

Questions and guide to answers

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Give an account on the following:

- (1) Chronic mucocutaneous candidiasis.
- (2) Role of rituximab in the management of vasculitic disorders.
- (3) Management of hyperuricemia in the presence of comorbidities.
- (4) Early detection and management of scleroderma renal crisis.
- (5) Difficulty of weaning from mechanical ventilation.
- (6) Pseudomembranous colitis.
- (7) Hyperviscosity syndromes.
- (8) Gangrene of the toes with normal pedal pulsations.

Q1 Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) refers to a heterogeneous group of disorders characterized by recurrent or persistent superficial infections of the skin, mucous membranes, and nails with *Candida spp.* organisms, usually *Candida albicans*.

These disorders are confined to the cutaneous surface, with little propensity for systemic dissemination. There are several subgroups of patients with CMC, and these can be identified by associated disorders such as autoimmune diseases, endocrinopathies, thymoma, and interstitial keratitis, as well as the distribution and severity of *Candida spp.* infections.

CMC does not represent a specific disease, but rather a phenotypic presentation of a spectrum of immunologic, endocrinologic, and autoimmune disorders. The unifying feature of these heterogeneous disorders is impaired cell-mediated immunity against *Candida spp.*

Associated disorders

- (1) Disturbances of both T-cell-mediated and humoral immunity, leading to many autoimmune manifestations – for example, autoimmune

- hemolytic anemia, immune thrombocytopenic purpura, and rheumatoid arthritis.
- (2) Various degrees of bone marrow failure with aplastic anemia.
- (3) Neoplastic diseases have occurred in several patients, mostly involving the mouth and esophagus. Benign and malignant thymomas have also been reported.

CMC usually manifests during infancy or early childhood (60–80% of cases), with a mean age of onset of 3 years. Delayed or adult onset of the disease is reported and can be associated with thymoma, myasthenia gravis, and bone marrow abnormalities.

Clinical manifestations oral thrush (that may extend to the esophagus) and thickened fragmented nails with or without periungual edema.

Diagnosis is made by means of physical examination, potassium chloride preparation results, fungal culture, and a history of recurrent and refractory candidiasis.

Forms of CMC

- (1) CMC without endocrinopathies.
- (2) CMC may occur as a part of autoimmune polyendocrinopathy syndrome type 1. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED). CMC, hypoparathyroidism, and Addison disease. Other autoimmune disorders may be associated, such as type 1 diabetes, autoimmune thyroiditis, Graves' disease, alopecia areata, vitiligo, hypogonadism, biliary cirrhosis, hepatitis, idiopathic

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thrombocytopenic purpura, and pernicious anemia.

APECED is inherited in an autosomal recessive manner and usually manifests early during childhood.

- (3) CMC with thymoma: Patients in this subgroup typically present after the third decade of life. These patients are at increased risk for myasthenia gravis and bone marrow abnormalities.

Laboratory diagnosis

Scrapings from the infected site are suspended in 10–20% potassium hydroxide and microscopically examined. The presence of yeast cells and pseudohyphae confirms the diagnosis.

Culture of *Candida* spp. organisms

Screening laboratory tests for a CMC-associated endocrine dysfunction: perform baseline and yearly follow-up tests to screen for associated endocrinopathy.

Consider a complete blood cell count, to screen for leukopenia, and an HIV test.

Consider cellular immunity tests and immunoglobulin subclasses to diagnose associated immune deficiencies.

Recently, anti-interferon-1 antibodies were found to be highly specific for APECED and to precede the appearance of CMC, suggesting an important new diagnostic test.

Skin biopsy is performed to assure the presence of *Candida* spp. and assure diagnosis.

Treatment: Relapses are common. Antifungal therapy (topical and systemic), replacement of the associated endocrinal deficiency, and immunomodulatory treatment are carried out. Immunosuppressives (e.g. prednisone, azathioprine, tacrolimus, and rituximab) are administered. Bone marrow transplantation is a future suggested line of treatment.

Q2 Role of rituximab in the management of vasculitic disorders

Rituximab is a monoclonal antibody against CD20. It is a B-cell-depleting agent. Its use is limited mainly to the induction of remission in antineutrophil cytoplasmic antibody-associated vasculitic disorders – that is, microscopic polyangiitis and granulomatous polyangiitis formerly known as Wegener's granulomatosis [1].

Its use is in cases of resistance or contraindication to cyclophosphamide. Cyclophosphamide resistance in

patients with polyangiitis (granulomatous polyangiitis and microscopic polyangiitis) is defined as one or both of the following despite immunosuppressive therapy for at least 1 month [2].

- (1) A progressive decline in renal function (i.e. increase in serum creatinine) with persistence of an active urine sediment.
- (2) Persistence or new appearance of any extrarenal manifestations.

Occasionally, patients have a contraindication to cyclophosphamide therapy or refuse such therapy because of concerns about fertility, hair loss, the risk for malignancy, or other issues. Rituximab is the drug of choice for such patients.

The main limitation for its use is its safety and the lack of long-term randomized controlled trials with long periods of follow-up. The FDA approved its use in the induction of remission in cases of polyangiitis of small-sized and medium-sized vessels in 2011 after a controlled trial by RAVE-ITN Research Group (197 patients followed up for assuring remission for 6 months). The trial showed its effectiveness (+prednisone) as compared with cyclophosphamide (+prednisone) for remission induction [3].

Rituximab may induce activation of many serious infections, mainly hepatitis B and C. Other bacterial and fungal infections may also occur.

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Q3 Management of hyperuricemia in the presence of comorbidities

- (1) Hyperuricemia in type 2 diabetes mellitus and metabolic syndrome:

Type 2 diabetes mellitus and the metabolic syndrome are associated with an increased incidence of uric acid stones, possibly related to reduced ammoniogenesis and decreased urinary pH. Why this occurs is not clear, but both diabetes and the metabolic syndrome are characterized by increased body weight, which is associated with both a more acidic urine pH and increases in urinary uric acid excretion and supersaturation in proportion to the increase in BMI.

As losartan has been found to have an uricosuric property, it may be worthwhile to use it in hypertensive patients with hyperuricemia who lack any contraindication to angiotensin receptor blockers. Hyperuricemia has also been evaluated as a risk factor for coronary heart disease.

(2) Uric acid nephrolithiasis:

Allopurinol is the mainstay of drug therapy in patients with hyperuricemia who develop uric acid stones. Patients with calcium stones who are hyperuricosuric may also benefit from allopurinol because urate crystals in the urine may act as a nidus for other stones to form.

(3) Tumor lysis syndrome (TLS)/acute urate nephropathy is an oncologic emergency that is caused by massive tumor cell lysis. Catabolism of the nucleic acids to uric acid leads to hyperuricemia; the marked increase in uric acid excretion can result in the precipitation of uric acid in the renal tubules and acute renal failure. Treatment is to a large extent prophylactic in the form of intravenous hydration, urine alkalinization, and hypouricemic drugs [1].

Because allopurinol acts by decreasing uric acid formation, it does not reduce the serum uric acid concentration before treatment is initiated. Thus, for patients with pre-existing hyperuricemia (serum uric acid ≥ 7.5 mg/dl), rasburicase is the preferred hypouricemic agent in TLS [2]. Rasburicase (0.15–0.25 mg/kg according to uric acid level) promotes the degradation of uric acid by the administration of urate oxidase (uricase), which catalyzes oxidation of uric acid to the much more water-soluble compound allantoin. Uricase is present in most mammals but not in humans [3].

In established TLS, proper hydration and patient monitoring are important. The preferred drug of choice is rasburicase. Renal replacement therapy may be initiated in certain situations not only to correct renal functions but also to washout excess uric acid.

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Q4 Early detection and management of scleroderma renal crisis

Diagnosis depends on the characteristic findings in high-risk patients with systemic sclerosis. The following criteria for the diagnosis of scleroderma renal crisis may be helpful:

- (1) New onset of blood pressure greater than 150/85 mmHg, measured at least twice over the preceding 24 h. However, normotensive scleroderma renal crisis has been described.
- (2) Progressive decline in renal function with rising serum creatinine.
- (3) Additional findings may include the following:
 - (a) Microangiopathic hemolytic anemia and thrombocytopenia.
 - (b) Acute retinal changes of malignant hypertension.
 - (c) New onset proteinuria or hematuria (excluding other causes).
 - (d) Flash pulmonary edema.
 - (e) Progressive oliguria or anuria.
 - (f) Characteristic changes on kidney biopsy (pauci-immune crescentic glomerulonephritis).

Rarely, severe hypertension associated with acute renal failure may occur in individuals who have features of systemic sclerosis but lack the characteristic skin changes, a disease subset called systemic sclerosis sine scleroderma. In this setting, other signs of systemic sclerosis should be sought.

Treatment: Close monitoring and proper control of blood pressure before irreversible renal changes take place is the most effective part of treatment. Angiotensin-converting enzyme inhibitors are the preferred antihypertensive. Addition of calcium channel blockers may be performed in resistant cases. β -Blockers are usually avoided because of fear of vasospasm (Raynaud's phenomenon).

Q5 Difficulty of weaning from mechanical ventilation

Mechanical ventilation is initiated in patients who are acutely ill or have chronic underlying health problems. In those with cardiac disease, weaning from mechanical ventilation can place an added stressor on an already distressed system. For that reason, we monitor patients closely during weaning from mechanical ventilation. There are standard parameters that are monitored. For example, vital signs, tidal volume, and mental status changes are all important determinants of the success or failure of a weaning trial.

Patients who require multiple weaning attempts are considered difficult-to-wean. This may include as many as 30% of mechanically ventilated patients.

Weaning attempts that are repeatedly unsuccessful usually signify the following:

- (a) Incomplete resolution of the illness that precipitated mechanical ventilation, or
- (b) Development of one or more new problems.

First, all potential causes of ventilator dependency should be identified and a plan should be developed that uses a multidisciplinary team approach to correct the reversible causes of weaning failure and facilitate weaning [1].

Factors that should be corrected before attempting weaning

Central nervous system: impaired level of consciousness and excessive use of sedatives and narcotics.

Cardiovascular system: shock and arrhythmias.

Renal/electrolytes:

Volume overload (syndrome of inappropriate antidiuretic hormone secretion), marked shifts of electrolyte or pH, or marked anemia that may affect the oxygen-carrying capacity.

Poor nutritional status affecting physiological reserve and impairing respiratory muscle function.

Second, ventilator settings should be optimized to minimize the work of breathing during mechanical ventilation and improve respiratory muscle rest between weaning trials. Among the pulmonary factors to be considered are ventilator settings, intrinsic positive end-expiratory pressure (i.e. intrinsic positive end-expiratory pressure or auto-positive end-expiratory pressure), chronic hypercapnia, airway patency, and respiratory muscle performance. Frequent reassessment and modification of all aspects of the plan should be performed according to the patient's progress [2].

Third, respiratory circuit-related problems should be considered in patients who are difficult-to-wean. These include equipment dead space, circuit compliance, gas compression volume, exhalation valve function, and resistance of the endotracheal tube, inspiratory circuit, and expiratory circuit [3].

Before weaning trial, patients with airway obstruction should receive bronchodilator therapy. In addition, all patients should be suctioned and placed in their preferred position.

Summary

- (1) Determine the cause of ventilator dependency.

- (2) Correct correctable problems.
- (3) Develop a weaning plan.
- (4) Use team approach.
- (5) Consider psychological factors:
 - (a) Inform patient of weaning plan and progress.
 - (b) Provide motivation and reassurance.
 - (c) Consider the use of biofeedback.
 - (d) Provide environmental stimulation.
 - (e) Anticipate setbacks.
- (6) Optimize the timing of weaning trials.
- (7) Ensure adequate sleep.
- (8) Optimize posture.
- (9) Optimize pulmonary care:
 - (a) Ventilator settings.
 - (b) Clearance of secretions.
 - (c) Bronchodilator therapy.
 - (d) Endotracheal tube size.
 - (e) Tracheostomy, if necessary.
 - (f) Respiratory muscle rest.
 - (g) Respiratory muscle training.
 - (h) Bedside fan.
- (10) Ensure adequate nutritional support.
- (11) Correct minerals and electrolyte disturbances.
- (12) Regulate acid–base status.
- (13) Optimize general aspects of care.
- (14) Consider ambulation

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Q6 Pseudomembranous colitis

This is a *Clostridium difficile* infection of the colon. The organism is an anaerobic, gram positive, spore-forming, toxin-producing bacteria that spreads through feco-oral route. Infection is usually precipitated by the use of broad spectrum antibiotics that disrupt the normal intestinal microbiome allowing overgrowth of *C. difficile*. The organism produces toxins (A, B) causing mucosal damage and inflammation of the colon, disrupting the epithelial cells and triggering an inflammatory cascade. The exudate forms a membrane seen in the colon (pseudomembrane). The condition manifests as acute watery diarrhea, which may be mild or severe, causing ileus and toxic megacolon and can result in death. Severity is defined according to the presence or absence of fever,

abdominal tenderness, leukocytosis (>15 000), and hypoalbuminemia (<3 g/dl).

Risk factors: Antibiotic exposure (especially prior 2 m), recent hospitalization (community-acquired cases have been reported), immunocompromised host (common in post-transplant patients), ICU patients, and older age.

Clindamycin, cephalosporins, fluoroquinolones, and penicillins have been commonly implicated. However, any antibiotic can precipitate pseudomembranous colitis.

Diagnosis: The most sensitive and specific is the PCR for *C. difficile* toxin genes in the stools. It is superior to enzyme immunoassay tests in the diagnosis of infection. However, regardless of the test and because of the high mortality, if the patient presents with severe illness and concern for *C. difficile* infection is high, empiric therapy should be initiated. Colonoscopy may be normal or show nonspecific colitis until severe cases where pseudomembrane is seen [1].

Treatment: The implicated antibiotic should be stopped. Clinical suspicion especially in severe cases should prompt empiric treatment while awaiting test results. Oral metronidazole (500 mg × 3/day) or vancomycin (125–250 mg, four times daily) are usually used for treatment. In severe cases, additional use of intravenous metronidazole (500 mg, three times daily) and vancomycin enemas may be used. Response is expected within 3–5 days. Treatment should be continued for 10–14 days. Unresponsive cases may require surgical consultation. Fecal transplantation has been used successfully in recurrent cases. Fecal transplantation aims at transplanting microbiota from a healthy host to restore the balance with bacteria flora [3].

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Q7 Hyperviscosity syndromes

Hyperviscosity may be secondary to the following: [1]

- (1) Increased plasma viscosity (hyperfibrinogenemia or hypergammaglobulinemia).
- (2) Increased number of red or white blood cells (polycythemia vera, or myeloid and monocytic leukemias).
- (3) Decreased deformability of cells (sickle cell disease).

Clinical sequelae

- (1) Central nervous system: headache, deafness, nystagmus, and convulsions.
- (2) Cardiovascular: myocardial infarction and cerebrovascular accidents.
- (3) Visual loss: fundal hemorrhages and papilledema.
- (4) Hepatic affection: Budd–Chiari syndrome.
- (5) Pulmonary circulation: pulmonary embolism.
- (6) Platelet dysfunction: bleeding and thrombosis (deep vein thrombosis).
- (7) Leukocyte dysfunction: sepsis.
- (8) Increased plasma volume: dilutional anemia.

Q8 Gangrene of the toes with normal pedal pulse [2]

- (1) Vasculitis (small vessel e.g. leucocytoclastic vasculitides).
- (2) Diabetes mellitus.
- (3) Hyperviscosity syndrome.
- (4) Thromboembolism.
- (5) Iatrogenic (excess ergot or dopamine)

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