The Critically-Ill Pediatric Oncology Patients
What the Intensivist Needs to Know?

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Abstract
Cancer is evolving cause of morbidity and mortality in children globally. In the recent decades, there has been a marked increase in overall survival of children with cancer, after applying multiple novel methods of treatment. However, the complexity of the disease itself, as well as the intensity and toxicity of treatment is such that many children require admission to pediatric intensive care unit (PICU) which are well equipped with personnel who have adequate training and expertise to provide optimum care to these complex patients.
Here we provide a summary of the essential current evidence from published reviews to help PICU physicians take care of this patient group.

Keywords: Oncology; Cancer; Pediatrics; Critical Care; Intensive Care

Background
The significant improvement in survival rate of cancer patients is a result of better understanding of disease process. Although the overall outlook of pediatric cancer is excellent according to recent data, this success has not been universal due to lack of medical or nursing expertise, limited access to anticancer treatments and absence of concepts such as multidisciplinary management.

Depend on that more dedicated knowledge and focus on Oncological problems is therefore warranted to achieve better outcomes [1-4] taking to the count that according to statistics one in three children with cancer is admitted to the PICU at least once during their illness [5-9].

Cancer can involve any organ system of human body and can compromise vital functions including respiratory, cardiovascular, hemodynamic, renal or neurological systems, often requiring advanced life support such as Mechanical Ventilation, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO).

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Additionally, some cancers either inherently, or because of therapy, behave like chronic diseases with periods of decompensation that need intensive care treatment such as congestive heart failure, chronic respiratory failure and encephalopathies.

**What intensivist needs to know?**

The specificity of such patient and their unique presentation require from the intensivist to know the following:

- The type of oncology illness and its stage.
- How malignant the illness is, the distribution of illness and metastasis if present?
- The availability of oncology service in the hospital as support side by side with the intensivist.
- The approved policies and regulations for the treatment, the expected complications or palliative care measures if needed.
- Medications side effects and oncology emergencies.
- The availability of equipment’s and other subspecialties if needed.

Indications for PICU admission can be broadly categorized into:

A) Oncological emergencies.

B) Decompensation from treatment and its side effects.

In reported statistics Respiratory failure accounts for 45% of all oncology admissions to PICU, Sepsis and Septic shock 30%, Neurological problems 15%, while Tumor lysis syndrome (TLS) and renal dysfunction account for 10% total admissions to PICU [8-12].

**Figure 1: Causes of PICU admission for oncology patients.**

**Oncology emergencies**

**Superior vena cava syndrome**

Superior vena cava syndrome (SVCS) refers to the symptoms resulting from compression or obstruction of the SVC.
The most common cause in children are compression of SVC by a malignant tumor mass such as lymphoma, neuroblastoma or a Germ Cell Tumor (GCT). Other causes such as a veno-occlusive thrombus as a paraneoplastic phenomenon or related to central venous access device (CVAD). SVCS resulting from a tumor mass typically presents at the time of diagnosis or relapse, while occlusive thrombus can lead to SVCS at any time during treatment.

Presenting features include cough, shortness of breath, wheezing, chest pain, facial swelling, syncope, headache, orthopnea, hoarse voice and jugular venous distention and blood pressure changes.

The diagnosis usually achieved by Chest X-Ray or Computed Tomographic (CT) scan demonstrating obstruction or narrowing of SVC either by a venous thrombus or by a tumor mass, alongside secondary features of pleural and pericardial effusions, pulmonary edema and cardiomegaly.

Treatment and recommendations
Supportive measures including optimal positioning of child to minimize the obstruction, oxygen inhalation and rarely mechanical ventilation. Endotracheal intubation in this circumstance can be extremely challenging and requires the most experienced physician.

Every effort should be made to establish the tissue diagnosis by means other than biopsy of the mediastinal mass, such as flow cytometry of peripheral blood/bone marrow aspirate, assay of tumor markers such as alfa fetoprotein (AFP) or beta subunit of human chorionic gonadotrophin (BHCG), urinary estimation of urinary vinyl mandelic acid (VMA) and Homovanlalic acid (HVA), pleural or pericardial fluid cytology. However, SVCS is a true Oncological emergency and justifies starting chemotherapy even before confirmation of histopathological diagnosis in the face of a patient who is clinically deteriorating, and the above investigation cannot be performed or has not established the diagnosis [13].

Spinal cord compression
It results from of a tumor mass invading the vertebrae leading to their collapse resulting in compression of nerve roots. Alternatively, increased pressure in the spinal canal causes cord edema, venous hemorrhage, and ischemia.

The most common oncological causes of spinal cord compression are neuroblastoma, Non-Hodgkin Lymphoma and sarcoma. Bony vertebral metastatic lesions can also result in spinal cord compression in some patients, although it occurs less frequently in pediatric practice.

Symptoms of spinal cord compression depend on the spinal level of involvement, but include back pain, relatively symmetrical motor weakness, gait abnormalities, bowel and bladder dysfunction, numbness, and decreased ability to differentiate between dull and sharp pain.

Diagnosis is based on a complete neurologic exam and typical features on magnetic resonance imaging (MRI) [14,15].

Treatment and recommendations
Treatment can include the use of high-dose steroids and urgent chemotherapy if the primary diagnosis is known.

The most immediate and effective treatment is neurosurgical decompression of the cord via laminectomies of the most affected vertebrae, as it leads to immediate relief of paraplegia in addition to providing access to all-important tissue for diagnosis.

Tumor lysis syndrome
Tumor lysis syndrome (TLS) is a potentially life-threatening condition for children with leukemia and some solid tumors with large tumor burden either due to cytotoxic therapy or less commonly, spontaneously. Various definitions of clinical and laboratory TLS have been devised, which mainly describe the severity of renal compromise.
Massive tumor cell turns over and cells lysis results in rapid release of potassium, phosphorus and nucleic acids, which are metabolized into hypoxanthine, then xanthine and finally uric acid. Hyperkalemia can cause cardiac arrhythmias. Hyperphosphatemia can cause secondary hypocalcemia, leading to neuromuscular tetany, and seizure. Uric acid can induce acute kidney injury not only by intra tubular crystallization but also by crystal-independent mechanisms, such as renal vasoconstriction, impaired autoregulation, decreased renal blood flow, oxidation, and inflammation [16].

Presenting features include electrolyte’s imbalances; high Potassium, phosphorus, magnesium and uric acids in the plasma, which can lead to uric acid crystallization in kidneys tubules lead to acute renal failure.

diagnosis Mainly achieved by strict follow up labs for electrolytes, LDH and uric acid level with frequency every 4 to 6 hours in order to prevent complications related to imbalances as well as strict input and output urine charts.

Treatment and recommendations

Goal of effective TLS management is maintenance or restoration of normal kidney function with rapid elimination of tumor lysis products [17]. There is a lot of treatment protocols for TLS but in general it’s all shares the same principles as following summary table.

| Clinical Problem                        | Approach     | Dosages                                                                 | Comments and recommendations                                                                 |
|-----------------------------------------|--------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Renal insufficiency and hypovolemia     | IV fluids    | 0.9% sodium chloride at 3 L/m²/day (or 200 ml/kg/day if the child is less than or equal to 10 kg). | • Use with caution in cases of kidney failure  
• Monitoring of serum sodium concentration (along with tumor lysis laboratory monitoring) is recommended to avoid hyper/hyponatremia, especially in the setting of impaired urine output  
• If requiring more than 3 L/m²/day IV hydration, the urine output should be approximately 100% of total fluid intake. Consider dialysis and expert consult                                      |
|                                        | dialysis     |                                                                         |                                                                                               |
| Hyperuricemia                           | Allopurinol  | Children < 6 years: 150 mg daily  
Children 6 to 10 years: 300 mg daily  
Children >10 years and Adolescents: 600 to 800 mg daily for 2 to 3 days in 2 to 3 divided doses  
Weight-directed dosing: 10 mg/kg/day divided every 8 hours  
maximum daily dose: 800 mg/day  
BSA-directed dosing: 50 to 100 mg/m²/dose every 8 hours  
maximum daily dose: 300 mg/m²/day  
IV: (BSA-directed dosing):  
Children and Adolescents: Initial: 200 mg/m²/day administered once daily or in equally divided doses at 6-, 8-, or 12-hour intervals | • Reduce dose in renal failure; multiple drug interactions (6-mercaptopurine and azathioprine)  
• IV allopurinol should be used only in patients unable to take oral medications                                                                 |
|                                        | Rasburicase  | 0.05 - 0.2 mg/kg IV once daily up to 5 days                           | • Contraindicated in G6PD deficiency  
• Risk of sensitization and allergic reactions                                                                 |
### Hyperphosphatemia

**Definition:** Phosphate level > 6.5 mg/mL (> 2.1 mmol/L)

| Agent | Dosage and Administration | Notes |
|-------|---------------------------|-------|
| Sevelamer | **Oral:** BSA ≥ 0.75 to < 1.2 m²: 800 mg 3 times daily with meals; titrate as needed by 400 mg per dose at 2-week intervals. BSA ≥ 1.2 m²: 1,600 mg 3 times daily with meals; titrate as needed by 800 mg per dose at 2-week interval should be limited to 1,500 mg/day of elemental calcium and total calcium intake (including dietary sources and calcium-based phosphate binders) should not exceed 2,000 mg/day of elemental calcium. | - Low phosphorus diet  
- Phosphorus-free IV fluids  
- Phosphate binders may interfere with drug absorption if no response to medical therapy. |
| Calcium carbonate | | |
| Insulin (regular) | 0.1 units per kg maximum dose of 10 units | To be given along with dextrose infusion to avoid hypoglycemia. |
| Dextrose (50%) | 0.5 g/kg over 30 minutes, by IV infusion over five minutes. | Monitor glucose level regularly.  
- Time to onset of action is immediate.  
- Children younger than five years of age - Give 10 percent dextrose (100 mg/mL) at a dose of 5 mL/kg.  
- Children five years of age and older - Give 25 percent dextrose (250 mg/mL) at a dose of 2 mL/kg (maximum dose 25 g). |
| Calcium gluconate (10%) | IV 100 mg/kg (maximum dose: 3,000 mg) may repeat in 10 minutes if necessary. | Rapid infusion may cause bradycardia.  
- In the clinical setting of a cardiac arrest or impending arrest, calcium chloride is typically used rather than calcium gluconate because it results in a more rapid increase in the serum ionized calcium.  
- At dose 20 mg/kg (maximum dose 1000 mg) given over 5 to 10 minutes. |
| Sodium bicarbonate | 1 mEq/kg (maximum dose 50 mEq), IV over 10 to 15 minutes. | Avoid giving at the same line of calcium as it will block the line if no good flush.  
- It can be given as 1 mL/kg of an 8.4 percent solution.  
- For children less than six months of age, as 2 mL/kg of a 4.2 percent solution. Although dosing can be repeated, there is a risk of developing hypernatremia with repeated doses. |
| Sodium polystyrene sulfonate (Kayexalate) | - Oral, nasogastric: 1 g/kg/dose every 6 hours; maximum dose: 15 g/dose  
- Rectal: 1 g/kg/dose every 2 to 6 hours maximum dose range: 30 to 50 g/dose | Oral route more effective than rectal.  
- In case of rectal administration retain at least 15 to 60 minutes. |

### Hyperkalemia

| Agent | Dosage and Administration | Notes |
|-------|---------------------------|-------|
| Sodium bicarbonate | 1 mEq/kg (maximum dose 50 mEq) IV over 10 to 15 minutes. | Avoid giving at the same line of calcium as it will block the line if no good flush.  
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### Albuterol Inhaled

Dialysis

| Neonates - 0.4 mg in 2 mL of saline. |
| Infants and small children < 25 kg |
| 2.5 mg in 2 mL of saline. |
| Children between 25 and 50 kg |
| 5 mg in 2 mL of saline. |
| Older children and adolescents > 50 kg |
| 10 mg in 2 to 4 mL of saline |

- Inhaled albuterol may also be administered by metered dose inhaler (MDI) as 4 to 8 puffs with a spacer.
- Can be given concomitantly with the combination of IV insulin and glucose, or sequentially for patients who may not respond adequately to insulin/glucose therapy.

### Calcium gluconate (10%)

- IV 100 mg/kg (maximum dose: 3,000 mg) may repeat in 10 minutes if necessary
- Only if symptomatic; repeat as necessary; use with caution in patients with severe hyperphosphatemia

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**Table 1:** Summary of TLS metabolic abnormalities and its treatment [18].

### Decompensation from treatment and its side effects

#### Cancer and respiratory system

Some children present with overwhelming lung infections with bacterial or fungal pathogens resulting in respiratory failure. Others who present with a clinical picture of sepsis, have poor peripheral perfusion and hypotension, which requires fluid resuscitation and inotropic support and if severe the patient commonly requires mechanical ventilation. The final common pathway in both situations is development of acute respiratory distress syndrome (ARDS), which is defined according to the American-European Consensus Conference [19] by criteria of: acute onset, PaO₂/FiO₂ ≤ 200 mmHg (regardless of positive end-expiratory pressure level), bilateral infiltrates on chest radiograph, and no evidence of left atrial hypertension. The SpO₂/FiO₂ ratio could be used in the evaluation of lung disease severity if an arterial catheter not available [20].

Noninvasive ventilation (NIV) is of interest in this group of patients as they are highly susceptible to infections taking to account their fragile mucosal barrier and high risk of mucositis that accompanies neutropenia.

Conventional invasive ventilation requires endotracheal tube, which is associated with risk of iatrogenic damage through pressure of inflated cuff, especially if mechanical ventilation is required for periods longer than two weeks.

The benefits of NIV for immunocompromised patients have been documented in both adults and children [21-25]. In retrospective studies by Schiller, et al. reported data from 14 pediatric haemato-oncology patients with ALI and 23 pediatric haemato-oncology patients with ARDS, respectively. All patients received NIV via a full-face mask or a helmet. Intubation was avoided in 12 of 14 and 13 of 23 patients, respectively.

Considering the potential benefits of early NIV documented in adults, it is important for the pediatric intensivist to consider a trial of NIV in this group of patients. However, there will always be situations where patients will require invasive ventilation depending on clinical severity and rate of progression of ARDS. In balance, close monitoring is essential in all cases, and a possible switch to invasive ventilation should be discussed if there is no improvement after the first 2 hours of ventilation.

The criteria identified as predictive of NIV failure in the general PICU population are the presence of a second organ failure, pH < 7.25 after or more than 2 hours of treatment, the need for a high level of support (mean pressure > 12 cmH₂O or FiO₂ > 0.6), and the presence of ARDS [26-28].

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Cancer and sepsis

Several factors put the child with cancer at risk of developing sepsis during their treatment. These include type of malignancy (hematological malignancies having a greater risk than solid tumors), time-point in treatment and chemotherapy regimen being applied (some drugs are more myelosuppressive than others), duration and depth of neutropenia, integrity of skin and mucosal barriers. Presence of comorbidities and indwelling catheters also increase the risk of developing sepsis [29,30].

The Sepsis-3 definitions call for a new clinical tool to replace the criteria for systemic inflammatory response syndrome (SIRS) in identifying patients with sepsis. Because SIRS definition are non-specific, as they are not present in all patients with infection, and they do not necessarily reflect an abnormal host response. Most cases of neutropenic fever are managed outside the PICU setting with broad spectrum antibiotics. Pediatric intensivist is only involved in cases with advanced sepsis or septic shock. It is useful to remember that the early warning sign of fever is often absent in the oncology patients. Physicians therefore must rely on other parameters to determine the stage in the sepsis cascade. Febrile or hypothermic child, with evidence of fluid redistribution (tachycardia, poor perfusion, hypotension are all signs of impending and current sepsis. High serum lactate levels raised inflammatory markers (CRP, procalcitonin) or organs dysfunction aid the diagnosis and used as orientation in treatment approach.

The corner stone of sepsis treatment remains the empirical use of broad-spectrum antibiotic therapy. A variety of approaches, including both mono therapeutic and multidrug regimens, have been demonstrated to be effective, although no one regimen has been proven to be superior to another. Changes in the epidemiology of infectious organisms and the growing emergence of highly drug-resistant strains make it necessary to continually reevaluate the antibiotic selection. Optimal management is directed by the findings of a clinical evaluation of the patient as well as an awareness of institutional patterns of infection and susceptibility of likely infecting organisms [31,32]. Evidence-based guidelines for the management of patients with neutropenic fever have been developed by the infectious disease society of America (IDSA). In practice patients have already received the first dose on the floor or emergency department before their admission to PICU. Subsequent antibiotic management is directed by blood/body fluid cultures and indirect evidence of pathogens if isolated. This group of patients is also at risk of contracting invasive fungal infections including candida species and invasive aspergillosis, especially those with prolonged neutropenia and hematopoietic stem cell transplant (HSCT) recipients. Patients with persistent fever are at a high risk of developing complications and need prompt consultation from an infectious disease’s physician [33-37]. In supportive measures, hematopoietic growth factors, including granulocyte colony stimulating factor (GCSF) administration should be part of the treatment of septic neutropenic patients at high risk of infectious complications, expected prolonged (>10 days) or profound severe neutropenia (ANC) less than 100, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction [38].

Cancer and cytokines release syndrome

New novel immunotherapies like chimeric antigen receptor (CAR) T cell therapies. have recently been applied into clinical practice after showing impressive therapeutic activity in treatment of refractory acute lymphoblastic B cell leukemia (B-ALL), as such therapy protocols will increasingly be used in clinical practice plus the fact of reported sever inflammatory response and cytokines release syndrome (CRS) generated after its use as reported by Foster and Maude in 2018, it becomes paramount that oncologists and intensive care specialists are familiar with the complications of such therapy. Cytokines release syndrome can affect multiple organs and systems.

The pathophysiology of observed signs and symptoms is poorly understood and still under investigation, Interleukin 6 (IL-6) hold a key role in CRS pathophysiology since highly elevated IL-6 levels are seen in patients with CRS [43-45]. Treatment require collaboration between oncologist and intensive care specialist even severe CRS has a relatively good prognosis when appropriately treated, patients with CRS should be offered the full spectrum of modern critical care including mechanical ventilation, CRRT, ECMO if necessary.

Symptomatic treatment with antihistamines, antipyretics and fluids can be the start in mild cases. While not enough in other sever cases where application of therapy directed toward the pathophysiology of CRS is warranted in form of tocilizumab. By binding to mem-

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| System involved                          | Observed Signs and symptoms reported                                                                                                                                                                                                 |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| General appearance                      | Mild symptoms of fever, fatigue, arthralgia and myalgia can be the start of CRS storm.                                                                                                                                                   |
| Hemodynamics and Cardiovascular system  | Tachycardia, hypotension and septic shock with the need of vasopressors and inotropic support in ICUs have been reported also high level of troponin and cardiac arrhythmias in form of prolong Q-T interval after treatment, cardiomyopathies and acute heart failure observed in some cases. |
| Respiratory system                      | Cough and tachypnea but can Progress to acute respiratory distress syndrome (ARDS) with dyspnea, hypoxemia, may pulmonary edema and respiratory failure.                                                                                           |
| Central Nervous System                  | Neurotoxicity have been reported. With wide range of clinical presentation from mild confusion with word-finding difficulty, headaches and hallucinations to aphasia, hemiparesis, cranial nerve palsies, seizures and sever encephalopathies.          |
| Gastrointestinal system                 | Sever acute mucosities, diarrhea and colitis.                                                                                                                                                                                        |
|                                         | Nausea and vomiting                                                                                                                                                                                                                   |
|                                         | Splenomegaly, Hepatomegaly, elevation of liver enzymes, liver failure.                                                                                                                                                               |
| Kidneys and urinary tract               | Acute kidney injury and hematuria                                                                                                                                                                                                     |
| Blood and Metabolic abnormalities       | Cytopenias, coagulopathy, disseminated intravascular coagulation                                                                                                                                                                     |
|                                         | High CRP, elevated ferritin levels, and hypertriglyceridemia                                                                                                                                                                          |

Table 2: Effect of cytokines release syndrome on organs and systems [39-42].

brane bound as well as soluble IL-6 receptor tocilizumab interferes with both classical and trans-signaling pathways. Subsequent studies confirmed that administration of monoclonal antibodies against IL-6 (siltuximab) and its receptor (tocilizumab) led to rapid resolution of CRS symptoms [46-49].

Cancer and nervous system

The brain, spinal cord and peripheral nervous system can be impacted by cancer in several ways. Neurological presentations also vary significantly depending upon the location, size and biological behavior of the tumor. Presenting symptoms of CNS tumors include headache, vomiting, altered consciousness, gait disturbance, cranial nerve palsies, long tract signs and behavior change, seizures, growth and endocrine disturbances among others. Metastatic deposits of tumors arising outside CNS can also present in similar fashion. Leukemic infiltration of CNS can vary in presentation from asymptomatic, to seizures and deposition of solid masses of leukemic blasts.

Treatment toxicity and side effects can present with signs of raised intracranial pressure, posterior reversible encephalopathy syndrome (PRES) and leukoencephalopathy secondary to chemotherapeutic agents. Spinal tumors often come to light with back pain or paraplegia. There are often subtle symptoms predating the catastrophic signs of cord compression.

Majority of CNS manifestations are seen and treated by the Neurology and Oncology teams. Only a small proportion of these children are admitted to the PICU at some point during their treatment due to:

- Post-operative monitoring after tumor resection or biopsy, external ventricular drainage or VP shunt insertions where close monitoring of signs of rising or change in ICP are required.
- Uncontrolled seizures/status epilepticus.
- Complications caused by increased pressure in the brain and obstructive hydrocephalus.
- Ischemic stroke, hemorrhage.
- Spinal cord compression.

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The treatment of neurological presentations/complications is directed at treating the primary cause. This involves directly neurosurgical intervention, or anticancer treatment in the form of chemotherapy or radiotherapy.

**Anticancer therapy requiring PICU support**

A lot of chemotherapy used in practice and it’s important to know its side effects in order to predict complications and to direct treatment accordingly.

### Table 3: Anti-cancer agents with indications for PICU involvement.

| Anti-Cancer Agents                                      | Indications for PICU involvement                               |
|---------------------------------------------------------|----------------------------------------------------------------|
| L-Asparaginase                                          | Acute Pancreatitis                                           |
| L-Asparaginase, Rituximab, Alumtuzumab, Gemtuzumab      | Allergic Reaction                                              |
| Anti-thymocyte Globulin, Gamma Globulin, Etoposide, Carboplatin |                                                                  |
| Blood Products (especially in post Stem Cell Transplant setting) |                                                                  |
| Antimetabolites (Cytarabine, Fludarabine, Capcitabine)  | Severe Bone Marrow Suppression (Neutropenia, Thrombocytopenia) |
| Alkylating agents (Busulfan, Cyclophosphamide, Ifosfamide) |                                                                  |
| Anthracyclines (Daunorubicin, Doxorubicin, Idarubicin, Mitoxantrone) |                                                                  |
| Anthracyclines, Cyclophosphamide, Ifosfamide, Cytarabine | Cardiac (Dysrhythmias, Heart Failure syndromes)                 |
| Methotrexate, Ifosfamide                                | Cytokine Release Syndrome                                     |
| Cyclophosphamide, Ifosfamide, Radiotherapy              | Encephalopathy                                                |
| All Trans Retinoic Acid                                 | Hemorrhagic Cystitis                                          |
| Actinomycin-D, Busulfan, Cyclophosphamide, Cytarabine, Fludarabine, Gemtuzumab, Mercaptopurine, Roxithromycin, Thioguanine, Vincristine | Veno-occlusive disease of the liver                           |

**Conclusion**

Following the updates in the treatment protocols in and rapid improvement in the care of cancer patients require awareness from PICU doctors as in almost every Pediatric intensive care unit around the globe such patients will be encountered, special training programs for oncology PICU exist and new trainees always needed.

The PICU doctors should be aware of the common diseases and complications may face them while taking care of such patients, developing protocols and multidisciplinary approach is crucial for successful treatment and better outcome.

**Competing Interests**

The authors declare that they have no competing interests.

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