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# HPV Vaccines in Adolesient Girls

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## Abstract

Adolescence is a transitional journey from childhood to adult life along with physical development and sexual maturation. This may be considered as physical, psychological and emotional rebirth. HPV is the cause of variety of proliferative lesions in humans including anogenital warts and neoplasia. Immunization is one of the most important, most beneficial and cost effective disease prevention measures that can be provided for adolescents. Bivalent and quadrivalent vaccines are available. The development of HPV vaccines is a major medical achievement of 21st century. Finally, there is hope that cervical cancer may be controlled globally.

**Keywords:** Adolescent, vaccine, cervical cancer, HPV, prevention.

## Introduction

Adolescence is a transitional journey from childhood to adult life along with physical development and sexual maturation. This may be considered as physical psychological and emotional rebirth.[1] Human Papillomavirus (HPV) a non enveloped DNA papovavirus, is the cause of a variety of proliferative epithelial lesions in humans including anogenital warts and neoplasia.[2] HPV with over 100 types have been characterized. HPV types have been decided as low and high risk depending on the types of lesions caused. Low risk HPV types such as 6 and 11can cause genital warts. HPV types 16,18,45 and 31 are the most important of the high risk or oncogenic types all around the world. Prevalence of HPV is greatest in women aged less than 25 years and can be acquired by skin-to-skin contact.[3] Spread primarily through sexual transmission, the human papilloma virus causes all type of cervical cancer cases a disease that too often, affects relatively young women in the height of their reproductive years. It also causes vaginal cancer in women, penile cancer in men, and throat and anal cancer in both men and women.[4] It causes more years of life lost than any other form of cancer, with immeasurable human costs. Every two minutes somewhere in the world, some women will lose her life to the disease.

High risk HPV are unusual viruses that are confined to the mucosal epithelial cells in the cervix or genital tract and do not spread to the rest of the body. They therefore stimulate epithelial cells that down-regulate the local response, and prior infection with this virus does not induce immunity against subsequent infection. The vaccine is given by intramuscular injection and thus escapes this down

regulation by stimulating a direct systemic response.[3]

Clinical studies carried out to date in 15-25 years old women, have shown that the vaccine prevents HPV 16 or 18 associated persistent infections, abnormal cytologies and CIN lesions.[3]

The immunization is one of the most important, most beneficial and cost-effective disease prevention measures that can be provided for adolescents. The adolescent's vaccination protects most of the world's adolescents from the number of infectious diseases that previously claimed millions of lives each year. Main aims of adolescent's vaccination are: to boost immunity status that is waning after completion of primary immunization or absence of "natural" boosting due exposure to particular disease.[5] Three important infections (Neisseria meningitidis, Pertussis and HPV) for which effective vaccination is now available are especially prevalent in the adolescent years, making the adolescent age group the ideal target age for prevention.

***The Primary Objective of an Anti-HPV Vaccine would be:***

- *Prophylactic:* To prevent primary infection in susceptible population
- *Therapeutic:* To eliminate infections in populations infected. Two prophylactic vaccines have already been marketed and others are under development. Therapeutic vaccines are still under research.[6]

There no drug therapy available against HPV virus unlike treatment of HIV infection. However prophylactic vaccines are currently marketed. The development of HPV vaccines is a major medical achievement of 21st century. Finally, there is hope that cervical cancer may be controlled globally.[7]

*Prophylactic HPV Vaccines*

Mechanism of action of Prophylactic HPV Vaccines

The most crucial factor that stimulated interest in HPV vaccine development was the evidence that protection against infection by papillomaviruses could be accomplished successfully. A successful immune response to genital HPV infections is characterized by strong, local cell mediated immunity that is associated with lesion regression and protection against a further infection with the same genotype of HPV. Humoral immunity (antibody) is generated in most, but not all infected individuals. Despite low antibody levels, seropositive individuals are protected, probably for life, against further viral challenge, thus suggesting that vaccines that generate neutralizing antibodies to HPV capsid protein will be effective prophylactically.

In contrast to most viral vaccines which are based on an attenuated form of virus (for example polio vaccine), the development of an attenuated HPV vaccine has been difficult because there is not effective cultural system to propagate the virus. An attenuated vaccine could also potentially cause disease in vaccinated subjects, particularly if they were immunocompromised. Thus, an optional VLP-based (virus like particles) vaccine will require multiple vaccine components to provide good coverage against diseases caused by more than one virus type.

Three doses of both vaccines are recommended.[8]

- *Bivalent vaccine*
  - Cervarix
  - Protect against HPV 16 and 18.
  - Delivered by intramuscular route as a 0.5ml dose.
  - Vaccine Schedule:

| | |
|---|---|
| Zero point | 1st dose |
| One month | 2nd dose |
| Six months | 3rd dose |

- *Quadrivalent vaccine*
  - Gardasil
  - Protects against HPV 6, 11, 16 and 18.
  - This vaccine also prevents cancer cervix, genital warts, vaginal intraepithelial neoplasia and vulval epithelial neoplasia.
  - Vaccine Schedule:

| | |
|---|---|
| Zero point | 1st dose |
| Two months | 2nd dose |
| Six months | 3rd dose |

It has become a part of routine national health care and cancer screening programme in many countries. They are manufactured by recombinant DNA technique producing non-infectious virus like particles (VPL) with HPVL1 protein. Hence, it is not a live vaccine.

*Target Population*

Since HPV vaccines are prophylactic vaccines, the most appropriate target population for HPV vaccination will depend on the age at which individuals first get exposed to HPV. This depends on the sociocultural behavior patterns of the region.

The Food and Drug Administration (FDA) has licensed the HPV vaccines for use in girls and women aged 9-26 years.[9] It can be started as early as 9 years but routinely in females at age 11-12 years. Vaccination of sexually active women of any age can be done but the benefits may be less if the subject is already infected with one or the other virus. The

vaccine is also recommended for 13-26 year old girls/ women who have not yet received or completed the vaccination series.

Since the vaccine does not protect against all types of HPV, it will not prevent all cases of cervical cancer or genital warts, so it will be important for women to continue getting screened for cervical cancer by regular PAP tests.Thus, even after vaccinations-creening programme should be continued as per schedule.[6] Some countries have licensed the vaccine for use in boys as well. The case for male vaccination against HPV relies on the establishment of herd immunity, thus reducing the chances of an infected individual transmitting the virus to a susceptible person. The quadrivalent vaccine immunize against HPV types that cause genital warts as well, so it may be more likely to be taken up by teenage boys.[6]

### *Immunogenicity*

Protection is observed among women with a wide range of antibody titers. Peak antibody titers in trial are achieved 1 month after dose 3, i.e., at month 7, after which detectable titers decline until about month 18, when the rate of decline decreases considerably and titer appear to stabilize over the next few months at or above titers observed in women with naturally acquired and cleared infections. The total duration of protection is not yet known.[6]

### *Adverse Effects*

- Reaction at injection site: pain, redness or swelling.
- Fever.
- Headache, fatigue, myalgia.
- Gastrointestinal complaints.
- Itching.[10,11]

Most adverse effects are mild to moderate in intensity. Thus, both vaccines generally appear to be safe and well tolerated.

## Discussion

The major obstacles to implementation of HPV vaccine programs include:

- Cost.
- Lack of public awareness and infrastructure.
- Concern about unknown side effects, social and religious barriers.
- Parental concerns which include the possibility of change in sexual behavior of teenagers due to a false sense of security against STIs which may lead to an increase in other STIs.
- Since HPV vaccines are cancer prevention vaccines it may be difficult for parents to understand the role of vaccinating 9 to 13 years old girls for a cancer that they are unlikely to develop for at least two to three decades.[6]

### *Future Prospects*

Most countries that introduce HPV vaccination will eventually want to switch to HPV-DNA testing as the primary screening test since it has better performance characteristics than cervical cytology and also using HPV testing for screening coupled with HPV genotyping will provide a simple strategy to monitor long-term protection among vaccinated women. Rapid and cheap HPV testing systems amenable to use in areas with limited health infrastructures are currently being developed and evaluated.[6]

### *Second Generation Vaccines*

The current VLP vaccines have fundamental weakness for achieving their goals, particularly in developing countries, where most cervical cancers occur. Attempts are been made to overcome these short comings. Some of the new generation of vaccines under study are:

- Additional VLP types: (HPV-31, 45, 33, 52 etc.)[12]
- Heat stabilized VLPs.[13]
- Slow-release formulations.[14]
- Oral vaccines.[15]
- Chimeric VLPs.[16]

Chimeric VLPs have been shown in preclinical studies to elicit both neutralizing antibodies to the VLP and T-cell responses to L1 and oncogenic protein E7, thus offering better protection. Polynucleotide vaccines are being considered because of the ease of production and delivery in the developing world and the ability to generate both B and T-cell responses.[17] Capsomere vaccine may offer a simplified, economical alternative to VLPs that is particularly suited to the developing world where the burden of cervical cancer is greatest.

### *Theraputic Vaccines*

Therapeutic vaccines are aimed at eradicating or reducing infected cells. They are based on the generation of cell-mediated immunity. Agents that are in or nearing clinical trials are:

- HPV peptides.
- Fusion protein of HPV-16 L2/E7 and dendritic cells.

Vaccine efficacy in preventing genital warts was 100%. Cross protection has also been reported against other high-risk HPV genotypes. In recent reports, comparable safety, efficacy and immunogenicity of HPV vaccines have been reported in women aged 24 to 45 years.

The ministry of health and family welfare, government of India should make the policy for adolescent vaccination and community at large need to be made more aware about the value of adolescent immunization. There is need to strengthen other areas like health care quality measures, quality surveillance and research.[6]

### *Building Confidence in the HPV Vaccine*

Building public trust is a crucial objective of immunization programs around the world, and this particularly true when a new vaccine is introduced. The vaccine is extremely safe and highly effective in protecting girls against the most dangerous strains of the virus. We must work together to reach women and girls - wherever they live in the world - with effective, high quality prevention including vaccination, screenings and treatment. No women should die from a preventable disease. Benefits of vaccination far outweigh positive risks of potential side effects.

## Conclusion

In developing countries, where screening services are sporadic because of unpredictable funding and poor infrastructure. HPV vaccination represents a great hope in the fight against cervical cancer. Public awareness activities are needed aiming to provide parents, young people, schools and health workers with fact-based information on HPV and cervical cancer.

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# Enteral Nutrition in the Pediatric Intensive Care Unit

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## Abstract

*Background*: Occurrence of malnutrition in critically ill children is associated with higher morbidity and mortality. Critically ill children have to face various challenges to meet adequate energy needs. It is important to identify patients who are already malnourished or might become so during their illness by appropriate nutritional assessment. The main purpose of this review article is to discuss various aspects of enteral nutrition in the pediatric intensive care units.

*Methods*: A literature search was conducted in the PubMed database using word combinations of controlled vocabulary (MeSH terms):'enteral nutrition' and 'critical illnesses'. The methodology used for literature retrieval has been discussed in details in the main text.

*Results*: To reach an optimal nutrition, target caloric and protein requirement should be calculated by indirect calorimetry (ideally) or by standard formulae (like Schofield or WHO equations). Nutrition (in critically ill children) should preferably be provided in the form of enteral nutrition as early as possible (if there are no contraindications). It is vital to know the indicators of feed intolerance and side effects/complications of enteral feeding. Feed interruptions are very frequently encountered in the pediatric intensive care units with most of them being (actually) avoidable interruptions.

*Conclusions:* All the available local data should be put together to develop locally-suited algorithms to initiate and maintain enteral feeding which should be implemented strictly by a multidisciplinary nutrition support team.

**Keywords:** Algorithm; Critically ill; Enteral feeding; Intensive care; Malnutrition; Mortality; Nutrition; Vasoactive agents.

## Introduction

Optimal nutrition is a key feature in the management of all pediatric patients, especially those with a critical illness. This is required to deal with the increased metabolic needs in critical illnesses, to promote tissue repair and wound healing, to prevent loss of muscle mass, to alleviate the dysfunction of the immune system and to improve the functioning of the gastrointestinal system.[1] There are international as well as Indian studies depicting the incidence of malnutrition in the pediatric intensive care units (PICUs). De Souza et al. reported an incidence of 45.5% of malnutrition in a prospective study conducted in 385 children in the PICU.[2] Chaitra et al. from India showed that 55% of the critically ill children admitted in the PICU had a suboptimal nutritional status.[3] Nutrition delivery has been found to be inadequate in mechanically ventilated patients with an overall energy and protein intake of only

38% and 43% of the prescribed goals (respectively) as reported by Mehta et al.[4] In critically ill patients, malnutrition develops rapidly due to acute phase responses, which promote catabolism and alter the response to nutritional support.[1] Poor nutrition in the form of over-nutrition or under-nutrition has been found to adversely affect the final outcome, the hospital stay and the incidence of hospital acquired infections.[2,5] Castillo et al. reported a mortality of 42.6% in malnourished children in their prospective observational study on 174 critically ill patients on continuous renal replacement therapy.[5] De Souza et al. reported that malnutrition was associated with a longer duration of mechanical ventilation and PICU length of stay.[2]

Therefore, timely assessment of nutritional status in critically ill patients is extremely important to prevent nutritional problems and to monitor adequacy of nutritional therapy. In addition, early nutritional screening is a key factor in initiating appropriate nutritional intervention that may reduce the length of ventilator dependency, the ICU/hospital stay and the mortality.[6]

The essential goals of appropriate nutrition in a critically ill child are accurate assessment of nutrition requirements, prevention of over-feeding and under-feeding, initiation of (early) enteral nutrition (EN) and monitoring for energy and protein imbalance.[7,8] Although nutrition in the ICU setting can be provided by enteral or parenteral methods, the scope of this article is limited to enteral nutrition only. The aim of this article is to discuss various aspects of enteral nutrition for pediatricians managing critically ill patients, postgraduate students and those interested in intensive care.

## Methodology

A literature search was conducted in the PubMed database using word combinations of controlled vocabulary (MeSH terms):'enteral nutrition' and 'critical illnesses'. These controlled vocabulary terms were combined using 'AND' Boolean connector. The results were limited to studies available in English language. The age limit was set from birth to 18 years of age with a period from 2004 to 2019 (1678 articles hits seen) and purely neonatal articles (60) were excluded from the articles thus retrieved. Final list included 1618 articles which were finally shortlisted to 46 to include citations relevant to our review (we excluded the articles whose results were already incorporated in the guidelines and other reviews) with an emphasis on review articles, landmark articles and a couple of book chapters were also included.

### *Nutrition assessment*

All patients should be screened for malnutrition (on admission to the PICU). In this way, those who are already malnourished at the time of admission, or those who are at-risk of becoming malnourished can be identified.[6] The SCCM (Society of Critical Care Medicine) & ASPEN (American Society of Parenteral & Enteral Nutrition) 2017 guidelines recommend nutritional assessment of all patients in PICU within 48 hours of admission and then once weekly to assess risks of nutritional deterioration in the PICU.[8] This assessment includes history, anthropometry, biochemical and immunological measurements.[9]

i. *History taking:* The first step in nutrition assessment is a complete history with special attention to nutrition history, acute presenting complaints, chronic illness/es, past hospitalizations and surgical procedures.[9]

ii. *Anthropometry*: Anthropometry measurements include weight for age, length or height for age, weight for height and Body mass index (BMI). Commonly recommended measurements by SCCM & ASPEN include BMI and weight for age in all children and head circumference in those less than 36 months.[8] In a multi-centric (over 90 PICUs) study conducted by Bechard et al., the BMI was correlated with outcome in mechanically ventilated patients in PICU.[10] Being underweight (BMI Z-score < -2) was associated with a higher chance of 60-day mortality and hospital-acquired infections; whereas obesity (BMI Z-score > 2) was significantly associated with longer hospital stay among survivors.[10] Lee et al. in their consensus statement on optimal nutrition (in the Asia Pacific and Middle East) recommend to use uniform reference standards within a country and international reference standards like WHO if robust regional data are not available.[9] The WHO terminologies for malnutrition (6 months to 5 years) include – Underweight (Weight for age <2 standard deviations of the WHO child growth standards median), Stunting (Height for age < 2 standard deviations of the WHO child growth standards median), Wasting (Weight for height < 2 standard deviations of the WHO child growth standards median) and Overweight (Weight for height >+2 standard deviations of the WHO child growth standards median)[11] (z scores are preferred over percentiles).

iii. *Biochemical markers*: These include albumin,

pre albumin, transferrin, urea, triglycerides and retinol binding protein but biochemical markers are not commonly recommended to assess nutritional status of critically ill patients in PICU.[8,9] Hulst JM et al.[12] conducted a prospective descriptive study finding the association between abnormal biochemical marker and outcome and changes in anthropometric parameters. Abnormalities of biochemical parameters did not predict changes in anthropometric parameters. Children with hypertriglyceridemia on admission had longer ventilator dependence (P<0.01) and length of stay (P<0.001) than children with normal triglyceride levels. No other biochemical parameter was found to be significantly correlated with the outcome. Patients with fluid overload may have unreliable anthropometry measurements whereas the biochemical parameters may be affected in acute inflammation.[9] Accurate assessment of nutritional status should be taught to the PICU working staff.

In developing countries, enough resources may not be available for evaluating all patients. In these circumstances, screening tests may prove useful to identify the high-risk patients.[8] The subjective global nutrition assessment (SGNA) is a validated tool for assessing malnutrition in children comprising history and physical examination but not yet accepted as a standard screening scale in PICU patients.[13] Another screening tool for assessment of nutrition is Pediatric Nutrition Screening Tool (PNST), which consists of 4 simple questions devised by Australian dieticians.[14] In a study conducted by White et al., the PNST score was found to be a simpler and valid alternative to old nutrition scales like Screening Tool Risk for the Assessment of Malnutrition in Pediatrics (STAMP), Screening Tool Risk on Nutritional status and Growth (STRONGkids) and Pediatric Yorkhill Malnutrition Score(PYMS). A definitive screening test has still not been developed which can be used uniformly in all countries.[8]

### *Energy and protein requirements*

After nutritional assessment, the next step is to determine the energy and protein requirements of the critically ill pediatric patients.

*i. Energy requirements*: Calculation of energy requirements for critically ill patients is difficult and varies through the ICU stay of the child. Measurement of resting energy expenditure (REE)with indirect calorimetry (IC) is the gold standard for calculation of energy requirement but requires a lot of expertise and specialized equipment.[8] It measures oxygen ($O_2$) consumption and carbon dioxide ($CO_2$) production.[15] It is a highly accurate and non-invasive method of determining the metabolic rate with an error rate of lower than 1%.[15] REE is calculated by the modified Weir formula[16]; REE (kcal/day):3.941($VO_2$) + 1.106($VCO_2$)] × 1440 where $VO_2$ is the volume of oxygen consumed and $VCO_2$ is the volume of $CO_2$ produced. This is not dependent on height and weight of the child. Chaparro et al. used indirect calorimetry to identify the energy requirement in critically ill children and noted that REE decreased with neuromuscular blockade and increased with rise in temperature in mechanically ventilated critically ill children.[17] If IC measurement of resting energy expenditure is not feasible/ available, the Schofield or Food Agriculture Organization (FAO) / World Health Organization (WHO) / United Nations University equations can be used (but without the addition of stress factors).[8] Studies show that this calculation/ formulae can lead to under-feeding or over-feeding. Mehta et al. reported that standard equations overestimated the energy expenditure leading to a high incidence of overfeeding (83%).[18] Sy et al. noted that the World Health Organization equation overestimated, and Schofield predictive equations underestimated the energy requirements (respectively) compared with those obtained by bicarbonate dilution kinetics.[19] Therefore, signs of over-feeding (like rapid weight gain, hyperglycemia, hypertriglyceridemia and increased $CO_2$ production) and signs of under-feeding (like weight loss, prolonged dependency on ventilation and increased PICU stay) should be monitored.[8,23] Underfeeding can lead to decreased respiratory muscle function and delayed wound healing while overfeeding can lead to increase in calories, which are converted to fat and cause more $CO_2$ production leading to increased work of breathing.[23] The Harris-Benedict equation used to calculate the basal energy expenditure is not recommended to calculate energy requirement in critically ill children as it is used for normal growing children and over predicts the energy requirements. The Schofield equation in males and females aged 0 to 3 years is 0.167W + 15.174H-617.6 and 16.252W + 10.232H-413.5 respectively.[20] The equations in males and females between 3 to 10 years are 19.59W + 1.303H + 414.9 and 16.969W + 1.618H + 371.2 respectively [where W is the weight (in kg) and H is the height (in cm)].[20] The WHO equations in males are 60.9W-54 between 0 to 3 years and 22.7W + 495 between 3 to 10 years.[20] In females it is 61W - 51 between 0 to 3 years and 22.5W + 499 between 3 to 10 years.[20] Wong et al. in their survey reported that dieticians preferred to use Schofield equation

whereas physicians chose total fluid requirement to develop the estimated energy goals.[21] Basal physiological processes in the body consume about 70% of the total energy requirements. Additional 10% energy is required for physical activity and 20% for digestion of macronutrients.[22,23] Addition of stress factors to resting energy expenditure can lead to inaccuracies.[20,21] There are certain situations where a percentage increase in the energy expenditure need to be calculated. These include fever (12%/*C above 37*C), cardiac failure (15-25%), major surgery (20-30%),burns (upto 100%) and severe sepsis (40-50%).[23]

*ii. Protein requirements*: The protein requirements in a critically ill child are much more than healthy children. Sick children have excessive catabolism which leads to a negative nitrogen balance due to proteolysis. Hence, it is necessary to start adequate protein intake early in the course of the illness to promote positive nitrogen balance which can lead to positive clinical outcomes.[8] Wong et al. reported (retrospective study) that early initiation of nutrition support and proteins was associated with lesser ICU mortality (p=0.002) and greater ventilator-free days (p=0.005) in ventilated children with acute respiratory distress syndrome (ARDS).[24] Similarly, Mehta et al. (observational prospective study) reported that adequate protein intake was associated decreased 60 day mortality in 985 patients (p<0.001).[25] Protein requirement can summarized (age-wise) as 0-2 years : 2-3 g/kg/day; 2-13 years : 1.5-2 g/kg/day and 13-18 years : 1.5 g/kg/day.[20]

### *Enteral Nutrition (EN) therapy*

The next step in nutrition management is the appropriate route of delivery. Nutrition can be provided by enteral or parenteral pathways. Enteral nutrition (EN) is the preferred mode of nutrition in patients with a functioning gastrointestinal system.[8] The functioning of the gastrointestinal tract is required to facilitate digestion, absorption and metabolism and to provide a barrier for infectious agents and toxins.[8] Factors affecting these functions include mucosal permeability, thickness and gut associated lymphoid tissue.[8] There are certain parameters that can assess the function of the gastrointestinal system like presence of bowel sounds, absence of abdominal distension and vomiting, absence of diarrhea after starting enteral feeds and absence of increase in abdominal girth by 10% from the baseline.[23]

i. *Benefits of enteral nutrition*: Enteral nutrition has been shown to improve the trophic stimulation of the gut and maintain the gastrointestinal barrier function.[8] It is also found to reduce the oxidative stress and reduce the metabolic and infectious complications. It prevents the translocation of bacteria and supports the gut associated lymphoid tissue. It is found to be safe, simple, economical and physiological.[8] Mehta et al. conducted an international prospective study in 31 PICUs in eight countries and followed patients during their PICU stay for a maximum of 10 days and subsequently followed them up until 60 days or till discharge.[4] They reported that enteral nutrition was started in 67% of the patients and a decreased incidence of 60-day mortality was observed in children receiving higher percentage of daily nutritional intake via the enteral route (p=0.002).[4]

ii. *When to start EN / initiation of EN*: It is recommended to start enteral nutrition early (within 24 to 48 hours of admission to intensive care) and reach up-to two thirds of the nutrient goal in the first week of the illness.[8] There have been various controversies regarding the role of early and delayed enteral feeding. In a retrospective study by Mikhailov et al. on 5105 patients, those receiving early enteral nutrition had an improved survival but did not affect length of stay or duration of mechanical ventilation.[26] A retrospective cross sectional study across six PICUS in the United States (US) conducted by Canarie et al. showed higher levels of respiratory support, increased severity of illness and gastrointestinal disturbances in patients as factors causing delayed nutrition.[27] Bagci et al. conducted a prospective observational study in nine PICUs in Turkey and stated that early enteral feeding is associated with early attainment of target enteral nutrition (patients who received more than 25% of the estimated energy requirement by enteral feeding within 48 hours of admission to PICU), which in turn improved the mortality.[28] Haney et al. showed that patients who received early enteral nutrition had a shorter PICU stay compared to those who did not.[29] Leroue et al. reported that 64% of the patients started enteral nutrition within 24 hours, with 72% achieving goal enteral nutrition rate within 72 hours and use of bi-level noninvasive positive pressure ventilation and continuous dexmedetomidine were independently associated with decreased likelihood of early enteral nutrition.[30] Early enteral nutrition has also been found to affect hospital

charges. In a retrospective study conducted by Mikhailov et al., early enteral nutrition in critically ill children was associated with lower total and daily hospital charges in 859 patients in 2 centers.[31] Balakrishnan et al. conducted a retrospective multicentric study in 416 children with head injury admitted in 5 PICUs and reported that delayed enteral nutrition (>48 hours) was associated with worse functional status at PICU discharge (p=0.02) but was not associated with mortality or increased length of stay.[32] Enteral nutrition should be started as early as possible in critically ill patients, as long as there are no contraindications and given cautiously in high risk cases (like those with high doses of inotropic supports or with risk of aspiration).[8] There is relative hypoperfusion to the gastrointestinal tract in hemodynamically unstable patients which is further aggravated by the use of vasoactive agents (like epinephrine, norepinephrine, dopamine, dobutamine, vasopressin and milrinone) by causing splanchnic vasoconstriction.[33] This theoretically increases the risk of multi system organ failure due to perfusion-reperfusion injuries to the gastrointestinal tract.[29] Therefore, enteral nutrition is given cautiously in those with high doses of vasoactive agents.[33] However, Panchal et al. conducted a retrospective study of 339 patients over 18 months and reported no adverse effects with the use of vasoactive agents during enteral nutrition.[33] Fluid restriction in certain conditions like acute or chronic kidney disease and congenital heart diseases can cause inadequate energy and protein intake in critically ill children. In a cross sectional study by Tume et al., various factors found to be associated with reduced energy delivery included fluid-restriction (60%), the child just being 'too ill' to feed (17%), post-surgery (16%), nursing staff slow in initiating feeds (7%), frequent procedures requiring fasting (7%) and hemodynamic instability (7%).[34]

*iii. Contraindications to EN*: Common contraindications for enteral feeding include intractable vomiting, high gastric aspirates, upper gastrointestinal bleeding, and use of inotropic or neuromuscular blocking agents.[23] Enteral feeding should be avoided in intestinal obstruction, paralytic ileus and bowel perforations.[23] Various aspects need to be checked before starting enteral feeding to confirm adequate intestinal function. Presence of bowel sounds; absence of abdominal distension and vomiting are some of these.[23] In the presence of these contraindications, they should be started on parenteral nutrition.

*iv. EN Interruptions*: Common problems which can act as a hindrance to enteral nutrition in PICUs include delayed initiation, interruptions due to perceived intolerance, and prolonged fasting around procedures. Interruptions are common due to intolerance to enteral feeding (emesis, diarrhea and high gastric residual volume), feeding tube issues (displaced or blocked tube) and pre-/ peri-procedure fasting (bedside or operating room procedures and endotracheal intubations/extubation).[35] There should be minimum interruptions in enteral feeding as far as possible. In a retrospective cohort study by Haney et al. over a 30 months period, feeding was interrupted in 19% of patients (mainly due to procedures) and most patients who developed feed intolerance were on inotropic agents.[29] Mehta et al. reported an interruption of enteral nutrition in 30% of patients with 58% of these being avoidable interruptions, especially in infants and those on mechanical ventilation.[36] A common criteria for perceived intolerance is high gastric residual volumes (GRV). GRV measurement in intermittent bolus feedings is performed prior to each feeds or every four hours in continuous feeding.[20] GRV is considered significant if it is 5 ml/kg or 150 ml or more than half the previous feeding volume.[20] In case of a high GRV, repeat measurement is done after 2 hours without any change in rate or volume of the feeds. If two consecutive GRVs are elevated, EN should be withheld and GRV should be monitored every four hours till it decreases. After reaching this point, feeds can be started again at 50% of the previous rate and volume.[20] Upper GI dysmotility (like abnormal fundal relaxation, antral and pyloric activity) is common in critically ill patients, which results in delayed gastric emptying.[35] This may occur due to inflammation, hypoperfusion, electrolyte abnormalities or drugs like sedatives & muscle relaxants (e.g. opiates).[35,37]

*v. Optimal route of enteral feeding*: Enteral feeding can be provided by the gastric or transpyloric pathway. Gastric feedings are

preferred as it is easier and does not require special expertise for insertion or feeding.[8] Transpyloric or postpyloric feeding is preferred when there is poor gastric emptying or failed trial of gastric feeding.[8] It decreases gastric aspiration and improves tolerance for feeding but requires great expertise.[8] Kamat et al. found no benefit in transpyloric over the gastric feeds and noted that those with transpyloric feeds had significant delays in initiating enteral nutrition due to the time required to insert the feeding tubes transpylorically.[38] Some patients may require long-term enteral nutrition by gastrostomy or jejunostomy.[8] Feeding can be given as bolus or continuous feeding.[23] Bolus feeding is more physiological, can allow movements of patients in between feeds and does not require infusion pumps.[23] Bolus feeding should be started at the rate of 10-15ml/kg every 3 hourly to a maximum of 20-30 ml/kg 4-5 hourly with an increase of 10-30 ml per feed.[23] Children aged 1-6 years should be given 5-10 ml/kg every 3 hourly increasing 30-45 ml per feed to a maximum of 15-20 ml/kg 4-5 hourly.[23] On the other hand, continuous feeding improves tolerance, absorption and adaptation but may require a pump for accurate delivery.[23] It can be started at 1-2 ml/kg/hour to a maximum of 6ml/kg/hour in infants. In children between 1-6 years, feeds can be started at 1ml/kg/hour with an increase of 1 ml/kg every 2-8 hours to a maximum of 5 ml/kg/hour.[23] Horn et al. noted no difference in feeding tolerance and gastric residual volumes between bolus (24 patients) and intermittent (22 patients) feeding groups.[39]

*vi. Complications of enteral nutrition*: Malpositioned feeding tubes may lead to perforation of pharynx, esophagus, stomach and sometimes even pneumothorax, which can occur at the time of insertion or later.[40] In some patients with high GRVs and gastric distention, there are chances of aspiration pneumonias.[40] Other side-effects include diarrhea, necrotizing enterocolitis and gastrointestinal hemorrhage.[40]

The SCCM &ASPEN guidelines (2017) recommend the use of parenteral nutrition (PN) as a supplement when children are not able to get enteral nutrition during the first week in the PICU.[8] In some critically ill children with intestinal failure, parenteral nutrition needs to be started immediately. It is important to use parenteral nutrition carefully as it is associated with complications like hyperglycemia, infection, hepatic and intestinal injury.[9]

For patients who are severely malnourished or at risk of nutritional deterioration, PN may be supplemented in the first week if they are unable to advance past low volumes of EN.[8] In stable patients, the total parenteral energy requirements can be calculated from resting energy requirements with adding constants for physical activity and catch-up growth. Lipid emulsions given intravenously is a major part of parenteral nutrition with a maximum limit of 3 g/kg/day. To prevent essential fatty acid deficiency, a minimum of 0.1 g/kg/day of linoleic acid should be added to the emulsion.[41] Immunonutrients (like glutamine, arginine, nucleotides, omega-3 fatty acids, fiber, antioxidants, selenium, copper, and zinc) are currently not recommended in critically ill children.[8]

### *Monitoring*

After starting EN, continuous monitoring of patients for maintenance of optimum nutrition is required. Various clinical and biochemical parameters need to be monitored for checking for optimal nutrition.[8] Daily weight, caloric and protein intake, abdominal girth and change in frequency and consistency of stools are the clinical parameters to be monitored daily.[8,23] Various biochemical parameters which can be monitored include serum prealbumin, procalcitonin, blood urea nitrogen, transferrin, C reactive protein, blood gas, glucose, triglyceride and retinal binding protein.[8,20] Monitoring is important to assess the clinical efficacy of enteral nutrition and identification of early signs of nutritional deficiencies.

It is important to monitor signs of overfeeding and underfeeding while on enteral nutrition. In a retrospective study conducted by Larsen et al.[42] reported that children who were overfed had significantly longer PICU stay compared to those who were appropriately or underfed. Children who were underfed had significantly higher CRP compared to those children in the appropriately fed and overfed groups.

### *Developing protocols/ algorithms/ other miscellaneous issues:*

It is important to develop guidelines for EN internationally, nationally and locally. There is a need to identify the problems with feeding at a local level so that they can be addressed as early as possible.[8] These guidelines should be taught to all the medical and paramedical (nursing) staff in charge of/

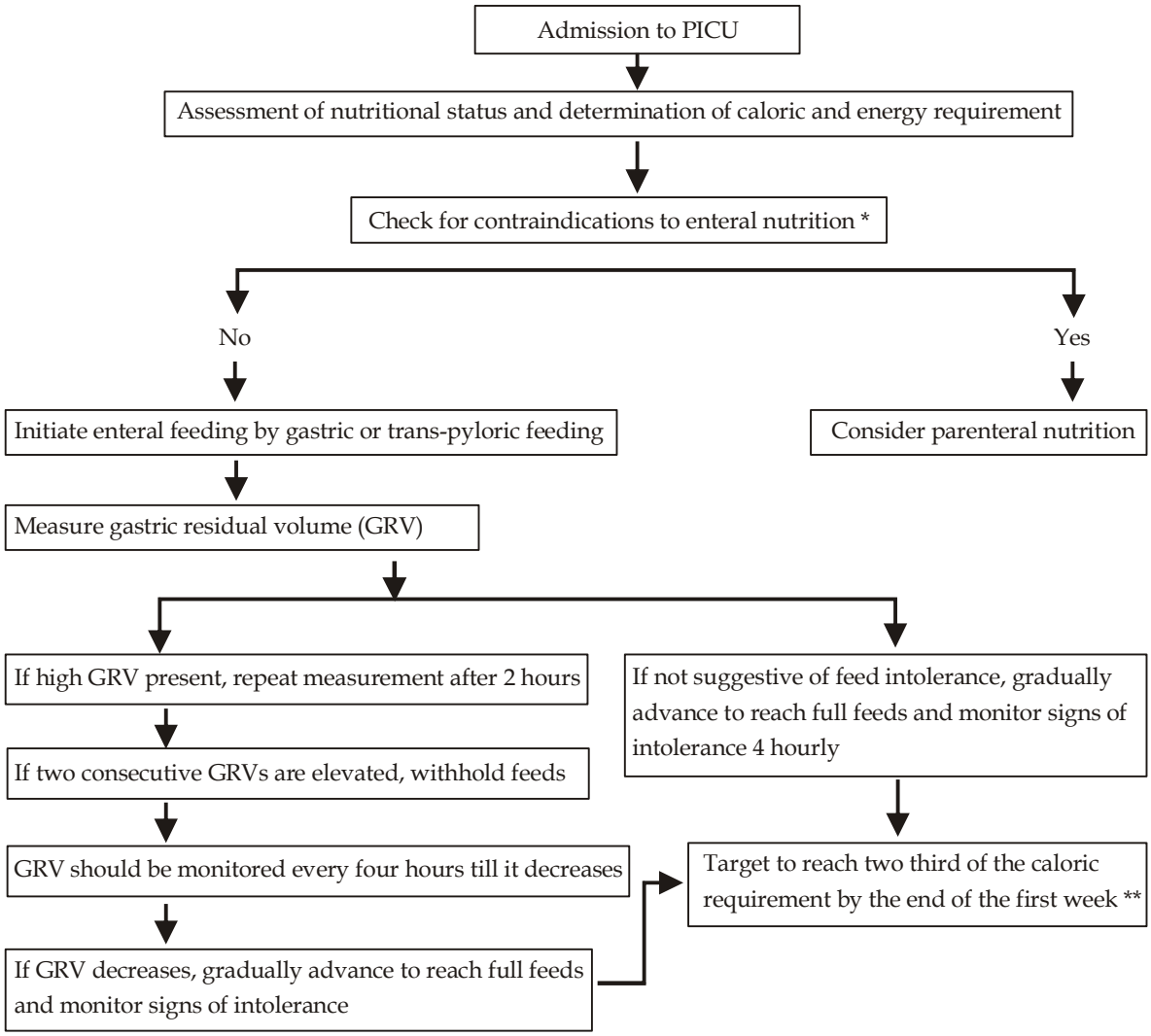


**Fig.:** Algorithm to follow enteral nutrition in the PICU.[36,37]

* Contraindications for enteral feeding: intractable vomiting, high gastric aspirates, upper gastrointestinal bleeding, and use of inotropic or neuromuscular blocking agents, intestinal obstruction, paralytic ileus and bowel perforation.

** Monitor for complications (malpositioned feeding tubes, aspiration pneumonias, diarrhea, necrotizing enterocolitis and gastrointestinal hemorrhage).

working in the critical care unit, with regular audits to evaluate adherence.[8] These stepwise algorithms should include bedside approach for increasing the rate of enteral nutrition and management of intolerance as well.[8]

A simple algorithm has been devised to be used for enteral nutrition in critically ill patients given in Figure 1.

In addition, there should be a multidisciplinary team including a dietician to follow these guidelines.[8] Apart from this, there should be six-monthly audits to check for compliance to these protocols and guidelines in the hospital.[40] Hamilton et al. developed an enteral nutrition algorithm for their hospital and carried out a prospective study on 80 patients pre and post implementation of thisalgorithm.[43] Deane et al. reported a decrease in avoidable episodes of EN interruption (p=0.0001) and decrease in the median time to reach their energy goals (p<0.0001), with a greater number of patients reaching this goal (p= 0.01).[37] Kaufman et al. examined the role of a protocol on EN and identified that use of the protocol increased the number of patients reaching daily caloric goals from 50.1% to 60.7% and those reaching protein goals increased from 51.6% to 72.7%.[44] Meyer et al. introduced a series of enteral feeding protocols in a PICU over 9 years and reported that these protocols shortened the time to initiate enteral nutrition (from 15 hours to 4.5 hours), increased the number of patients receiving

enteral nutrition (from 89% to 96%) and decreased the number patients receiving parenteral nutrition (from 11% to 4%).[45] Mehta et al. also reported a lower prevalence of hospital acquired infections in those patients admitted to PICUs following a feeding protocol independent of the amount of protein and energy intake.[4] A stepwise algorithm for enteral nutrition has been developed by Mehta based on the existing local nutritional practices.[40] In a survey conducted by Wong et al., only 13 (37%) of centers had a dedicated dietician in their PICU with anthropometry being the most common screening tool used by them.[21] Those centers with a dietitian had a regular assessment of their patients compared to those who did not ($p<0.001$).[21]

New home based enteral nutrition has also been started especially in the European countries where oral or tube feeding has been tried in patients with a neurodisability or those with a chronic illness to improve the physical and psychological condition of the child. It additionally reduces the costs of the hospital for these patients with chronic illnesses. Lezo et al. conducted a survey in Italy over 22 centers in the age group of 0 to 19 years and noted a dramatic increase in the number of patients using home based enteral nutrition.[46] A survey conducted by Diamanti et al. reported the use of home parenteral nutrition in pediatric patients of chronic intestinal failure like short bowel syndrome (SBS), Hirschsprung's disease and congenital intestinal pseudo-obstruction syndromes (CIPOS).[47]

***The SCCM &ASPEN 2017 recommendations[8]:***

There has been a recent update in the recommendation of ASPEN (in year 2017) with regards to nutrition in a critically ill child. These SCCM & ASPEN guidelines recommend that all patients in PICU should undergo a detailed nutritional assessment within 48 hours of admission with re-evaluation weekly while in the hospital, with anthropometry (z scores) being the main method to screen patients for malnutrition. Recommended energy requirement should be calculated by indirect calorimetry when available, or else by Schofield/ FAO/WHO equations with the objective of reaching two thirds of the prescribed daily energy intake by the end of the first week. Proteins should be started early in the ICU with a minimum intake of 1.5 g/ kg/day. Enteral nutrition is the preferred mode of nutrition in critically ill children; especially those started on EN early (within 24-48 hours) and achieving two third of the nutrition goal in the end of the first week have better outcomes. They also suggest a stepwise algorithmic approach and a nutrition support team to initiate and maintain the enteral nutrition.

## Conclusions

Optimal nutrition is important for critically ill children with enteral nutrition being the most common way of administering the same. It is important to assess patients at the time of admission by anthropometric and biochemical parameters. Enteral feeding should be initiated as early as possible by nasogastric or transpyloric methods. It is vital to identify the contraindications and side effects of enteral nutrition. To follow the recommendations, it is important to have a specialized dedicated nutrition support team and local protocol/ algorithm of initiating and maintaining the enteral nutrition.

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# Anesthetic and Airway Management of Post Burn Microstomia: A Case Report

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## Abstract

Anesthetic and airway management of microstomia patients is challenging for anesthesiologists and requires special care and preparation during intubation and extubation.

Back up plan with other airway management equipment's should be available at hand before dealing with these patients, Decision of extubation is crucial and senior anesthetist should be available in the operating room. In case of prolonged surgery elective ventilation should be done in these cases.

**Keywords:** Anesthetic; Difficult; airway; Post burn; One contract.

## Introduction

*Microstomia*- "Congenital or acquired reduction in the size of oral aperture" that leads to compromise in cosmesis, nutrition and quality of life. Most common cause in pediatric patient Oro facial burn. Air way management in micro stoma patient is challenging. We aim to describe the successful management of micro stomiafoc using on the challenges during nasotracheal intubation and extubation.

## Case Report

A 6 year old Male patient admitted with history of or facial burn 1 year back, presented with complaint of post burn contracture over face and neck resulting in microstomia.

Preoperative assessment of the patient Weight-29kg, Height-107cm, average built No history of any chronic and congenital disease. On general examination Patient conscious, oriented, well hydrated, a febrile, HR- 89/min , BP- 128/76 mm Hg, Sp02-99% on Room Air, with no active intra oral infection or pathology. Systemic examination revealed CVS examination: S1,S2 heard with no murmurs.

On neurological examination patient conscious oriented to time, place and person with GCS-15/ 15,Respiratory examination: B/L Air entry equal with no added sounds.

Airway examination shows mouth opening was less than one finger Fig 1 Mallampatti grading- can't be assessed because of burn contracture Thyromental distance: 4cm. Adequate nasal patency Slight restriction of neck movement Surgery planned was ontracture release and reconstruction.

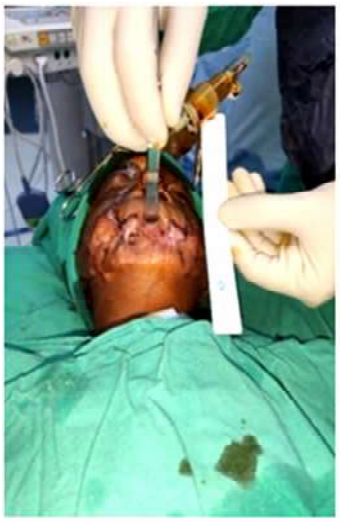

**Fig. 1:** Mouth opening

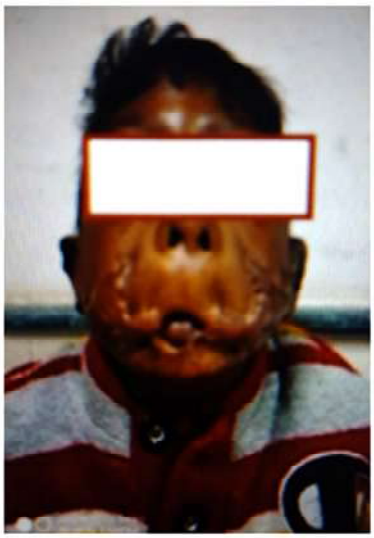

**Fig. 2:** Glottic exposure on FOB

### *Anaesthesia Plan*

*Combined balanced General Anaesthesia Preparation* Nebulization with Topical lignocaine 4% Nasal instillation of oxymetazoline 0.1%, 2% lignocaine+ Adrenaline soaked cotton pellet placed in nasal cavity.

Premedicated with Inj. Glycopyyrolate 0.1mg iv, Inj Midazolam 1mg.IV Induction with Inj Propofol in titrated dose, Inj. Fentanyl iv 50mcg.

Intubation done under fiber optic guidance. Pediatric fiber optic loaded with endotracheal cuffed tube size 4.5mm ID After localization of epiglottis, fiber optic proceeded Tracheal scope position was confirmed, Oral Pack was inserted. tube was advanced position confirmed by bilateral chest rise & auscultation and EtCO2 Anaesthesia Maintained with IV Atracurium, Isoflurane and 50% O2+ air with Volume-Controlled mode of Ventilation.

Planed Extubation on table, oral pack removed under vision and under mild sedation and spontaneous respiration Guarded extubation done with ventilating bougie passed inside trachea. After extubation, laryngospasm noted EtCO2 not recordable.

Immediately patient ventilated with 100% O2 given with CPAP, Jaw Thrust, suctioning done, Deepened anesthesia withpropofol, Larson's manoeuvre . Airway was collapsing dynamically-Re intubation trail given using 4.5 mm ID uncuffed tube intubation failed and then Nasopharyngeal endotracheal tube of 3.5mm ID passed through nostril. Saturation maintained >95% on manual ventilation Surgical Tracheostomy done.

Patient shifted to ICU for elective ventilation and management.

## Discussion

*Main Challenge for Anaesthesiologist:* Securing airway. In our case mask ventilation was difficult so nasopharyngeal catheter was used for mask ventilation. Use of LMA and oropharyngeal airway not possible-Restricted mouth opening. Blind nasal intubation avoided due to risk of bleeding and trauma Following the difficult airway algorithm of difficult airway society (DAS): Fiber optic wing chosen and proceeded. Difficult intubation anticipated surgical team on standby for tracheostomyDuring Extubation: episode of laryngospasm noted We followed difficult airway society (DAS) difficult extubation guideline "AT Risk" algorithm.

## Conclusion

Anesthetic and airway management of microstomia patients is challenging for anesthesiologists and requires special care during intubation and extubation. Meticulous monitoring, adequate plane of anesthesia and avoidance of unnecessary airway manipulation is the keymof successful anesthetic management. Surgical team should always be on standby for tracheostomy.

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- No repetition of data in tables and graphs and in text.
- Actual numbers from which graphs drawn, provided.
- Figures necessary and of good quality (color)
- Table and figure numbers in Arabic letters (not Roman).
- Labels pasted on back of the photographs (no names written)
- Figure legends provided (not more than 40 words)
- Patients' privacy maintained, (if not permission taken)
- Credit note for borrowed figures/tables provided
- Manuscript provided on a CDROM (with double spacing)

**Submitting the Manuscript**

- Is the journal editor's contact information current?
- Is the cover letter included with the manuscript? Does the letter:

1. Include the author's postal address, e-mail address, telephone number, and fax number for future correspondence?
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