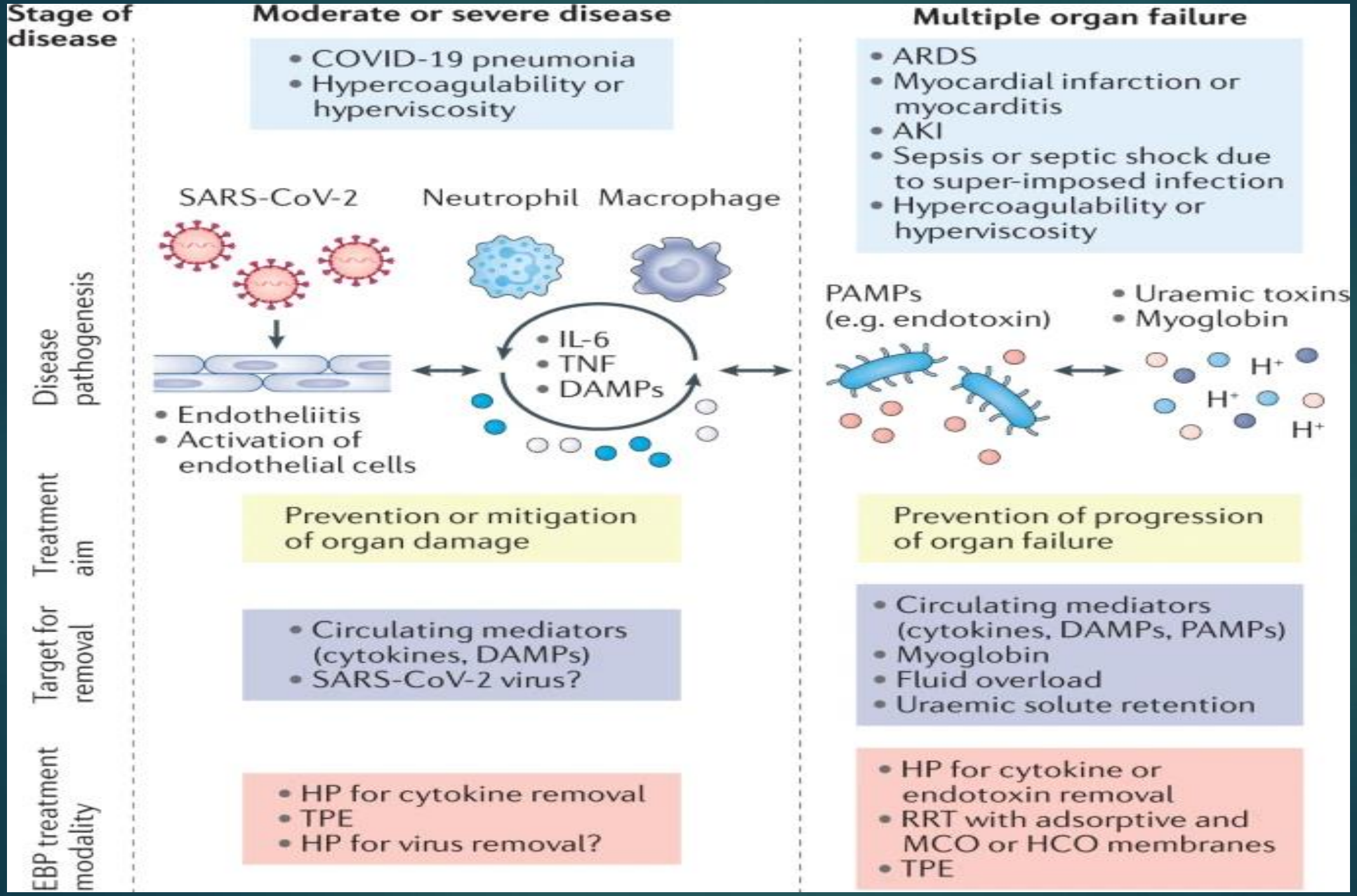

# Pathogenesis of COVID-19 AKI

# Pathogenesis of COVID-19 AKI



# Stage-based management of COVID-19 AKI






**Potential extracorporeal blood purification treatment options based on underlying COVID-19 pathophysiology**

# Ischemic ATN

- Prerenal AKI and ischemic ATN are part of a spectrum of manifestations of renal hypoperfusion:

Prerenal AKI ⟶ Ischemic ATN

- *ATN differs from prerenal AKI in that the renal tubular epithelial cells are injured in the latter.*

- *Recovery typically takes 1–2 weeks after normalization of renal perfusion, as it requires repair and regeneration of renal cells.*

# Nephrotoxic ATN

- Drugs: Antibiotics-NSAIDs-Antiviral agents…
- Rhubdomyolysis
- Contrast agents

# Potential Risk Factors for COVID-19 A

## Demographic risk factors

- Older age
- Diabetes mellitus
- Hypertension
- Cardiovascular disease or congestive heart failure
- High body mass index
- Chronic kidney disease
- Genetic risk factors (e.g. *APOL1* genotype; *ACE2* polymorphisms)
- Immunosuppressed state
- Smoking history

## Risk factors for AKI at admission

- Severity of COVID-19
- Degree of viraemia
- Respiratory status
- Non-respiratory organ involvement, e.g. diarrhoea
- Leukocytosis
- Lymphopaenia
- Elevated markers of inflammation, e.g. ferritin, C-reactive protein, D-dimers
- Hypovolaemia/Dehydration
- Rhabdomyolysis
- Medication exposure, e.g. angiotensin-converting-enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARBs), statins, nonsteroidal anti-inflammatory drugs (NSAIDs)

## Risk factors for AKI during hospitalization

- Nephrotoxins (medications, contrast exposure)
- Vasopressors
- Ventilation, high positive end-expiratory pressure
- Fluid dynamics (fluid overload or hypovolaemia)

## Factors that may contribute to CoVID-19-associated acute kidney injury

**Acute tubular injury**

- Regional inflammation
- Direct viral infection
- Renal compartment syndrome
- Tissue hypoxia hypoperfusion leading to hypoxaemia, hypotension, hypovolaemia and heart failure
- Nephrotoxic- induced injury (potentially associated with the use of antibiotics (vancomycin, aminoglycosides, colistin) or antivirals (remdesivir, ritonavir))
- Rhabdomyolysis

**Vascular injury**

- Endotheliitis
- Microthrombi
- Thrombotic microangiopathy

**glomerular injury**

- Collapsing glomerulopathy (potentially caused by interferon- associated podocyte injury)
- Glomerulonephritis

**Interstitial injury**

- Acute interstitial nephritis; infiltration by immune cells
- Interstitial oedema

## Key points

- Over a quarter of patients hospitalized with coronavirus disease 2019 (COVID-19) have been reported to develop acute kidney injury (AKI).

- Low molecular weight proteinuria, Fanconi syndrome and histological findings point towards tubular injury.

- Analyses of kidney biopsy samples from patients with COVID-19 and AKI have inconsistently reported **viral infection of kidney cells**.

- Collapsing glomerulopathy has been identified in patients with high- risk APOL1 genotypes, mostly in those without severe respiratory symptoms.

- Regional inflammation, endothelial injury and renal microthrombi have been reported but their implication in the pathogenesis of COVID- associated AKI remains uncertain.

- Anti- inflammatory drugs (for example, steroids and IL-6 receptor blockers) seem to limit the development of severe AKI in patients with COVID-19.

# راهنمای تشخیص و درمان کووید- ۱۹ در سطوح ارائه خدمات سرپایی و بستری- نسخه هشتم

عوارض کلیوی در بیماری کووید- ۱۹

۶۰ ٪ گزارش - ۵٪ و میزان مرگ ومیر ۹۰ - حدود ۱۵ MERSو SARSدر عفونتهای ( )AKIشیوع نارسایی حاد کلیه ۳٪ بوده است ولی در مطالعات بعدی - کم و حدود ۸ COVID-در عفونت ۱۹ AKIشده است در مطالعات اولیه خطر تا ۳۷ درصد گزارش شده است. یک مطالعه کوهورت آینده نگر بزرگ در حدود ۷۰۰ بیمار در چین انجام AKIشیوع در موقع بستری پروتئینوری داشتند و در حدود ۲۶ درصد COVID-شد که ۴۴ درصد بیماران مبتلا به عفونت ۱۹ به eGFRآنها هم هماچوری مشاهده گردید. در حدود ۱۳ تا ۱۴ درصد از بیماران افزایش اوره و کراتینین و کاهش در ( 1.73 )AKIسطح بدن دیده شد. در این مطالعه، نارسایی حاد کلیه mکمتر از ۶۰ میلی لیتر در دقیقه به ازای ۲ موجب افزایش خطر مرگ و میر در بیمارستان نیز بود. از طرف دیگر در سایر AKI %5مواردمشاهده گردید در ضمن بالاتر ) ۲۵ ٪( بوده و موجب بدتر شدن پیش آگهی و افزایش خطر مرگ AKIشیوع ARDSمطالعات در مبتلایان به از ایتالیا آمده است COVID-ومیر در این بیماران گردیده است. در گزارشی که در بیش از دو هزار بیمار مبتلا به ۱۹ حدود ۲۸ ٪ می باشد. معهذا در گزارشات اخیر شیوع درگیری کلیوی ARDSشیوع نارسایی حاد کلیه در افراد مبتلا به آلبومینوری شدید داشته و COVID-بالاتر بوده است در یک مطالعه در روز اول بستری ۳۴ ٪ از بیماران با عفونت ۱۹ در ۲۷ ٪ کل افراد و در دو سوم %63 . BUNآنها در مابقی روزهای بستری در بیمارستان دچار پروتئینوری شده اند با شدت بیماری ارتباط دارد به طوری که در بیمارانی که تحت AKIبیمارانی که فوت شدند بالا بوده است. شیوع ٪ مکانیکال ونتیلاتور قرار می گیرند تا ۹۰ ٪ ولی در بیمارانی که وضعیت بحرانی ندارند شیوع کمتری داشته و تا ۲۲ شامل سن بالا، دیابت، هیپرتانسیون، بیماری قلبی و عروقی، مکانیکال ونتیلاسیون AKIذکر شده است. پره دیکتورهای و استفاده از داروهای وازوپرسور می باشد.

# راهنمای تشخیص و درمان کووید- ۱۹ در سطوح ارائه خدمات سرپایی و بستری- نسخه هشتم

## مکانیسمهای AKIدرCOVID-19

شواهد هیستوپاتولوژی کلیه در اتوپسی و بیوپسی شاملATN،کلاپسینگ گلومرولوپاتی وRPGNبوده است.
با توجه به شیوع درگیری کلیوی در این عفونت و تاثیر آن در پیش آگهی و عاقبت بیماری، توصیه می شود در بیمارانی که علامت دارند یا به هر علتی در بیمارستان بستری می شوند باید آزمایشات مربوط به عملکرد کلیه )اندازه گیری اوره و کراتینین سرم( و آزمایش کامل ادرار انجام شود و و برای احتمال بروز رابدومیولیز باید سطوح کلسیم، فسفر، اسید اوریک و پتاسیم سرم اندازه گیری شود که در رابدومیولیز هیپوکلسمی، هیپرفسفاتمی، هیپراوریسمی و هیپرکالمی دارند. ارزیابی نارسایی حاد کلیه در افراد بستری:
در بیماران باCOVID-19 مشکوک یا اثبات شده که مبتلا به AKIشده اند باید متوجه عوامل پره رنال بود و وضعیت هیدراسیون بیمار را ارزیابی کرده و مانع کمبود حجم شده و از طرف دیگر هم نباید آورهیدراسیون نیز صورت گیردزیرا باعث بدتر شدن وضعیت تنفسی به خصوص در بیماران باARDS می گردد. ارزیابی اتیولوژی AKIمانند سایربیماران بحرانی در موارد غیر کرونایی می باشد. بعضی تستها نظیر آزمایش کامل ادرار و اندازه گیری اوره و کراتینین به سهولت انجام می شود ولی انجام سونوگرافی کلیه ها و مجاری ادراری که در ارزیابی مبتلایان بهAKI غیر کرونایی باید انجام شود در بیماران مبتلا به کرونا با دشواری مواجه است زیرا تماس پرسنل با بیماران کرونایی باید کمتر صورت گیرد.

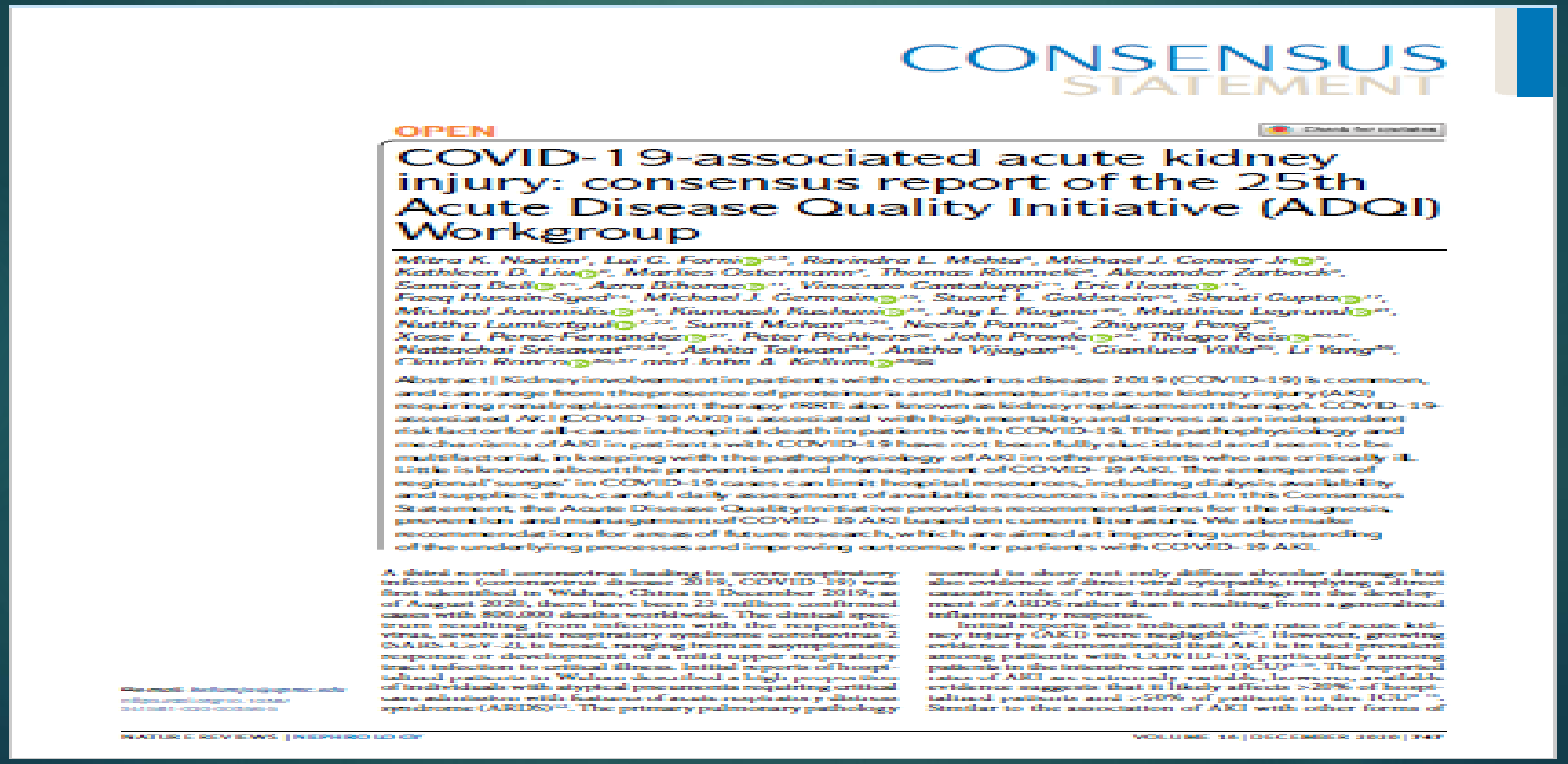
# راهنمای تشخیص و درمان کووید- ۱۹ در سطوح ارائه خدمات سرپایی و بستری- نسخه هشتم

**درمانAKI بیماران بستری:**

درمانAKI این بیماران فرقی با سایر بیماران غیر کرونایی ندارد ولی باید توجه داشت که نباید باعث آورهیدراسیون شد. اندیکاسیونهای همودیالیز در بیماران مبتلا بهCOVID-19 فرقی با سایر بیماران غیر کرونایی ندارد نظیر آورلود، هیپرکالمی شدید مقاوم به درمان، اسیدوز شدید مقاوم به درمان، پریکاردیت و غیره.

باید توجه داشت که این بیماران باید از سایر بیماران تحت همودیالیز جداسازی شده و در یک اطاق مجزا در صورت امکان و فقط توسط یک پرسنل همودیالیز شوند و پرسنل مربوطه نیز تمام موارد حفاظت شخصی را باید مراعات نمایدو در بیماران بد حال هم بهتر است دیالیز در بخش ICU انجام شود. اگر همودینامیک بیمار تثبیت شده است از دستگاه همودیالیز معمولی استفاده می شود ولی اگر وضعیت همودینامیک بیمار مختل باشد ازدستگاه CRRTبهتراست استفاده کرد و در مراکزی که فاقد این دستگاه می باشند می توان از روش prolonged intermittent renal replacement therapy یا sustained low-efficiency dialysis (SLED) که با خیلی از دستگاههای جدیدهمودیالیز قابل انجام است استفاده کرد.

# Potential management strategies for COVID-19 AKI



CONSENSUS STATEMENT

OPEN

## COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup

*Mitra K. Nadim, Luiz G. Forni, Ravindra L. Mehta, Michael J. Connor Jr, Kathleen D. Liu, Marlies Ostermann, Thomas Rimmelé, Alexander Zarbock, Samira Bell, Azra Bihorac, Vincenzo Cantaluppi, Eric Hoste, Faeq Husain-Syed, Michael J. Germain, Stuart L. Goldstein, Shruti Gupta, Michael Joannidis, Kianoush Kashani, Jay L. Koyner, Matthieu Legrand, Nuttha Lumlertgul, Sumit Mohan, Neesh Pannu, Zhiyong Peng, Xose L. Perez-Fernandez, Peter Pickkers, John Prowle, Thiago Reis, Nattachai Srisawat, Ashita Tolwani, Anitha Vijayan, Gianluca Villa, Li Yang, Claudio Ronco and John A. Kellum*

Abstract | Kidney involvement in patients with coronavirus disease 2019 (COVID-19) is common, and can range from the presence of proteinuria and haematuria to acute kidney injury (AKI) requiring renal replacement therapy (RRT; also known as kidney replacement therapy). COVID-19-associated AKI (COVID-19 AKI) is associated with high mortality and serves as an independent risk factor for all-cause in-hospital death in patients with COVID-19. The pathophysiology and mechanisms of AKI in patients with COVID-19 have not been fully elucidated and seem to be multifactorial, in keeping with the pathophysiology of AKI in other patients who are critically ill. Little is known about the prevention and management of COVID-19 AKI. The emergence of regional 'surges' in COVID-19 cases can limit hospital resources, including dialysis availability and supplies; thus, careful daily assessment of available resources is needed. In this Consensus Statement, the Acute Disease Quality Initiative provides recommendations for the diagnosis, prevention and management of COVID-19 AKI based on current literature. We also make recommendations for areas of future research, which are aimed at improving understanding of the underlying processes and improving outcomes for patients with COVID-19 AKI.

A third novel coronavirus leading to severe respiratory infection (coronavirus disease 2019, COVID-19) was first identified in Wuhan, China in December 2019, as of August 2020, there have been 23 million confirmed cases with 800,000 deaths worldwide. The clinical spectrum resulting from infection with the responsible virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is broad, ranging from an asymptomatic response or development of a mild upper respiratory tract infection to critical illness. Initial reports of hospitalized patients in Wuhan described a high proportion of individuals with atypical pneumonia requiring critical care admission with features of acute respiratory distress syndrome (ARDS)[1–3]. The primary pulmonary pathology seemed to show not only diffuse alveolar damage but also evidence of direct viral cytopathy, implying a direct causative role of virus-induced damage in the development of ARDS rather than it resulting from a generalized inflammatory response.

Initial reports also indicated that rates of acute kidney injury (AKI) were negligible[4–7]. However, growing evidence has demonstrated that AKI is in fact prevalent among patients with COVID-19, particularly among patients in the intensive care unit (ICU)[8–15]. The reported rates of AKI are extremely variable; however, available evidence suggests that it likely affects >20% of hospitalized patients and >50% of patients in the ICU[8–15]. Similar to the association of AKI with other forms of

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# Potential management strategies for COVID-19 AKI

- ***Standard measures***

| Therapy | Rationale | Recommendation |
|---|---|---|
| Standard measures based on AKI risk and stage | Prevention and management depend on the risk and stage of AKI | Strategies based on KDIGO and other relevant guidelines are appropriate for risk- and stage-based prevention and management of COVID-19 AKI |
| Measurement of kidney function | Serum Cr and urine output are the current gold standards for the evaluation of kidney function, although neither is kidney specific or sensitive for detection of early kidney injury | We recommend monitoring kidney function using a minimum serum Cr and urine output with careful consideration of the limitations of both |
| Haemodynamic optimization | Hypovolaemia, hypotension, and vasoplegia may occur in patients with COVID-19. Fluid & vasopressor resuscitation using dynamic assessment of cardiovascular status may reduce the risk of renal injury and respiratory failure | We recommend individualized fluid and haemodynamic management based on dynamic assessment of cardiovascular status |
| Fluid management | The composition of crystalloids for volume expansion is important. Individual trials in non- COVID patients have shown reduced risk of AKI with use of balanced fluids fori nitial volume expansion, especially in sepsis | We recommend using balanced crystalloids as initial management for expansion of IV volume in pts at risk of or with COVID-19 AKI unless an indication for other fluids exists |
| Glucose management | Insulin resistance and a hypercatabolic state are common in COVID-19 and contribute to hyperglycaemia | We suggest monitoring for hyperglycaemia and use of intensive glucose- lowering strategies in high- risk patients |
| Nephrotoxin management | The risks and benefits of nephrotoxic medications & their alternatives need to be closely & frequently assessed. This includes assessment of NSAID use | We recommend limiting nephrotoxic drug exposure where possible and with careful monitoring when nephrotoxins are required |
| Use of contrast media | Sodium bicarbonate and N- acetylcysteine have not been shown to prevent contrast- media- associated AKI | We recommend optimization of intravascular volume status as the only specific intervention to prevent contrast- media- associated AKI |

# Potential management strategies for COVID-19 AKI

- ***Experimental strategies***

| Therapy | Rationale | Recommendation |
|---|---|---|
| Antivirals | Some evidence suggests that direct viral infiltration of tubular cells and podocytes has an impact on tubule function and glomerular filtration | Evidence that antivirals may reduce the risk of COVID-19 AKI is indirect and limited |
| Immunomodulatory agents(e.g.HCQ,corticosteroids,tocilizumab,imatinib,ciclosporin,IVIG) | Immunomodulatory agents have the potential to attenuate cytokine production or block cytokine-receptor activation & inhibit autophagy & lysosomal activity to modulate inflammation in host cells | Existing data on immunomodulation in COVID-19 do not show an impact on the development or progression of AKI |
| Systemic anticoagulation | Thrombi in the renal microcirculation may contribute to the development of AKI | No data are available to show that anticoagulation strategies reduce the risk of AKI or mitigate AKI progression. Systemic anticoagulation may be needed to maintain filter patency during RRT |
| Statins | Statins inhibit the production of pro- inflammatory Cytokines & the activation & proliferation of T cells, potentially leading to Immunomodulation | No data are available to show that statins reduce the risk of AKI or mitigate progression |
| ACE- I and/or ARBs | ACE- I and ARBs increase ACE2 levels and may rescue cellular ACE2 activity | The impact of RAAS inhibitors on the development or prevention of COVID-19 AKI is uncertain |
| NSAIDs | Anti- inflammatory properties | Effect unknown |
| Recombinant ACE2 | Potential to neutralize the SARS- CoV-2 and rescue cellular ACE2 activity | Under investigation |
| Serine inhibitors | Blockage of transmembrane protease serine 2 activity and prevention of viral infiltration | Under investigation |

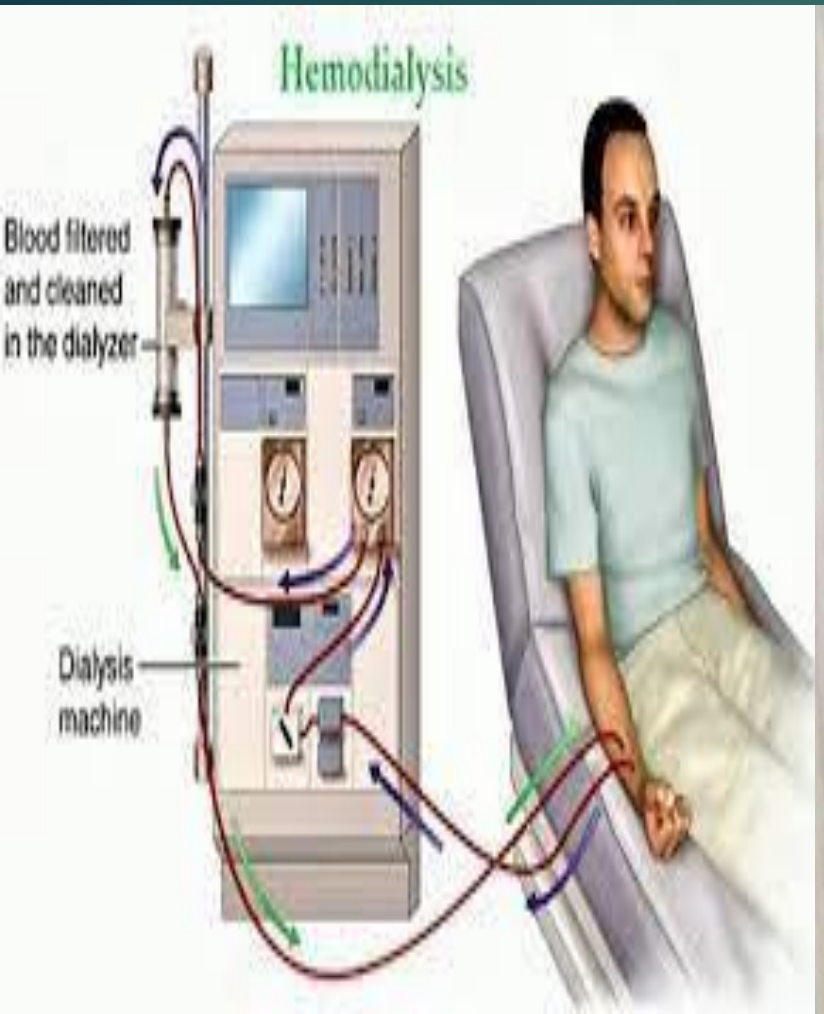
# Renal Replacement Therapy

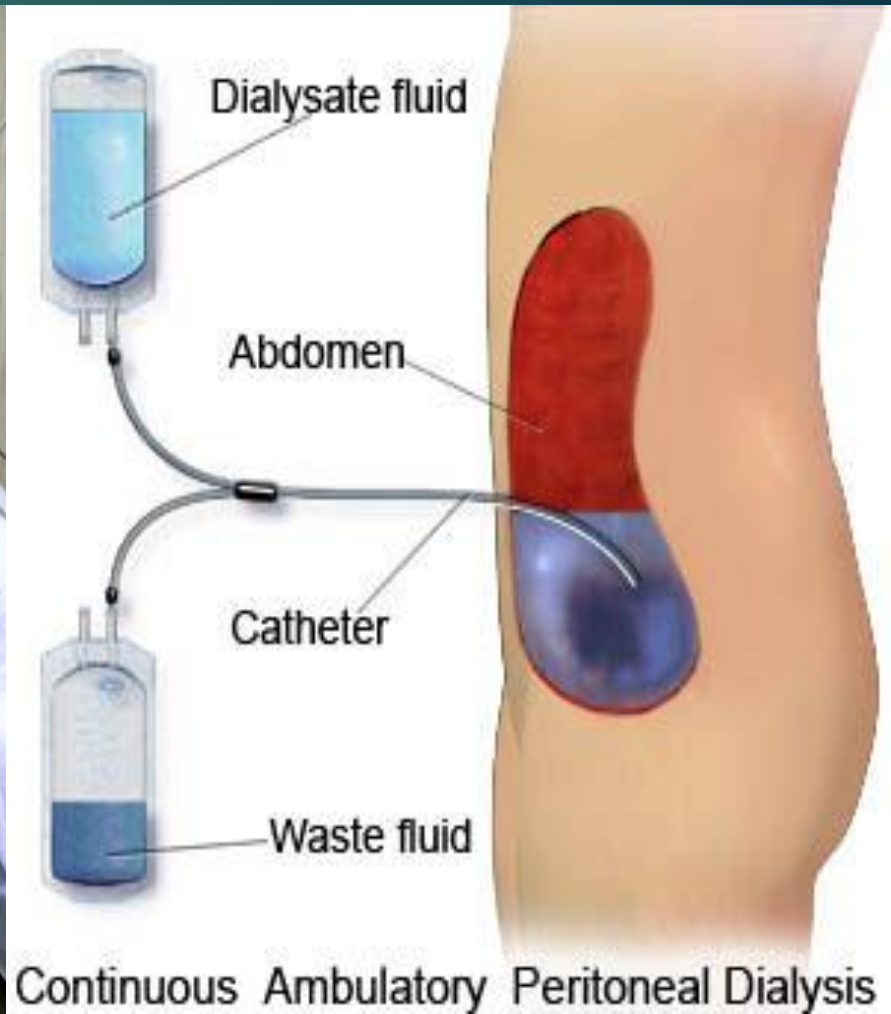
## Hemodialysis

- Intermittent hemodialysis
- Continuous renal replacement Therapy(CRRT)

## Peritoneal Dialysis

# Renal Replacement Therapy



# A E I O U - Acute Indications for Dialysis

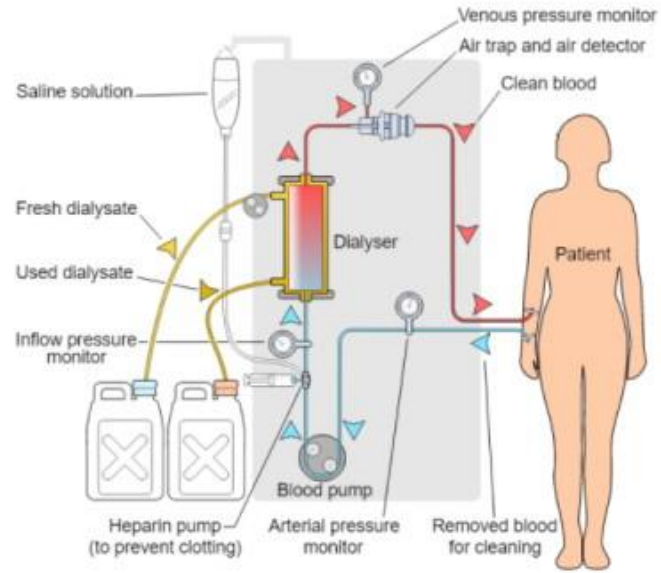
**A** **A**cidosis
(pH < 7.1)

**E** **E**lectrolytes
Refractory Hyperkalemia

**I** Intoxication / **I**ngestions
Toxic Alcohols, Salicylates, Lithium, etc

**O** **O**verload
Congestive Heart Failure

**U** **U**remia
Uremic Pericarditis, Uremic Encephalopathy

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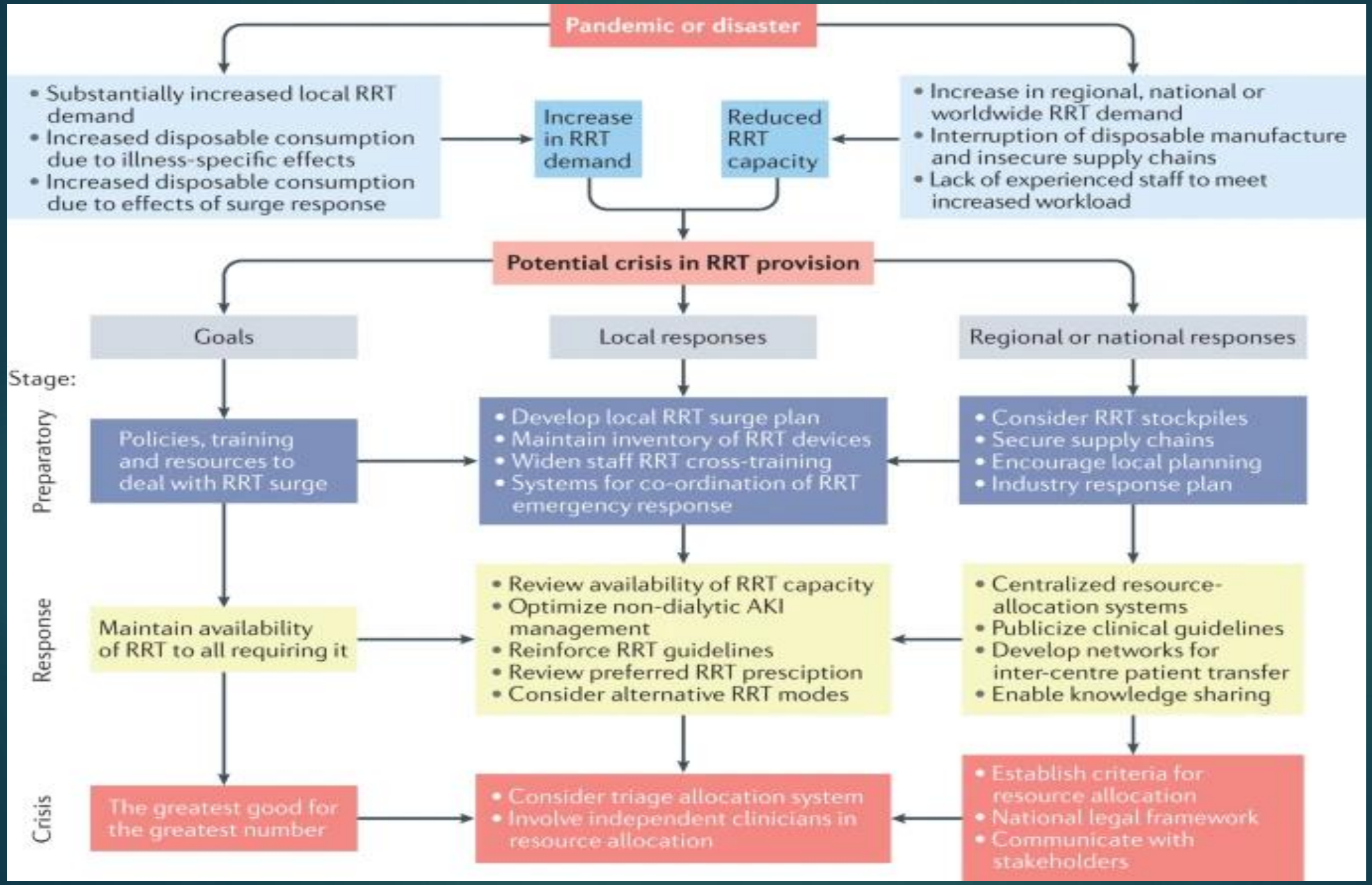


Fig. 3: Step-wise plan to prepare for a surge in RRT demand during a pandemic or disaster.