UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

COMPARAÇÃO DAS ESTRATÉGIAS DE TERAPIA NUTRICIONAL ENTERAL HIPOCALÓRICAS VERSUS NORMOCALÓRICAS EM PACIENTES CRÍTICOS COM INSUFICIÊNCIA RESPIRATÓRIA AGUDA: REVISÃO SISTEMÁTICA E METANÁLISE DE ENSAIOS CLÍNICOS RANDOMIZADOS

OELLEN STUANI FRANZOSI

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OELLEN STUANI FRANZOSI

Orientador: Prof. Dra. Sílvia Regina Rios Vieira

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BANCA EXAMINADORA

Prof. Dr. Edison Capp

Prof. Dr. Luciano Zubaran Goldani

Profa. Dra. Ingrid Dalira Schweigert Perry

Prof. Dr. Márcio Manozzo Boniatti

DEDICATÓRIA

Dedico esta tese de mestrado ao meu esposo Diego, meu amor. Meu colega na realização do mestrado e meu companheiro em todos os momentos da minha vida.

Dedico esta tese de mestrado aos meus pais Tarcísio e Sueli, minha irmã Michelle e meu cunhado Ricardo, pelo apoio nas minhas escolhas e decisões e pela compreensão nos momentos de ausência.

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RESUMO

Base teórica: Existem controvérsias quanto à quantidade ideal de calorias que pacientes críticos com insuficiência respiratória aguda devem receber, bem como aos efeitos das estratégias de terapia nutricional hipocalórica *versus* normocalórica nos desfechos clínicos e de tolerância gastrointestinal.

Objetivo: Comparar o efeito de duas estratégias de terapia nutricional enteral (nutrição hipocalórica versus normocalórica) nos desfechos clínicos e na tolerância gastrointestinal de pacientes criticamente doentes em insuficiência respiratória aguda.

Bases de dados pesquisadas: MEDLINE, EMBASE, SCOPUS e Cochrane Central Register of Controlled Trials até o período de agosto de 2014.

Seleção dos estudos: Ensaios clínicos randomizados que compararam o efeito das estratégias de nutrição hipocalórica *versus* normocalórica nos desfechos clínicos principais [mortalidade na unidade de terapia intesiva (UTI), tempo de internação na UTI e tempo de ventilação mecânica] e nos sinais e sintomas gastrointestinais (regurgitação, aspiração, vômito, diarreia, constipação, distensão abdominal, elevado volume de resíduo gástrico e uso de agentes pró-cinéticos).

Extração dos dados: Informações sobre a execução e qualidade dos estudos e características dos pacientes e dos desfechos de interesse foram extraídas. As estimativas de risco relativo (RR) e média da diferença (MD) foram sintetizadas sob o modelo de efeitos aleatórios. A heterogeneidade foi avaliada com Teste Q e I^2. A análise de sensibilidade foi conduzida através de análise de subgrupos os quais foram classificados conforme a estratégia de terapia nutricional enteral utilizada (nutrição trófica *versus* nutrição hipocalórica moderada). A metanálise foi realizada com apoio do software RevMan v5.3.

Resultados: Dentre os 798 estudos encontrados, quatro ensaios clínicos randomizados que avaliaram 1540 pacientes foram incluídos na avaliação qualitativa e quantitativa. Não houve diferença na mortalidade geral (RR, 0.92; 95% CI, 0.73 – 1,19; I^2 31% p=0.23 para heterogeneidade). A análise de subgrupos verificou mortalidade geral significativamente menor no subgrupo que recebeu 59-72% das necessidades nutricionais (RR, 0.72; 95% CI, 0.53 – 0.98; I^2 0% p=0.78 para heterogeneidade). Não foram encontradas diferenças entre os grupos quanto à mortalidade na UTI, tempo de permanência na UTI ou hospitalar e tempo de ventilação mecânica. Quanto à avaliação da tolerância gastrointestinal, o grupo que recebeu nutrição hipocalórica foi associado a uma menor ocorrência de vômitos, diarreia e constipação

quando comparado ao grupo nutrição normocalórica. Não foram verificadas diferenças entre os grupos quanto aos sintomas de aspiração e distensão abdominal.

Conclusão: A estratégia de terapia nutricional enteral hipocalórica em aporte moderado (59-72%) foi associada à menor mortalidade geral. A tolerância gastrointestinal foi superior no grupo que recebeu nutrição hipocalórica. A oferta de terapia nutricional enteral hipocalórica em aporte moderado deve ser preferida em pacientes criticamente doentes.

Descritores: *Enteral nutrition, critical care, mortality, respiration artificial, length of stay, signs and symptoms digestive.*

Número do registro da revisão sistemática: Registro internacional prospectivo de revisões sistemáticas: identificador CRD42014013041.

ABSTRACT

Context: Controversy exists regarding the optimal amount of calories that critically ill patients with acute respiratory failure should consume as far as clinical outcomes and gastrointestinal tolerability are concerned.

Objective: To compare the effect of two enteral nutrition strategies (underfeeding versus full-feeding) on clinical outcomes and gastrointestinal tolerability in critically ill patients with acute respiratory failure.

Data Sources: MEDLINE, EMBASE, SCOPUS and the Cochrane Central Register of Controlled Trials up to August 2014.

Study Selection: Randomized Controlled Trials that compared the effects of underfeeding with full-feeding strategies on major clinical outcomes (ICU and overall mortality, ICU and hospital length of stay and mechanical ventilation) and gastrointestinal signs and symptoms (regurgitation, aspiration, vomiting, diarrhea, constipation, abdominal distention, elevated gastric residual volume and use of prokinetic agents).

Data extraction: Studies' information, patient's characteristics and outcomes were extracted. Risk ratio (RR) and Mean Difference (MD) estimates were synthesized under a random-effects model. Heterogeneity was evaluated using the Q test and I^2. A sensitivity analysis on overall mortality was conducted, wherein the groups were classified according to the feeding strategy used (trophic versus hypocaloric nutrition). Meta-analyses were performed using RevMan v5.3 analysis software.

Data synthesis: Among the 798 studies retrieved, four studies of 1540 patients were included. Interventional studies comparing underfeeding with full-feeding were not associated with significant difference in overall mortality (RR, 0.92; 95% CI, 0.73 – 1,19; I^2 31% p=0.23 for heterogeneity). Subgroup analysis of the groups according to the amount of delivered calories showed that the overall mortality was significantly lower in the subgroup that achieved 59-72% of energy intake than in the full-feeding group (RR, 0.72; 95% CI, 0.53 – 0.98; I^2 0% p=0.78 for heterogeneity). No differences were found between the underfeeding versus full-feeding groups regarding in the ICU mortality, ICU and hospital length of stay and duration of mechanical ventilation. As far as gastrointestinal tolerability is concerned, the underfeeding group showed lower occurrence of vomiting, regurgitation, use of prokinetic agents, elevated gastric residual volume occurrence, diarrhea and constipation when

compared with the full-feeding strategy. No differences between the two groups were found for aspiration and abdominal distention.

Conclusion: The underfeeding strategy was associated with lower overall mortality in the subgroup that achieved initial moderate intake. Gastrointestinal tolerability was improved by the underfeeding strategy. Initial moderate intake should be preferred rather than trophic or full-feeding in critically ill patients.

Key Words: Enteral nutrition, critical care, mortality, respiration artificial, length of stay, signs and symptoms digestive.

Systematic review registration number: International prospective register of systematic reviews: identifier CRD42014013041.

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LISTA DE SIGLAS E ABREVIATURAS

ASPEN - *American Society for Parenteral and Enteral Nutrition*

GALT - G*ut-associated Lymphoid Tissue*

IMC – Índice de massa corporal

IrPA – Insuficiência respiratória aguda

SOFA - *Sequential Organ Failure* Assessment Score

SAPS - *Simplified Acute Physiology Score II*

TGI – Trato gastrointestinal

TNE – Terapia nutricional enteral

UTI – Unidade de Terapia Intensiva

VMI – Ventilação Mecânica Invasiva

SUMÁRIO

1. INTRODUÇÃO

A desnutrição hospitalar é associada a piores desfechos em pacientes cirúrgicos desde a década de 1930 [1] e reiterada por Charles E. Butterworth [2]. Apesar de hoje mais facilmente identificada, segue sendo uma condição prevalente. No inquérito brasileiro de avaliação nutricional hospitalar, desnutrição foi a condição nutricional mais frequentemente encontrada, acometendo 48,1% dos pacientes internados, e destes 12,6% a forma grave [3]. Em pacientes críticos, o panorama não é diferente, cerca de 50% dos pacientes são desnutridos [4, 5].

Pacientes críticos são um grupo de doentes caracterizados por elevado catabolismo decorrente da resposta metabólica ao estresse. Há aumento da proteólise muscular para síntese de novas proteínas na fase aguda da doença, desta forma aminoácidos livres são utilizados para geração de proteínas nos locais de injúria tecidual bem como para regulação da resposta inflamatória e imunológica [6]. O estudo de Gamrin [7] foi pioneiro em avaliar aspectos bioquímicos da musculatura esquelética de pacientes críticos através de biópsia muscular e evidenciou a redução da concentração de proteínas em 12% entre a primeira e a segunda semana de internação na Unidade de Terapia Intensiva (UTI).

Em adição à alteração metabólica imposta pela doença, pacientes críticos estão propensos a desenvolver déficit energético e proteico decorrentes da incapacidade total ou parcial de receber alimentação por via oral, por esta razão a via enteral torna-se importante rota terapêutica [8].

O suporte nutricional na população de doentes críticos, tradicionalmente considerado adjuvante ao tratamento, restringia-se a fornecer substratos exógenos para manutenção do paciente durante a fase de resposta ao estresse. Recentemente a denominação foi alterada para terapia nutricional considerando os objetivos que têm sido atribuídos à terapêutica, dentre eles, atenuação da resposta metabólica ao estresse, prevenção de injúria celular oxidativa e modulação favorável da resposta imune [9].

Apesar de farta documentação que relaciona déficit calórico e proteico a piores desfechos, ainda hoje a oferta de energia e nitrogênio dificilmente ultrapassa a faixa mínima preconizada de 65% do planejado [9-11].

A recomendação padrão é que a terapia nutricional enteral (TNE) seja iniciada em 24-48 horas da admissão na UTI, com progressão para aporte nutricional pleno nas próximas 48-72h. No período de 7 a 10 dias, o aporte nutricional deve estar próximo de 100% das necessidades do paciente [9, 12]. Ressalta-se ainda que esforços sejam feitos para estabelecer uma oferta de pelo menos 50-65% do planejado ao final da primeira semana de internação [9].

Entretanto, recentemente tem-se questionado a necessidade de atingir aporte nutricional pleno neste grupo de pacientes, considerando os dados de adequação da terapia nutricional que mostram limitação no alcance desta prática [11], bem como a hipótese de que o benefício da terapia nutricional estaria centrado na implementação da terapêutica na fase inicial da doença [13, 14] independentemente da quantidade de calorias administrada. Neste cenário, surgem as estratégias de terapia nutricional enteral hipocalóricas, destacando-se a nutrição trófica ou "*trophic nutrition*" e nutrição hipocalórica permissiva ou "*permissive underfeeding*", que foram propostas como estratégias alternativas para manutenção da integridade gastrointestinal e redução de complicações associadas à TNE.

Neste contexto, esta revisão sistemática com metanálise busca demonstrar o nível de evidência das práticas atuais bem como comparar as estratégias de TNE hipocalóricas (nutrição trófica e nutrição hipocalórica permissiva) *versus* TNE normocalórica em pacientes críticos com insuficiência respiratória aguda (IrPA) necessitando de assistência ventilatória invasiva quanto a desfechos clínicos e tolerância gastrointestinal.

2. REVISÃO DA LITERATURA

2.1 ESTRATÉGIAS PARA LOCALIZAR E SELECIONAR AS INFORMAÇÕES

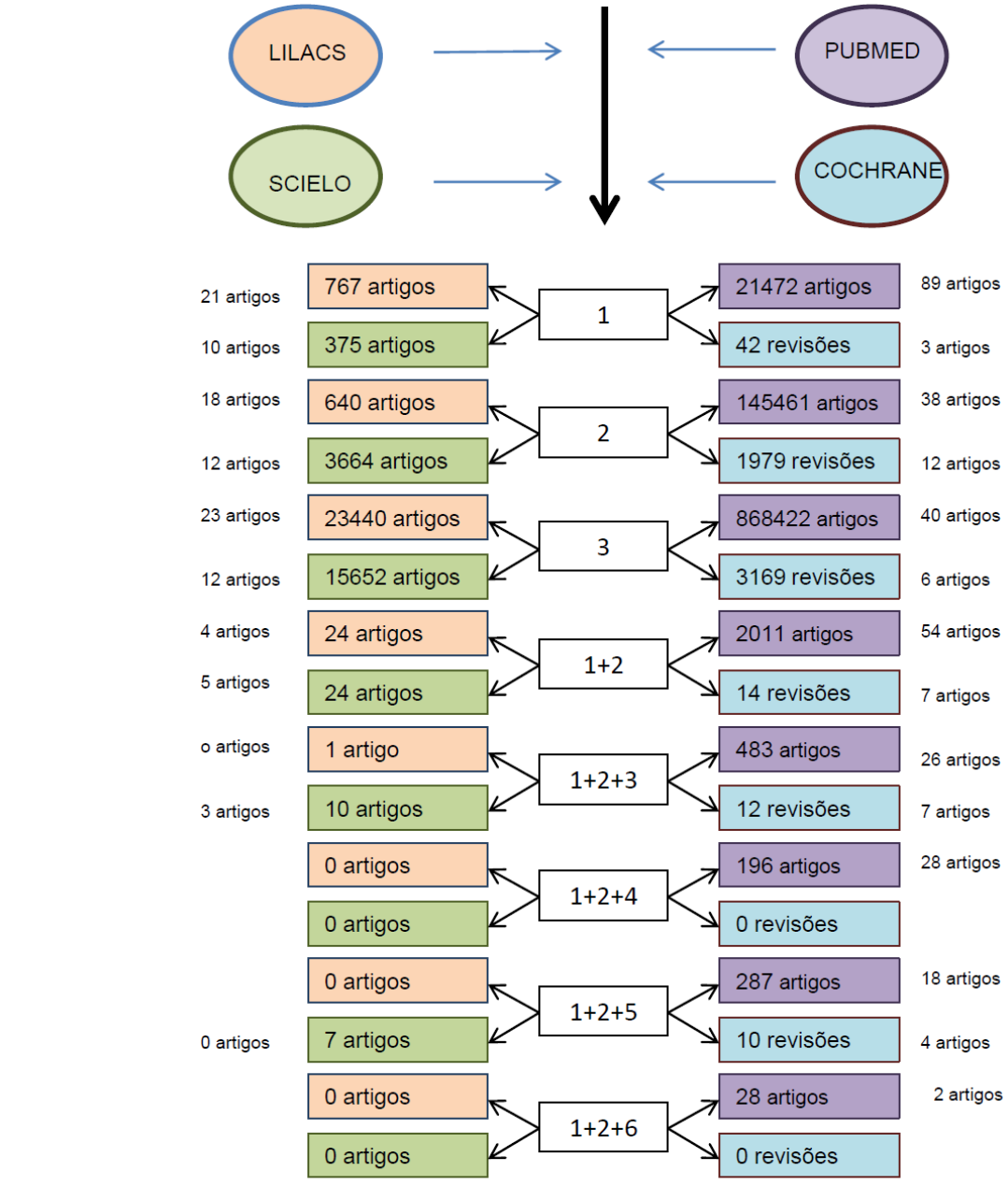
Esta revisão da literatura contempla aspectos relacionados às diferentes estratégias de terapia nutricional enteral empregadas em pacientes críticos.

A busca contemplou a intervenção (nutrição enteral), a população em estudo (pacientes críticos) e os desfechos de interesse principais (mortalidade, ventilação mecânica, tempo de internação e tolerância gastrointestinal).

A estratégia de busca envolveu as bases de dados: LILACS, SciELO, MEDLINE - MEDLINE e Cochrane no período de 1946 a 2014. Foram realizadas as buscas através dos descritores controlados *"enteral nutrition", "critical care", "mortality", "artificial respiration", "length of stay" e "Signs and Symptoms, Digestive"e* seus sinônimos *(entry terms).*

A estratégia de busca está ilustrada na Figura 1.

Figura 1: estratégia de busca de referencias bibliográficas



Em cada caixa de texto central os números indicados correspondem aos descritores de fator de estudo e população: (1) enteral nutrition, (2) critical care e aos descritores de desfecho: (3) mortality, (4) artificial respiration, (5) length of stay e (6) signs and symptoms digestive. Cada caixa de texto lateral corresponde ao resultado da pesquisa na base de dados correspondente à cor. Lateralmente esta descrito quantos artigos foram selecionados para leitura completa.

2.2 TNE EM PACIENTES CRÍTICOS

2.2.1 Definições, indicações e contraindicações

Terapia nutricional é definida pela *American Society for Parenteral and Enteral Nutrition* (ASPEN) [9] como fornecimento de nutrição por via enteral ou por via parenteral. Por via enteral, os nutrientes podem ser administrados através de sondas oro- ou nasogástricas (extremidade distal no estômago), oro- ou nasoentéricas (extremidade distal no intestino), gastrostomias (incisão cirúrgica ou endoscópica no estômago) ou jejunostomias (incisão cirúrgica no jejuno).

As principais indicações de TNE em pacientes críticos são decorrentes da indisponibilidade da via oral por necessidade de ventilação mecânica invasiva (VMI) e ausência de sensório adequado para permitir alimentação via oral segura sem riscos para a via aérea em pacientes não entubados. Em algumas patologias específicas como pancreatite grave e fístulas digestivas altas, a TNE é utilizada como alternativa à via oral visto que permite o posicionamento da sonda na porção do trato gastrointestinal (TGI) viável/desejável e a utilização de fórmulas especializadas. Ainda como indicação de TNE em pacientes críticos, podemos citar quadros clínicos de elevada demanda energético-proteica na qual o consumo espontâneo por via oral é insuficiente (queimados graves, politraumatizados, etc.) [12].

Contraindicações de TNE se sustentam na não funcionalidade do TGI ou quando o mesmo é impérvio. Dentre as contraindicações, podemos citar quadros clínicos de obstrução intestinal, íleo paralítico, vômitos intratáveis, isquemia gastrointestinal, peritonite difusa, diarreia intratável ou recusa do paciente (por se tratar de um tratamento médico, é necessária a autorização do paciente ou responsável legal) [15]. Nos casos de pacientes instáveis hemodinamicamente, com hipofluxo sistêmico e/ou que necessitam de drogas vasoativas em elevadas doses com sinais de baixa perfusão tecidual, a contraindicação de TNE é temporária até a melhora dos padrões hemodinâmicos e de perfusão [12].

Uma vez indicada a TNE, esta deve iniciar o quanto antes possível [13, 14]. Geralmente nutrição precoce, ou seja, iniciada nas primeiras 24-48h da admissão na UTI é possível mesmo em doentes com patologia abdominal complexa ou síndromes clínicas graves [16-18].

2.2.2 TNE e preservação do TGI

No final da década de 1970, estudos experimentais lançaram as primeiras evidências das alterações hormonais e estruturais na mucosa do trato gastrointestinal submetido à privação alimentar. Animais alimentados exclusivamente por via parenteral apresentaram redução da altura das vilosidades, lentificação na proliferação de células epiteliais e inibição da função pancreática (atividade das dissacaridases) [19-21].

Alguns anos após os achados iniciais, dois estudos de Kudsk [22, 23]e colaboradores avaliaram o efeito da administração de uma solução de nutrição parenteral por via enteral *versus* intravenosa primeiramente em ratos desnutridos e em estudo posterior em ratos bem nutridos submetidos à indução de modelo de sepse. Em ambos os experimentos foram verificadas taxas de mortalidade significativamente mais baixas nos grupos que receberam a solução por via enteral. Os autores ressaltaram os efeitos induzidos pela presença de nutrientes no TGI na resposta do organismo contra insultos bem como no papel fundamental da via de administração na retomada da capacidade absortiva de vilosidades atrofiadas por desnutrição ou privação alimentar.

Desde então, ensaios clínicos têm reiterado o papel da TNE na preservação e funcionalidade do TGI bem como na importância deste como modulador da resposta imunológica por reduzir as complicações sépticas em pacientes críticos [24-26].

Uma das hipóteses para a menor incidência de complicações sépticas em pacientes alimentados por via enteral é a ligação interdependente entre a mucosa gastrointestinal e mucosas de outros sítios. Teoria conhecida como “Hipótese da Mucosa Imune Comum” sustenta que células processadas no sistema linfoide associado à mucosa intestinal (GALT, do inglês *gut-associated lymphoid tissue*) podem migrar para outras porções do TGI bem como para locais externos ao intestino e induzir imunidade específica [27].

Um epitélio trófico e um GALT igualmente trófico, além de um ambiente com menor permeabilidade e, consequentemente, menor chance de absorção de toxinas ou translocação bacteriana (alterações associadas ao funcionamento inadequado da barreira intestinal) são justificativas para o uso do TGI como via preferencial para terapia nutricional [9, 28].

2.2.3 TNE precoce

A oferta precoce é vista como sendo uma estratégia terapêutica que poderia reduzir a severidade da doença, diminuindo as complicações, reduzindo o tempo de internação na UTI e impactando de forma positiva nos desfechos clínicos de paciente crítico [9, 13, 14]. Dentre as razões para oferecer TNE precoce podemos citar a manutenção da integridade do TGI e a modulação da resposta imune sistêmica.

As recomendações de TNE precoce são sustentadas pelas premissas de que balanço energético negativo se associa a piores desfechos [14] e que o quanto antes for ajustada a oferta, menor a chance de extremos no balanço energético [29].

Doig e colaboradores [14] verificaram em uma metanálise que o início da TNE em 24 horas teve impacto significativo na redução da mortalidade (OR 0.34 ; IC 0.14-0.85). Posteriormente, em 2011, em nova metanálise com base em três estudos randomizados composto por 126 pacientes vítimas de trauma internados na UTI, verificaram que TNE precoce foi associada à redução da mortalidade (OR, 0,20, 95% CI, 0,04-0,91, p= 0,04) [13].

2.2.4 TNE e complicações gastrointestinais

A TNE é o método de escolha para nutrir pacientes críticos que não podem receber alimentação por via oral ou na qual esta é insuficiente [9]. Apesar de segura e conferir benefícios ao TGI, complicações são atribuídas à terapêutica. Dentre os sintomas gastrointestinais reportados podemos citar: elevado resíduo gástrico, náuseas e vômitos, distensão abdominal, diarreia e constipação [30].

Trabalho realizado em cinco UTIs do Reino Unido que avaliou problemas associados à administração de TNE destacou maior incidência de elevado resíduo gástrico (56%) e náuseas e vômitos (50%) seguido por distensão abdominal (28%), diarreia (11%), sangramento gastrointestinal (11%) e dor abdominal (7%)[31]. Em estudo prospectivo que incluiu 1,312 pacientes críticos adultos, os sintomas gastrointestinais mais incidentes foram vômitos e regurgitação (41,3%), elevado resíduo gástrico (22,7%), diarreia (14%), distensão abdominal (10,6%) e sangramento gastrointestinal (7,4%) [32]. Estudo multicêntrico realizado na Colômbia verificou incidência de complicações em 43,7% dos pacientes em uso de TNE. A complicação mais frequente foi resíduo gástrico elevado (24,2%) seguido de diarreia em 12,6% dos pacientes [33].

Estudo observacional prospectivo [34] que avaliou intolerância à terapia nutricional enteral através de medidas de resíduo gástrico verificou que 46% dos pacientes apresentaram valores entre 150ml-500ml em dois momentos distintos após duas medidas consecutivas ou resíduo gástrico >500ml ou episódio de vômito. Os autores ressaltam que a intolerância ocorreu precocemente (mediana de dois dias após início da TNE), foi mais prevalente em pacientes em uso de sedativos ou catecolaminas e foi associada a maior incidência de pneumonia nosocomial, maior tempo de internação e mortalidade na UTI.

Análise da incidência de diarreia nas duas primeiras semanas de internação em uma UTI terciária na suíça verificou taxa de 5,2 por 100 pacientes/dia ou 14%. O sintoma iniciou em média no sexto dia de internação e 89% dos pacientes apresentaram até quatro dias de diarreia. Dentre os fatores de risco verificados, receber TNE *per se* não foi associada ao sintoma, porém receber TNE com aporte > 60% das necessidades energéticas foi um fator de risco. Nos pacientes que receberam TNE com aporte > 60% das necessidades energéticas, o risco de diarreia foi aumentado pelo uso de antibióticos ou drogas antifúngicas [35].

Constipação pode estar associada ao aumento da pressão intra-abdominal, aumento da proliferação bacteriana, lesão e translocação de bactérias pela mucosa intestinal [36]. Estudo observacional que avaliou constipação em pacientes críticos internados por pelo menos três dias na UTI verificou incidência de 69,9%. Dentre as condições estudadas, TNE precoce foi associada a menor incidência do sintoma mesmo após análise multivariada [37]. Mostafa e cols [38] em estudo prospectivo verificaram incidência de constipação em 78% dos pacientes cirúrgicos avaliados e em 85% do pacientes clínicos. Pacientes constipados apresentaram mais falhas no desmame da VMI. A permanência na UTI e a proporção de pacientes que não

conseguiram se alimentar por via enteral foi maior no grupo de pacientes constipados apesar de não ter significância estatística.

Menor intervalo de tempo entre a admissão na UTI e a primeira evacuação foi associado a menores valores do escore de avaliação de disfunção orgânica (SOFA, do inglês "*Sequential Organ Failure* Assessment Score"), tempo de VMI e internação na UTI. A distensão abdominal causada pela constipação em pacientes críticos pode dificultar a ação do diafragma, diminuir a complacência pulmonar e aumentar o trabalho respiratório [39].

2.2.5 Estratégias de TNE normocalóricas

A maioria das diretrizes (nacional e internacionais) de terapia nutricional convergem na recomendação de aporte calórico entre 20-30kcal/kg/dia ou uso de equações preditivas para estimativa das necessidades nutricionais [9, 12, 40, 41]. Nos serviços que dispõem de calorimetria indireta, esta ferramenta deve nortear a dose de nutrição a ser administrada e contribuir para a quantificação da oferta relativa entre os principais constituintes da nutrição, ou seja, carboidratos, lipídeos e proteínas.

O débito energético acumulado na primeira semana de internação na UTI é descrito como um forte preditor de desfechos clínicos. Um estudo suíço [42] verificou após ajuste para escore de gravidade (SAPS, do inglês *"Simplified Acute Physiology Score II"*), SOFA, idade e índice de massa corporal (IMC), que o déficit energético cumulativo foi associado a maior tempo de internação da UTI, maior período em VMI e complicações clínicas.

O déficit energético foi independentemente associado à mortalidade na UTI em um estudo francês [43] que acompanhou pacientes em ventilação mecânica por período superior a sete dias.

Ensaio clínico randomizado [44] que avaliou o efeito da terapia nutricional guiada por medidas repetidas de calorimetria *versus* estimativa pontual por fórmula de bolso verificou maior balanço energético positivo diário e cumulativo no grupo orientado pela calorimetria. Tendência de menor mortalidade no grupo intervenção (p=0,058) quando avaliado por intenção de tratar, e quando analisado por protocolo, menor mortalidade (p=0,023).

As diretrizes nacionais e internacionais [9, 12, 40, 41] vigentes recomendam que o aporte nutricional administrado seja o mais próximo das necessidades do paciente, para evitar deficiências nutricionais, atenuar perda de massa magra, evitar complicações e melhorar desfechos clínicos.

2.2.6 Estratégias de TNE hipocalóricas

TNE hipocalórica tem sido proposta como uma alternativa para nutrir pacientes críticos. Os benefícios da terapêutica estão centrados na oferta de nutrientes para manutenção da integridade do TGI e na redução de complicações.

Krishnan e cols [45] avaliaram o aporte calórico com os desfechos clínicos em pacientes críticos com ≥ 96 horas de internação na UTI. O aporte calórico recebido foi categorizado em tercis, 0-32% (tercil 1), 33-65% (tercil 2) e ≥ 66% (tercil 3). Quando comparado ao tercil 1, o tercil 2 foi associado a maior probabilidade de sobrevida na alta hospitalar enquanto o tercil 3 a menor sobrevida. O tercil 2 foi associado a maior probabilidade de alta da UTI com ventilação espontânea enquanto o tercil 3 a menor probabilidade. Quando analisado o subgrupo de pacientes com SAPS II > 50, os tercis 2 e 3 foram associados a menor probabilidade de alta com vida. Assim, este estudo sugere que uma oferta calórica diária menor que as médias até aqui propostas por outros estudos se associava a melhores desfechos, de acordo com um emergente conceito apresentado na literatura pertinente, hipoalimentação permissiva. Os autores discutem que as complicações da TNE podem ter contribuído para atenuar os benefícios potenciais da TNE normocalórica.

Ensaios clínicos [46, 47] que compararam nutrição trófica (infusão de nutrição enteral à 10ml/h) *versus* nutrição plena (25-30kcal/kg de calorias não proteicas) durante os seis primeiros dias de internação na UTI não encontraram diferença na mortalidade hospitalar, dias de ventilação mecânica e dias livres de UTI, porém verificaram menor ocorrência de episódios de intolerância gastrointestinal no grupo que recebeu nutrição trófica.

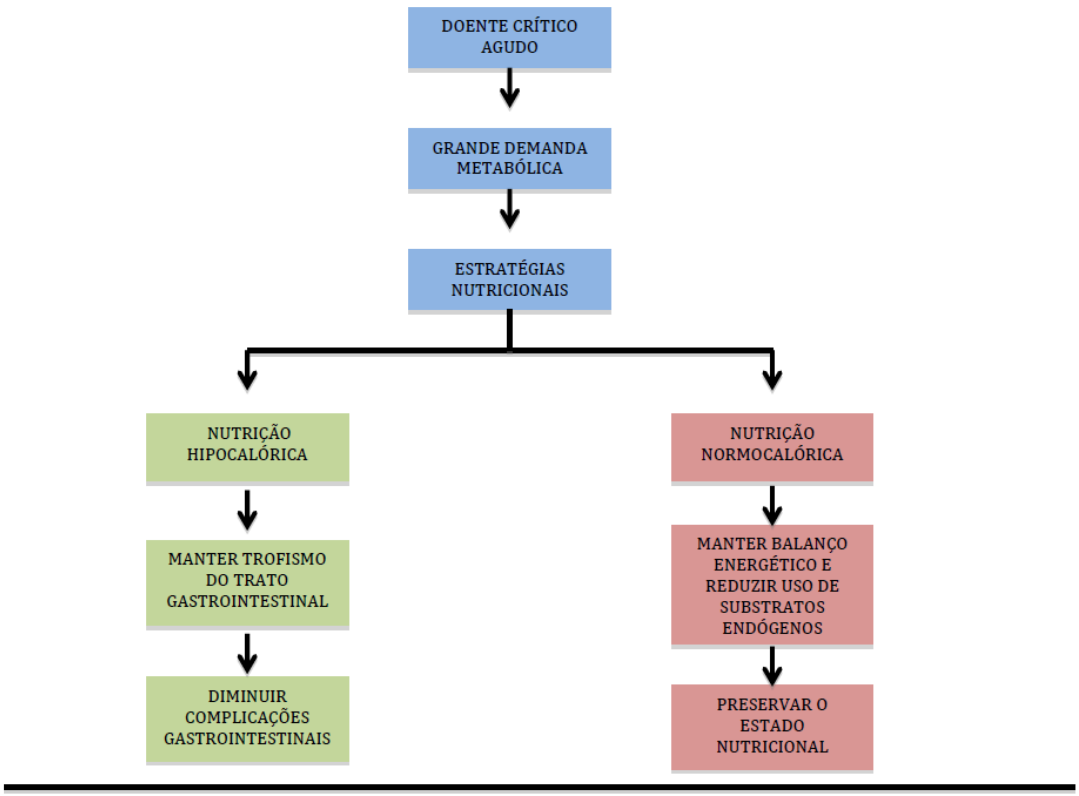
Resultado semelhante foi encontrado no estudo de Arabi e colaboradores [48] no qual pacientes críticos foram randomizados para receber nutrição hipocalórica permissiva ou nutrição normocalórica (60-70% *versus* 90-100% das necessidades nutricionais estimadas).

Os autores verificaram menor mortalidade hospitalar no grupo que recebeu nutrição hipocalórica permissiva.

3. MARCO TEÓRICO CONCEITUAL ESQUEMÁTICO

O marco teórico que fundamenta as estratégias de TNE comparadas nesta revisão sistemática e metanálise está ilustrado na Figura 2.

Figura 2: Marco teórico



TGI: trato gastrointestinal

4. JUSTIFICATIVA

Apesar de a TNE ser recomendada como a terapia de primeira escolha em pacientes graves com IrPA, segue incerta a quantidade de calorias que esse grupo de pacientes deve receber.

TNE normocalórica é recomendada pelas principais sociedades nacionais e internacionais de terapia nutricional parenteral e enteral [9, 12, 40, 41]. É sabido que oferecer aporte nutricional normocalórico com objetivo de reduzir o déficit na fase inicial da doença está associado à preservação de massa muscular, função imune, redução do déficit energético e desfechos clínicos favoráveis.

Por outro lado, TNE hipocalórica está sendo proposta como uma estratégia para manutenção da integridade do TGI aliada à redução dos sintomas de intolerância gastrointestinal [46-48].

Recentemente têm-se discutido se seria necessário atingir o aporte nutricional estimado (TNE normocalórica) nos primeiros dias de internação na UTI ou se nutrição hipocalórica seria suficiente para manutenção do TGI e redução de complicações gastrointestinais associadas à terapêutica.

No atual contexto de incerteza acerca do aporte nutricional em pacientes críticos, insere-se a relevância da comparação das estratégias de TNE em relação aos desfechos clínicos de interesse e tolerabilidade gastrointestinal.

5. OBJETIVOS

5.1. OBJETIVO PRIMÁRIO

Esta revisão sistemática tem como objetivo responder a seguinte questão de pesquisa: “Em pacientes críticos com insuficiência respiratória aguda, estratégias de TNE hipocalóricas são superiores às estratégias normocalóricas em relação aos desfechos clínicos?”.

5.2. OBJETIVO SECUNDÁRIO

Comparar as estratégias de TNE hipocalóricas versus normocalóricas em pacientes críticos com insuficiência respiratória aguda em relação à tolerabilidade gastrointestinal.

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7. ARTIGO

Comparison of underfeeding with full-feeding strategy in critically ill patients with acute respiratory failure: a systematic review with meta-analysis of randomized controlled trials

Oellen S Franzosi [1], Anize D von Frankenberg [2], Diego S L Nunes [1], Sérgio H Loss [1,3], Sílvia R R Vieira [1,3,4]

[1]Post-Graduate Medical Sciences Program, School of Medicine, *Universidade Federal do Rio Grande do Sul*, Porto Alegre, Brazil

[2]Post-Graduate Endocrinology Program, School of Medicine, *Universidade Federal do Rio Grande do Sul*, Porto Alegre, Brazil

[3]Intensive Care Unit, *Hospital de Clínicas de Porto Alegre*, Porto Alegre, Brazil.

[4]Department of Internal Medicine, *Universidade Federal do Rio Grande do Sul*, Porto Alegre, Brazil.

Corresponding author:

Oellen Stuani Franzosi

Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos. 2350 – Sala 445.

90035-003. Porto Alegre. RS – Brazil. Phone: +55 51 33598530.

E-mail: oellen.franzosi@gmail.com

Running title: Enteral nutrition strategies for critically ill patients.

Keywords: Enteral nutrition, critical care, mortality, respiration artificial, length of stay, signs and symptoms digestive.

ABSTRACT

Context: Controversy exists regarding the optimal amount of calories that critically ill patients with acute respiratory failure should consume as far as clinical outcomes and gastrointestinal tolerability are concerned.

Objective: To compare the effect of two enteral nutrition strategies (underfeeding versus full-feeding) on clinical outcomes and gastrointestinal tolerability in critically ill patients with acute respiratory failure.

Data Sources: MEDLINE, EMBASE, SCOPUS and the Cochrane Central Register of Controlled Trials up to August 2014.

Study Selection: Randomized Controlled Trials that compared the effects of underfeeding with full-feeding strategies on major clinical outcomes (ICU and overall mortality, ICU and hospital length of stay and mechanical ventilation) and gastrointestinal signs and symptoms (regurgitation, aspiration, vomiting, diarrhea, constipation, abdominal distention, elevated gastric residual volume and use of prokinetic agents).

Data extraction: Studies' information, patient's characteristics and outcomes were extracted. Risk ratio (RR) and Mean Difference (MD) estimates were synthesized under a random-effects model. Heterogeneity was evaluated using the Q test and I^2. A sensitivity analysis on overall mortality was conducted, wherein the groups were classified according to the feeding strategy used (trophic versus hypocaloric nutrition). Meta-analyses were performed using RevMan v5.3 analysis software.

Data synthesis: Among the 798 studies retrieved, four studies of 1540 patients were included. Interventional studies comparing underfeeding with full-feeding were not associated with significant difference in overall mortality (RR, 0.92; 95% CI, 0.73 – 1,19; I^2 31% p=0.23 for heterogeneity). Subgroup analysis of the groups according to the amount of delivered calories showed that the overall mortality was significantly lower in the subgroup that achieved 59-72% of energy intake than in the full-feeding group (RR, 0.72; 95% CI, 0.53 – 0.98; I^2 0% p=0.78 for heterogeneity). No differences were found between the underfeeding versus full-feeding groups regarding in the ICU mortality, ICU and hospital length of stay and duration of mechanical ventilation. As far as gastrointestinal tolerability is concerned, the underfeeding group showed lower occurrence of vomiting, regurgitation, use of prokinetic agents, elevated gastric residual volume occurrence, diarrhea and constipation when

compared with the full-feeding strategy. No differences between the two groups were found for aspiration and abdominal distention.

Conclusion: The underfeeding strategy was associated with lower overall mortality in the subgroup that achieved initial moderate intake. Gastrointestinal tolerability was improved by the underfeeding strategy. Initial moderate intake should be preferred rather than trophic or full-feeding in critically ill patients.

Key Words: Enteral nutrition, critical care, mortality, respiration artificial, length of stay, signs and symptoms digestive.

Systematic review registration number: International prospective register of systematic reviews: identifier:CRD42014013041.

INTRODUCTION

Critically ill patients are a group characterized by high metabolism due to stress response. Cytokine and stress hormones predispose patients to have high protein catabolism, due to muscular proteolysis, allowing the synthesis of acute-phase protein[1]. As a result of this stress response, critically ill patients are bound to develop protein and energy deficit, added by total or partial inability of oral feeding. In order to prevent nutrition deficits and their associated worse clinical outcomes, nutritional therapy is required[2].

Despite enteral nutrition (EN) being the recommended first-line therapy, there is still no consensus regarding the optimal amount of calories that the above-mentioned group of patients should consume. Full-feeding is the EN strategy recommended by the main nutrition guidelines[3-5]. It is emphasized that nutritional intake should be as close as possible to the patient's needs to prevent nutritional deficits, mitigate lean mass loss, prevent complications and improve clinical outcomes. However, recently there has been a question whether it would be necessary to provide full-feeding to critically ill patients, considering the worldwide failure to meet energy and protein targets[6].

Alternatively, underfeeding has been proposed as a strategy to maintain gut integrity and function due to the reduced feeding complications and gastrointestinal intolerances. Interventional studies suggest no difference in hospital mortality, duration of mechanical ventilation and intensive care unit-free days, but show fewer episodes of gastrointestinal intolerances in the initial trophic feeding (EN infusion rate of 10ml/h) compared to the full-feeding strategy[7, 8]. In a randomized controlled study, patients were randomly assigned to permissive underfeeding or target feeding groups (60-70% compared to 90-100% of estimated energy requirement), with a lower hospital mortality being detected in the permissive underfeeding group[9]. Observational data also suggest improved mortality and reduced mechanical ventilation days in the underfeeding (33-65% of target) group. Authors assign the lack of benefits of full-feeding to gastrointestinal intolerances[10].

Considering the contradictory data, this study aimed to systematically review and analyze randomized controlled trials (RCTs) comparing the effects of underfeeding with full-

feeding strategy in patients with acute respiratory failure requiring mechanical ventilation on clinical outcomes and gastrointestinal tolerability.

METHODS

Protocol and registration

A predetermined protocol established according to Cochrane Handbook recommendations[11] was registered at the international prospective register of systematic reviews (PROSPERO) under the number CRD42014013041. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement is used to improve the reporting of results[12].

Inclusion and exclusion criteria

We considered all RCTs comparing underfeeding with full-feeding strategy in adult patients with acute respiratory failure requiring mechanical ventilation. Data from at least one major clinical outcome [intensive care unit (ICU) mortality, overall mortality, ICU length of stay, hospital length of stay and duration of mechanical ventilation] had to be available for study inclusion. In addition to clinical outcomes, gastrointestinal signs and symptoms (regurgitation, aspiration, vomiting, diarrhea, constipation, abdominal distention, elevated gastric residual volume (GRV) and use of prokinetic agents) were analyzed. If data necessary for the review were missing, we contacted the authors by e-mail. The study was excluded if no answer was received within four weeks. We also excluded studies that did not report outcomes and/or included parenteral nutrition. No language, date or publication status restrictions were imposed.

Search strategy and information sources

We searched MEDLINE, EMBASE, SCOPUS and the Cochrane Central Register of Controlled Trials (up to August 2014). The initial search included the following Medical Subject Headings (MeSH) terms and their entry terms: *enteral nutrition* and *critical care.* We also included entry terms designed by the Cochrane Collaboration for RCTs identification (available at http://www.sign.ac.uk/methodology/filters.html#random). The complete strategy for MEDLINE search is available at Supplemental Content. The studies were identified by database searching, scanning reference lists of articles and consultation with experts in the field. We checked the Annual Congresses of the following societies: American Society for Parenteral and Enteral Nutrition (ASPEN), European Society for Clinical Nutrition and Metabolism (ESPEN), Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM). Hand search was made for original papers published in relevant journals in the nutrition field: *Nutrition in Clinical Practice, The American Journal of Clinical Nutrition, Journal of Parenteral and Enteral Nutrition, European Journal of Clinical Nutrition, Journal of Nutrition and Metabolism, Clinical Nutrition and Nutrition*.

Data collection process

Titles, abstracts and full texts were reviewed by two independent reviewers (OSF and ADVF). Disagreements regarding study inclusion were solved by a third investigator (SHL). Data were extracted independently by two reviewers using a piloted form.

The data extracted included the studies' methods and quality information (authors, publication year and journal, number of participants, study design, trial duration, randomization mode, allocation concealment, blinding, loss of follow-up and selective reporting), patient's demographic and baseline clinical characteristics (age, gender, body mass index (BMI), admission category, prevalence of sepsis, use of vasopressor agents, Acute Physiology and Chronic Health Evaluation (APACHE II or APACHE III) score or Simplified Acute Physiology Score (SAPS II) and PaO2/Fio2 ratio. Nutrition strategy characteristics included intervention period, energy intake target, achieved energy intake, initial dose,

increasing feeding rate and GRV. Data regarding outcomes included: ICU mortality, overall mortality (considered as hospital mortality [7, 9, 13] or 60-days mortality [8]), ICU and hospital length of stay, duration of mechanical ventilation and symptoms of gastrointestinal intolerance (diarrhea, constipation, abdominal distention, vomiting, aspiration, regurgitation, elevated GRV) and use of prokinetic agents.

Assessment of Methodological Quality

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers (OSF and ADVF). Biases were classified into six domains: Selection bias, Performance bias, Detection bias, Attrition bias, Reporting bias and other. The "other" domain included the assessment of potential bias arising from the financing of nutrition industries. According to the Cochrane collaboration tool for assessing risk of bias, each domain was classified as high, low or unclear [11]. Regarding funding risk of bias, it was classified as "low" if the author described the funding/support sources or "unclear" if the information was not reported.

Statistical Analysis

ICU and overall mortality were analyzed through Mantel-Haenszel method [14, 15] and summarized as risk ratio (RR). ICU length of stay, hospital length of stay and duration of mechanical ventilation through inverse variance method [11] and the effect measure as mean difference (MD). Diarrhea, constipation, distention, vomiting, aspiration, regurgitation, GRV and use of prokinetic agents were analyzed through inverse variance method [11] and summarized as RR after logarithmic transformation. For both RR and MD, their corresponding 95% confidence intervals (CIs) were estimated. Heterogeneity between studies was assessed by the Cochran's x test (Q test) (significant at P for trend ≤0.10). The I^2 test was also performed to evaluate the magnitude of heterogeneity and it was considered high if $I^2 \geq$ 50.0%. Considering the conservative characteristic of the random-effects model [16], this

approach was used to summarize RR and MD estimates. To detect publication bias, we performed Begg's and Egger's tests [17, 18]. We conducted a sensitivity analysis (subgroup analysis) wherein the groups were assigned according to the achieved energy intake [trophic nutrition (16 – 25% of target) and hipocaloric nutrition (59 - 72% of target)]. Meta-analyses were performed using RevMan v5.3 analysis software of the Cochrane Collaboration [19].

RESULTS

Study selection

The flow diagram for the selection of eligible studies is presented in **Figure 1**. Through database searching we identified 796 studies and through other sources two more studies were added. For full text examination we selected 16 studies (see data collection process) and after exclusions, four studies were included in the final qualitative and quantitative analysis [7-9, 13]. We identified a RCT protocol report [20] and contacted the corresponding author but the study results are not available yet. The characteristics of included studies are presented in **Table 1** while those related to the nutritional strategy are showed in **Table 2.**

Studies included 100 to 1000 patients of both genders and with mean age of 54 years. Mean BMI was not different between underfeeding and full-feeding groups for all studies, ranging from 25.0 to 30.4 kg/m². Three studies reported the admission category, with samples mainly composed of medical patients (average of 71%) [8, 9, 13]. Although studies have used different scores for severity assessment, there were not differences between underfeeding and full-feeding groups for all studies. Three studies showed data of baseline sepsis diagnosis, use of vasopressor agents and PaO_2:FiO_2 ratio [7-9]. Despite not being different within studies, baseline sepsis diagnosis and use of vasopressor agents were higher in one study [9] and baseline PaO_2:FiO_2 ratio in were lower in another study [8].

As far as nutritional strategies are concerned, the intervention period was similar between studies [113h (about 5 days) [13] to 7 days [9]]. The estimated energy goal of full-feeding groups ranged from 23 to 30 kcal/kg/d and that of underfeeding groups from 17 to 30 kcal/kg/d. The achieved energy intake in full-feeding groups ranged from 71 to 93% of the estimated energy goal between the four studies; on the other hand, it widely varied in underfeeding groups, reaching 16-25% in two studies (trophic nutrition) [7, 8] and 59-72% in the other two (hypocaloric nutrition) [9, 13]. The initial dose in full-feeding groups was similar in three studies [7-9], while, in a single study, EN was started at optimal flow rate (25 Kcal/kg day)[13]. In the four studies, the initial dose in underfeeding groups ranged from 10 – 30 mL/h.

The increasing feeding rate in full-feeding groups was also similar in three studies [7-9], ranging from 10 to 30 mL/h, guided by protocols that considered GRV as a sign of EN tolerance. In the underfeeding groups, two studies did not increase the feeding rate during the intervention period, keeping the initial dose [7, 8], one study increased the feeding rate of 25 mL/h every 24h [13], and one study increased the feeding rate of 10 mL every 12h according to EN tolerance until reaching the energy goal [9]. GRV used in the feeding protocols ranged from 150 to 400 mL in the four studies.

Risk of Bias assessment

Risk of bias assessment of the included studies in this systematic review and meta-analysis is summarized in **Figure 2.** The risk of bias for random sequence generation was low in three studies [7-9]. In one study [13], it was high due to more patients were admitted after surgery in the underfeeding group and more patients were admitted for trauma in the full-feeding group. Allocation concealment risk of bias was low in all studies. Performance risk of bias was high for all studies considering that in none of them the researchers were blinded due to the need of adjustments of the feeding rates according to the protocols. Detection risk of bias was low in all studies, taking into account that the outcomes measurements were not likely to be influenced by lack of blinding. Attrition bias was low in all studies in view of the fact that outcome data were complete and the rate of discontinued intervention was low. Reporting risk of bias was low in three studies [7-9], but in one study [13] the risk was unclear due to the absence of separate reporting of some gastrointestinal outcomes according to the groups. Regarding funding bias, it was low in three studies [7-9] that showed information about funding/support sources, none having received funding from nutrition industries. In one study it was unclear due to the absence of data [13].

Concerning publication bias, both Begg's ($p=0.31$) and Egger's ($p=0.37$) tests did not achieve significance, providing evidence of absence of publication bias.

Effects on Overall and ICU mortality

Meta-analysis of overall and ICU mortality between underfeeding and full-feeding are presented in **Figure 3**.

All included studies evaluated the effects of underfeeding versus full-feeding on overall mortality. Pooled data from these four studies did not show differences between underfeeding and full-feeding strategies in the risk of overall mortality (RR, 0.92; 95% CI, 0.73 – 1,19; I^2 31% p=0.23 for heterogeneity). Although low heterogeneity was found, studies showed opposite directions in RR. Two studies [9, 13] favored underfeeding while other two [7, 8] showed benefit in the full-feeding strategy. Sensitivity analyses (subgroup analysis) showed different results according to the amount of delivered calories (trophic or hypocaloric nutrition). In the hypocaloric nutrition subgroup (59 - 72% of achieved energy intake) [9, 13], the overall mortality was significantly lower (RR, 0.72; 95% CI, 0.53 – 0.98; I^2 0% p=0.78 for heterogeneity) than in the full-feeding group. In the trophic nutrition subgroup (16 – 25% of achieved energy intake) [7, 8] no difference in overall mortality was found when compared to the full-feeding group (RR, 1.06; 95% CI, 0.86 – 1.31; I^2 0% p=0.77 for heterogeneity).

Among the four selected studies, two were excluded from the ICU mortality analysis due to the absence of data [7, 8]. There was no difference in the ICU mortality between the two strategies (RR, 0.9; 95% CI, 0.57 – 1.42; I^2 0% p=0.38 for heterogeneity).

Effects on ICU and hospital length of stay and duration of mechanical ventilation

Forest plots of the effects of underfeeding versus full-feeding on ICU and hospital length of stay and duration of mechanical ventilation are showed in **Figure 4**.

Two studies [9, 13] reported the effects of nutritional strategies on ICU and hospital length of stay. Regarding ICU length of stay, one study [13] reported the same period of hospitalization between the groups while the other [9] showed longer length of stay in the full-feeding group. In the meta-analysis, no significant differences were found (MD, -1.81; 95%

CI, -4.43 – 0.82; I^2 6% p=0.30 for heterogeneity). As far as hospital length of stay is concerned, no differences were found in the meta-analysis (MD, -0.84; 95% CI, -19.17 – 17.49; I^2 0% p=0.67 for heterogeneity).

The duration of mechanical ventilation was evaluated by three studies [7-9] and did not significantly differ between the groups (MD, -0.44; 95% CI, -1.86 – 0.98; I^2 23% p=0.28 for heterogeneity).

Effects on gastrointestinal tolerability

Effects of underfeeding versus full-feeding on gastrointestinal signs and symptoms are shown in **Figure 5.**

Among the four selected studies, three [7, 8, 13] reported data for vomiting, regurgitation, use of prokinetic agents and high GRV. Vomiting was 21% lower (RR, 0.79; 95% CI, 0.63 – 1.00; I^2 0% p=0.87 for heterogeneity) and regurgitation 44% lower in the underfeeding group (RR, 0.56; 95% CI, 0.39 – 0.80; I^2 0% p=0.73 for heterogeneity). The use of prokinetic agents was less common in the underfeeding group (RR, 0.72; 95% CI, 0.55 – 0.92; I^2 0% p=0.99 for heterogeneity) as well as elevated GRV occurrence (RR, 0.39; 95% CI, 0.25 – 0.61; I^2 0% p=0.72 for heterogeneity)**.**

Two studies [7, 8] analyzed the effects of underfeeding versus full-feeding on diarrhea, constipation, aspiration and distention. Diarrhea was 15% less experienced (RR, 0.85; 95% CI, 0.74 – 0.99; I^2 0% p=0.50 for heterogeneity) and constipation showed the same trend with 33% less occurrences in underfeeding considering the feeding days (RR, 0.67; 95% CI, 0.67 – 0.85; I^2 0% p=0.50 for heterogeneity). Aspiration and abdominal distention were not different between the groups (RR, 0.69; 95% CI, 0.44 – 1.08; I^2 0% p=0.35 for heterogeneity and RR, 0.86; 95% CI, 0.70 – 1.06; I^2 0% p=0.32 for heterogeneity respectively, forest plots not shown).

DISCUSSION

This systematic review and meta-analysis of randomized controlled trials enabled us to assess the effects of two different feeding strategies on clinical outcomes and gastrointestinal tolerability in critically ill patients. Studies that compared underfeeding with full-feeding were not associated with differences in overall mortality [7-9, 13]. Sensitivity analysis performed by subgroup analysis showed different effects according to the achieved energy intake. In the subgroup that reached 59 – 72% of the energy requirement [9, 13], the overall mortality was significantly lower in the underfeeding group than in the full-feeding one, while no differences were found in the subgroup [7, 8] that reached 16 – 25% of requirements. The two strategies evaluated in this study were not associated with differences in ICU mortality. Since only two studies [9, 13] have reported ICU mortality data, it was not possible to perform subgroup analysis. Regarding ICU and hospital length of stay and duration of mechanical ventilation, this study did not add evidence of benefits in outcomes between the two feeding strategies assessed.

Early enteral nutrition is considered a therapeutic strategy associated with decreased disease severity and complications, as well as reduced ICU length of stay thus positively impacting on clinical outcomes in critically ill patients [4, 21, 22]. Among the reasons for offering early enteral nutrition, maintaining of the gut integrity and systemic immune response system are to be considered. However, despite the recommendation of early enteral nutrition by current clinical practice guidelines, it remains unclear the amount of energy that critically ill patients should consume considering the conflicting evidence that supports both initial underfeeding and full-feeding strategy [7-10, 23-25].

Our subgroup analysis showed benefits on the overall mortality in the subgroup that reached 59-72% of the energy requirements. This adequacy fits the proposed minimum cutoff value suggested by ASPEN [4] for the first week of ICU and is similar to the average adequacy found in international multicenter studies [6, 26]. Our data suggest that initial moderate intake of enteral feeding should be considered rather than trophic feeding (16-25% of requirements) or full-feeding.

Concerning gastrointestinal signs and symptoms, this study shows interesting data. Differently from the study of Choi *et al* [27],which pooled data on the incidence of serious gastrointestinal intolerances (vomiting, regurgitation and diarrhea) and found no differences between the feeding strategies, we decided to observe separately gastrointestinal signs and symptoms for better understanding of the effects of the strategies evaluated in the results. Three studies [7, 8, 13] evaluated vomiting, regurgitation, use of prokinetic agents and high GRV. Underfeeding was associated with low occurrence of all upper digestive intolerance signs and symptoms and the protective effect ranged from 21% for vomiting to 61% for elevated GRV occurrence. Upper digestive intolerance signs and symptoms are associated with a higher incidence of nosocomial pneumonia, longer ICU stay and higher ICU mortality [28]. Data show that symptoms occur early, and are more frequent in patients using sedation or catecholamines [28]. Two studies assessed diarrhea and constipation [7, 8]. For both lower gastrointestinal tract symptoms, underfeeding showed the same trend, lowering the occurrence by 15% for diarrhea and 33% for constipation. Abdominal distention was not different between the groups, but meta-analysis showed a trend of benefit for the underfeeding strategy. Diarrhea, which is the gastrointestinal symptom most commonly experienced by critically ill patients, and the respective contribution of feeding, were explored by Thibault *et al* [29]. They reported that the median day of diarrhea onset was the sixth day and most patients had ≤ 4 diarrhea days. As an important result, enteral covering of > 60% of energy target was associated with 75% more occurrences of diarrhea. These findings are consistent with our observations that diarrhea was less experienced in the underfeeding group. Constipation, prevalent symptom in critically ill patients [30, 31], is associated with delays in weaning from mechanical ventilation that can be explained by distention, discomfort and restlessness experienced by patients and by the inability of the ventilator muscle to cope with increased workload caused by distention [30]. Early defecation is associated with a shorter duration of mechanical ventilation and ICU length of stay [32, 33]. Even after multivariate analysis, observational data showed lower incidence of constipation when early enteral nutrition was implemented [31]. Our results are consistent with these findings, since underfeeding was associated with 33% less occurrence of the symptom. The above may suggest that the benefit could be centered in the introduction of nutrients in the gastrointestinal tract rather than in the achievement of energy targets. No difference was found for aspiration, a symptom that occurred rarely (one study [7] reported one episode in the underfeeding group and the other [8] reported occurrence of 0.2-0.3% of feeding days).

Although the literature search was conducted in multiple databases and no restrictions concerning language, publication date or publication status were imposed, this meta-analysis has some limitations. First, the small numbers of studies retrieved did not allow us to perform meta-regression. Because of this, only subgroup analysis was performed. Second, none of the studies was designed in a double-blinded format. Third, studies did not report data of all outcomes evaluated in this meta-analysis, thus some analyses included two or three studies instead of all. Fourth, the full-feeding strategies did not achieve the energy targets, ranging from 71 – 93% of requirements.

In conclusion, in the subgroup analysis, the underfeeding strategy was associated with lower overall mortality in the subgroup that achieved 59-72% of energy intake [9, 13] compared with the full-feeding group. These results are in accordance with the minimum cutoff value proposed for the first week in the ICU [4] and the average adequacy found worldwide in multicenter studies [6, 26]. Underfeeding was associated with fewer occurrences of gastrointestinal signs and symptoms evaluated. Based on the results of overall mortality and gastrointestinal tolerability, initial moderate intake should be preferred rather than trophic or full-feeding. Results from the large multicenter randomized controlled trial which is being conducted [20] will likely allow more definitive evaluation of the feeding strategies in critically ill patients.

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Conflict of interest:

None of the authors had a conflict of interest.

SUPPLEMENTAL CONTENT

Pubmed Search strategy

Intervention: Enteral Nutrition *OR* Nutrition, Enteral *OR* Enteral Feeding *OR* Feeding, Enteral *OR* Force Feeding *OR* Feeding, Force *OR* Feedings, Force *OR* Force Feedings *OR* Tube Feeding *OR* Feeding, Tube *OR* Gastric Feeding Tubes *OR* Feeding Tube, Gastric *OR* Feeding Tubes, Gastric *OR* Gastric Feeding Tube *OR* Tube, Gastric Feeding *OR* Tubes, Gastric Feeding

Study population: Critical Care *OR* Care, Critical

Type of study: randomized controlled trials *OR* randomized controlled trial *OR* random allocation *OR* double blind method *OR* single blind method *OR* clinical trial *OR* exp clinical trials *OR* clinic adj trial *OR* single *OR* double *OR* triple *AND* blind *OR* mask *OR* placebos *OR* randomly allocated *OR* allocated adj random *NOT* case report *OR* letter *OR* historical article *OR* review multicase *OR* review of reported cases.

Figure 1 - PRISMA Flow Diagram of literature search and studies selection

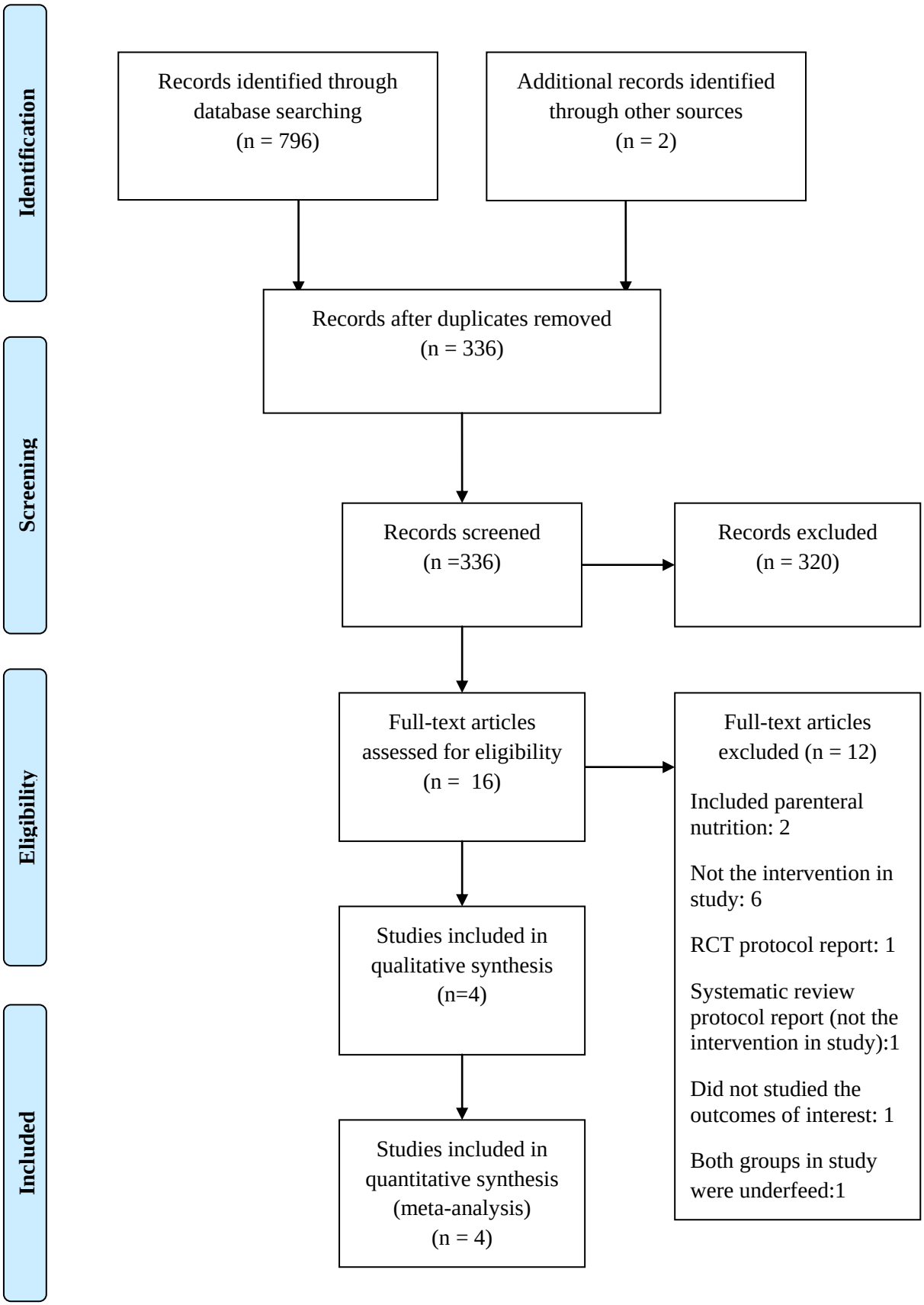
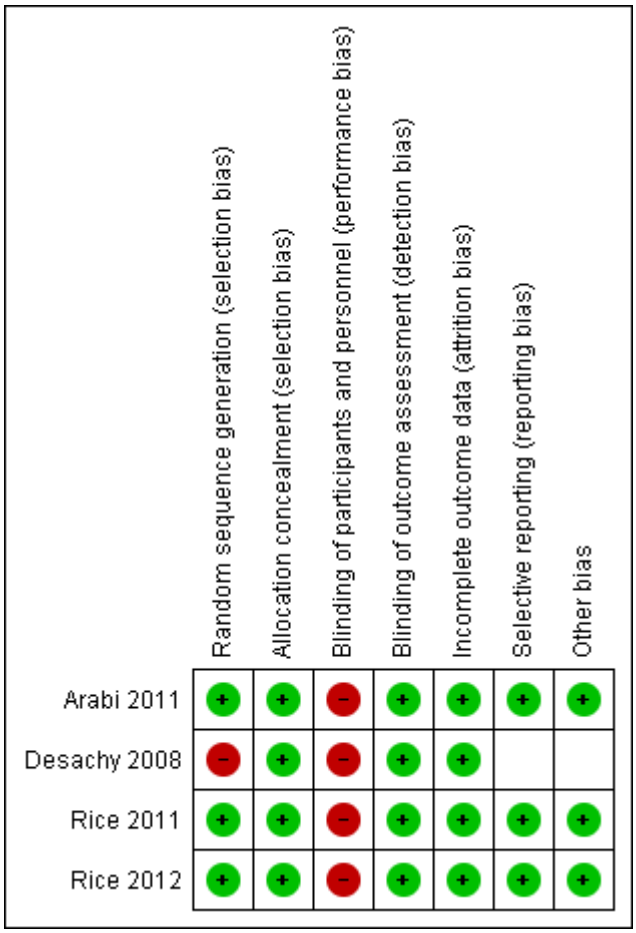
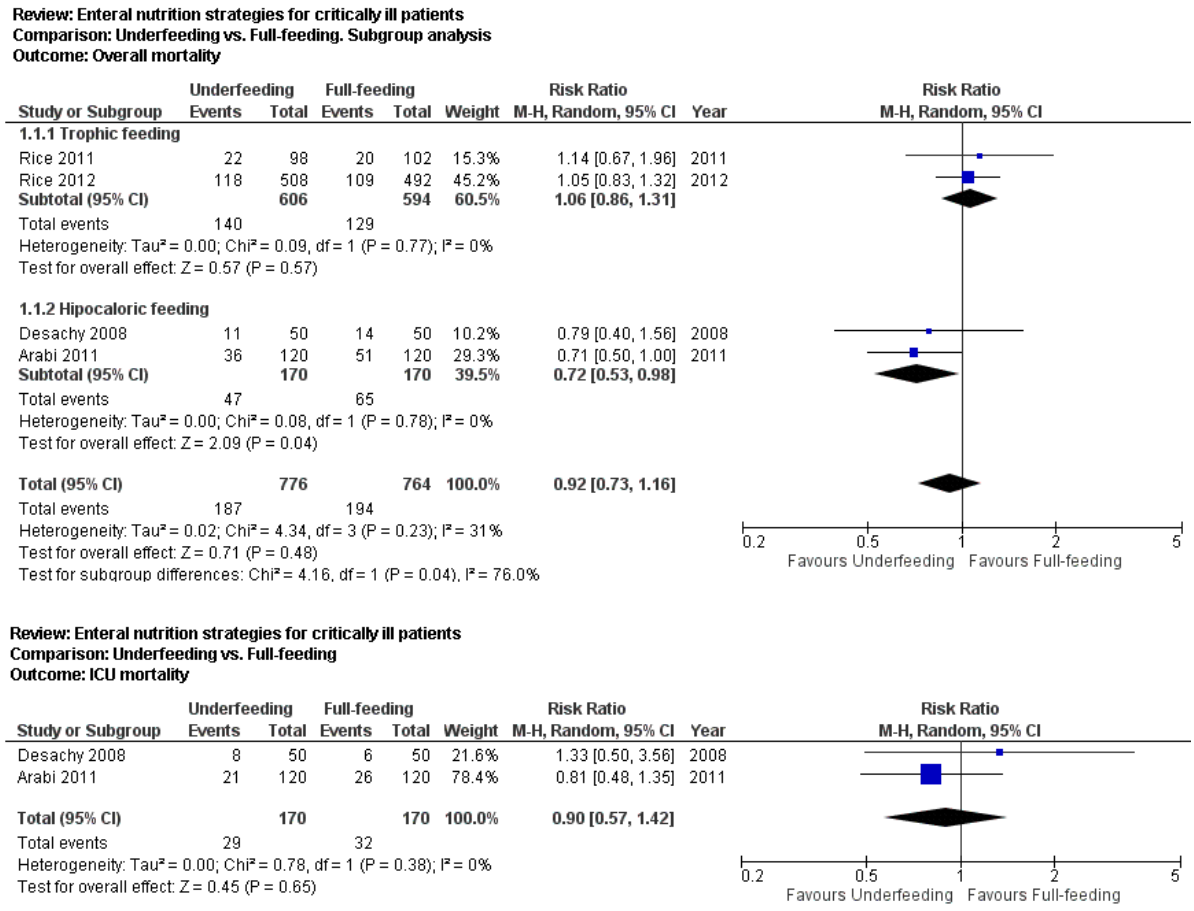


Figure 2 - Risk of bias assessment of included studies in this systematic review and meta-analysis



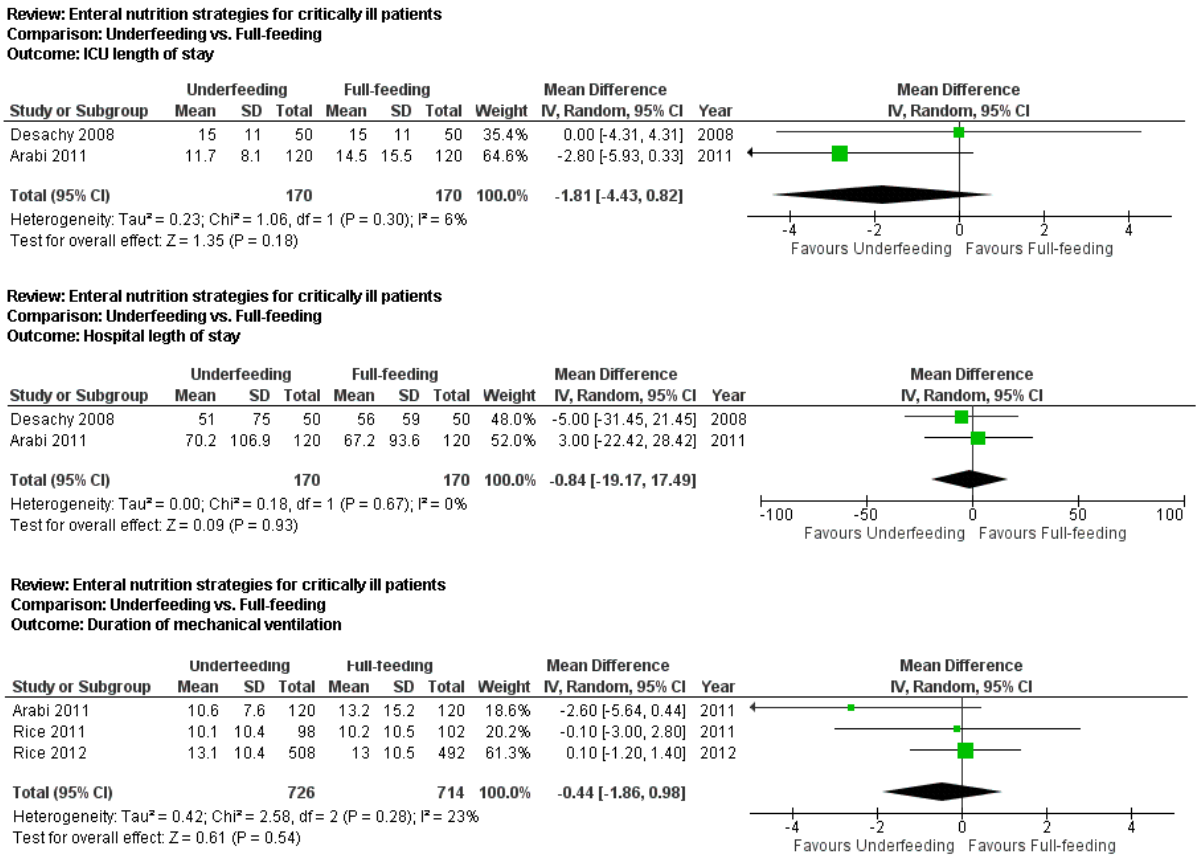
(+) low risk; (-) high risk; (no symbol), unclear risk. "Other" bias domain included the assessment of potential bias arising from the financing of nutrition industries

Figure 3 - Forest plots (meta-analyses, random-effects models) of overall and intensive care unit (ICU) mortality between underfeeding and full-feeding in critically ill patients.



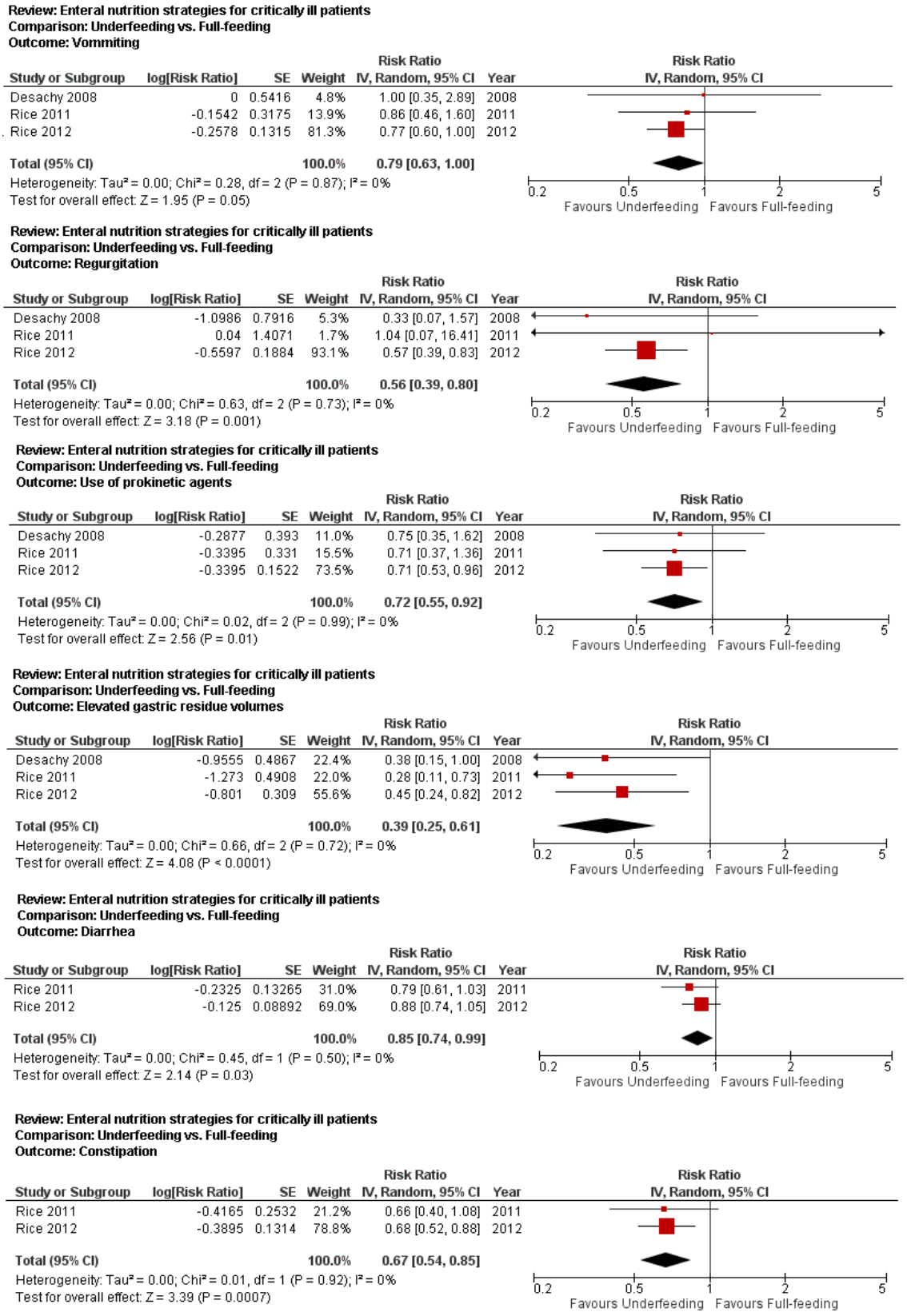
CI, confidence interval.

Figure 4 - Forest plots (meta-analyses, random-effects models) of intensive care unit (ICU) and hospital length of stay and duration of mechanical ventilation between underfeeding and full-feeding in critically ill patients.



CI, confidence interval; SD, standard deviation; IV, inverse variance.

Figure 5 - Forest plots (meta-analyses, random-effects models) of gastrointestinal signs and symptoms between underfeeding and full-feeding in critically ill patients



CI, confidence interval; SE, standard error; IV, inverse variance

TABLE 1 - Characteristics of Included Studies

Author, Year	Sample	BMI[1] (kg/m²)	Admission category: Medical n (%)	Severity[1]	Sepsis n (%)	Vasopressor n (%)	PaO_2:FiO_2 ratio[1]
Desachy A, 2008	UF: 50 subjects, 62% male, 64±13y FF: 50 subjects, 76% male, 58±19y	UF: 27.0±5.0 FF: 25.0±3.0	UF: 35 (70%) FF: 33 (66%)	SAPS II: UF:40.0±11.0 FF:42.0±17.0	UF: NR FF: NR	UF: NR FF: NR	UF: NR FF: NR
Arabi YM, 2011	UF: 120 subjects, 72% male, 50±21y FF: 120 subjects, 65% male, 52±22y	UF: 28.5±7.4 FF: 28.5±8.4	UF: 95 (79%) FF: 103 (86%)	APACHE II: UF: 25.2±7.5 FF: 25.3±8.2	UF:35 (29%) FF: 37 (31%)	UF:77 (64%) FF: 78 (65%)	UF: 202±106 FF: 208±97
Rice TW, 2011	UF: 98 subjects, 40% male, 53±19y FF: 102 subjects, 46% male, 54±17y	UF: 29.2±10.2 FF: 28.2±9.4	UF: NR FF: NR	APACHE II: UF: 26.9±8.1 FF: 26.9±6.6	UF: 10(10%) FF: 12(12%)	UF: 35(36%) FF: 42(41%)	UF: 181±110 FF: 183±122
Rice TW, 2012	UF: 508 subjects,53% male, 52±17y FF: 492 subjects, 49% male, 52±16y	UF: 29.9±7.8 FF: 30.4±8.2	UF: 309 (61%) FF: 309 (63%)	APACHE III: UF:92.0±28.0 FF 90.0±27.0	UF: 82(16%) FF: 63 (13%)	UF:188(37%) FF:190(39%)	UF: 168±79 FF: 164±82

1 Mean ± SD; BMI, body mass index; UF, underfeeding; FF, Full-feeding; APACHE II or III, Acute Physiology and Chronic Health Evolution II or III, SAPS II Simplified Acute Physiology Score II, NR, not reported.

TABLE 2: Nutritional strategy characteristics

Author, Year	Intervention Period	Estimated energy goal	Achieved energy intake	Initial dose	Increasing feeding rate	GRV (ml)
Desachy A, 2008	UF: 127±46h[1] FF: 113±50h[1]	UF: 25 kcal/kg/d FF: 25 kcal/kg/d	UF: 1297 kcal/d (72%) FF: 1715 kcal/d (93%)	UF: 25 mL/h FF: 25 kcal/kg/d (started at target FR)	UF: 25 mL/h 24/24h FF: 0	300
Arabi YM, 2011	UF: 7 days FF: 7 days	UF: 60-70% of SCR FF: 90-100% of SCR	UF: 1067 kcal/d (59%) FF: 1252 kcal/d (71%)	UF: 30 mL/h FF: 30 mL/h	UF: 10 mL/h 12/12h FF: 10 mL/h 4/4h	150
Rice TW, 2011	UF: 6 days FF:6 days	UF: 25 – 30 kcal/kg/d of NPC FF: 25 – 30 kcal/kg/d of NPC	UF: 300 kcal/d (16%) FF: 1418 kcal/d (75%)	UF: 10 mL/h FF: 25 mL/h	UF: 0 FF: 25 mL/h 6/6h if no GI	300
Rice TW, 2012	UF: 6 days FF:6 days	UF: 25 – 30 kcal/kg/d of NPC FF: 25 – 30 kcal/kg/d of NPC	UF: 400 kcal/d (25%) FF: 1300 kcal/d (80%)	UF: 10 mL/h FF: 25 mL/h	UF: 0 FF: 25 mL/h 6/6h if no GI	400

Mean ± SD; UF, underfeeding ; FF, full-feeding; GI, gastrointestinal intolerance; SCR, standard caloric requirement estimated by Harris-Benedict equation + injury factor; GRV, gastric residue volume; NPC, non protein calories; FR, flow rate

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8. CONSIDERAÇÕES FINAIS

Esta revisão sistemática e metanálise que comparou duas estratégias de terapia nutricional em pacientes críticos verificou mediante análise de subgrupos que o consumo moderado de calorias (59-72% das necessidades nutricionais estimadas) foi associado com menor mortalidade geral na estratégia de nutrição hipocalórica. Os valores de adequação de 59-72% estão de acordo com o ponto de corte mínimo proposto para a primeira semana de internação na UTI [9] e com a média de adequação verificada em estudos observacionais multicêntricos [10, 11]. A estratégia de nutrição hipocalórica também foi associada a menor ocorrência de sinais e sintomas de intolerância gastrointestinal.

Com base nos resultados desta metanálise, em especial de menor mortalidade e menor ocorrência de sintomas de intolerância gastrointestinal, a oferta moderada (59-72% das necessidades nutricionais estimadas) deve ser preferida quando comparada às estratégias de nutrição trófica ou normocalóricas.

9. PERSPECTIVAS FUTURAS

Integrar os resultados do ensaio clínico randomizado multicêntrico que está sendo conduzido por Arabi e colaboradores [49] mediante nova revisão sistemática e metanálise possivelmente irá permitir melhor avaliação das estratégias de terapia nutricional em pacientes críticos.