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the SQUARE Healthcare bulletin

Since 1993

- Acute Kidney Injury
- Pelvic Inflammatory Disease
- COVID-19 and Diabetes
- Monkeypox Outbreak
- Product Profile- Magnide™

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the SQUARE
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Contents

Editorial

Dear Doctor,

We welcome you to this addition of *"the SQUARE"* healthcare bulletin!

At first, let us take the opportunity to offer you all our best wishes from our editorial team!

In this issue we have presented a blend of topics. At first we focused on "Acute Kidney Injury", which is a serious public health issue, with an increasing incidence and significant associated deleterious effects. We have highlighted on "Pelvic Inflammatory Disease", which result in infertility, ectopic pregnancies, as well as chronic pelvic pain. Besides, we have presented a feature on "Covid – 19 and Diabetes". Evidence implies that patients with diabetes are at a higher risk of severe disease or death due to COVID-19 than individuals without diabetes. We have also published an article on "Monkeypox Outbreak", which came again into limelight for its recent multi-country outbreak. You will also find our regular feature, "Test Yourself" & "Product Profile" in this issue.

We hope you will find this healthcare bulletin both interesting and informative!

On behalf of the management of SQUARE we wish you all healthy, prosperous and long lives!

Thank you!

Omar Akramur Rab

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Acute Kidney Injury

The term Acute Kidney Injury (AKI) was used for the first time by William MacNider in 1918 in a situation of acute mercury poisoning but became the preferred term in 2004 when ARF was redefined. The concept of Acute Renal Failure (ARF) has undergone significant re-examination in recent years. Traditionally, emphasis was given to the most severe acute reduction in kidney function, as manifested by severe azotaemia and often by oliguria or anuria. However, recent evidence suggests that even relatively mild injury or impairment of kidney function manifested by small changes in serum creatinine (SCr) and/or urine output (UO) is a predictor of serious clinical outcomes. AKI results in the abrupt loss of kidney function, which encompasses both injury and impairment leading to the retention of waste products, electrolyte disturbances and volume status changes.

The term AKI has recently replaced the term ARF because smaller changes in kidney function without overt failure can result in significant clinical consequences and increased morbidity and mortality.

Defining AKI

Until a decade ago, there was a lack of uniform diagnostic criteria for AKI that led to a number of various definitions being used. Several consensus definitions of AKI have been developed over time to improve the recognition and reporting of AKI. In 2004, the risk, injury, failure, loss, end-stage renal disease (RIFLE) criteria for AKI was established. In 2007, the AKI Network (AKIN) modified RIFLE criteria with the inclusion of an absolute change of serum creatinine (SCr). RIFLE and AKIN were later unified in 2012 by Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The KDIGO criteria define and stage patients (three severity stages) according to changes in SCr levels and urine output.

RIFLE Criteria: In 2004, the Acute Dialysis Quality Initiative published the risk, injury, failure, loss, end-stage (RIFLE) criteria. The RIFLE classification is based on changes in two markers: SCr and urinary output. The classification includes three graded stages of AKI - risk, injury and failure-with two outcomes: loss of kidney function greater than 4 weeks and end-stage renal disease greater than 3 months. The RIFLE-defined period for change in SCr or urinary output is 7 days.

AKIN Criteria: In 2007, AKIN updated and modified the RIFLE criteria to define AKI and the staging system. The definition of AKI is an abrupt increase in SCr of 0.3 mg/dL over baseline within 48 hours, a 50% or greater increase in SCr within 7 days or urinary output of less than 0.5 mL/kg/hour for more than 6 hours. Studies had shown significantly increased mortality with small elevations in SCr (0.3–0.5 mg/dL) over a short period (24–48 hours). The AKIN staging system corresponds with the RIFLE categories. The loss and end-stage renal disease categories are removed from staging and consid- ered outcomes.

RIFLE		AKIN		RIFLE/AKIN
Category	**SCr or ↓ GFR**	**Stage**	**Increase in SCr**	**Urinary Output Change**
Risk	1.5-fold ↑ SCr **or** 25% ↓ GFR	1	1.5- to 1.9-fold ↑ SCr or ↑ SCr ≥ 0.3 mg/dl	<0.5 mL/kg/hr for 6-12 hr
Injury	2-fold ↑ SCr **or** 50% ↓ GFR	2	2- to 2.9-fold ↑ SCr	<0.5 mL/kg/hr for ≥12 hr
Failure	3-fold ↑ SCr **or** SCr >4 mg/dl with acute risk > 0.5 ,g/dl **or** 75% ↓ GFR	3	3-fold SCr or SCr > 4 mg/dl with acute risk > 0.5 mg/dl **or** RRT	<0.3 mL/kg/hr for ≥24 hr or anuria for ≥ 12 hr

AKI = acute kidney injury; RRT = renal replacement theraphy.
Information from: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guidelline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.

KDIGO Criteria: In 2012, the KDIGO clinical practice guidelines defined AKI as an SCr increase of 0.3 mg/dL within 48 hours or a 50% increase in SCr within the previous 7 days. The staging system was maintained the same as AKIN; however, a GFR of less than 35 mL/minute/1.73 m^2 was added for pediatric patients as a criterion for stage 3 AKI.

Stage	Increase in serum creatinine	Urine output
1	≥0.3 mg/dl (26.5 μmol/L within 48 h or 1.5-1.9 times baseline within 7 days)	<0.5 mL/kg/h for 6-12 h
2	2.0-2.9 times baseline within 7 days	<0.5 mL/kg/h for ≥12 h
3	≥3.0 times baseline or ≥4.0 mg/dL (354 μmol/L) increase within 7 days or in patients <18 years of age, decrease in estimated GFR to <35 μmL/min/1.73 m^2	<0.3 mL/kg/h for ≥24 h Anuria ≥12 h

Despite the uniform AKI criteria that have been developed, AKI remains a clinical diagnosis and has to be put into the clinical context where it occurs. The AKI criteria should not be used as an absolute 'truth', rather as a frame for decisions, when to initiate measures aimed at preventing further damage to the kidney.

Kidney Injury Biomarkers

By the time KDIGO SCr criteria for AKI met the decline in glomerular filtration rate (GFR) and likely structural damage that preceded the decline have been present for several hours. It has been hypothesized that delayed detection of AKI is one of the reasons of failure of treating AKI. Therefore, a lot of effort has been put into finding biomarkers that could detect kidney injury earlier, before functional biomarkers (SCr and serum cystatin C) have changed and which would be related to the clinical course of AKI, predict the need of dialysis or other complications. These biomarkers provide information on tubular injury, which commonly precedes functional decline. Most well-studied biomarkers are liver type fatty acid binding protein (L-FABP), neutrophil gelatinase associated lipocalin (NGAL), the combination of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7). NGAL and interleukin 18 (IL-18), both in plasma and urine are being tested as early markers

Type of biomarker	Biomarker	Description	Kinetics
Tubular injury	Kidney injury molecule 1	Tested in urine. Upregulated after injury to proximal tubuli. Activates immune cells leading to clearance and remodeling of injured cells.	Detected 12-24 h after injury and will peak at 48-72 h post-injury
	IL-18	Tested in urine and serum. Upregulated after ischemic injury to proximal tubuli. Has pro-inflammatory characteristics.	Detected within the first 6 h after injury, and will peak at 12-72 h post-injury
	NGAL	Tested in urine and serum. Is released both from distal and proximal tubuli from damaged cells and actives protective enzymes and prevents production of radicals. NGAL is also released from liver and neutrophils in sepsis.	Detected within 3 h of injury and will peak at 6 h post-injury
	L-FABP	Tested in urine. Protein that is expressed in proximal tubuli after ischemic injury.	Detected within 1 h after injury and will peak within 6 h post-injury
	TIMP-2 and IGFBP-7	Tested in urine. Both these biomarkers induce G1 cell cycle arrest that prevents proliferation of endothelial cells.	Detected within 12 h of injury
Glomerular filtration	Cystatin C	Tested in serum. Protein, which is produced at a constant rate and filtered freely, reabsorbed and metabolized in the proximal tubuli.	Detected 12-24 h after injury and will peak within 48 h post-injury

Biomarkers of acute kidney injury

of injury following cardiac surgery. However, the ability of any of these markers to predict AKI was modest.

Recently, the combination of two biomarkers for tubular cell cycle arrest, TIMP-2 and IGFBP-7, has shown promising diagnostic performance to predict a doubling of SCr within 12 hours in patients with sepsis.

Risk factors for AKI

The onset of AKI is multifactorial and several patient specific factors can contribute to the risk of AKI. Risk factors for AKI include age, comorbid diseases, proteinuria, nephrotoxic exposures, major surgery, sepsis, fluid resuscitation and volume status. Older age increases the risk of AKI. Comorbid conditions including CKD, DM, hypertension, coronary artery disease, heart failure, liver disease and chronic obstructive pulmonary disease are risk factors for AKI. Proteinuria with a GFR greater than 60 mL/minute/1.73 m^2 or an elevated urinary albumin/creatinine ratio is associated with an increased risk of AKI. Hospitalized patients, especially critically ill patients are often exposed to several nephrotoxins and contrast exposure. Antimicrobials, NSAIDs and proton pump inhibitors are common medications administered in this population. Acute kidney injury is common after cardiac surgery and is less common in the non cardiac surgery population. Sepsis is a common predisposing factor to AKI and the development of AKI further increases the risk of mortality. Choice of fluid for resuscitation may be a risk factor for AKI because hydroxyethyl starch has been associated with increased risk of AKI compared with crystalloids. High volume resuscitation with crystalloids has a higher risk of AKI than balanced salt solutions because of the deleterious effects of chloride loading. Fluid overload and therapies to treat volume overload increase the risk of AKI. Fluids are the mainstay for preventing and treating AKI. However, certain fluids have been associated with an increased risk of AKI.

Etiology and types of AKI

Causes of AKI can be classified into three broad groups: (1) prerenal or hemodynamic (i.e. hypoperfusion to the kidney), (2) Renal or intrinsic (i.e. structural damage to the kidney) and (3) postrenal (i.e. obstruction of urinary outflow). It is important to determine the cause and assess for reversibility in order to identify appropriate strategies for minimizing the severity of injury.

1) Prerenal AKI: Prerenal AKI is the leading cause of kidney injury. Decreased renal perfusion of the kidney can cause AKI with or without systemic arterial hypotension. Inadequate fluid intake, excessive vomiting, diarrhea and fever can lead to dehydration. Trauma resulting in massive hemorrhage decreases circulating volume, resulting in hypoperfusion to the kidney.

Prerenal
- ACEIs/ARBs
- Calcineurin inhibitors
- COX-2 inhibitors
- Diuretics
- NSAIDs

Glomerular Injury
- Interferon
- Pamidronate

Acute Interstitial Nephritis
- Allopurinol
- Azathioprine
- Chinese herbs - *Stephania tetrandra, Magnlia officinalis, Aristolochia fangchi*
- Cimetidine
- Diuretics (thisazides, furosemide)
- NSAIDs
- Phenytoin
- Proton pump inhibitors
- Quinolones
- Rifampin
- Semisynthetic penicillins (ampicillin, nafcillin, oxacillin)
- Sulfonamides
- Vancomycin

Acute Tubular Necrosis
- Aminoglycosides
- Amphotericin B
- Carboplatin
- Cisplatin
- Cyclophosphamide
- Ifosfamide
- Pentamidine
- Radiocontrast media
- Vancomycin

Crystal Nephropathy
- Acyclovir
- Allopurinol
- Indinavir
- Methotrexate
- Nelfinavir
- Quinolones
- Sulfonamide
- Triamterene

ACEI = angiotensin converting enzyme inhibitors; AIN = acute interstitial nephritis; AKI = acute kidney injury; ARB = angiotensin II receptor blockers; ATN = acute tubular necrosis; COX II = cyclooxygenase 2.

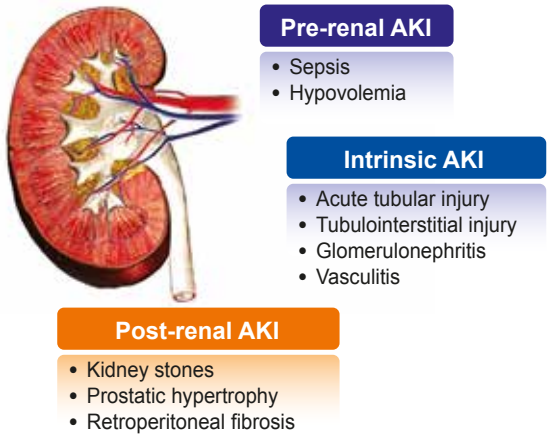
Sepsis, heart failure and cirrhosis are disease states in which there is reduced perfusion to the kidneys. Sepsis and septic shock are the most common causes of AKI in the ICU. Although the mechanism

that causes sepsis and septic shock is still unknown, it likely involves the inflammatory response to infection that leads to hypoperfusion and multi organ failure. Cardiac surgery and heart failure are the second most common causes of AKI.

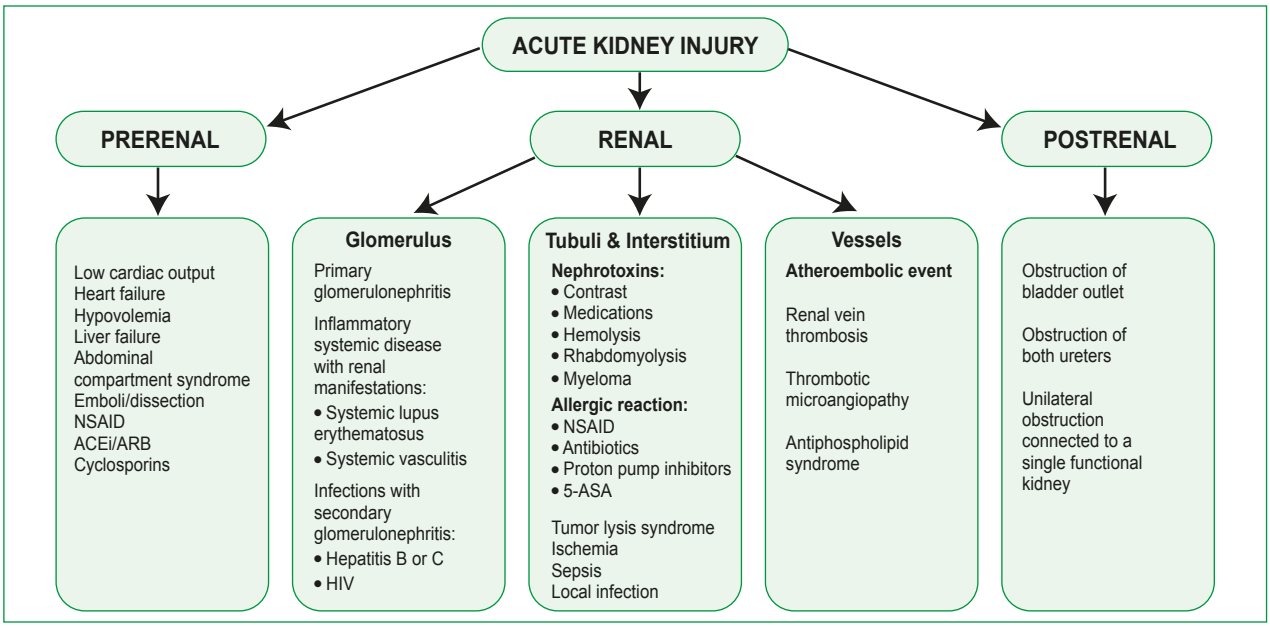
Hepatorenal syndrome, burns and trauma can also cause hypoperfusion of the kidneys. The mechanisms are thought to be from shock, abdominal compartment syndrome, inflammatory mediators and changes in tissue perfusion.

2) Renal or intrinsic AKI: Intrinsic kidney injury includes damage to the glomerulus, tubules, interstitium and vasculature. These conditions are quite different from a pathophysiologic standpoint and include a wide spectrum of etiologies, disease conditions (infection, sepsis, renal ischemia, malignant hypertension or inflammation e.g. glomerulonephritis, vasculitis, allergic reaction etc) or nephrotoxic drugs and other nephrotoxins. The immune system plays a major role in glomerular disorders, interstitial injury and vascular injury. Drugs causing intrinsic injury may be direct nephrotoxins or they may stimulate an immune response. In some cases, drugs can cause injury through more than one mechanism (i.e., tubular injury and interstitial injury).

3) Postrenal AKI: Postrenal AKI is caused by an obstruction of urinary flow. The most common causes of post-renal AKI include nephrolithiasis, benign prostatic hypertrophy and surgical causes. A number of other causes exist as urethral stricture, pelvic or abdominal cancers, neurological causes as multiple sclerosis or ureter injury following surgery or trauma. The initial action is to exclude urinary outflow obstruction and thereafter, ultrasound should be performed to rule out hydronephrosis. In cases where flank pain is present, the preferred imaging should be computed tomography without contrast in order to rule out kidney stones.



Combination of prerenal and renal AKI: In many cases, prerenal and renal AKI exist concurrently. AKI may occur in sepsis, despite the absence of hypotension. The causes are multifactorial including sympathetic activation, hormonal and inflammatory mediation.



Causes & types of AKI

Concomitant prerenal and renal AKI is also observed in disorders such as rhabdomyolysis and hypercalcemia, in which severe hypovolemia combined with the toxic effects of myoglobin and calcium causes AKI. Rhabdomyolysis is commonly associated with hypovolemia, thus leading to prerenal AKI and direct nephrotoxic effects of myoglobin and heme proteins may also lead to intraluminal cast formation and tubular obstruction. After cardiac surgery the causes of AKI are often a combination of ischemia, inflammation, hypotension, embolism and free hemoglobin from blood transfusions.

Diagnosis

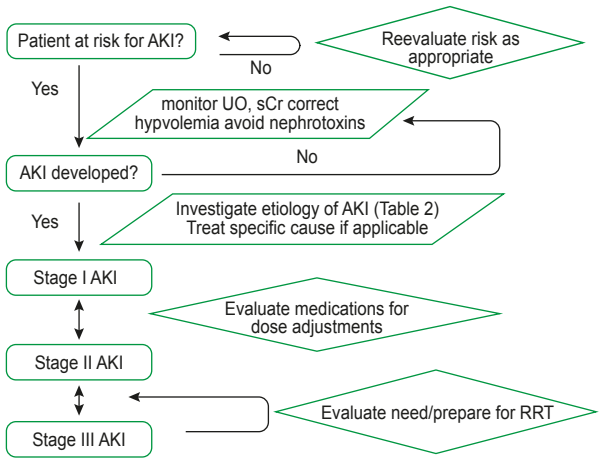
AKI is rarely symptomatic and signs and symptoms are related to the underlying cause rather than AKI itself.

Examinations and treatments are dependent on the clinical setting and underlying causes. The medical history should be reviewed including exposure to nephrotoxic agents. Urinary outflow obstruction should be excluded. If the underlying cause of AKI is not obvious, renal ultrasound should be performed in order to exclude hydronephrosis and to assess kidney size, where a kidney length <8 cm may be indicative of CKD instead of AKI, but does not exclude acute on CKD. Blood and urine samples should be collected in order to analyze blood cell counts, electrolytes, SCr, serum albumin, standard bicarbonate and dipstick urine analysis.

Management of AKI

General principles:

The treatment of AKI focuses on treating the underlying cause, limiting damage and preventing further loss of GFR. There are several key principles to follow, where the most important are to treat the underlying cause and to achieve normovolemia and hemodynamic stability. In addition, electrolyte disturbances should be treated, nephrotoxic drugs discontinued or dose adjusted and drugs with renal elimination should be dose adjusted. Potassium sparing diuretics and ACE inhibitors should be discontinued in order to avoid progression of AKI and hyperkalemia. Acid-base disturbances, mainly in the form of metabolic acidosis, are frequent in moderate to severe AKI (stages 2 and 3), where treatment of the underlying causes is the primary objective.



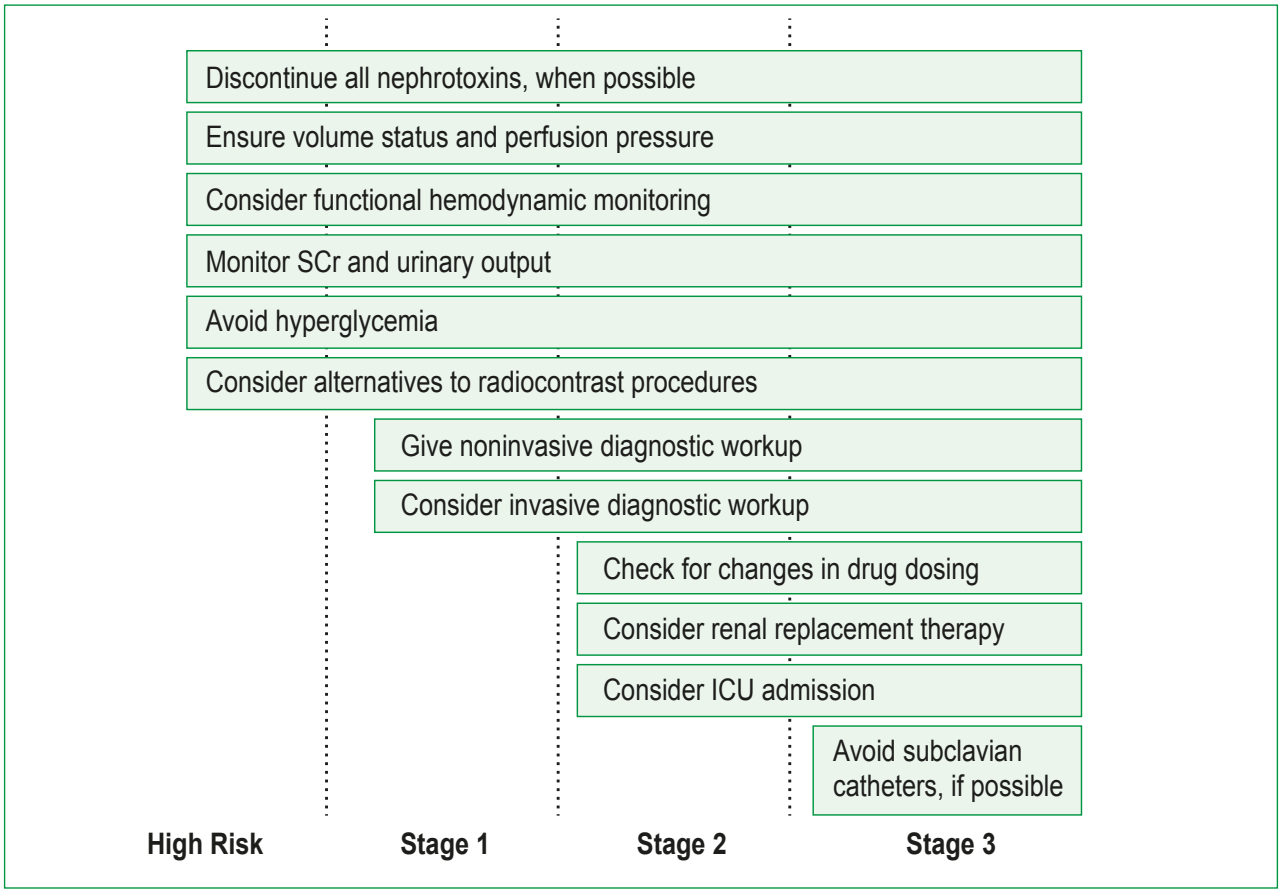
Conceptual model for the diagnosis and treatment of acute kidney injury (AKI). Abbreviations: UO, urine output; RRt, renal replacement therapy; sCr, serum creatinine.

Urine Indices	Prerenal/Hemodynamic	Acute Tubular Necrosis	Postrenal Obstruction
Urine sodium (mEq/L)	< 20	> 40	> 40
FENa (%)	< 1	> 2	> 1
Urine osmolality (mOsm/k)	Up to 1200	< 300	< 300
Urine creatinine/ plasma SCr ratio	> 40:1	< 20:1	< 20:1
Specific gravity	> 1.010	< 1.010	Variable

Summary of urinary indices for differential diagnosis

Analysis of urinary sediment may also be a guide to determine the etiology of AKI. Urine output should always be monitored in patients with AKI because oliguria and anuria is common and is an earlier marker of progressive AKI than SCr.

A cornerstone of the management of all patients with AKI is to monitor urine output and to initially monitor SCr several times a day. Several drugs have been tested for AKI, but none has been established as standard treatment in clinical practice.



Stage-based management of AKI.

Fluid therapy:

For all cases in which hypovolemia is the suspected cause of AKI, the first priority is to restore fluid balance with the aim to increase cardiac output, in order to stabilize hemodynamics and renal blood flow, without inducing fluid overload. Evaluation of hydration status is difficult and several methods have recently become available in clinical practice such as measuring bioimpedance and ultrasound assessment of vena cava and left ventricle dimensions. Crystalloids and colloids are common solutions used for volume repletion in patients with prerenal AKI. Crystalloid solutions are more commonly used than colloids for resuscitation, especially in the initial resuscitation phase in patients with AKI. The rate of rehydration should be individually assessed.

Diuretics:

Diuretics have long been a mainstay in preventing and treating AKI. Volume overload is common and diuretics facilitate fluid management. Furosemide has several renoprotective characteristics like blocking of oxygen consuming sodium channels in the tubules, increased diuresis leading to a reduced oxygen demand in the kidney and washout of kidney toxic molecules. However, clinical studies have failed to demonstrate that furosemide improves the prognosis in AKI, except in patients with fluid overload. The use of furosemide as prevention of AKI in conjunction with cardiac surgery or contrast exposure has been linked to a higher risk of AKI. Sometimes, loop diuretics are recommended for treating volume overload and hyperkalemia as consequences of AKI.

Vasopressors:

Vasopressors are used to maintain an adequate mean arterial pressure (MAP) for organ and tissue perfusion.

Often, fluid resuscitation alone is insufficient and vasoactive agents must be considered. Persistent hypotension, even after fluid resuscitation, increases the risk of AKI. No one vasopressor is most effective in AKI, rather choice of vasopressor depends on the cause of hypotension and hypoperfusion. Of the vasopressors, dopamine was long considered preferred because it is a renal vasodilator acting on both the pre and postglomerular arterioles and thereby increasing renal blood flow. The administration of a low dose of dopamine has been thought to increase renal perfusion. Norepinephrine is the most commonly used vasopressor and is vasopressor of choice in sepsis. It has greater effects on α-receptors than on β-receptors. Adverse effects include ischemia from vasoconstriction and deleterious cardiac effects. Vasopressin is another non-adrenergic vasopressor drug that increases blood pressure. It is an endogenous hormone that increases vascular tone, improves blood pressure and enhances diuresis. Vasopressin commonly used as a second line drug in conjunction with norepinephrine in order to stabilize hemodynamics.

Sodium bicarbonate:

Sodium bicarbonate has been used for the treatment and prevention of AKI associated with heme- pigment nephropathies (myoglobin, hemoglobin and bilirubin) and in tumor lysis syndrome. Sodium bicarbonate is thought to increase the solubility of these products preventing the formation of obstructive methemoglobin cylinders and crystals in the tubules. In addition, sodium bicarbonate is thought to reduce oxidative stress and free radicals. This led to the hope that sodium bicarbonate may prevent AKI.

Renal replacement therapy (RRT) for AKI

Renal replacement therapy is required in 5%–6% of critically ill patients who develop AKI and is associated with increased mortality. The current recommen- dation on when to start RRT involves life threatening changes in fluids, electrolytes, the acid–base balance or uremic complications.

However, controversy exists over the benefit of initiating dialysis at an early stage, when life threatening complications have not yet developed. Despite advances in RRT, questions arise on how to optimize RRT for AKI to improve patient outcomes. Factors to consider in the prescription and delivery of RRT include timing of RRT, modality of RRT, treatment dose or intensity and type of clearance provided by RRT (e.g., diffusion, convection).

Summary

AKI is common and associated with poor outcomes. It can be caused by several conditions and should be considered a syndrome rather than an injury alone because of the many complications and effects on other organs. It is very important to identify and avoid nephrotoxins, optimizing medication therapy during an AKI episode and accurately estimating kidney function in patients receiving or not receiving dialysis to improve AKI outcomes. No effective treatment or prevention of AKI has yet been found. Therefore, efforts should be made to limit damage in patients with AKI. In addition, patient education on appropriate follow up and avoiding nephrotoxins may play significant role to minimize the risk and recurrent AKI and progression to CKD.

Abbreviations: AIN-Acute interstitial nephritis; AKI-Acute kidney injury; AKIN-Acute Kidney Injury Network; ATN-Acute tubular necrosis; CKD-Chronic kidney disease; eGFR-Estimated glomerular filtration rate; KDIGO-Kidney Disease Improving Global Outcomes; RIFLE-Risk, injury, failure, loss, end- stage; RRT-Renal replacement therapy.

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- CCSAP 2017 Book 2 Renal/Pulmonary Critical Care

Pelvic inflammatory disease (PID) is an infection induced inflammation of the female upper reproductive tract (the endometrium, fallopian tubes, ovaries or pelvic peritoneum); it has a wide range of clinical manifestations. Inflammation spreads from the vagina or cervix to the upper genital tract, with endometritis as an intermediate stage in the pathogenesis of disease. The hallmark of the diagnosis is pelvic tenderness combined with inflammation of the lower genital tract; women with pelvic inflammatory disease often have very subtle symptoms and signs. Many women have clinically silent spread of infection to the upper genital tract, which results in subclinical pelvic inflammatory disease.

It is a major concern because it can result in long-term reproductive disability, including infertility, ectopic pregnancy and chronic pelvic pain. After the introduction of laparoscopy in the 1960s, research on pelvic inflammatory disease proliferated through the 1970s, 1980s and 1990s, leading to major breakthroughs in the understanding of the microbial causes of the disease and its relationship to reproductive disability, as well as enabling the standardization of antimicrobial treatment. According to a national estimate, in 2001 more than 750,000 cases of pelvic inflammatory disease occurred in the United States. Over the past two decades, the rates and severity of pelvic inflammatory disease have declined in North America and western Europe. These declines have occurred in association with public health efforts to control Chlamydia trachomatis and Neisseria gonorrhoeae infection. Despite progress, however, pelvic inflammatory disease remains a problem because reproductive outcomes among treated patients are still suboptimal, subclinical pelvic inflammatory disease remains poorly controlled and programs aimed at the prevention of pelvic inflammatory disease are not feasible in much of the developing world.

Pathophysiology

Most cases of PID are presumed to occur in 2 stages. The first stage is acquisition of a vaginal or cervical infection. This infection is often sexually transmitted and may be asymptomatic. The second stage is direct ascent of microorganisms from the vagina or cervix to the upper genital tract, with infection and inflammation of these structures.

The mechanism by which microorganisms ascend from the lower genital tract is unclear. Studies suggest that multiple factors may be involved. Although cervical mucus provides a functional barrier against upward spread, the efficacy of this barrier may be decreased by vaginal inflammation and by hormonal changes that occur during ovulation and menstruation.

In addition, antibiotic treatment of sexually transmitted infections can disrupt the balance of endogenous flora in the lower genital tract, causing normally nonpathogenic organisms to overgrow and ascend. Opening of the cervix during menstruation, along with retrograde menstrual flow, may also facilitate ascent of microorganisms.

Intercourse may contribute to the ascend of infection through rhythmic uterine contractions occurring during orgasm. Bacteria may also be carried along with sperm into the uterus and fallopian tubes.

In the upper genital tract, a number of microbial and host factors appear to influence the degree of inflammation that occurs and thus, the amount of subsequent scarring that develops. Infection of the fallopian tubes initially affects the mucosa, but inflammation may rapidly become transmural. This inflammation, which appears to be mediated by complement, may increase in intensity with subsequent infections.

Inflammation may extend to uninfected parametrial structures, including the bowel. Infection may extend via spillage of purulent materials from the fallopian tubes or via lymphatic spread beyond the pelvis to produce acute peritonitis and acute perihepatitis (Fitz-Hugh−Curtis syndrome).

Pregnancy related factors

PID rarely occurs in pregnancy; however, chorioamnionitis can occur in the first 12 weeks of gestation, before the mucous plug solidifies and seals off the uterus from ascending bacteria. Fetal loss may result. Concurrent pregnancy influences the choice of antibiotic therapy for PID and demands that an alternative diagnosis of ectopic pregnancy be excluded. Uterine infection is usually limited to the endometrium but may be more invasive in a gravid or postpartum uterus.

Genetic factors

Genetically mediated variation in immune response plays an important role in susceptibility to PID. Variants in the genes that regulate toll-like receptors (TLRs), an important component in the innate immune system, have been associated with an increased progression of C. trachomatis infection to PID.

Researchers found a possible contributing role of 5 single-nucleoside polymorphisms (SNPs) in 4 genes encoding pattern recognition receptors in local tubal cells and circulating immune cells (eg, macrophages). The presence of 2 or more SNPs appeared to correlate with increased laparoscopically identifiable tubal pathology.

Etiology

The organisms most commonly isolated in cases of acute PID are N. gonorrhoeae and C. trachomatis. C. trachomatis is an intracellular bacterial pathogen and the predominant sexually transmitted organism that causes PID.

In the United States, N. gonorrhoeae is no longer the primary organism associated with PID, but gonorrhea remains the second most frequently reported sexually transmitted disease, after chlamydial infection. Clinically, gonorrheal infection may be asymptomatic or may manifest similarly to chlamydial infection; however, it more often produces more acute symptomatic disease. An estimated 10-20% of untreated chlamydial or gonorrheal infections progress to PID.

Cultures of specimens collected during laparoscopy have demonstrated that PID is a polymicrobial infection in as many as 30-40% of cases. Polymicrobial PID may begin as an isolated infection with N. gonorrhoeae or C. trachomatis, which causes inflammation of the upper genital tract that facilitates the involvement of other pathogens (anaerobes, facultative anaerobes and other bacteria). These other organisms are increasingly isolated as inflammation increases and abscesses form.

In addition to N. gonorrhoeae and C. trachomatis organisms involved in PID include the following:
Gardnerella vaginalis
Mycoplasma hominis
Mycoplasma genitalium
Ureaplasma urealyticum
Herpes simplex virus 2 (HSV-2)
Trichomonas vaginalis
Cytomegalovirus (CMV)
Haemophilus influenzae
Streptococcus agalactiae
Enteric gram-negative rods (eg, Escherichia coli)
Enterococcus, described in 2 individuals post IUD insertion
Peptococcus species
Anaerobes

The microbiology of PID reflects the predominant sexually transmitted pathogens within a specific population, as well as some organisms less commonly seen in that population. Bacterial vaginosis (BV) may lead to vaginal inflammation, which could

Clinical Classification of Pelvic Inflammatory Disease and Likely Microbial Causes.

Clinical Syndrome	Causes
Acute pelvic inflammatory disease (≤30 days duration)	Cervical pathogens (Neisseria gonorrhoeae, Chlamydia trachomatis and Mycoplasma genitalium)
	Bacterial vaginosis pathogens (peptostreptococcus species, bacteroides species atopobium species, leptotrichia species, M. hominis, Ureaplasma urealyticum and clostridia species)
	Respiratory pathogens (Haemophilus influenzae, Streptococcus pneumoniae, group A streptococci and Staphylococcus aureus)
	Enteric pathogens (Escherichia coli, Bacteroides fragilis, group B streptococci and campylobacter species)
Subclinical pelvic inflammatory disease	C. trachomatis and N. gonorrhoeae
Chronic pelvic inflammatory disease (>30 days' duration)	Mycobacterium tuberculosis and actinomyces species

facilitate ascending infection with bacterial vaginosis (BV)-associated organisms (eg, G. vaginalis). However evidence is unclear if detecting and treating BV reduces PID related infection. In some regions, PID may be from a granulomatous salpingitis caused by Mycobacterium tuberculosis or Schistosoma species.

In a cross-sectional study of 736 women with PID, patients with Trichomonas infections demonstrated a 4-fold increase in the histologic evidence of acute endometritis. Coinfection with HSV-2, N. gonorrhoeae, C. trachomatis and BV were associated with histologic evidence of acute endometritis. HSV-2 was associated with fallopian tube inflammation and lower tract ulcerations that may contribute to disruption of the endocervical canal mucous barrier.

HIV infection is associated with an increased incidence of infection with C. trachomatis, Candida and human papillomavirus (HPV). N. gonorrhoeae can facilitate HIV transmission via modulation of HIV- specific immune responses. Women with HIV infection also have an increased risk of progression to PID and Tubo-Ovarian Abscess (TOA).

Microbial virulence appears to play a significant role in PID. In a study, different chlamydial strains recovered from patients with PID and found less symptomatic disease in infection produced by a less virulent variant strain. Features that may increase the likelihood that a lower tract infection will progress to frank PID include expression of chlamydial heat shock protein 60 (CHSP60) in C. trachomatis and expression of P9Opa(b) protein in N. gonorrhoeae.

Risk factors

Risk factors for PID include multiple sexual partners, a history of prior STIs and a history of sexual abuse. Frequent vaginal douching has been considered a risk factor for PID, but studies reveal no clear association. Gynecologic surgical procedures which affect the cervix such as endometrial biopsy, curettage and hysteroscopy break the cervical barrier, predisposing women to ascending infections.

Younger age has been found to be associated with an increased risk of PID. Likely reasons include increased cervical mucosal permeability, a larger zone of cervical ectopy, a lower prevalence of protective antichlamydial antibodies and increased risk-taking behaviors. Older women with PID are more likely to be affected with non STI organisms.

Contraception

Different forms of contraception may affect the incidence and severity of PID. Appropriately used barrier contraception has clearly been shown to decrease the acquisition of most STIs.

Studies of oral contraceptive pills (OCPs) have found differing effects on PID risks. On one hand, some authors suggest that OCPs increase the risk of endocervical infection, probably by increasing the zone of cervical ectopy. On the other hand, some evidence indicates that OCPs can decrease the risk of symptomatic PID, possibly by increasing cervical mucus viscosity, decreasing menstrual anterograde and retrograde flow and modifying local immune responses. Still other studies have suggested that OCPs may not have any effect on PID incidence.

Use of an intrauterine device (IUD) has been linked to a 2- to 9-fold increased risk of PID, but current IUDs may pose a substantially lower risk. In a large retrospective cohort study from 2012, the overall risk of PID in women receiving IUDs was 0.54%. A study reported 9.6 cases of PID per 1,000 IUD insertions, with the most significant risk in the first 20 days. Another study validated the risk of PID within the first month after insertion and also found that the risk appears to be modified by the patient's number of sexual partners and age and by the community prevalence of STIs. The CDC notes that the risk of PID is greatly reduced by testing for-and if necessary, treating-STI before IUD insertion. This testing can be completed in the same day as insertion and patients confirmed to have STI's should be treated. Additionally, IUDs need not be removed if PID is detected. Patients should be treated and re-evaluated clinically. If pain persists or symptoms are not improving, that is an indication to remove the IUD.

PID may have a different microbial profile in IUD users. A study found that in women with PID, Fusobacterium and Peptostreptococcus species were significantly more common in IUD users than in non-IUD users. Actinomyces species were found almost exclusively in patients with IUDs.

Bilateral tubal ligation (BTL) has not been found to provide protection against PID. However, patients with BTL may have delayed or milder forms of PID.

Epidemiology

United States statistics

Among 1,171 sexually experienced reproductive-aged women in the 2013-2014 National Health and Nutrition Education Survey (NHANES) the prevalence of self-reported lifetime PID was 4.4%. Therefore approximately 2.5 million women aged 18–44 nationwide have received a diagnosis of PID in their lifetime (95% CI = 1.8–3.2 million). The CDC has estimated that more than 1 million women experience an episode of PID every year. The disease leads to approximately 2.5 million office visits and 125,000-150,000 hospitalizations yearly.

International statistics

No specific international data are available for PID incidence worldwide. In 2005, however, the World Health Organization (WHO) estimated that approximately 448 million new cases of curable STIs occur annually in individuals aged 15-49 years. Factors contributing to the difficulty of determining the actual worldwide incidence and prevalence of PID include the following:

- Nonrecognition of disease on the part of patients
- Difficulties in obtaining access to care
- The often subjective method of disease diagnosis
- The lack of diagnostics and laboratory facilities in many developing countries
- Underfunded and overstretched public health systems

Worldwide, WHO has determined that STIs rank in the top 5 disease categories for which adults seek care. Women in resource-poor countries, especially those in sub-Saharan Africa and Southeast Asia, experience an increased rate of complications and sequelae.

The annual rate of PID in high-income countries has been reported to be as high as 10-20 per 1000 women of reproductive age. Public health efforts implemented in Scandinavia to decrease the prevalence of STIs have been quite effective in reducing the incidence of PID.

Signs & symptoms

Women with PID present with a variety of clinical signs and symptoms that range from subtle and mild to severe. PID can go unrecognized by women and their health care providers when the symptoms are mild. Despite lack of symptoms, histologic evidence of endometritis has been demonstrated in women with subclinical PID. When present, signs and symptoms of PID are nonspecific, so other reproductive tract illnesses and diseases of both the urinary and the gastrointestinal tracts should be considered when evaluating a sexually active woman with lower abdominal pain. Pregnancy (including ectopic pregnancy) must also be excluded, as PID can occur concurrently with pregnancy.

When symptoms are present, the most common symptoms of PID are-

- Abdominal pain
- Cervical motion tenderness
- Increased vaginal discharge
- Irregular menstrual bleeding
- Painful and frequent urination
- Pelvic organ tenderness
- Abdominal tenderness
- Pain with intercourse
- Adnexal tenderness
- Inflammation
- Fever (>38° C)
- Mild pelvic pain
- Uterine tenderness

Diagnosis

The wide variation in symptoms and signs associated with PID can make diagnosis challenging. No single historical, physical or laboratory finding is both sensitive and specific for the diagnosis of PID. Clinicians should therefore maintain a low threshold for the diagnosis of PID, particularly in young, sexually active women. Criteria have been developed for the diagnosis of PID.

Presumptive treatment for PID should be initiated in sexually active young women and other women at risk for STDs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified and if one or more of the following minimum clinical criteria are present on pelvic examination:

- Cervical motion tenderness or
- Uterine tenderness or
- Adnexal tenderness.

The requirement that all three minimum criteria be present before the initiation of empiric treatment could result in insufficient sensitivity for the diagnosis of PID. After deciding whether to initiate empiric treatment, clinicians should also consider the risk profile for STDs.

More elaborate diagnostic evaluation frequently is needed because incorrect diagnosis and management of PID might cause unnecessary morbidity. For example, the presence of signs of lower genital tract inflammation (predominance of leukocytes in vaginal secretions, cervical exudates or cervical friability), in addition to one of the three minimum criteria, increases the specificity of the diagnosis. One or more of the following additional criteria can be used to enhance the specificity of the minimum clinical criteria and support a diagnosis of PID:

- Oral temperature >101°F (>38.3°C);
- Abnormal cervical mucopurulent discharge or cervical friability;
- Presence of abundant numbers of WBC on saline microscopy of vaginal fluid;
- Elevated erythrocyte sedimentation rate;
- Elevated C-reactive protein; and
- Laboratory documentation of cervical infection with N. gonorrhoeae or C. trachomatis.

Most women with PID have either mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of a saline preparation of vaginal fluid (i.e., wet prep). If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely and alternative causes of pain should be considered. A wet prep of vaginal fluid also can detect the presence of concomitant infections (e.g., BV and trichomoniasis).

The most specific criteria for diagnosing PID include:

- Endometrial biopsy with histopathologic evidence of endometritis;
- Transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid filled tubes with or without free pelvic fluid or tubo-ovarian complex or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia); or
- Laparoscopic findings consistent with PID.

A diagnostic evaluation that includes some of these more extensive procedures might be warranted in some cases. Endometrial biopsy is warranted in women undergoing laparoscopy who do not have visual evidence of salpingitis, because endometritis is the only sign of PID for some women.

A serologic test for human immunodeficiency virus (HIV) is also recommended. A pregnancy test should always be performed to exclude ectopic pregnancy and because PID can occur concurrently with pregnancy. When the diagnosis of PID is questionable or when the illness is severe or not responding to therapy, further investigation may be warranted using other invasive procedures (endometrial biopsy, transvaginal ultrasonography, magnetic resonance imaging or laparoscopy).

Treatment

PID treatment regimens must provide empiric, broad spectrum coverage of likely pathogens. Several parenteral and oral antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short term follow up. However, only a limited number of investigations have assessed and compared these regimens with regard to elimination of infection in the endometrium and fallopian tubes or determined the incidence of long term complications (e.g., tubal infertility and ectopic pregnancy) after antimicrobial regimens. The optimal treatment regimen and long term outcome of early treatment of women with subclinical PID are unknown. All regimens used to treat PID should also be effective against N. gonorrhoeae and C. trachomatis bec- ause negative endocervical screening for these organisms does not rule out upper reproductive tract infection.

The need to eradicate anaerobes from women who have PID has not been determined definitively.

Anaerobic bacteria have been isolated from the upper reproductive tract of women who have PID and data from in vitro studies have revealed that some anaerobes (e.g., Bacteroides fragilis) can cause tubal and epithelial destruction. BV is present in many women who have PID. Until treatment regimens that do not cover anaerobic microbes have been demonstrated to prevent long term sequelae

(e.g., infertility and ectopic pregnancy) as successfully as the regimens that are effective against these microbes, the use of regimens with anaerobic activity should be considered. Treatment should be initiated as soon as the presumptive diagnosis has been made, because prevention of long term sequelae is dependent on early administration of appropriate antibiotics. When selecting a treatment regimen, healthcare providers should consider availability, cost and patient acceptance. In women with PID of mild or moderate clinical severity, parenteral and oral regimens appear to have similar efficacy. The decision of whether hospitalization is necessary should be based on provider judgment and whether the woman meets any of the following suggested criteria:

- Surgical emergencies (e.g., appendicitis) cannot be excluded;
- Tubo-ovarian abscess;
- Pregnancy;
- Severe illness, nausea and vomiting or high fever;
- Unable to follow or tolerate an outpatient oral regimen; or
- No clinical response to oral antimicrobial therapy.

No evidence is available to suggest that adolescents have improved outcomes from hospitalization for treatment of PID and the clinical response to outpatient treatment is similar among younger and older women. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women.

Parenteral treatment

Several randomized trials have demonstrated the efficacy of parenteral regimens. Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24-48 hours of clinical improvement. In women with tubo-ovarian abscesses, at least 24 hours of inpatient observation is recommended.

Prevention

The most important public health measure for the prevention of pelvic inflammatory disease is the prevention and control of sexually transmitted infections with C. trachomatis or N. gonorrhoeae. Many high-income countries have implemented programs to screen and treat women for asymptomatic C. trachomatis infection, on the basis of evidence from randomized controlled trials indicating that screening for and treating cervical C. tracho- matis infection can reduce a woman's risk of pelvic inflammatory disease by approximately 30 to 50% over 1 year. The U.S. Preventive Services Task Force, CDC and other professional organizations recommend annual C. trachomatis screening for all sexually active women younger than 25 years of age and older women at increased risk for infection (e.g., women with multiple or new sex partners). These groups also recommend testing for N. gonorrhoeae among women at increased risk for infection (e.g., women with multiple sex partners or previous gonorrhea infection and women living in communities with a high prevalence of disease).

Comprehensive sex education, promotion of the use of condoms and provision of condoms are cornerstones of the prevention of sexually transmitted infection globally and also have benefits for the prevention of pelvic inflammatory disease. Data from the PEACH (PID Evaluation and Clinical Health) study showed that persistent condom use during follow up was associated with reduced risks of recurrent pelvic inflammatory disease, chronic pelvic pain and infertility. In women with pelvic inflammatory disease due to N. gonorrhoeae or C. trachomatis, reinfection and repeat pelvic inflammatory disease are common. Thus, prompt evaluation and empirical treatment of male sex partners of women with pelvic inflammatory disease or cervical infection are essential.

If sex partners cannot be linked to care, expedited treatment of the partner (e.g., providing prescriptions or medications to a patient to take to her partner, without the clinician examining the partner) is a useful approach and has been shown to reduce the risk of reinfection.

References:

- Emedicine.medscape.com
- NEJM
- Centers for Disease Control and Prevention

Diabetes is one of the most prevalent non-communicable diseases globally and currently, the disease is a major public health issue in developing countries because of its chronic nature, rapidly increasing prevalence, related complications and the requirement of long-term care. This pandemic has shown that people with diabetes are at higher risk than people without diabetes of having a severe illness of COVID-19 and also dying of COVID-19.

The World Health Organization (WHO) has declared the COVID-19 outbreak to be a public health emergency of international concern. People of all ages can be infected. Older people and people with pre-existing medical conditions (such as diabetes, heart disease and asthma) appear to be more vulnerable to becoming severely ill with the COVID-19 virus. When people with diabetes develop a viral infection, it can be harder to treat due to fluctuations in blood glucose levels and, possibly, the presence of diabetes complications. There appear to be two reasons for this. Firstly, the immune system is compromised, making it harder to fight the virus and likely leading to a longer recovery period. Secondly, the virus may thrive in an environment of elevated blood glucose. People with diabetes are more likely to have serious complications from COVID-19.

People with diabetes seem to develop more severe COVID-19 disease. It's not that people with diabetes are more prone to COVID-19, but if they develop COVID-19, the disease is much more severe and seems to progress quicker. That seems to happen both with type 2 and type 1 diabetes, and both seem to be prone to more severe disease though Type 1 patients may do better because they're younger.

Type 1 diabetes is a disorder in which most of the insulin producing cells in the body are destroyed by an immune process. Type 2 diabetes involves an interaction between genetic predisposition and the environment, so the environment in the sense that increased food intake, decreased physical activity, increased weight, interact with their family history which provides the genes.

In people with diabetes there is more inflammation in the body. And so, with COVID-19, that inflammatory state gets worse much more quickly, so that could be one reason. The second reason is people with diabetes may be more prone to having problems with their circulation. They may already have had a bypass or a stroke or low blood flow to the legs or something like that. And then this was since that, because there's an addition circulatory problem on top of a background of circulatory issues. Blood flow because of clotting problems could be exaggerated by COVID-19. So, within each one of these bigger reasons there may be smaller reasons nested.

Evidence for human studies published between Dec 1, 2019, and Sept 6, 2021. These were small studies (<1000 people) limited to short follow-up periods (up to 3 months) showed that people with COVID-19 might be at increased risk of incident diabetes. A large-scale in-depth assessment of the risks and burdens of incident diabetes over a longer time horizon has not been done. In this study, to examine the post-acute risk and burden of diabetes in people who survived the first 30 days of SARS-CoV-2 infection.

There is evidence to suggest that beyond the acute phase of COVID-19, survivors might be at an increased risk of developing incident diabetes and increased risk of incident antihyperglycemic use in the post-acute phase of the disease. Diabetes should be considered as a facet of the multifaceted long COVID-19 syndrome. Post acute care strategies of people with COVID-19 should integrate screening and management of diabetes.

Pathogenesis

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to increased levels of inflammatory mediators in the blood, including lipopolysaccharide, inflammatory cytokines and toxic metabolites. Modulation of natural killer cell activity (increased or decreased) and IFNγ production can increase the interstitial and/or vascular permeability for proinflammatory products. In addition, infection with SARS-CoV-2 leads to increased reactive oxygen species (ROS) production. These effects lead to lung fibrosis, acute lung damage and acute respiratory distress syndrome (ARDS). ROS production and viral activation of the renin angiotensin aldosterone system (RAAS) (via increased angiotensin II expression) cause insulin resistance, hyperglycaemia and vascular endothelial

damage, all of which contribute to cardiovascular events, thromboembolism and disseminated intravascular coagulation (DIC). Infection also causes increases in the clotting components fibrinogen and D-dimer, leading to increases in blood viscosity and vascular endothelial damage and xxxxx

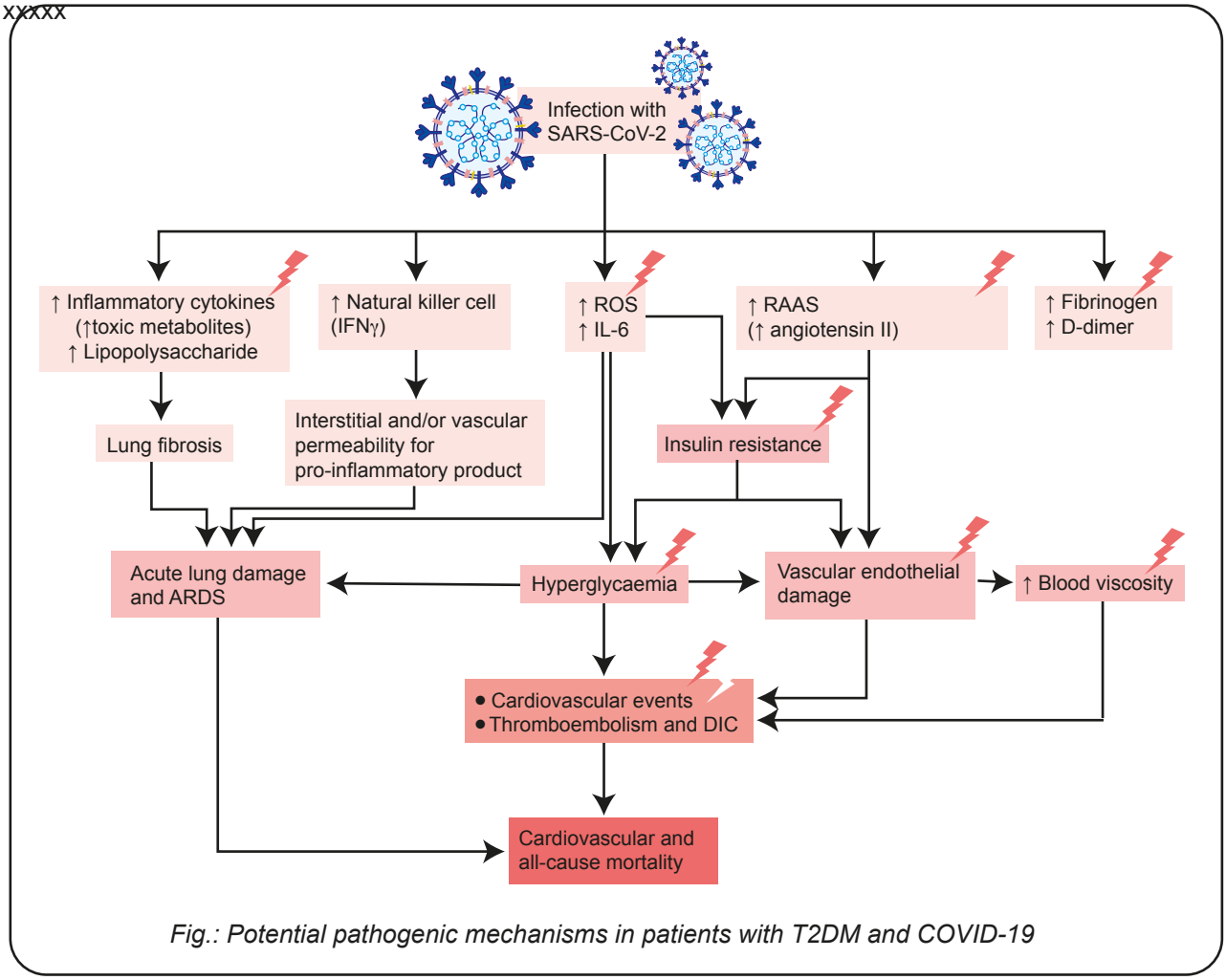

Fig.: Potential pathogenic mechanisms in patients with T2DM and COVID-19

associated cardiovascular events, thromboembolism and DIC.

Management

Underlying diabetes mellitus are considered risk factors for increased coronavirus disease severity and worse outcomes, including higher mortality.

During the COVID-19 pandemic, tight control of glucose levels and prevention of diabetes complications might be crucial in patients with diabetes mellitus to keep susceptibility low and to prevent severe courses of COVID-19.

Evidence suggests that insulin and dipeptidyl peptidase 4 inhibitors can be used safely in patients with diabetes mellitus and COVID-19; metformin and sodium glucose cotransporter 2 inhibitors might need to be withdrawn in patients at high risk of severe disease.

Pharmacological agents under investigation for the treatment of COVID-19 can affect glucose metabolism, particularly in patients with diabetes mellitus; therefore, frequent blood glucose monitoring and personalized adjustment of medications are required.

As COVID-19 lacks definitive treatment so far, patients with diabetes mellitus should follow general preventive rules strictly and monitor glucose levels more frequently, engage in physical activity, eat healthily and control other risk factors.

General guideline

During COVID-19 pandemic, patients with diabetes mellitus should be aware that COVID-19 can increase blood levels of glucose and, as such, they should follow clinical guidelines for the management of diabetes mellitus more strictly. Follow general guidance for patients and healthcare providers: patients should be extra vigilant regarding their adherence to prescribed medications (including insulin injections) and their blood levels of glucose, which should be checked more frequently than previously. In the light of current global quarantine policies, more emphasis needs to be placed on healthy food intake and physical activity in patients with diabetes mellitus. If patients experience symptoms such as a dry cough, excessive sputum production or fever or show a sudden rise in glucose level, they should be advised to consult their physician immediately. Most importantly, general precautions should be strictly followed by both healthcare providers and their patients, such as social distancing, wearing a mask, washing hands and using disinfectants, to reduce the risk of infection in patients with diabetes mellitus.

Telehealth or remote consultations might help reduce the risk posed by direct physical contact between patients and medical personnel. These could be further ways to minimize the risk of SARS-CoV-2 transmission and at the same time provide continued and safe medical care to the general population.

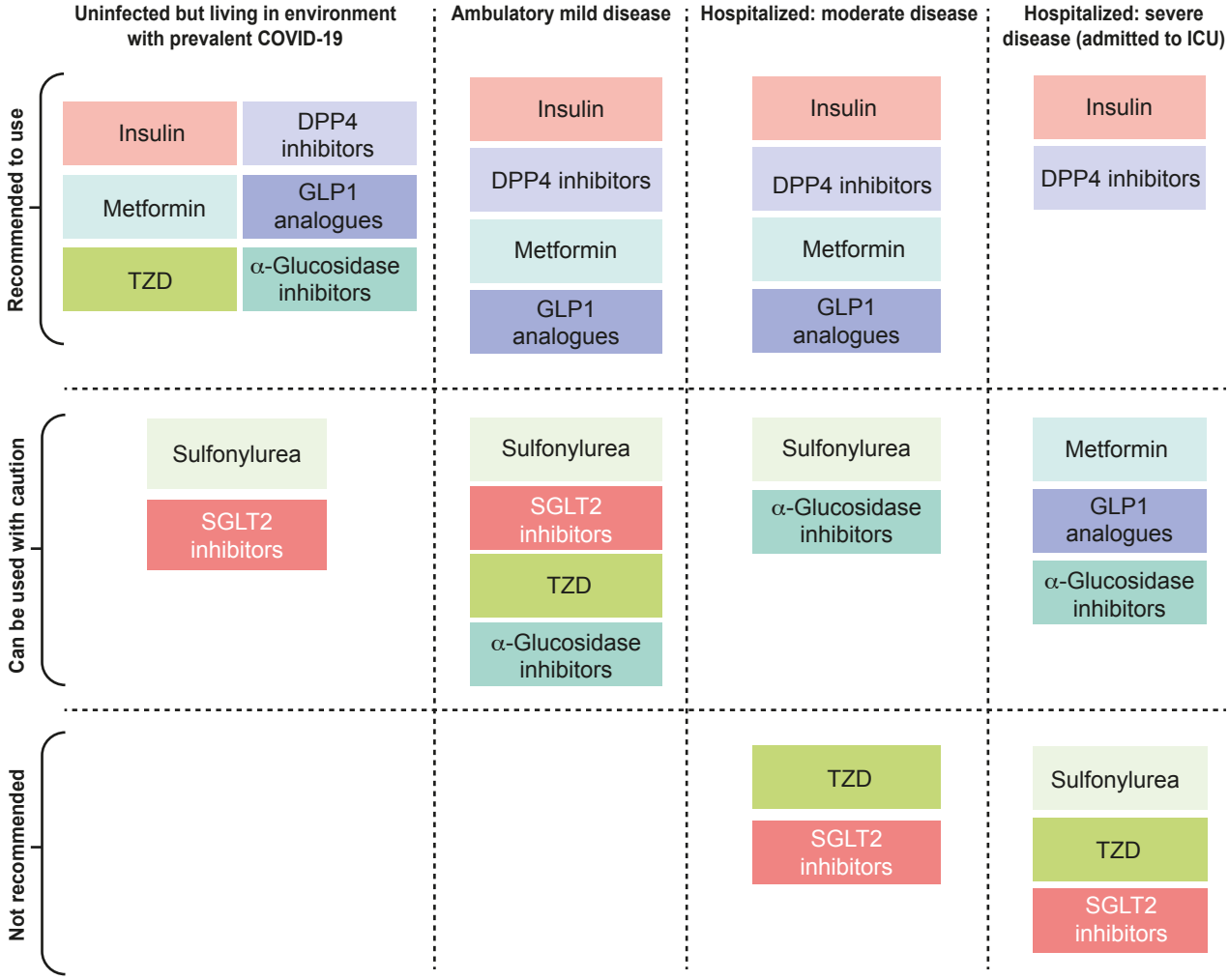

Fig.: Use of antidiabetic medications in patients with T2DM and COVID-19

Use of antidiabetic medications

Coronavirus disease severity is based on the WHO clinical progression scale. Insulin is mainly recommended for critically ill patients with diabetes mellitus infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Optimal glucose control using insulin infusion statistically significantly reduced inflammatory cytokines and improved severity of COVID-19. Metformin can be used for uninfected patients with type 2 diabetes mellitus (T2DM) or ambulatory patients with mild COVID-19. However, it should be noted that metformin is not encouraged for use in critically ill patients. Sulfonylurea can be used in uninfected patients with T2DM, but it is not recommended in patients with severe COVID-19 because it can provoke hypoglycaemia. Thiazolidinediones have the potential to mediate protective effects on the cardiovascular system. However, thiazolidinedione therapy induces weight gain and oedema and tends to aggravate heart failure. These results do not support its use in patients with severe COVID-19. Dipeptidyl peptidase 4 (DPP4) inhibitors are one of the most frequently prescribed medications without serious adverse events. DPP4 inhibitor therapy has proved neutral in terms of major adverse cardiac events in previous cardiovascular outcome trials. Therefore, DPP4 inhibitors can be recommended for use in most patients with a broad spectrum of severity of COVID-19. Given that beneficial roles of glucagon like peptide 1 (GLP1) analogues for the prevention of cardiovascular disease (CVD) and kidney disease are well established, these drugs could be an ideal option for the treatment of patients with T2DM at risk of CVD and kidney disease. Sodium glucose cotransporter 2 (SGLT2) inhibitor treatment induces osmotic diuresis and potentially dehydration, which has been suggested to be a risk factor for acute kidney injury and ketoacidosis. As such, the use of SGLT2 inhibitors is not recommended in patients under critical care.

Other medications

Coronavirus infections are proven to have a huge effect on the management of diabetes mellitus because they aggravate inflammation and alter immune system responses, leading to difficulties in glycaemic control. SARS-CoV-2 infection also increases the risk of thromboembolism and is more likely to induce cardiorespiratory failure in patients with diabetes mellitus than in patients without diabetes mellitus. All of these mechanisms are now believed to contribute to the poor prognosis of patients with diabetes mellitus and COVID-19. During the COVID-19 pandemic, tight glycaemic control and management of cardiovascular risk factors are crucial for patients with diabetes mellitus. Medications used for both diabetes mellitus and CVD should be adjusted accordingly for people at high risk of SARS-CoV-2 infection.

COVID-19 vaccination

In view of increased risk of poor health outcomes as a consequence of COVID-19, it is important that people with diabetes are included among priority groups for vaccination programs.

International diabetes federation (IDF) strongly recommends governments to prioritise access to vaccines for people living with diabetes and other health conditions, and advises people living with diabetes to get themselves vaccinated at the earliest opportunity that is offered to them.

Conclusion

The COVID-19 global pandemic poses considerable health hazards, especially for patients with diabetes mellitus. A definitive treatment has yet to be discovered. Therefore, preventing infection in the first place is still the best solution. Under these circumstances, patients with diabetes mellitus should make a determined effort to maintain a healthy lifestyle and to decrease potential risk factors.

References:

- American Diabetic Association (ADA)
- World Health Organization (WHO)
- International Diabetes Federation (IDF)

Surprisingly, Monkeypox virus is spreading around the world again. Till now 257 confirmed and 127 suspected cases are identified across 25 countries. On this incidence, WHO found it alarming and assuming its further outbreak. This time first infected person found in UK. After that, positive cases also found in Spain, Germany, Portugal, Belgium, France, Netherlands, Italy & Sweden.

Monkeypox is a viral zoonosis (transmitted from animals to humans) with symptoms very similar to smallpox with less severity. Human monkeypox was first identified in humans in 1970 in the Democratic Republic of the Congo in a region where smallpox had been eliminated in 1968. Since then, most cases have been reported from rural regions of the Congo Basin. Scientists at the Centers for Disease Control and Prevention (CDC) are collaborating with the Massachusetts Department of Public Health to investigate the U.S. resident tested positive for monkeypox on May 18, 2022 after returning from Canada. CDC is also tracking multiple clusters of monkeypox cases reported in early to mid-May in several countries. Since 1970, human cases of monkeypox have been reported in 11 African countries. A concurrent outbreak of chickenpox and monkeypox was found which could explain real or apparent changes in transmission dynamics in this case. Since 2017, Nigeria has experienced a large outbreak with over 500 suspected and 200 confirmed cases and a fatality ratio of approximately 3%. In 2003, forty-seven confirmed and probable cases were reported. This was the first time that human monkey-pox was reported outside of Africa. On that year, it was the first outbreak in the USA and it was linked to contact with infected pet prairie dogs. This outbreak led to over 70 cases of monkeypox in the U.S.

Animal to human transmission can occur from direct contact with the blood, bodily fluids or cutaneous lesions of infected animals. In Africa, evidence of monkeypox infection has been found in many animals including rope squirrels, tree squirrels, Gambian poached rats, dormice, different species of monkeys and others. The natural reservoir of tis has not yet been identified, though rodents are the most likely. Eating inadequately cooked meat and other animal products of infected animals is a possible risk factor. Human to human transmission can result from respiratory secretions, skin lesions of an infected person or recently contaminated objects. It can also occur via the placenta from mother to fetus or during close contact during and after birth. Monkeypox transition specifically through sexual routes is yet unclear. The incubation period of monkeypox is usually from 6 to 13 days. It is usually a self-limiting disease with the symptoms lasting from 2 to 4 weeks. Severe cases occur more commonly among children and are related to the extent of virus exposure, patient health status and nature of complications. Although vaccination against smallpox was protective in the past, today persons younger than 40 to 50 years of age may be more susceptible to monkeypox due to cessation of smallpox vaccination campaigns globally after eradication of the disease. Complications of monkeypox can include secondary infections, bronchopneumonia, sepsis, encephalitis and corneal infection. The case fatality ratio has historically ranged from 0 to 11 % in the general population and has been higher among young children. In recent times, the case fatality ratio has been around 3-6%.

In suspected cases, a sample must be collected and transported to an appropriate laboratory. Polymerase chain reaction (PCR) is the preferred laboratory test. Where feasible, biopsy is an option. Clinical care for monkeypox should be to alleviate symptoms, manage complications and prevent long term sequelae. Patients should be offered fluids and food to maintain adequate nutrition. Secondary bacterial infections should be treated as indicated. An antiviral agent Tecovirimat, is licensed by the European Medical Association (EMA) for monkeypox in based on data in animal and human studies. Vaccination against smallpox was about 85% effective in preventing monkeypox. Thus, prior smallpox vaccination may result in milder illness. At the present time, first-generation smallpox vaccines are no longer available to the general public. Still newer vaccines have been developed. Among them JYNNEOS also known as Imvanex which is based on a modified attenuated vaccinia virus (Ankara strain) has been approved in USA for prevention of monkeypox specifically.

References:

❏ WHO-who.int/news-room/fact-sheets/detail/monkeypox ❏ CDC-cdc.gov/poxvirus/ monkeypox ❏ PubMed- pubmed.ncbi.nlm.nih. gov/24158414

Product Profile- Magnide™

Composition

Magnide™ Tablet: Each tablet contains 605.33 mg Magnesium Oxide BP equivalent to 365 mg Magnesium.

Pharmacokinetics

Absorption of a micronutrient as Mg is affected by other nutrients and reaches an estimated 30–50% of dietary Mg intake at basal conditions, while the absorption fraction declines with age and raising Mg intake. The drug absorption depends on both the kind of Mg salt and other food elements that may either augment or abate it.

Distribution of Mg is mainly intracellular, <1% circulates in the blood (both extracellularly and intracellularly), and total serum Mg comprises three states with roughly 60% ionized, 33% protein bound and 7% anion complexed.

Elimination of Mg is handled by renal filtration with 25% being reabsorbed in the proximal convoluted tubule and further 50-60% being reabsorbed in the loop of Henle. Around 70–80% of plasma Mg undergoes glomerular filtration, but merely 3% is eventually excreted in the urine.

Indication

Magnide™ is indicated for the treatment of following condition:

- Relieving the symptoms of magnesium deficiency
- Cardiovascular system: Rapid heartbeat, heart rate irregularity, heart attack, angina pectoris, mild severe hypertension
- Nervous system and muscles: Sudden and excessive contractions (tetania) in the muscles, muscle cramp, gastrointestinal cramps, increased stimulability of muscles and nerves, calf cramps, cramp conditions in newborn and young children and stress
- Gynecological diseases, birth and pregnancy: Preterm contraction, cervical insuciency, premature membrane rupture, contractions during pregnancy (eclampsia/preectampsia), tocolysis requiring the use of beta mimetic (interruption of the uterine contractions), dysmenorrhea.
- Orthopedics: Calcification and ossification
- Prevention of kidney stone formation (prevention of recurrence of calcium oxalate urolithiasis)
- Diabetes treatment and migraine

Dosage & Administration

Magnesium supplements must be taken with meal to reduce stomach upset and diarrhea. The recommended daily dose for adults and adolescents is 1-2 tablets.

Use in pregnancy and lactation

The recommended daily dose in pregnancy and lactation is 1-2 tablets. (During pregnancy & lactation, this product should be used only when clearly needed)

Use in special populations

Kidney failure: Should not be used in patients with severe kidney insuciency.

Liver failure: There are no data on patients with liver insuciency.

Usage in elderly: There is no data on the use in elderly patients.

Side effects

Mild side effects include-Nausea, Vomiting, Diarrhea, Cramp, Tiredness, Weakness, Confusion. These side effects disappear when the dose is reduced or treatment is discontinued. Serious side effects include-low blood pressure, changes in the ECG, depression, severe allergic reaction (e.g. swelling in mouth and throat, itching, rash, redness), respiratory depression, coma. These may require emergency medical treatment. These serious side effects occur very rarely.

Precaution

This product may contain inactive ingredients, which can cause allergic reactions or other problems. If anyone have the following health problem, he/she should consult with doctor before using this product: kidney disease, alcohol dependence, liver disease, phenylketonuria (PKU) or any other condition that requires limit/avoid these substances from diet.

Test Yourself - 52

1. **The followings are true for "Pelvic Inflammatory Disease (PID)" except:**
   a. PID often have very subtle symptoms and signs.
   b. Most cases of PID are presumed to occur in two stages.
   c. Uterine infection is not usually limited to the endometrium.
   d. N. gonorrhoeae and C. trachomatis are the organisms most commonly isolated in cases of acute PID.

2. **All the followings are correct for "Acute Kidney Injury (AKI)" except:**
   a. Kidney injury biomarker 'Cystatin C' is a marker of tubular injury.
   b. The onset of AKI is multifactorial.
   c. Hypertension, Diabetes Mellitus, Coronary Artery Disease, Heart Failure are risk factors for AKI.
   d. Pre-renal AKI is the leading cause of kidney injury.

3. **All the below are true for "Pelvic Inflammatory Disease (PID)" except:**
   a. Treatment should be initiated as soon as the presumptive diagnosis is made.
   b. 'Laparoscopic findings consistent with PID', is one of the non-specific criteria for diagnosing PID.
   c. Endometrial biopsy, curettage, hysteroscopy are the risks factors for PID.
   d. Different forms of contraception may affect the incidence and severity of PID.

4. **All the followings are correct for "Acute Kidney Injury (AKI)" except:**
   a. Most common causes of post-renal AKI include nephrolithiasis, benign prostatic hypertrophy and surgical causes.
   b. Acute Kidney Injury is always symptomatic and signs and symptoms are related to AKI itself.
   c. The treatment of AKI focuses on treating the underlying cause, limiting damage and preventing further loss of GFR.
   d. AKI is common and associated with poor outcomes.

5. **The followings are right for "Pelvic Inflammatory Disease (PID)" except:**
   a. There are wide variation of symptoms and signs associated with PID.
   b. The annual rate of PID in high-income countries has been reported to be high as 60-70 per 1000.
   c. PID treatment regimens must provide empiric, broad spectrum coverage of likely pathogen.
   d. Prevention and control of sexually transmitted infection with C. trachomatis or N. gonorrhoeae is the most important public health measure to prevent PID.

6. **All the followings are correct for "Covid -19 and Diabetes" except:**
   a. People especially with diabetes are most likely to have serious complications from Covid -19.
   b. Infection with SARS-CoV-2 can lead to increased levels of inflammatory mediators in blood.
   c. DPP4 inhibitors is not recommended for use in most patients with a broad spectrum of severity of Covid -19.
   d. Metformin is not encouraged for use in critically ill patients with Covid -19.

Axlovir™ Combipack

Nirmatrelvir INN 150 mg Tablet & Ritonavir USP 100 mg Tablet

Step forward to fight against COVID-19

Dosage & Administration:
Axlovir™ Combipack is administered as three tablets (two tablets of nirmatrelvir and one tablet of ritonavir) taken together orally twice daily for five days, for a total of 30 tablets.

Molvir™ 200

Molnupiravir INN 200 mg **Capsule**

Dosage & Administration:
The recommended dose is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days

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