Case on Hemato-oncology
(allogeneic stem cell transplantation)

D. Séguy (FR)
Allogeneic hematopoietic stem cell transplantation (allo-HCT)

D Seguy
Lille University Hospital, France
Clinical Case

- 47 year-old male, pharmacist without medical history
- Asthenia + gingival hypertrophy + hyperleukocytosis (35 000 WBC/mm³)
- Myelogram > 90% of blasts, myelomonocytic (Acute Myeloid Leukemia 4)
- **Month -4** induction chemotherapy
  * Daunorubucin 60 mg/m² (3 days)
  * Aracytin 200 mg/m² (7 days)
- **Month -3** first course of consolidation: aracytin 2000 mg/m² (days 1, 3, 5)
- **Month -2** second course of consolidation chemotherapy
- Myelogram: patient in remission (< 5% of blasts)

→ Indication of allo-HCT

- Pretransplantation evaluation
  * Karnofsky PS 80% (normal activity with effort, some signs/symptoms of disease)
  * No organ failure
  * Sibling related donor (sister, HLA 10/10)

→ Bone marrow allo-HCT following myeloablative conditioning regimen
Allogeneic hematopoietic stem cell transplantation process

> 20,000 allo-HCT / year are performed all over the world

* Graft sources
  - Bone marrow 45%
  - Peripheral blood 50%
  - Umbilical cord blood < 5%

* Donor
  - A sibling
  - Other relative
  - An unrelated person

* Conditioning therapies
  - Myeloablative (MAC)
  - Reduced-intensity (RIC)
  - Non-myeloablative


Patient characteristics

Hematological malignancy characteristics

Graft infusions

#1 #2 d-7 d0 d30 d100

Supportive care

GvHD prophylaxis +/- treatment

Chimerism

WBC/mm³

aGvHD

Clinical Case

- **Day -6** myeloablative conditioning
  * Fludarabin 40 mg/m²/day (day -6 to day -3)
  * Busulfan 3,2 mg/kg/day (day -6 to day -3)
  * Rest (2 days)

- **Day -5**
  * Nausea despite anti-nausea medications
  * Bloated abdomen, diarrhea
  * Anorexia (food intake < 50% of usual intake, < 1000 kcal/day)
  * Weight 62 kg (usual weight 60 kg for 1.73 m)
  * Albumin 38 g/L
How would you characterize the nutritional status of this patient?

A. Severe malnutrition
B. Moderate malnutrition
C. Risk of malnutrition
D. Satisfactory nutritional status
E. Impossible to characterize

Correct answer: C. Risk of malnutrition
<table>
<thead>
<tr>
<th>Tool</th>
<th>Items</th>
<th>Score</th>
<th>Cutoff</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRI</td>
<td>Albumin + % of weight loss</td>
<td>101</td>
<td>&gt; 100</td>
<td>Well nourished</td>
</tr>
<tr>
<td>MST*</td>
<td>Weight loss % of W loss</td>
<td>0</td>
<td>≥ 2</td>
<td>No risk</td>
</tr>
<tr>
<td></td>
<td>Appetite</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUST*</td>
<td>BMI % of weight loss</td>
<td>0</td>
<td>≥ 2</td>
<td>High risk</td>
</tr>
<tr>
<td></td>
<td>Acute disease effect</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS-2002*</td>
<td>Impaired nutritional status</td>
<td>2</td>
<td>≥ 3</td>
<td>High risk</td>
</tr>
<tr>
<td></td>
<td>Severity of disease</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFNEP oncology</td>
<td>IMC &lt; 18.5</td>
<td>0</td>
<td>1</td>
<td>At risk</td>
</tr>
<tr>
<td></td>
<td>Weight loss ≥ 5%</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Food intake &lt; 70%</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ESPEN guidelines on nutrition in cancer patients

Allo-HCT process: a model of malnutrition

- Mucositis
- Intestinal GvHD
- GI disorders
- Malabsorption / enteropathy
- Taste and smell disorders
- Chemotherapy
- Low bacterial diet
- Anorexia
- Extended length of stay
- Decrease of physical activity
- Depressive mood / stress / isolation
- Corticosteroid regimen
- Myelotoxicity of treatments
- Pain/fever
- Haematological disease
- Sepsis / inflammation
- Chemotherapy
- Mucositis
- GI disorders
- Malabsorption / enteropathy
- Undernutrition
- Myelotoxicity of treatments
- Allo-HCT process: a model of malnutrition

Corticosteroid regimen
How would you manage the patient at this moment?

A. No specific nutritional support
B. Oral fasting
C. Adaptation and enrichment of meal trays
D. Oral nutritional supplements
E. Parenteral nutrition
Day 0, patient is transferred in the transplantation unit to receive the graft

* He is isolated in a high-efficiency particulate air filtered (HEPA) room
* He is in deep aplasia (WBC < 10 /mm³)
* He receives a low-microbial, highly controlled oral diet (< 1000 CFU/g of food)
Low bacterial diet

- Recommended during transplant process and while immunocompromised
- To reduce the risk of food borne infections from bacteria, yeasts, molds, viruses, and parasites

<table>
<thead>
<tr>
<th>Food Groups</th>
<th>Do Not Eat (DIII)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy</td>
<td>Nonpasteurized or raw milk.</td>
</tr>
<tr>
<td></td>
<td>Milk products made from nonpasteurized or raw milk.</td>
</tr>
<tr>
<td></td>
<td>Cheese from delicatessen.</td>
</tr>
<tr>
<td></td>
<td>Cheese containing chili peppers or other uncooked vegetables</td>
</tr>
<tr>
<td></td>
<td>Cheese with molds (such as blue, Stilton, Roquefort, gorgonzola)</td>
</tr>
<tr>
<td></td>
<td>Mexican-style soft cheese such as queso fresco, queso blanco</td>
</tr>
<tr>
<td>Meat and meat substitutes</td>
<td>Raw or undercooked meat, poultry, fish, game, tofu.</td>
</tr>
<tr>
<td></td>
<td>Raw or undercooked eggs and nonpasteurized egg substitutes; no eggs over easy, soft boiled eggs, or poached eggs.</td>
</tr>
<tr>
<td></td>
<td>Meats and cold cuts from delicatessen.</td>
</tr>
<tr>
<td></td>
<td>Hard cured salami in natural wrap.</td>
</tr>
<tr>
<td></td>
<td>Uncooked refrigerated smoked seafood such as salmon or salmon labeled as &quot;nova-style,&quot; &quot;lox,&quot; &quot;kippered,&quot; &quot;smoked,&quot; or &quot;jerky&quot;</td>
</tr>
<tr>
<td></td>
<td>Pickled fish.</td>
</tr>
<tr>
<td></td>
<td>Tempe (tempel) products.</td>
</tr>
<tr>
<td>Fruits and nuts</td>
<td>Unwashed raw fruits.</td>
</tr>
<tr>
<td></td>
<td>Fresh or frozen berries.</td>
</tr>
<tr>
<td></td>
<td>Unwashed raw nuts.</td>
</tr>
<tr>
<td></td>
<td>Brushed nuts in the shell.</td>
</tr>
<tr>
<td></td>
<td>Nonpasteurized fruit and vegetable juices.</td>
</tr>
<tr>
<td></td>
<td>Fresh vegetables found in the grocery refrigerator case</td>
</tr>
<tr>
<td></td>
<td>Nonpasteurized items containing raw vegetables found in the grocery refrigerator case</td>
</tr>
<tr>
<td>Entrees, soups, vegetables</td>
<td>All miso products (such as miso soup and miso paste).</td>
</tr>
<tr>
<td></td>
<td>Unwashed raw vegetables or herbs.</td>
</tr>
<tr>
<td></td>
<td>Fresh nonpasteurized vegetable salsa found in the grocery refrigerator case</td>
</tr>
<tr>
<td></td>
<td>Nonpasteurized items containing raw vegetables found in the grocery refrigerator case</td>
</tr>
<tr>
<td></td>
<td>All raw vegetables.</td>
</tr>
<tr>
<td></td>
<td>Alfalfa sprouts, clover sprouts, bean sprouts, all others</td>
</tr>
<tr>
<td></td>
<td>Salads from delicatessen.</td>
</tr>
<tr>
<td>Bread, grain, and cereal products</td>
<td>Raw (not baked or cooked) grain products (such as raw oats)</td>
</tr>
<tr>
<td>Beverages</td>
<td>Unboiled milk water.</td>
</tr>
<tr>
<td></td>
<td>Unpasteurized tea made with warm or cold water</td>
</tr>
<tr>
<td></td>
<td>Nonpasteurized fruit and vegetable juices.</td>
</tr>
<tr>
<td></td>
<td>Wine, nonpasteurized beer.</td>
</tr>
<tr>
<td></td>
<td>(Note: all alcoholic beverages should only be consumed following physician approval.)</td>
</tr>
<tr>
<td>Desserts</td>
<td>Unrefrigerated cream-filled pastry products (not shelf-stable)</td>
</tr>
<tr>
<td>Fats</td>
<td>Fresh salad dressings (stored in the grocer’s refrigerated case) containing raw eggs or cheeses listed as “Do Not Eat” under “Dairy”</td>
</tr>
<tr>
<td>Other</td>
<td>Raw honey; honey in the comb.</td>
</tr>
<tr>
<td></td>
<td>Herbal and nutrient supplement preparations</td>
</tr>
<tr>
<td></td>
<td>Brewers yeast, if uncooked.</td>
</tr>
</tbody>
</table>

Centers for Disease Control (CDC) guidelines, Tomblyn et al. Biol Blood Marrow Transplant; 15:1143-238
153 patients induction therapy for acute myeloid leukemia (RCT)

* Raw food versus cooked food (fruits and vegetables)
* Both groups received antibacterial/antiviral/antifungal

**Fig 2.** Probability of major infection in cooked, raw, and nonrandomized groups; the nonrandomized group ate only cooked food (log-rank test, $P = .50$ for three-way comparison and $P = .44$ for comparison of cooked and raw groups).

**Fig 3.** Probability of death in cooked, raw, and nonrandomized groups (log-rank test, $P = .32$ for three-way comparison and $P = .36$ for comparison of cooked and raw groups).

Few evidence-based guidelines

- 3 RCTs during chemotherapy induced neutropenia (no allo-HCT)
  * No evidence that LBD prevents infections and related outcome
  * But “No evidence of effect” is not the same as “Evidence of no effect”
    Van Dalen et al. Cochrane Database Syst Rev 2016; 4

- ESPEN guidelines

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>C4 – 3</th>
<th>High-dose chemotherapy and HCT: Low bacterial diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td></td>
<td>There are insufficient consistent clinical data to recommend a low bacterial diet for patients more than 30 days after allogeneic transplantation</td>
</tr>
<tr>
<td>Questions for research</td>
<td></td>
<td>Definition of factors predicting beneficial effects of a low bacterial diet Comparing benefits of food safety guidelines vs neutropenic diet</td>
</tr>
</tbody>
</table>


- Probiotic therapy is not recommended in the immunocompromised patient
  * Lactobacillus bacteremia Cesaro et al. Support Care Cancer 2008; 8:504-5
  * Saccharomyces fungemia Lherm et al. Intensive Care Med 2002; 78:797-801
**Day 0, evolution**

* Improvement of digestive disorders
* Food intake > 60% of usual intake
* Stable weight (62 kg)
What nutritional support would you offer in addition to oral spontaneous consumption?

A. Nothing

B. Oral nutritional supplements (ONS)

C. Enteral nutrition

D. Parenteral nutrition

E. Parenteral nutrition + IV glutamine
Counterproductive effects of IV glutamine (allo/auto-HCT)

- IV glutamine may reduce clinical infections ($P=0.03$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous glutamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziegler 1992</td>
<td>3</td>
<td>24</td>
<td>9</td>
<td>21</td>
<td>15.1%</td>
<td>0.29 [0.09, 0.94]</td>
</tr>
<tr>
<td>Schloerb 1993</td>
<td>6</td>
<td>16</td>
<td>5</td>
<td>13</td>
<td>8.7%</td>
<td>0.97 [0.38, 2.48]</td>
</tr>
<tr>
<td>Pytlík 2002</td>
<td>3</td>
<td>21</td>
<td>1</td>
<td>19</td>
<td>1.7%</td>
<td>2.71 [0.31, 23.93]</td>
</tr>
<tr>
<td>Blijlevens 2005</td>
<td>7</td>
<td>16</td>
<td>11</td>
<td>16</td>
<td>17.3%</td>
<td>0.64 [0.33, 1.21]</td>
</tr>
<tr>
<td>de Gama Torres 2008</td>
<td>21</td>
<td>27</td>
<td>24</td>
<td>26</td>
<td>38.6%</td>
<td>0.84 [0.67, 1.06]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>104</td>
<td>95</td>
<td>81.4%</td>
<td></td>
<td></td>
<td>0.75 [0.58, 0.97]</td>
</tr>
</tbody>
</table>

Crowther et al. BMT 2009; 44:413-25

- But may also increase the rate of relapse (autologous-HCT, RCTs)

Pytlík et al. BMT 2002; 30: 953-61
Sykorová et al. Neoplasma 2005; 52:476-82
Evolution of guidelines (allo-HCT)

- **ESPEN guidelines 2006**
  

  3.4. Is there an indication for routine EN during autologous or allogeneic hematopoietic stem cell transplantations (HSCT)?

  No. There are no proven effects on tumour response, therapy-associated side effects, graft survival, graft-versus-host disease or overall survival. The routine use of EN, therefore, is not recommended (C). In addition, if oral intake is decreased, the increased risk of haemorrhage and infections associated with enteral tube placement in immuno-compromised and thrombocytopenic patients has to be considered; in certain situations, therefore (e.g. allogeneic HSCT) parenteral nutrition (PN) may be preferred to TF (C).

- **ASPEN guidelines 2009**
  
  August et al. JPEN 2009; 33:472-500

  Enteral nutrition should be used in patients with a functioning gastrointestinal tract in whom oral intake is inadequate to meet nutrition requirements. (Grade: C)

  When parenteral nutrition is used, it should be discontinued as soon as toxicities have resolved after stem cell engraftment. (Grade: B)

- **ESPEN guidelines 2017**
  
  Arends et al, Clin Nutr 2017; 36:11-48

  | C4 − 2 | High-dose chemotherapy and HCT: Enteral and parenteral nutrition |
  | Strength of recommendation | If oral nutrition is inadequate we suggest preferring enteral tube feeding to parenteral nutrition, unless there is severe mucositis, intractable vomiting, ileus, severe malabsorption, protracted diarrhea or symptomatic gastrointestinal graft versus host disease (GvHD). |
  | Level of evidence | Weak |
  | Questions for research | Comparing efficacy of enteral vs parenteral nutrition on clinical outcome and complication rates |
EN and neutrophil engraftment (allo-HCT)

- In adults (94 EN vs. 27 PN$^\S$)
  * Monocentric prospective study
  * 20 [17-23] vs. 24 [20-31], $P=0.004$
  * EN was a protective factor
    (HR=2.17; 95% CI=1.24-3.81; $P=0.007$)

- In children (97 EN vs. 97 PN)
  * Multicentric retrospective study
  * Patients closely matched
  * Delays of engraftment were similar
  * Use of GM-CSF more frequent in PN group: 11% vs. 36%; $P<0.0001$

$^\S$ 22 PN + OF and 5 OF

**Graphs**

- Neutrophils > 1.0 x 10^9/L vs. PNN > 0.5 G/L
  - Time (d)
  - HR_EN = 0.81; 95% CI_EN [0.62; 1.04]

References:

Gonzales et al. 2017 submitted
EN and sepsis (allo-HCT)

- **Adults (94 EN vs. 27 PN)**
  * Fever duration, Med [IQR]: 7 [3-11] vs. 8 [5-12]; $P=0.07$
  * ≥ 2 episodes of infection: 3% vs. 90%; $P=0.03$
  * Nonbacterial infections: 9% vs. 41%; $P=0.01$
    

- **Adults (25 EN vs. 28 PN, retrospective)**
  * Fever duration, Med [range]: 2 [0-8] vs. 5 [0-17]; $P=0.004$
  * Central venous catheter removal: 11% vs. 32%; $P=0.051$
    
EN and platelet engraftment (allo-HCT)

- In adults (94 EN vs. 27 PN)
  * 22 [19-28] vs. 30 [23-41], \( P=0.004 \)
  * PN delayed platelet engraftment (HR=0.57; 95% CI=0.33-0.99; \( P=0.046 \))

- In children (97 EN vs. 97 PN)
  * 92% vs. 78%; \( P<0.0001 \)

Gonzales et al. 2017 submitted
Deleterous effect of PN on platelets (auto-HCT)

- Autologous HCT 30 TPN (30 kcal/kg/d) vs. 31 PPN (340 kcal/d)

<table>
<thead>
<tr>
<th></th>
<th>TPN</th>
<th>PPN</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usage of antibiotics (d)</td>
<td>12.03 ± 2.73</td>
<td>11.16 ± 4.36</td>
<td>0.356</td>
</tr>
<tr>
<td>Febrile day ((&gt;38.1^\circ\mathrm{C}))</td>
<td>4.03 ± 3.40</td>
<td>5.70 ± 3.76</td>
<td>0.064</td>
</tr>
<tr>
<td>Culture positivity ((n))</td>
<td>20 (64.5%)</td>
<td>12 (40%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Oral mucositis (d)</td>
<td>5.46 ± 1.55</td>
<td>6.63 ± 2.15</td>
<td>0.070</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>13.90 ± 3.68</td>
<td>13.20 ± 2.68</td>
<td>0.360</td>
</tr>
<tr>
<td>RBC transfusion (U)</td>
<td>3.58 ± 1.85</td>
<td>2.76 ± 1.43</td>
<td>0.118</td>
</tr>
<tr>
<td><strong>Platelet transfusion (U)</strong></td>
<td><strong>1.93 ± 1.26</strong></td>
<td><strong>1.16 ± 0.94</strong></td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>

PPN, partial parenteral nutrition; RBC, red blood cell count; TPN, total parenteral nutrition.

*Cetin et al. Nutrition 2002;18:599-603*
### EN on transfusion needs (allo-HCT)

<table>
<thead>
<tr>
<th></th>
<th>Adults (Seguy 2012)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EN (n=94)</td>
<td>PN (n=27)</td>
<td>P</td>
<td>EN (n=97)</td>
<td>PN (n=97)</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>83 [74-90]</td>
<td>75 [67-81]</td>
<td>0.008</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hemorrhagic events (%)</td>
<td>5%</td>
<td>23%</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transfusion needs (unit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, Med [IQR]</td>
<td>6 [4-12]</td>
<td>15 [6-22]</td>
<td>0.004</td>
<td>5 [3-9]</td>
<td>11 [6-22]</td>
</tr>
</tbody>
</table>
EN and early overall survival (allo-HCT)

- In adults (94 EN vs. 27 PN)
  * OS 92% vs. 67%, $P=0.0008$
  * EN was a protective factor, $P=0.019$ (Cox)

- In children (97 EN vs. 97 PN)
  * OS 99% vs. 87%, $P=0.0127$

**Seguy et al. Transplantation 2012; 94:287-94**

**Gonzales et al. 2017 submitted**
What is the right time to place the enteral tube feeding?

A. During the conditioning regimen

B. Day 0 (graft infusion)

C. As soon as possible after the day of graft infusion

D. When requested by the patient

E. When the patient no longer eats
Enteral tube feeding (allo-HCT)

- Place the tube at day +1 “in the eye of the cyclone” to improve its tolerance
  * Nausea of conditioning has usually disappeared
  * Mucositis is not yet present
  * Recipient is in the best psychological disposition
    
    * Sefcick et al. Bone Marrow Transplant 2001; 28:1135-9
    * Seguy et al. Transplantation 2006; 82:835-39

- In practice
  * Nasogastric tube (easier to replace in case of vomiting)
  * Low diameter (6 to 9 fr) tube, radiopaque
  * Overnight continuous infusion using peristaltic pump
  * Polymeric hyperenergetic/hyperproteic solution with fibers
  * Goal of 1000-1500 kcal/day
  * Starting at 20 mL/h within 10 h (increasing by 10 mL/h/night)
  * Oral intake encouraged during the day

  * Seguy et al, Transplantation 2012; 94:287-94
Clinical Case

- **Day +1**
Which objective seems unnecessary to achieve with this EN?

A. To complete oral food intake

B. To avoid using parenteral nutrition

C. To improve the weight

D. To improve intestinal trophicity

E. To reduce the risk of intestinal bacterial translocation

✓ C. To improve the weight
Weight evolution following allo-HCT

- In adults (94 EN vs. 27 PN)
- In children (97 EN vs. 97 PN)

Gonzales et al. 2017 submitted
Fluid overload following allo-HCT

- In adults (94 EN vs. 27 PN)
- In children (97 EN vs. 97 PN)
  * Edema: 21% vs. 58%; p<0.0001


Gonzales et al. 2017 submitted
Intestinal mucosal atrophy (ileum) in mice receiving low protein diet

- Intestinal mucosal height reduced by greater than 75% after 3 weeks
- Higher bacterial translocation after a challenge with an endotoxin
- Lack of intraluminal glutamine may contribute to impair intestinal barrier

*Deitch et al. Gut 1994; 35:S23-7*
15 critically ill patients underwent enteral fasting for a mean of 8 days and were compared to 28 healthy volunteers.

Influence of enteral fasting on intestinal mucosal trophicity

<table>
<thead>
<tr>
<th>Duodenal Mucosal Morphometry and L/M Ratio in Patients and Controls (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Villous height (μm)</td>
</tr>
<tr>
<td>Crypt depth (μm)</td>
</tr>
<tr>
<td>VH/CD ratio</td>
</tr>
<tr>
<td>L/M ratio</td>
</tr>
</tbody>
</table>


TPN before laparotomy was an independent factor of BT

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Bacterial translocation</th>
<th>Univariate P*</th>
<th>Multivariate P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>927</td>
<td>130 (14.0)</td>
<td>0.021</td>
</tr>
<tr>
<td>Preoperative TPN No</td>
<td>866</td>
<td>115 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61</td>
<td>15 (25)</td>
<td></td>
</tr>
</tbody>
</table>

Evolution of plasma citrulline after allo-HCT with MAC

Impairment of intestinal mucosa during allo-HCT

- Reduction of oral intake potentiates the impairment of intestinal mucosa
- Early EN would limit mucosal atrophy and bacterial translocation


* p < 0.04

* Compared to day -6 level
Day +10, oral mucositis appears

* Grade III mucositis (ulcers with extensive erythema)
* Swallowing becomes impossible
* Odynophagia requiring the introduction of subcutaneous morphine
What do you suggest?

A. Stop meals and remove the probe + Prescription of ONS

B. Stop meals + Prescription of ONS + Continuation of overnight EN

C. Stop meals and remove the probe + Prescription of ONS + Start PN

D. Ad libitum oral intake + Overnight EN + EN during the day

E. Exclusive PN
Tolerance of EN during allo-HCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Up-front EN (n)</th>
<th>Overall duration (day), Med</th>
<th>EN without further PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papadopoulou</td>
<td>1998</td>
<td>21</td>
<td>17</td>
<td>71%</td>
</tr>
<tr>
<td>Langdana</td>
<td>2001</td>
<td>42</td>
<td>41</td>
<td>86%</td>
</tr>
<tr>
<td>Azarnoush*</td>
<td>2012</td>
<td>65</td>
<td>22</td>
<td>77%</td>
</tr>
<tr>
<td>Gonzales*</td>
<td>2017</td>
<td>97</td>
<td>23</td>
<td>71%</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seguy*</td>
<td>2006</td>
<td>22</td>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>Seguy*</td>
<td>2012</td>
<td>94</td>
<td>14</td>
<td>65%</td>
</tr>
<tr>
<td>Guièze</td>
<td>2013</td>
<td>28</td>
<td>14</td>
<td>57%</td>
</tr>
</tbody>
</table>

* Lille University Hospital

→ **Tolerance of EN is good and**

→ **Improves with the confidence of staff members in enteral feeding**
Day +21, profuse diarrhea
* > 20 stools/day (volume > 1.5 L/day)
* Refractory to drugs
* Non-infectious
* Grade 3 Intestinal GvHD confirmed by
  - Sigmoidoscopy
  - Video-capsule endoscopy
  - Barium meal follow through

→ Indication of IV corticoids (2 mg/kg/day)
What do you suggest?

A. Ad libitum oral feeding
B. Oral feeding during the day + Overnight EN
C. Exclusive EN
D. Exclusive PN
E. PN covering 80% of needs + EN for the remaining 20%
Pathophysiology of acute GvHD (aGvHD)
Influence of oral feeding on aGvHD

- Cumulative incidence of aGvHD grades III–IV depending on number of days with no oral intake (n=241)

  OR = 7.66
  IC95% 1.44 – 40.7
  p = 0.016

- Two studies found a reduction in aGvHD with oral glutamine (n=241)
  * RR 0.42, 95% CI 0.21–0.85
Influence of digestive decontamination on aGvHD

- Metronidazole + Ciprofloxacin vs. Ciprofloxacin (5 weeks), RCT

- Fluconazole during 75 days (400 ml/d) vs. PCB; RCT

Beelen et al. Blood 1999;93:3267-75

Influence of EN on aGvHD

- In adults (94 EN vs. 27 PN)
  * 9% vs. 37%; P=0.0004
  * EN was a protective factor
    (HR=0.19; 95% CI=0.05-0.72; P=0.01)

- In children (97 EN vs. 97 PN)
  * 18% vs. 34%; P=0.033

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Gonzales et al. 2017 submitted
Influence of EN on aGvHD

EN would limit intestinal mucosal atrophy and bacterial translocation

<table>
<thead>
<tr>
<th>100-day aGvHD location</th>
<th>Adults (Seguy 2012)</th>
<th></th>
<th></th>
<th>Children (Gonzales 2017)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EN (n=94)</td>
<td>PN (n=27)</td>
<td>P</td>
<td>EN (n=97)</td>
<td>PN (n=97)</td>
<td>P</td>
</tr>
<tr>
<td>Gut</td>
<td>15%</td>
<td>37%</td>
<td>0.008</td>
<td>16%</td>
<td>32%</td>
<td>0.014</td>
</tr>
<tr>
<td>Liver</td>
<td>4%</td>
<td>22%</td>
<td>0.0003</td>
<td>2%</td>
<td>7%</td>
<td>0.10</td>
</tr>
<tr>
<td>Skin</td>
<td>35%</td>
<td>52%</td>
<td>NS</td>
<td>45%</td>
<td>51%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Influence of intestinal health before allo-HCT on aGvHD

- Cohort study in adults undergoing allo-HCT and receiving early EN (d+1)

Early administration of EN does not abolish aGvHD

Hueso et al. Biol Blood Marrow Transplant 2017; 23:913-21
Influence of intestinal health before allo-HCT on aGvHD

* Citrulline ≤ 20 μmol/L was an independent factor for aGvHD development (HR = 4.43, 95% CI 1.43-13.75; P = 0.01)

→ Suggests the existence of pretransplantation subclinical intestinal damage in the aGvHD group

Hueso et al. Biol Blood Marrow Transplant 2017; 23:913-21
Hueso et al. ESPEN 2017 oral communication: 0R57
**Day +36**, intestinal GvHD was sensitive to corticoids

* Diarrhea has improved dramatically, no abdominal pain
* Weight 55 kg with lower limb edema
* Albumin 30 g/L
* Patient covers half of his needs with oral feeding and receives overnight EN
* Oral corticosteroids 40 mg/d and cyclosporine 120 mg/d should be continued
What do you suggest for the discharge?

A. No discharge until the weight normalized

B. Ad libitum oral feeding without any restriction

C. Ad libitum oral feeding with some restrictions

D. Ad libitum oral feeding with some restrictions + ONS

E. Ad libitum oral feeding + Home EN until the weight normalized
Epilogue

* Patient was discharged 38 days after his transplantation
* 6 months were necessary to recover his usual body weight
* He resumed his professional activity after 12 months
* Currently, he’s still in remission
Every patient undergoing MAC allo-HCT require early nutritional support

Degree of intestinal damage caused by conditioning is potentiated by post-transplantation oral/enteral fasting

Rather than being opposed strategies, enteral and parenteral routes are complementary for the prevention and care of allo-HCT-related malnutrition

Despite the lack of randomized controlled studies, EN appears to be useful for limiting gut atrophy and bacterial translocation, which can promote sepsis and acute GvHD

The day following the transplantation is the best time to start EN

Tolerance of EN is good and improves with the confidence of staff members in enteral feeding

PN becomes a rescue option when oral/enteral intake is insufficient or impossible, but cannot substitute for the effects of EN on gut trophicity
The golden nutrition support team of Lille University Hospital