Kliiniline küsimus nr 24

Kas enneaegsete vastsündinute parema ravitulemi saavutamiseks tuleb eelistada varast enteraalset toitmist võrreldes hilise enteraalse toitmise alustamisega?
- rinnapiim võrreldes doonorrinnapiim
- doonorrinnapiim/rinnapiim võrreldes enneaegse vastsündinu piimasegu
- kogused, skeem

Tulemusnäitajad: lapse peamised tulemusnäitajad, kaaluiive neonataalses perioodis, rinnapiimaga toitmise kestus

Süstemaatilised ülevaated
Kokkuvõte süstemaatilistest ülevaadetest, süstemaatilistest kirjanduse ülevaadetest ja ühest randomiseeritud uuringust aastatel 2009-2015:

- **rinnapiim võrreldes doonorrinnapiim**

Enneaegse sünnituse korral mõjutavad rinnapiima kogust ja koostist erinev hormonaalne profiil, hilinenud imetamine või rinnapiima pumpamine/lüpsmine, ema stress ja vähenenud rinnapiima kogus. Vaatamata sellele on enneaegsete vastsündinute toitmisel rinnapiimaga eelised nagu väiksem infektsioonide, NEK`i, kõhulahtisuse ja urotrakti infektsioonide, hilise sepsise, otiidi esinemissagedus. IgA, laktoferriin, lüsosüüm, oligosahhariidid, nukleotiidid, tsütokiinid kasvufaktorid, ensüümid, antioksütandid ja spetsiifilised aminohapped aitavad kaasa organismi vastupanuvõimele. Rinnapiimaga toitmine soodustab pikemas perspektiivis neurokognitiivset arengut, üldisi tervisenäitajaid, nägemisfunktsiooni, vähendab enneaegsete retinopaatia (ROP) esinemissagedust ja kaitseb allergiliste haiguste eest atoopia riskiga lapsi. Paremat neuroloogilist kaugtulemust seostatakse pika ahelaga polüküllastamata rasvhapete, kolesterooli, antioksüdantide, tauriini, kasvufaktoritega. Rinnapiimatoidul olevate laste toidutaluvust parandavad kiirem mao tühjenemine ja parem laktaasi aktiivsus [1,2,3,4,15,18].

Enneaegsetel vastsündinutel sünnikaaluga 500-2,200 g on piisava kaaluiibe saavutamiseks valgu- ja energiavajadus palju suurem kui ajalisena sündinud lastel. Life Sciences Research Office (LSRO) on soovitanud, et valgu vajadus <1,200 g on 3,4-4,3 g/kg/die ja European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) on soovitanud 4.0–4.5 g/kg/die. Kui laps saab valku vähem, on vajalik rinnapiima tõhustamine nii enneaegsetel kui ka ajalistel lastel. Doonorpiima sagedaseim valgusisaldus on 1g/dl, kuid enneaegsete laste emade rinnapiima valgusisaldus on esimesel 4 kuni 6 nädalal pärast sünnitust 1.2 kuni 1.5g /dl, mistõttu doonorrinnapiima tõhustamine on laialt levinud. Seda ei mõjuta pastöriseerimine, vaid rinnapiima doonoriteks on tavaliselt ajaliselt sünnitanud terved naised. Selleks, et saavutada energiabilanss >100 kcal/kg/die, peaks vastsündinu saama rinnapiima >140 ml/kg/die. Kuna selline eesmärk ei ole tavaliselt saavutatav, rakendatakse koos parnteraalset ja minimaalset enteraalset toitmist [1,2,3].
McCormic F Cochrane Systemic Review`s 2010 näitas, et 12 kuu vanuselt on kaaluiive, pikkus- ja peaümbermõõdu kasv statistiliselt tõepäraselt parem tõhustatud versus tõhustamata rinnapiimatoidul olevatel lastel. Neurokognitiivset arengut 18 elukuu korrigeeritud vanuses ei selles ülevaates käsitletud [1].

Pastöriseerimise toime rinnapiimale
Pastöriseerimine kaitseb bakteriaalsete ja viirushaiguse eest, kuid selle käigus saavad mõjutada mõned rinnapiima unikaalsed põletikuvastased omadused. Rinnapiim sisaldab ema T rakke, B rakke, makrofaage ja neutrofiile, mis kõik inaktiveeruvad pastöriseerimisel. Sekretoorse lgA tase väheneb 28 % kuni 60%, laktoferriini ja lüsosüümi aktiivsus väheneb vastavalt 80% ja 60%. Pastöriseerimine ei mõjuta rinnapiima oligosahhariidide taset kuid nende koostis võib olla ema rinnapiimast erinev. Enamus uuringuid näitavad, et pastöriseerimine ei mõjuta rinnapiima valgu, rasva ja süsivesikute taset, kuid asendamatute pika süsinikuahelaga polüküllastamata rasvhapete DHA ja ARA sisaldus ei ole adekvaatne. Enamus vitamiinide ja mineraalide tase püsib endine, kuid piima antioksüdantne toime väheneb oluliselt.

Table 2. Protein and energy concentrations in preterm and term human milk

	Protein*				Energy**			
	day 7	day 14	day 21	day 28	day 7	day 14	day 21	day 28
Milk								
Preterm	2.0	1.67	1.63	1.48	73.86	74.59	73.84	73.33
Term	1.78	1.58	1.45	1.31	73.62	71.81	70.40	72.71

Adapted from Lemons et al. [62]. * Protein in g/dl (nitrogen × 6.25). ** Energy in kcal/dl.

NEK ja doonorpiim. Ei ole avaldatud uuringuid, kus oleks võrreldud ema rinnapiimaga ja tõhustatud doonorpiimaga toitmist ning NEK`i. Võrreldud on piimasegu ja doonorrinnapiima dieeti enneaegsetel vastsündinutel. Nendes uuringutes doonorrinnapiim vähendab NEK riski võrreldes piimaseguga.
VLBW vastsündinu kasvamine ja doonorpiim. Sarnaselt rinnapiimale kasvab doonorpiimga toidetud laps esialgu aeglasemalt võrreldes piimaseguga toitmisel. Paremad tulemused on saadud doonorpiima valgusisalduse tõstmisel rinnapiima tõhustajatega.
Doonorpiim ja totaalne parenteraalne toitmine (TPN), haiglas viibimise aeg. Tõhustatud doonorrinnapiim ei ole mõjutanud TPN kasutamist ja haiglas viibimise aega. Rinnapiimaga toitmine (EHM-exclusive human milk) lühendab TPN vajadust võrreldes piimaseguga [1,3].

- **doonorrinnapiim/rinnapiim võrreldes enneaegse vastsündinu piimasegu**

Rinnapiima kasutamine väga väikese sünnikaaluga vastsündinute toiduks võrreldes enneaegsete piimaseguga vähendab haigestumust, kaasaarvatud nekrootilise enterokoliidi (NEK), hilise sepsise, bronhopulmonaalse düsplaasia (BPD), raske enneaegsete retinopaatia (ROP) esinemissagedust ja suremust. Rinnapiimatoidul olevatel vastsündinutel on lühem haiglas viibimise aeg, neil esineb vähem rehospitaliseerimisi kui kunstlikul toidul olevatel lastel. On leitud, et nende psühhomotoorne ja neurokognitiivne areng 18.-22., 30. elukuul ja 7.-8. eluaastal on parem võrreldes kunstlikul toidul olevate lastega [3,6].
Kui toitmine vastsündinu ema enda rinnapiimga ei ole võimalik, siis on alteranatiivseteks valikuteks kas doonorrinnapiim või piimasegu. Üheksa randomiseeritud kontrolluuringu põhjal näidati, et toitmine piimaseguga annab lühiaegselt kiirema kaaluiibe, kuid on kõrgema riskiga NEK`i tekkeks. Enamus uuritavatest (n=1070) olid stabiilses üldseisundis <32 rasedusnädala ja < 1800 g sünnikaaluga vastsündinud. Hinnati sünnikaalu jõudmise aega, kaaluiivet, pikkuskasvu, peaümbermõõtu, pikemaajalist kasvukõverat, üldist suremust, NEK`i esinemissagedust, täienteraalsele toidule jõudmise aega, toidutaluvust ja invasiivsete infektsioonide esinemist. Kuue uuringu meta-analüüs näitas, et kunstlik toit rohkem kui

kahekordistab NEK riski. Toitmine doonorrinnapiimaga on edukam, kui seda lisatakse ema enda rinnapiimale või kui laps on täielikult tõhustatud doonorrinnapiima toidul. Vähe on uuringuid, kus oleks võrreldud tõhustatud doonorrinnapiima toidul olevaid vastsündinuid kunstlikul toidul olevatega, kuid rinnapiima tõhustamine on vastsündinute intensiivravi osakondades levinud tava [1,5,6,7].

- **kogused, skeem**

Varane troofiline toitmine ehk minimaalne enteraalne toitmine (TN) on tavaliselt defineeritud kui piimaga toitmine väikestes kogustes ilma toidukoguseid suurendamata esimesel 5-7 postnataalsel päeval [*McClure RJ.2001*]. Troofiline toitmine on 10-24 ml/kg/die, tavaliselt 12-24 ml/kg/die . Varase troofilise toitmise mõju rinnapiimaga ebaküpse vastsündinu seedetraktile võib vähendada NEK`i riski, vähendab seedetrakti permeaabelsust, stimuleerib rakkude proliferatsiooni, soodustab mao tühjenemist ja aitab kaasa varasemale jõudmisele täielikule enteraalsele toitmisele [2,8,9, 17].
Hilinenud või aeglane/vähene enteraalne toitmine võib nõrgendada seedetrakti funktsionaalset adapatasiooni ja häirida mikroobide kolonisatsiooni struktuuri. Seedetrkti düsmotoorika võib põhjustada toidutalumatust, mis viib hilinenud enteraalsele toitmisele ja seetõttu pikendab parenteraalse toitmise vajadust, mis omakorda võib luua soodsamad tingimused hilise sepsise tekkeks [10].

Cochrane süstemaatilised ülevaated troofiline toitmine vs. kiire enteraalne toitmine:
Morgan J et al 2013, 9 uuringut: VLBW n=754. Mõned patsiendid olid <28 GN või ELBW:<1000g või IUGR. Ülevaade ei näidanud tõenduspõhiselt, et varane troofiline toimine mõjutab toidutaluvust või kasvukiirust. Kuigi mõned uuringud toovad välja vastukäivaid ja statistiliselt mitte tõepäraseid tulemusi, et troofiline toitmine aitab kaasa jõudmisele kiiremini täisenteraalsele toitmisele ja sünnikaalu.
Morgan J et al 2013, 5 RCT uuringut: n=588, VLBW, vähem ELBW vastsündinuid. Aeglane toitmine 15-20 ml/kg/die, kiire toitmine 30-35 ml/kg/die. Metaanalüüs ei leidnud statistiliselt tõepäraselt, et oleks suurenenud NEK risk või üldine suremus. Aeglasel toitmisel olevad lapsed jõudsid sünnikaalu (keskmine erinevus 2 ja 6 päeva) ja saavutasid täisenteraalse toitmise hiljem (2-5 päeva). Analüüs ei näidanud, et oleks olnud mõjutatud hiliste infektsioonida esinemissagedus ja haiglaravil viibimise aeg.
Morgan J et al 2013, 7 RCT uuringut: n=964, hiline toitmise alustamine 5.-7. elupäeval, varane enne 4. elupäeva. Metaanalüüs ei leidnud statistiliselt tõepäraselt mõju NEK`i esinemissagedusele või üldisele suremusele.
Leaf A et al 2012, 3 suurt uuringut (kaasaarvatud UK ja Iirimaa 54 keskust hõlmav uuring): Vastava alagrupi metaanalüüs ei leidnud statistiliselt tõepäraselt mõju NEK`i esinemissagedusele või üldisele suremusele. Lapsed, keda hakati toitma hiljem, jõudsid hiljem täisenteraalsele toitmisele (keskmine erinevus 2-4 päeva) [10].
Morgan J et al 2014, 9 RCT: n=1106 , mõned enneaegsed <28 GN VLBW ja ELBW , uuritavate alagrupid: 1. kunstlikul toidul vastsündinud 2. rinnapiimatoidul (emapiim või doonorpiim) vastsündinud 3. enamus uuritvatest olid < 1000 g sünnikaaluga või < 28 GN sündinud 4. IURG vastsündinud või need, kellel antenataalselt puudus Doppler ultraheliuuring või oli negatiive vool loote aordis või a. umbilicalise`s [11].
Järeldus: Toitmise alustamine enne 4. elupäeva ja toidukoguse suurendamine rohkem kui 24 ml/kg/die ei tõsta NEK`i riski VLBW vastsündinutel. See järeldus langeb kokku ka Skandinaaviamaad kogemusega, kus toitmist alustatakse 24-48 tunni jooksul pärast sündi [7,8,9].

SIFT - Speed of Increasing Feed Trial – käigus olev RCT, mis hõlmab 2500 VLBW vastsündinut. Võrreldakse toidukoguseid 30 ml/kg/die vs. 18 ml/kg/die. Grupp hõlmab nii rinnapiimatoidul kui ka segutoidul olevaid lapsi. Kokkuvõte tehakse 2 aasta vanuselt. Hinnatakse suremust, haigestumust, antibiootikumide kasutamist ja haiglas viibimise aega. Plaanis on hinnata ka kulutõhusust. SIFT uuring on paralleeluuring teisele Suurbritannias käigus olevale suurele uuringule, kus hinnatakse profülaktilise enteraalse laktoferriini toimet väga enneaegsetele vastsündinutele (*ELFIN- Trial Investigators Group. Lactoferrin immunoprophylaxis for very preterm infants. Arch Dis Child Fetal Neonatal Ed 2013;98:F2–4.*) [9].

Rinnapiima tõhustamine on näidustatud alates toidukogusest 100 ml/kg/die [2,11].

Toitmine boolustena versus pidev nasogastraalne toitmine:
Pidev enteraalne toitmine võib parandada energia tasakaalu tõstes energia absorbtsiooni ja vähendades selle kulutamist, soodustada kasvu ja toidutaluvust . Samas on võimalik, et pidev toitmine mõjutab seedetrakti hormoonide tsüklilist vabanemist (gastriin, gastriini inhibiitor peptiid ja enteroglükagoon), metaboolset homeostaasi ja häirib alumise söögitoru sfinkteri funktsiooni, soodustades gastroösofagiaalse refluksi (GÖR) arengut.
Toitmine boolustena on füsioloogilisem soodustades seedetrakti hormoonide tsüklilist vabanemist, mida on näidatud ajalistel vastsündinutel. See võib olla oluline seedetrakti arengule. Samas võib see olla ebaküpsele seedetraktile koormav, soodustada toidutalumatust ja toitmisega seoatud apnoesid [10,12].
Cochrane andmebaasi süstemaatiline ülevaade (6 RCT aastatel 1992-2005, n=511) ei näinud erinevust täisenteraalsele toitmisele jõudmises, lapse kasvamises ja NEK`i esinemissageduses võrreldes pideval ja boolustena toitmisel olevaid vastsündinuid [11]. Samas näitasid *Dsilna A, Christesson K 2005* oma uuringus, et pideval toitmisel olevad vastsündinud jõudsid täisenteraalse toitmiseni kiiremini ja see oli ilmsem kõige väiksematel (sünnikaal ≤ 850 g) vastsündinutel. Toetudes sellele, uurisid *Dani C, Pratesi S, 2013* pideva ja boolustena toitmise mõju AGA ja SGA enneaegsetel vastsündinutel hinnates põrna regionaalset oksügenisatsiooni (splanchnic regional oxygenation - rSO2S) kasutades NIRS`i (Doppler ultrasound and near-infrared spectroscopy) ja hinnates Doppler ultraheliuuringuga verevoolu ülemises mesenteriaalarteris. Selle uuringu alusel järeldati, et pidev toitmine võib olla soodsam jõudmaks kiiremini täisenteraalsele toimisele ja vähendes raskes seisundis enneaegsetel vastsündinutel seedetrakti hüpoksilis-isheemilise kahjustuse riski. See kehtib eriti SGA ja ≤ 850 g sünnikaaluga enneaegsetel.
Lyanne W. W. et al 2015 (RCT, Netherland) uuringus osalesid vastsündinud sünnikaaluga < 1750 g ja < 32 GN. Minimaalset enteraalset toitmist (TN) alustati esimesest elupäevast 0,5, 1 või 2 ml iga nelja tunni järel (sünnikaal vastavalt 500-749 g, 750-1249 g ja 1250-1749 g). Lapsed olid nii rinnapiimatoidul kui ka kunstlikul toidul. Kui ei esinenud avatud arteriaalset juha (PDA) või hüpoksiat sünnil, alustati toidukogusest 24 ml/kg/die. Parenteraalset toitmist redutseeriti vastavalt enteraalse toiduhulga suurenemisega ja arvestades lapse vajadust elupäevade järgi ning lõpetati kui toidu kogus oli 120 ml/kg/die , ~100 kcal/kg/day. Ideaalsetes tingimustes jõuti selleni 6. elupäevaks. SGA ja PDA korral suurendati toidukoguseid ettevaatlikumalt ja nemad jõudsid eelpool toodud eesmärgini 2 päeva hiljem.
Täisenteraalne toimine on toidukogus on 150 ml/kg/die 72 tundi järjest.
Pidev toitmine n=121, boolustena n=125.
Täisenteraalne toitmine vastavalt 7 (5-10) vs. 6 (5-8) päeva.
Maojäägid olid väiksemad booluste grupis 4.8 vs 3.9 ml/die.
Toitmise katkestamist vajati harvem booluste grupis 76 vs 59, erinevus 16% (3-28%).

Järeldati, et nii pidev kui ka boolustena toitmine on sobilik enneaegsetele vastsündinutele, kuigi toitmine boolustena on eelistatum [13].

Practice of Enteral Nutrition in Very Low Birth Weight and Extremely Low Birth Weight Infants [14]
Koletzko B, Poindexter B, Uauy R (eds): Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2014.

Table 1. Reasonable strategy to optimize enteral feeding practices in ELBW (<1,000 g) and VLBW (1,000–1,499 g) infants

	ELBW	VLBW
Preferred milk	HM*	HM*
First feeding	between 6 and 48 h of life	between 6 and 48 h of life
Initial feeding (MEF)	0.5 ml/kg/h or 1 ml/kg q2h	1 ml/kg/h or 2 ml/kg q2h
Duration of MEF	1–4 days	1–4 days
Feeding advancement	15–25 ml/kg/day	20–30 ml/kg/day
If continuous feeding	+0.5 ml/kg/h q12h	+1 ml/kg q8h
If q2h intermittent feeding	+1 ml/kg q12h	+1 ml/kg q8h
HM fortification	before 100 ml/kg/day	before 100 ml/kg/day
Target energy intakes	110–130 kcal/kg/day	110–130 kcal/kg/day
Target protein intakes	4–4.5 g/kg/day	3.5–4.0 g/kg/day

* Own mother's breast milk or donor HM, but adapted preterm infant formula may also be used if there is no access to HM.

Guidelines for Feeding Very Low BirthWeight Infants. Review 2015, Canada [15].

Level of evidence (LOE) as per the Centre for Evidence-based Medicine, United Kingdom. The outline of the LOE for therapy trials is as follows:

1a Systematic review (with homogeneity) of randomized controlled trials (RCT)
1b Individual RCT with narrow confidence interval (CI)
2a Systematic review (with homogeneity) of cohort studies
2b Individual cohort studies and low-quality RCTs
3a Systematic review (with homogeneity) of case-control studies
3b Individual case-control studies
4 Case series, poor-quality cohort and poor-quality case-control studies
5 Expert opinion without explicit critical appraisal
If a minus sign is suffixed (e.g., 1a− or 1b−), it denotes either a single study with wide CI or a systematic review with troublesome heterogeneity.
Täisenteraalsele toitmisele jõudmise aeg (~150-180 ml/kg/die) umbes kahe nädala jooksul <1000 g sünnikaaluga vastsündinutel ja ja umbes ühe nädalal jooksul 1000-1500 g sünnikaaluga vastsündinutel. Vajadusel individuaalne patsiendipõhine lähenemine (LOE 2b).
Toitmise sageduse >1250 g sünnikaaluga vastsündinutel 3 tunni intervalliga. Ei ole tõenduspõhiselt näidatud, et kahe tunni intervalliga toitmisel ≤1250 g sünnikaaluga vastsündinutel oleks erinevust toidutaluvuse, apnoede, hüpoglükeemia, NEK`i esinemissageduses (LOE 2b).
Mõnede uuringute alusel on soovitav ≤1250 g sünnikaaluga vastsündinuid toita kahe tunnise intervalliga (LOE 4).

Troofiline toitmine: alustamine, kogus, kestvus. Troofilise toitmise ehk minimaalse enteraalse toitmise kogus on 10-15 ml/kg/die. Soovitav alustamise aeg on esimese 24 tunni

jooksul. Ettevaatlikumalt suhtuda ELBW ja IUGR vastsündinutesse. Kui esimese 24-48 tunni jooksul ema rinnapiima või doonor rinnapiima ei ole võimalik anda, kaaluda piimaseguga toitmist (LOE 1d-).

Enteraalne toitmine (kogus, sagedus): <1 kg sünnikaaluga vastsündinutel alustada toitmist 15-20 ml/kg/die ja tõsta toidukogust 15-20 ml/kg/die 2-3 päeva jooksul. Kui toidutaluvus on hea, kaaluda kiiremini koguse suurendamist. ≥1 kg sünnikaaluga vastsündinutel alustada toitmist 30 ml/kg/die ja tõsta kogust 30 ml/kg/die (LOE 1a, 1b ja 2b).

Enteraalne toitmine (kogus, sagedus): <1 kg sünnikaaluga vastsündinutel alustada toitmist 15-20 ml/kg/die ja tõsta toidukogust 15-20 ml/kg/die 2-3 päeva jooksul. Kui toidutaluvus on hea, kaaluda kiiremini koguse suurendamist. ≥1 kg sünnikaaluga vastsündinutel alustada toitmist 30 ml/kg/die ja tõsta kogust 30 ml/kg/die (LOE 1a, 1b ja 2b).

Toitmist alustada ema rinnapiimaga või kolostrumiga (värske või eelnevalt külmutatud). Teine valik on doonorrinnapiim. Kolmas valik on piimasegu. (LOE I-A).

Mitteinvasiivsel hingamistoetusel olevatel lastel tõsta toidukogust ettevaatlikult, kõhu distensiooni mitte hinnata toidutaluvuse häireks (LOE 4).

Feeding Practices and NEC [16]
Manimaran Ramani, MD [Assistant Professor] and Namasivayam Ambalavanan, MD [Professor]
Birmingham,UK, 2013

Rinnapiim võrreldes piimaseguga vähendab NEK esinemissagedust enneaegsetel vastsündinutel (LOE I-A).

Troofiline toitmine on ohutu enne ega suurenda NEK`i esinemissagedust väga enneaegsetel vastsündinutel. Kliiniliselt stabiilsetel VLBW vastsündinutel ei tõsta varane ja kiirem (30-35 ml/kg/die) toidukoguse suurendamine NEK`i esinemissagedust (LOE I – B).

Aeglane (15–20 ml/kg/die) ja kiire (30–35 ml/kg/die) toidukoguse suurendamine enneaegsetel vastsündinutel on ohutu. Varane troofilise toitmisega alustamine aitab jõuda kiiremini täisenteraalselt toitmisele (LOE I-B).

Kuigi boolustena toitmine on füsioloogilisem võrreldes pideva toitmisega, ei ole tõenduspõhisust, et üks võrreldes teisega vähendaks NEK`i esinemissagedust, haigestumust ja suremust enneaegsetel vastsündinutel (LOE I-B).

Inimese rinnapiimal põhinevad rinnapiima tõhustajad vs. lehampiimapõhised tõhustajad võivad vähendada NEK`i riski, kuid edasised uuringud on vajalikud (LOE I-B)[16].

Donor Human Milk for Preterm Infants: Current Evidence and Research Directions
2013 ESPHAGAN [17].
Vedelikuvajadus: soovitatud enteraalne vedeliku kogus 135-200 ml/kg/die, tavaliselt 150-180 ml/kg/die.
Energia: terve enneaegse vastsündinu kasvamiseks adekvaatse valgu pakkumise juures soovitatud energia vajadus on 110-135 kcal/kg/die.

Valk: Sünnikaal < 1000 g, valgu vajadus 4,0-4,5 g/kg/die
Sünnikaal 1000-18000g, valgu vajadus 3,5-4,0 g/kg/die [14].
NEK: kolm RCT (Boyd CA, 2007; Quigley MA, 2007; McGuire W, 2003), DHM vs piimasegu, kliiniline järeltulem. Kõik ülevaatd järeldavad, et DHM omab NEK`i vastu kaitsvat mõju.
Viie kõrge kvaliteediga uuringu metaanalüüs näitas statistiliselt tõepäraselt kõrgemat NEK`i esinemissagedust kunstlikul toidul olevatel vastsündinutel (RR 2.5, 95% [CI] 1.2–5.1).

-A.S.P.E.N. Clinical Guidelines 2012: Nutrition Support of Neonatal Patients at Risk for Necrotizing Enterocolitis [18]
Erica M. Fallon, MD; Deepika Nehra, MD; Alexis K. Potemkin, RN, BSN; Kathleen M. Gura, PharmD, BCNSP; Edwin Simpser, MD; Charlene Compher, PhD, RD, CNSC, LDN, FADA; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors; and Mark Puder, MD, PhD
Journal of Parenteral and Enteral Nutrition Volume 36 Number 5 September **2012** 506-523

Soovitused:

- Minimaalset enteraalset toitmist alustada kahe esimese elupäeva jooksul ja jõuda 30 ml/kg/die vastsündinutel ≥1000g. (**Nõrk soovitus**)

- Kasutada pigem rinnapiima kui lehmapiima põhist piimasegu. (**Nõrk soovitus**)

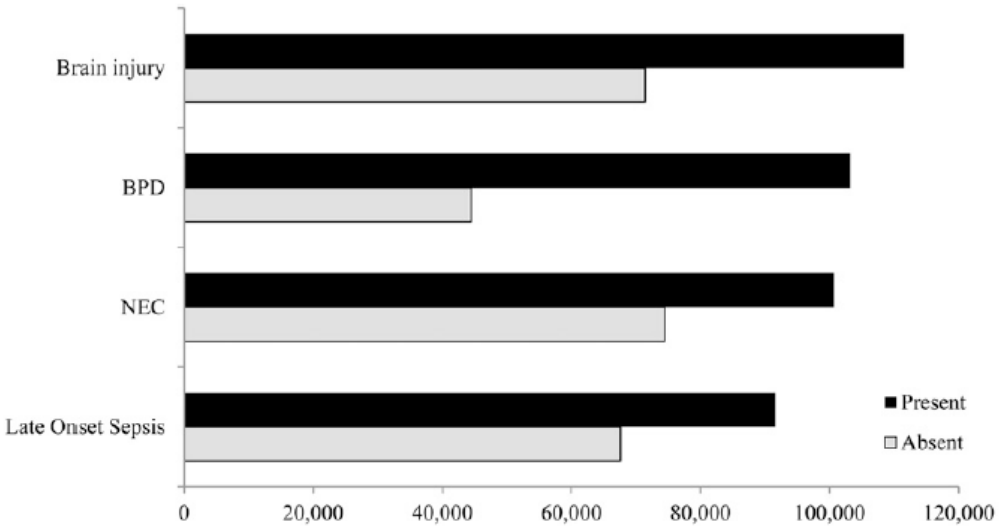
Table 1. Nutrition Support Guideline Recommendations for Neonatal Patients at Risk for Necrotizing Enterocolitis

Question	Recommendation	Grade
When and how should feeds be started in infants at high risk for NEC?	We suggest that minimal enteral nutrition should be initiated within the first 2 days of life and advanced by 30 mL/kg/d in infants ≥1000 g.	Weak
Does the provision of mother's milk reduce the risk of developing NEC relative to bovine-based products or formula?	We suggest the exclusive use of mother's milk rather than bovine-based products or formula in infants at risk for NEC.	Weak
Do probiotics reduce the risk of developing NEC?	There are insufficient data to recommend the use of probiotics in infants at risk for NEC.	Further research needed
Do certain nutrients either prevent or predispose to the development of NEC?	We do not recommend glutamine supplementation for infants at risk for NEC.	Strong
	There is insufficient evidence at this time to recommend arginine and/or long-chain polyunsaturated fatty acid supplementation for infants at risk for NEC.	Further research needed
When should feeds be reintroduced to infants with NEC?	There are insufficient data to make a recommendation regarding time to reintroduce feedings to infants after NEC.	Further research needed

Abbreviation: NEC, necrotizing enterocolitis.

Rinnapiimatoidul olevate enneaegsete vastsündinute ravi maksumuse eelis seisneb nende spetsiifiliste haiguse esinemissageduse vähenemises ja vastsündinu oma ema rinnapiima kättesaadavuse ja säilitamise lihtsamates tingimustes[19]:

FIGURE 1 Comparison of hospital direct costs with and without specific morbidities in 2009 US$. BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis.



VLBW vastsündinute välditavate haiguste haiglaravi maksumuse võrdlus:

TABLE 1 Comparison of costs of preventable morbidities in VLBW infants[1]

Morbidity and authors	Type of costs	BW or GA	Cost as reported by authors	Year of costs	Cost inflated to 2011 US$
Brain injury					
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$12,045	2009	$13,305
BPD					
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$31,565	2009	$34,868
Late-onset sepsis					
Payne et al. (6)	Unadjusted costs	VLBW (401–1500 g)	$54,539 ($104,473 vs. $49,934)	1999	$90,316
Payne et al. (6)	Adjusted incremental cost	VLBW (401–1500 g)	$5,875, BW 401–750 g	1999	$9729
			$12,480, BW 751–1000 g		$20,667
			$9,583, BW 1001–1250 g		$15,869
			$6,276, BW 1251–1500 g		$10,393
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$10,055	2009	$11,107
NEC					
Medically managed only					
Bisquera et al. (7)	Unadjusted charges	VLBW (<1500 g)	$73,700	1992–1994	$144,910
Ganapathy et al. (7)	Adjusted incremental cost	≤28 wk GA	$74,004	2011	$76,716
Surgically managed only					
Bisquera et al. (7)	Unadjusted charges	VLBW (<1500 g)	$186,200	1992–1994	$366,110
Ganapathy et al. (8)	Adjusted incremental cost	≤28 wk GA	$198,040	2011	$205,299
Medically and surgically managed					
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$15,440	2009	$17,056

[1] Costs inflated to 2011 US$ using the Consumer Price Index for medical care (9). BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; NEC, necrotizing enterocolitis; VLBW, very low birth weight.

TABLE 2 Impact of human milk on costs of preventable morbidities in VLBW infants[1]

Authors	Type of costs	BW	Morbidity	Cost savings of HM	Year of costs
Ganapathy et al. (8)	Incremental cost due to reduction in NEC: HM bovine	≤1250 g	NEC	Bovine milk associated with $8167 higher cost than HM	2011
Patel et al. (13)	Incremental cost, after controlling for sepsis: <25, 25–49.99, and ≥50 mL · kg^{-1} · d^{-1}	<1500 g	Sepsis	<25 mL · kg^{-1} · d^{-1} HM had $31,514 higher cost than ≥50 mL · kg^{-1} · d^{-1} HM and $20,384 higher cost than 25–49.99 mL · kg^{-1} · d^{-1} HM	2010

[1] BW, birth weight; HM, human milk; NEC, necrotizing enterocolitis.

Rinnapiima väljalüpsmiseks ja säilitamiseks haiglas on vaja rinnapumpasid, kogumisnõusid ja säilituskonteinereid. Jegier et al 2010 ja 2013 näitas, et vastsündinu enda ema rinnapiima

keskmine hind 100 ml päevas on 7,93 UDS/100 ml (ööpäevane piima kogus <100 ml/die) kuni 0,51 USD/100 ml (ööpäevane piima kogus >700 ml/die). Võrdluseks doonorpiima hind 14,84 USD 100 ml umbes 7. päeval pärast lüpsmist ja kunstliku toidu hind 3,18 USD/100 ml pärast 19. päeva kui ema lüpsab rinnapiima <100 ml päevas. Kui ema lõpsis rinnapiima >400 ml päevas, siis oli selle hind odavam doonorrinnapiimast 4. päeval ja kunstlikust toidust 10. päeval [13].

Ravijuhendid

Soovitused enneaegse vastsündinu enteraalse toimise kohta on kahes AGREE-ga hinnatud ravijuhendis (2009 ja 2014).

Enteral Nutrition administration. In A.S.P.E.N. enteral nutrition practice recommendations. Guideline summary NGC-7287.

Bibliographic Sourse(s): Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, Lyman B, Metheny NA, Mueller C, Robbins S, Wessel J. JPEN J Parenter. Enter. Nutr. **2009** Mar-Apr;33(2):149-58 (88 references).

Soovituste aste:

A. There is good research-based evidence to support the quideline (prospective, randomized trials).
B. There is fair research-based evidence to support the quideline (well Designer studies without randomization).
C. The quideline is based on expert opinion and editorial consensus.

Praktilised soovitused enneaegsete vastsündinute toitmiseks:

1. Enneaegsed vastsündinud, kes kaaluvad < 1500 g ja kellel on risk nekrootilise enterokoliidi tekkeks, nende emasid peab julgustama ja soodustama nende laktatsiooni **(A).**
2. ELBW ja VLBW vastsündinute minimaalne enteraalne toitmine peaks olema edukas alustades aeglasel 0,5-1,0 ml/kg/die kuni 20 ml/kg/die **(B).**
3. Edasine VLBW ja ELBW vastsündinute toidukogus peaks suurenema 10-20 ml/kg/die **(C).**

Care of extremely premature infants

A guideline for the care of children born before 28 full weeks of pregnancy have passed

The Swedish National Board of Health and Welfare September 2014
ISBN 978-91-7555-206-4 Article number 2014-9-10

Rinnapiim peaks olema vastsündinu esimene toit.
Recommended nutritional intake:

Nutrient (kg/d)[a]	Day 0[b]	Day 4[c]	EN full dose[d]	TPN full dose[e]
Liquid (ml)	80-100	130-160	135-200	135-180
Energy (kcal)	50-60	105-125	115-135	90-115
Protein/aa (g)	2-2.4	3.5-4.5	4.0-4.5	3.5-4
Carbohydrates (g)	7-10	11-16	9-15	13-17
Glucose (mg/kg/min)	5-7	-	-	9-12
Fat (g)	1.0-1.5	4-6	5-8	3(-4)
DHA (mg)	-	-	12-60	11-60
Arachidonic acid	-	-	18-45	14-45

(mg)				
Na (mmol)	0-1	2-4	3-7	3-7
P (mmol)	0-1	1.0-2.5	2-3	2-3
Cl (mmol)	0-1	2-4	3-7	3-7
Ca (mmol)	0.5-1.5	2.2-2.7	3.0-3.5	1.5-2
P (mmol)	0.5-1.5	1.7-2.5	2-3	1.5-1,9
Mg (mg)	0-4	6-11	8-15	4,3-7,2
Fe (mg)	-	0	2-3	0,1-0.2
Zn (mg)	-	1-1.5	1.5-2.5	0.4-0.45
Cu (Mg)	-	70-110	120-200	20-25
Se (Mg)	-	2-5	2-7	2-5
Mn (Mg)	-	0-4	1.0-7.5	0-1
I (Mg)	-	10-30	10-50	10
Vit A (RE) (IE)	-	1 000-2 300	1 300-3 300	700-1 500
Vit D (IE)	-	220-600	400-1 000	40-160
Vit E (TE) (mg)	-	2.2-7	2.2-11	2.8-3.5
Vit K (Mg)	-	4.4-20	4.4-28	4.4-16
Vit C (mg)	-	13-35	11-46	15-25
Thiamine B1 (Mg)	-	140-300	140-300	200-350
Riboflavin B2 (Mg)	-	150-300	200-400	150-200
Pyridoxine B6 (Mg)	-	45-250	45-300	150-200
Niacin (NE) (mg)	-	0.4-7,0	0.4-5,5	4-7
Pantethine (mg)	-	0.3-2,0	0.3-2,1	1-2
Biotin (Mg)	-	1.7-12,0	1.7-16,5	5-8
Folate (Mg)	-	35-90	35-100	35-80
Vit B12 (Mg)	-	0.1-0.6	0.1-0/77	0.1-0.5

[a] Per kilo body weight and day for all units. The relevant weight is used for body weight except for the first few days when the birth weight is used until it has been achieved and passed.

[b] Here, day 0 is defined as the date of the birth, i.e. from the birth until the morning of the next day. The recommendation applies to a full day and needs to be individually adjusted down depending on the time when the child is born

[c] The child ought to be given a full dose of nutrition at least as of the fourth day of life (but still with some fluid restriction). The recommendation in this column is approximate and is based on 50 per cent enteral and 50 per cent parenteral nutrition. The exacta targets (which must be individually calculated) depend on the proportions of the parenteral supply of the nutrient in question, so the target will be slightly lower than stated if the child receives a greater share of parenteral nutrition for example.

[d] Recommended intake for full enteral nutrition (EN).

[e] Recommended intake for total parenteral nutrition (TPN).

Kulutõhusus: Economic Benefits and Costs of Human Milk Feedings: A Strategy to Reduce the Risk of
Prematurity-Related Morbidities in Very-Low-Birth-Weight Infants REVIEWS FROM ASN EB 2013 SYMPOSIA

Tricia J. Johnson, Aloka L. Patel, Harold R. Bigger, Janet L. Engstrom, Paula P. Meier
Adv. Nutr. 5: 207–212, 2014.

Süstemaatiliste ülevaadete, ülevaateartiklite viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Key messages: - Human milk is the preferred feeding for premature infants. - Both mother's own milk and donor human milk will need to be fortified in very-low-birth-weight infants. - Attention to growth and assuring appropriate fortification is extremely important. The compositional differences between term and preterm human milk are caused by a variety of reasons including early interruption of pregnancy, variable hormonal profile [*Anderson GH:1984*] , delay in initiation of pumping, maternal anxiety and decreased milk flow. Nonetheless, the benefits of providing human milk for premature infants are numerous and are listed: [*Bhatia J 2007; Johnston M 2012*] . **Host defense benefits** Lower incidence of infections Decreased NEC Decreased diarrhea and urinary tract infections Decreased late-onset sepsis Decreased otitis media sIgA, lactoferrin, lysozyme, oligosaccharides, nucleotides, cytokines, growth factors, enzymes, antioxidants, and specific amino acids may all contribute to the improved host defense **Neurodevelopment** Improved long-term cognitive development 'Intention' to breastfeed may also influence outcome by positiive health behaviors in the mothers Improved visual function Decreased retinopathy of prematurity Protective effect against atopic disease in infants at high risk for atopy Factors that influence neurodevelopmental outcome are not clear and may include the long-chain polyunsaturated fatty acids, cholesterol, antioxidants, taurine, growth factors, and unknown maternal factors **Gastrointestinal effects** More rapid gastric emptying Improved lactase activity Table 2 depicts concentrations of protein and energy in preterm and term human milk through 28 days of age:	1.**Human Milk and the Premature Infant** Jatinder Bhatia USA 2013

Table 2. Protein and energy concentrations in preterm and term human milk

	Protein*				Energy**			
	day 7	day 14	day 21	day 28	day 7	day 14	day 21	day 28
Milk								
Preterm	2.0	1.67	1.63	1.48	73.86	74.59	73.84	73.33
Term	1.78	1.58	1.45	1.31	73.62	71.81	70.40	72.71

Adapted from Lemons et al. [62]. * Protein in g/dl (nitrogen × 6.25). ** Energy in kcal/dl.

When compared to the protein and energy intakes needes to achieve fetal weight gain as summarized by Ziegler [*Ziegler EE 2011*] , preterm human milk falls short for both components from body weights of 500–2,200 g. Protein requirements, for example, for infants <1,200 g that have been recommended by the Life Sciences Research Office (LSRO) are 3.4–4.3 g/ kg/day [*Klein CJ, 2002*] , and by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 4.0–4.5 g/kg/day [*Agostoni C, 2010*] , underscoring the need for supplementation of human milk, both preterm and term. Supplementation is widely used especially in donor milk with a typical protein concentration of 1.0 g/dl. To achieve >100 kcal/kg/day, human milk would have to be fed at >140 ml/kg/day, a target not usually achievable in the first weeks of life where a mixture of parenteral nutrition and minimal enteral nutrition provides the nutrition supply.

Human Milk and NEC

In an older prospective multicenter study [*Lucas A,1990*] , NEC developed in 5.5% (51 infants) of 926 preterm infants assigned to their early diet. In exclusively formula-fed infants, confirmed disease was 6–10 times more likely than in those fed breast milk and 3 times more common in those with mixed feeds. Pasteurized donor milk was found to be as protective as mother's own milk. In a systematic review, Quigley et al. [*Quigley MA, 2007*] reported a statistically significantly higher incidence of NEC in the formula-fed versus nutrient-fortified donor breast milk group (typical relative risk 2.5, 95% confidence interval 1.2, 5.1).

Infants fed their own mother's milk achieved full enteral feeds significantly earlier than those fed preterm formula Human Milk and the Gastrointestinal Tract.

Feeding of human milk improves gut motility and promotes gastric emptying [*Donovan SM, 2006, Heiman H,2006*] . In addition, infants fed their own mother's milk achieved full enteral feeds significantly earlier than those fed preterm formula [*Schanler RJ,1999*] . Infants fed donor milk demonstrated less feeding intolerance [*Gross SJ:1983*] . Meta-analyses did not demonstrate differences in feeding tolerance between infants fed fortified versus unfortified human milk or formula [*Quigley MA 2007; Kuschel CA,2004*]

A Cochrane Systematic Review [*McCormick F, 2010*] cited one study

where weight, length, and head circumference were statistically significantly greater in infants fed fortified human milk for 12 weeks after discharge compared to a control group; the assessments were performed at 12 months' corrected age No neurodevelopmental benefits were found at 18 months' corrected age. **Better weight gain and improved gains in length were observed in infants fed fortified versus unfortified human milk.** **Feeding of mother's own milk and, in its absence, donor human milk provides multiple benefits to preterm infants compared to formula.** **Conclusions** In summary, meta-analyses and randomized controlled trials indicate that feeding of mother's own milk and, in its absence, donor human milk provides multiple benefits to preterm infants compared to formula. However, in the absence of human milk, mother's or donor, preterm formula is an appropriate option. The American Academy of Pediatrics and ESPGHAN recommend human milk as the preferred feeding for all infants including preterm infants, although fortification and/or supplementation must be provided in very preterm infants to meet the nutrient needs of the growing premature infant. In the balance, in the absence of contraindications to human milk feeding, human milk should be the preferred source of nutrition for all infants.	
Some of the trophic effects of human milk on the gastrointestinal tract are listed: **Table 4.** Effects of early feeding of human milk May reduce the incidence of NEC [46] Trophic effects of human milk on the immature gastrointestinal tract [47, 48] • reduces intestinal permeability [49] • stimulates cell proliferation [50] • enhances gastric emptying [51] • facilitates earlier achievement of full feedings [52] *46- Kamitsuka MD,2000* *47- Donovan SM, 2006* *48- Walker A, 2010* *49- Taylor SN,2009* *50- Hirai C,2002* *51- Van den Driessche M,1999* *51- Sisk PM,2008* Human milk keeps the risk of NEC to a minimum and is therefore the preferred feeding for premature infants . Because it usually takes some days for maternal milk to become available, donor milk is often used as initial trophic feeding in order to start gut stimulation in a timely manner, i.e. on the first day of life. As maternal milk becomes available, it then replaces donor milk. Gastric residuals need to be monitored and their size taken into account in decisions about	**2.Meeting the Nutritional Needs of the Low-Birth-Weight Infant** Ekhard E. Ziegler USA 2011

advancing feedings. It is probably prudent to keep the volume of trophic feedings low (10 ml/kg/day) until gastric residuals are substantially diminished. But there is no consensus whether feedings should be kept at trophic levels for a fixed number of days or whether cautious advancement should begin sooner. At some point, fortification of human milk must be initiated. An enteral feeding volume of 100 ml/kg/day seems to be the most widely used point at which addition of human milk fortifier (HMF) is initiated.	
As evidence of differences in outcomes of very low birthw eight(VLBW) infants fed maternal human milk compared with those fed infant formula has mounted, doonor human milk has become an increasing used intervention when maternal milk is unavailable. Use of maternal milk during the birth hospitalization in VLBW infants has been associated with lessened in-hospital morbidity including lower rates of necrotizing enterocolitis (NEC),a late-onsept sepsis, a bronchopulmonary dysplasia, the composite outcome of NEC or death,and severe retinopathy of prematurity.Maternal milk diets have been associated with shorter hospidal stays and lower incidence of rehospitalization than preterm formula diets. Most important for lifelong benefit, maternal milk intake in preterm infants has also been associated with superior neurodevelopmental outcomes compared with formula diets, measured at 18 to 22 months [*VohrB R, 2006*], 30 months [*VohrB R,2007*] and 7 to 8 [*Lucas A, 1992*]years with demonstration of a significant dose-response relationship [*VohrB R, 2006, Lucas A,1992*]. **Pasteurization and Effects on Human Milk:** The good: prevention of bacterial and viral disease transmissioon. The bad: pasteurization negatively affects some of the unique anti-infectious properties of human milk. Human milk contains active maternal T cells [*WirtD P, 1992*], B cells, macrophages,and neutrophils [*Field C J,2005*], all of which are inactivated by pasteurization [*Lawrence RA, 1999*]. ln addition, secretory lgA levels are reduced by 28 % to 60% with Holder pasteurization [*Braga LP,2007; Akinbi H,2010; Czank C,2009*], and lactoferrin and lysozyme activity are reduced up to 80% and 60%, respectively [*Czank C,2009*]. Pasteurization does not affect the levels of human milk oligosaccharides [*Bertino E,2008*] and although patterns and levels of these compounds may differ between donor and maternal milk fed to VLBW infants in neonatal intensive care units(NlCUs) [*Marx C,2014*],the significance of this is unclear. Most studies report that pasteurization does not affect proteiin, fat and carbohydrate levels of human milk [*Braga LP,2007; Valentine CJ,2010*]. Levels of most vitamins and minerals are not affected by pasteurization *[Goes H C,2002; Ewaschuk JB,2011]*, although milk antioxidant capacity is significantly reduced [*Silvester D,2008*]. Protein content of doonor human milk approaches the generallay accepted standard estimate of 1 g/dl for term hurman milk [*Wojcik K Y,2009*], but typically does not reach the levels of 1.2 to 1.5g /dl reporter for milk expressed by mothers delivering preterm in the first 4 to 6 weeks a fter delivery [*Schanler RJ,1980*]. This is a consequence not of pasteurization but of	**3.Donor Human Milk for Preterm Infants What lt ls, What lt Can Do, and What Still Needs to Be Learned** Tarah f. Colaizy, MD, MP; Clin Perinatol 41 (2014)4 37450

donors donating later in lactation arter having delivered term infants. **Current State of the Evidence: Differences Between Maternal and Donor Milk** -Pasteurization results in inactivation of white blood cells, bacteria and viruses in human milk. -Pasteurization also results in loss of some protective compounds present in milk,whereas others are not affected. -Donor milk obtained from term donors contains less fat and protein than typical preterm maternal milk, and may not contain adequate DHA and ARA. -Differences between maternal and donor milk should be recognized and addressed when doonor milk is fed to VLBW infants. **Current State of the Evidence: NEC and Donor Milk**: -The most common mode of doonor milk use(ie,as a supplement to maternal milk with BHMF)is poorly studied with regard to risk of NEC compared with formula supplementation, but such use may be protective. -NEC risk of doonor milk plus BHMF as a sole diet has not been compared with the risk with preterm formula. -The EHM diet shows pomise as an intervention that may be superior to formula use;both sole formula diets and maternal milk diets supplemented with formula. **Current State of the Evidence: Growth in VLBW lnfants Fed Donor Human Milk** -VLBW infants fed human milk are typically r ported to grow more slowly during birth hospitalization than Athose fed formula, when both maternal and doonor milk are studied. - Recent studies report improved rates of growth with dietary strategies that focus on proteiin supplementation beyond standard fotifier use according to manufacturer recommendations. -These strategies should be used,or neonatologists should at least be aware that additional protein supplementation may be needes in VBLW infants fed donor human milk. **Current State of the Evidence**:**Donor Human Milk and Hospital Stay, TPN Use** -Donor human milk,fortified with bovine fortifier and used as a suplement to maternal milk, has not been shown to affect TPN usage or length of hospital stay. -Donor human milk,forlified with human HMF and used as a suplement to maternal milk,has not been shown to affect length of stay or TPN use compared with the use of bovine fortifier and formula supplements to maternal milk. -An EHM diet is associated with shorter length of TPN use compared with preterm formula in infants receiving no maternal milk.	
The patient's clinical condition and activities dictate the daily energy requirements as follows: ●Average daily energy requirements for enteral fed premature infants are 120 kcal/kg per day [*Sinclair JC.1971*]. ●Energy requirements are reduced to 80 to 100 kcal/kg per day in infants fed parenterally because of less fecal energy loss, fewer	**4. Approach to enteral nutrition in the premature infant** ***Disclosures:*** **Richard J**

episodes of cold stress, and somewhat less activity. ● Total energy needs in infants with chronic illness, such as bronchopulmonary dysplasia, increase up to 150 kcal/kg per day because of increased resting energy expenditure, activity, and possibly fecal losses [*Weinstein MR 1981; Yunis KA, 1989*]. **Our approach — The approach we use is as follows:** ● Directly after birth, parenteral fluids with glucose are initiated to meet the immediate fluid and energy requirements of the premature infant until enteral feeds are established. ● Parenteral nutrition solutions (glucose, amino acids, calcium, vitamins, and lipids) are started as early as feasible to begin to address energy and nutrient needs. ● Enteral feedings are initiated in the first two to five days after birth to prime the gastrointestinal (GI) tract in the VLBW infant (birth weight <1500 g) and to begin feeds in the more mature infant. Feeding is begun with unfortified human milk or 20 kcal/oz preterm formula. ● Milk volume is advanced to provide enteral nutrition when the infant is clinically stable and minimal feedings are tolerated. The volume of parenteral nutrition solution is simultaneously reduced. Specific volumes of milk administered for nutritive feeding depend upon the size, maturity, and feeding tolerance of the infant. Feeding (unfortified human milk or 20 kcal/oz preterm formula) is started at 20 mL/kg per day. After a period of a few days of GI priming, feedings are advanced at a rate of 15 to 30 mL/kg per day. ● When the infant tolerates at least 100 mL/kg per day or has been fed unfortified human milk for at least one week, the caloric density of milk is increased by either switching to 24 kcal/oz preterm formula or adding human milk fortifier. ● The final goal is 150 to 160 mL/kg per day of 24 kcal/oz preterm formula or 160 to 180 mL/kg per day of fortified human milk. The target volume generally is one that supports a weight gain of more than 15 g/kg per day.	**Schanler, MD** Consultant/Advisory Boards: Medela [Breastfeeding (Breast pumps, collection kits)]. **Steven A Abrams, MD** Grant/Research/Clinical Trial Support: Mead-Johnson, Nutrition [Pediatric Nutrition (Infant formulas)]. Consultant/Advisory Boards: MilkPrep [dairy products (fluid milk)]. **Alison G Hoppin, MD** Nothing to disclose. Literature review current through: Sep 2015.
Background When sufficient maternal breast milk is not available, alternative sources of enteral nutrition for preterm or low birth weight infants are donor breast milk or artificial formula. Donor breast milk may retain some of the non-nutritive benefits of maternal breast milk for preterm or low birth weight infants. However, feeding with artificial formula may ensure more consistent delivery of optimal levels of nutrients. Uncertainty exists about the balance of risks and benefits of feeding formula versus donor breast milk for preterm or low birth weight infants. **Objectives** To determine the effect of feeding with formula compared with donor breast milk on growth and development in preterm or low birth weight infants. **Search methods** We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 3), MEDLINE (1966 to March 2014), EMBASE (1980 to March 2014), CINAHL (1982 to March 2014),	**5.Formula versus donor breast milk for feeding preterm or low birth weight infants** Maria Quigley, William McGuire [Intervention Review]Cochr. 2014

conference proceedings and previous reviews.
In total, 1070 infants participated in the included trials.Most participants were clinically stable preterm infants of gestational age less than 32 weeks or birth weight less than 1800 g. Most of the trials specifically excluded infants who were small for gestational age at birth and infants with congenital anomalies, or gastrointestinal or neurological problems.

Interventions

The trials varied according to type of formula, whether doonor breast milk feeds were fortified and whether the intervention was a sole diet or a supplement to mother's own milk:
-Four trials compared feeding with term formula milk versus donor breast milk [*Davies 1977; Gross 1983; Raiha 1976;Schultz 1980*]. In all of these trials term formula or donor breast milk was the sole diet.
-Five trials compared feeding with preterm formula milk versus donor breast milk [*Lucas 1984a; Lucas 1984b; Schanler 2005; Tyson 1983; Cristofalo 2013*].
-In three of these trials preterm formula milk or donor breast milk was the sole diet [*Lucas 1984a; Tyson 1983; Cristofalo 2013*]. In the other two trials preterm formula milk or donor breast milk was given as a supplement to maternal breast milk [*Lucas 1984b; Schanler 2005*].

Five trials used donor breast milk collected from mothers who had delivered an infant at term [*Davies 1977; Lucas 1984a; Lucas 1984b; Raiha 1976; Schultz 1980*]. Two of these trials used 'drip' breast milk [*Lucas 1984a; Lucas 1984b*]. One trial used preterm donor breast milk [*Schanler 2005*], one trial used both term and preterm milk [*Gross 1983*] and two trials did not specify the type of donor breast milk [*Tyson 1983; Cristofalo 2013*]. In all trials except Tyson 1983, the donor breast milk was pasteurised. Only the two more recent trials used nutrient-fortified doonor breast milk [*Schanler 2005;Cristofalo 2013*]. In general, feeds were allocated for several weeks, or until participating infants reached a specified weight (generally over 2 kg).

Formula milk versus donor breast milk for feeding preterm or low birth weight infants

When a mother's own breast milk is not available for feeding her preterm or low birth weight infant, the alternatives are either formula or expressed breast milk from a donor mother ('donor breast milk'). This review of nine randomised controlled trials suggests that feeding with formula increases short-term growth rates, but is associated with a higher risk of developing the severe gut disorder called 'necrotising enterocolitis'. There is no evidence of an effect on longer-term growth or on development. Further trials that compare these two strategies are needed. These should probably compare formula adapted for preterm infants with donor breast milk supplemented with extra nutrients.
Meta-analysis of data from six trials suggests that feeding with formula more than doubles the risk of necrotising enterocolitis. The observed effect sizes were similar across the trials and there was no statistical evidence of heterogeneity. The pooled estimate suggests that one extra case of necrotising enterocolitis will occur in every 25

infants who receive formula. This beneficial effect of donor breast milk exists even when donor breast milk is given as a supplement to maternal breast milk rather than as a sole diet and also when the donor breast milk is fortified. However, only one of the trials was able to blind caregivers and assessors to the intervention. This methodological weakness may have resulted in surveillance and ascertainment biases that contributed to the higher rate of detection of necrotising enterocolitis in formula-fed infants. Finally, caution should be exercised in applying these data to growth-restricted preterm infants or sick infants, since these infants, although at high risk of developing necrotising enterocolitis, were generally excluded from the included trials. **Quality of the evidence** The trials contain various methodological quality weaknesses, specifically uncertainty about adequate allocation concealment methods in three trials and lack of blinding in most of the trials. Parents, caregivers, clinicians and investigators were likely to have been aware of the treatment group to which infants had been allocated and this knowledge may have affected some care practices or investigation strategies including thresholds for screening or diagnosing for necrotising enterocolitis, which may have affected the outcomes assessed. **Authors' conclusions** In preterm and low birth weight infants, feeding with formula compared with donor breast milk results in a higher rate of short-term growth but also a higher risk of developing necrotising enterocolitis. Limited data on the comparison of feeding with formula versus nutrient-fortified donor breast milk are available. This limits the applicability of the findings of this review as nutrient fortification of breast milk is now a common practice in neonatal care. Future trials may compare growth, development and adverse outcomes in infants who receive formula milk versus nutrient-fortified donor breast milk given as a supplement to maternal expressed breast milk or as a sole diet.	
Fluid We regard 135mL/kg/day as the minimum fluid volume and 200 mL/kg/day as a reasonable upper limit. For routine feeding, rates of 150 to 180 mL/kg/day nutrient intake when standard formula or fortified breast milk is used are likely to achieve meeting nutrient requirements. Some infants may need higher volumes to meet requirements of substrates ohter than fluid. **Energy** A reasonable range of energy intake for healthy growing preterm infants with adequate protein intake is 110 to 135 kcal/kg/day. Increasing energy intake may not be appropriate for infants whose growth appears inadequate (without evidence of fat malabsorption) because it is more likely that ohter nutrients (eg, protein) are rate limiting. **Energia**: terve enneaegse vastsündinu kasvamiseks adekvaatse valgu	**6. Enteral Nutrient Supply for Preterm Infants: Commentary From the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition 2010** C. Agostoni, G. Buonocore, V.P. Carnielli, M. De Curtis, D. Darmaun,

pakkumise juures soovitatud energia vajadus on 110-135 kcal/kg/die. **Protein** Some excess of protein intake over requirements was not shown to cause detrimental effects in preterms, but a small deficit will impair growth. We therefore recommend aiming at 4.0 to 4.5 g/kg/day protein intake for infants up to 1000 g, and 3.5 to 4.0 g for infants from 1000 to 1800 g that will meet the needs of most preterm infants. Protein intake can be reduced towards discharge if the infant's growth pattern allows for this. The recommended range of protein intake is therefore 3.5 to 4.5 g/kg/day or 3.2 to 4.1 g/100 kcal.	T. Decsi, M. Domellöf, N.D. Embleton, C. Fusch, O. Genzel-Boroviczeny, O. Goulet, S.C. Kalhan, S. Kolacek, B. Koletzko, A. Lapillonne, W. Mihatsch, L. Moreno, J. Neu, B. Poindexter, J. Puntis, G. Putet, J. Rigo, A. Riskin, B. Salle, P. Sauer, R. Shamir, H. Szajewska, P. Thureen, D. Turck, J.B. van Goudoever, and E.E. Ziegler, for the ESPGHAN Committee on Nutrition
Human milk is not a uniform body fluid but a secretion of the mammary gland of changing composition. Foremilk differs from hindmilk, and colostrum is strikingly different from transitional and mature milk. Milk changes with time of day and during the course of lactation. Human milk consists not only of nutrients, such as proteins, lipids, carbohydrates, minerals, vitamins, and trace elements that are of paramount importance to fulfill the nutritional needs of young infants and ensure normal growth and development. Human milk also contains numerous immune-related components such as sIgA, leukocytes, oligosaccharides, lysozyme, lactoferrin, interferon-g, nucleotides, cytokines, and others. Several of these compounds offer passive protection in the gastrointestinal tract and to some extent in the upper respiratory tract, preventing adherence of pathogens to the mucosa and thereby protecting the breast-fed infant against invasive infections. Human milk also contains essential fatty acids, enzymes, hormones, growth factors, polyamines, and other biologically active compounds, which may play an important role in the health benefiits associated with breast-feeding. Breast-feeding is the natural and advisable way of supporting the healthy growth and development of young children. There are numerous indicators of benefits of breast-feeding on child health, both during infancy and later in life; a reduced risk of infectious diarrhoea and acute otitis media are the best documented effects. Exclusive breast-feeding for around 6 months is a desirable goal, but	**7. Breast-feeding: A Commentary by the ESPGHAN Committee on Nutrition 2009** ESPGHAN Committee on Nutrition:Carlo Agostoni, Christian Braegger, Tamas Decsi, Sanja Kolacek, Berthold Koletzko, Kim Fleischer Michaelsen, Walter Mihatsch, Luis A. Moreno, John Puntis, Raanan Shamir, Hania Szajewska, Dominique Turck and Johannes van Goudoever

partial breast-feeding as well as breast-feeding for shorter periods of time are also valuable. Continuation of breast-feeding after the introduction of complementary feeding is to be encouraged as long as mutually desired by mother and child. Although it is acknowledged that parents are responsible for decisions on breast-feeding of their infants, the role of health care workers, including paediatricians, is to protect, promote, and support breast-feeding.	
INTRODUCING AND ADVANCING ENTERAL FEEDS The timing of introduction and the rate of advancement of enteral milk feeds for very preterm or VLBW infants has the potential to influence important outcomes including the risk of NEC and late-onset infection. Observational studies have suggested that delaying the introduction of progressive enteral feeding until about 5–7 days after birth and increasing the volume of milk feeds slowly (<24 ml/kg/ day) is associated with a lower risk of developing NEC [*Henderson G,2009; Hartel C,2009*]. However, there are also potential disadvantages associated with conservative enteral feeding regimens. Delayed or slow enteral feeding may diminish the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonisation [*Stewart CJ;2013; Berrington JE,2013*]. Intestinal dysmotility may exacerbate feed intolerance leading to a delay in enteral feeding independently of parenteral nutrition. Prolonging the duration of parenteral nutrition may be associated with infectious and metabolic complications that increase mortality and morbidity, prolong hospital stay, and adversely affect growth and development [*Rønnestad A,2005; Rees CM,2007*]. EVIDENCE-BASE FOR EARLY ENTERAL FEEDING STRATEGIES Given the potential for early enteral feeding strategies to affect important outcomes, it is essential that policy and practice is based on the best quality evidence possible. Currently, wide variation in policy and practice exists internationally, and between and within neonatal units [*Klingenberg C, 2012*]. Observational data may be confounded by known and unknown factors, for example, clinician preferences or ohter care practices, that affect outcomes independently of the feeding method. Adequately powered randomised controlled trials obviate these issues and provide the least biased assessment of the impact of different feeding methods. Cochrane systematic reviews seek to identify and appraise randomised trials to provide a synthesised summary of the evidence. Three Cochrane reviews of enteral feeding strategies focus on distinct clinical scenarios [*Morgan J,2013 Cochrane Database Syst Rev 2013; 3:CD000504.; Morgan J, Cochrane Database Syst Rev 2013:5 CD001970; Cochrane Database Syst Rev 2013:3 CD001241*]. EARLY TROPHIC FEEDING VERSUS ENTERAL FASTING Early trophic feeding is conventionally defined as giving small	**8.Early enteral feeding strategies for very preterm infants: current evidence from Cochrane reviews** The SIFT Investigators Group 2013 Correspondence to Professor William McGuire, NIHR Centre for Reviews and Dissemination, University of York, York, UK

volumes of milk (typically 12–24 ml/kg/day) without advancing the feed volumes during the first five to seven postnatal days(20). The primary aim is to accelerate gastrointestinal physiological, endocrine and metabolic maturity and so allow infants to transition to full enteral feeding independent of parenteral nutrition more quickly. The Cochrane review of trophic feeding versus enteral fasting for very preterm or VLBWinfants includes nine trials in which a total of 754 infants participated [*Morgan J,2013 Cochrane Database Syst Rev 2013; 3:CD000504*]. Few participants were extremely preterm (<28 weeks) or extremely low birthweight (ELBW: <1000 g) or growth restricted. None of the trials specifically recruited infants with absent or reversed end end diastolic flow velocities on antenatal Doppler studies. These trials did not provide evidence that early trophic feeding affected feed tolerance or growth rates. Although some trials reported that trophic feeding reduced the time taken to establish full enteral feeds, meta-analysis of all of the available data did not detect a statistically significant effect. The trial data do not suggest that early trophic feeding is associated with important harms. Meta-analyses did not detect statistically significant effects on the incidence of NEC, late-onset infection or all-cause mortality (figures 2 and 3).

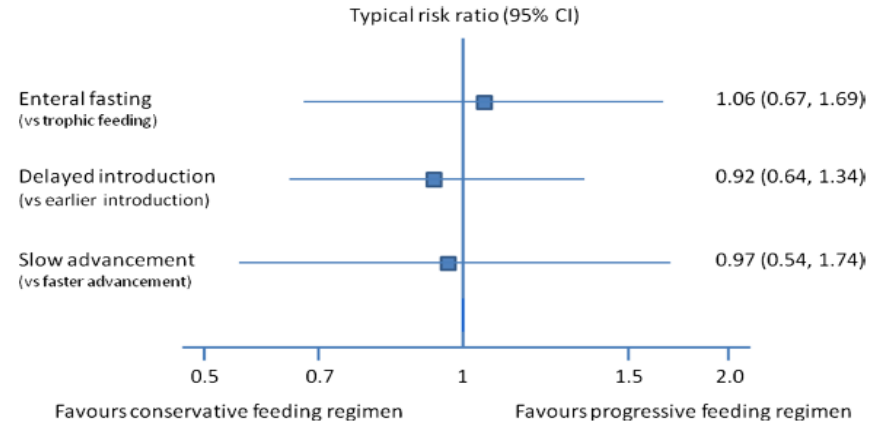


Figure 2 Summary meta-analyses of conservative versus progressive early enteral feeding: incidence of necrotising enterocolitis.

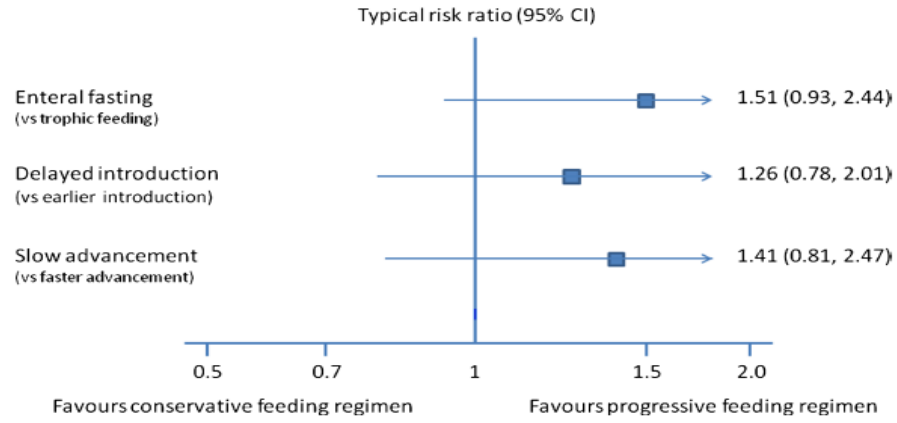


Figure 3 Summary meta-analyses of conservative versus progressive early enteral feeding: all-cause mortality.

The trials found inconsistent effects on short-term growth and meta-analysis did not reveal a significant difference in the time taken to regain birthweight. One trial reported that mothers who expressed breast milk for early trophic feeding were more likely to continue to provide breast milk as the ongoing Principel form of nutrition for their infants [*Schanler RJ,1999*]. Further study to confirm and define the mechanism of this association is merited given that feeding with breast milk compared to formula reduces the risk of NEC in very preterm or VLBWinfants [*Quigley MA,2007*].

Delayed versus early introduction of progressive enteral feeds
The Cochrane review of delayed versus early introduction of progressive enteral feeding identified seven randomised controlled trials in which a total of 964 infants participated (18).The trials defined delayed introduction as later than 5–7 days after birth and early introduction as up to 4 days after birth. Meta-analyses did not detect statistically significant effects on the risk of NEC or all-cause mortality (figures 2 and 3). Three of the trials (including a recent, large, UK and
Ireland 54-centre trial) restricted participation to growth-restricted infants with Doppler ultrasound evidence of abnormal fetal circulatory distribution or flow (23). Planned subgroup analyses of these trials did not find any statistically significant effects on the risk of NEC or all-cause mortality. Infants who had delayed introduction of enteral feeds took longer to establish full enteral feeding (median difference 2 to 4 days). It is not yet known whether this is associated with important clinically adverse consequences such as a higher rate of late-onset infection secondary to prolonged use of parenteral nutrition or a longer duration of hospidal admission.

Slow versus faster advancement of enteral feed volumes The Cochrane review identified five randomised controlled trials in which a total of 588 infants participated [*Morgan J et al, Cochrane Database Syst Rev 2013;3:CD001241*]. Few participants were extremely preterm, ELBW or growth restricted. The trials defined slow advancement as daily increments 15–20 ml/kg and faster advancement as 30–35 ml/kg. Meta-analyses did not detect statistically significant effects on the risk of NEC or all-cause mortality (figures 2 and 3). Infants who had slow advancement took significantly longer to regain birthweight (median differences 2 to 6 days) and to establish full enteral feeding (2–5 days). The trial data did not provide evidence of an effect on the incidence of late-onset infection or the duration of hospital stay.

LIMITATIONS OF EVIDENCE
The randomised controlled trials included in these Cochrane reviews were generally of good methodological quality but none of the trials masked caregivers and clinical assessors to the nature of the intervention. Although the lack of blinding may have resulted in surveillance and ascertainment biases, this is more likely to have caused an overestimation of the incidence of NEC in infants whose

feed volumes were introduced earlier or advanced faster. The assessment of abdominal radiographs for signs of NEC was masked in most trials to ensure that the diagnosis of severe NEC (confirmed by the radiological detection of gas in the bowel wall or portal tract) was not prone to bias. However, since the microbial generation of gas in the bowel wall is substrate-dependent, infants who received more enteral milk (substrate) may have been more likely to demonstrate this radiological sign than infants with equally severe bowel disease who had received less milk. This 'substrate effect' is also more likely to cause over-ascertainment of NEC in the infants who had faster rates of feed volume advancement [*Tyson JE et al 2007*].

IMPLICATIONS FOR PRACTICE

The available trial data suggest that introducing progressive enteral feeding before 4 days after birth and advancing the rate of feed volumes at more than 24 ml/kg/ day does not increase the risk of NEC in very preterm or VLBW infants. These findings are consistent with policy and practice in some countries, notably in Scandinavia, where very early introduction and advancement of enteral feeds (often within 24 to 48 h after birth) has not been associated with a higher incidence of NEC [*Klingenberg C et al,2012; Fellman V et al,2009*]. Delayed introduction or slow advancement results in several days of delay in the time taken to regain birthweight and establish full enteral feeds. The long-term clinical importance of these effects is unclear. However, the generalisability of these data for extremely preterm or ELBWinfants is unclear as this group contributed only a minority of the total participants in the existing trials. Uncertainty also exists about the riskbenefit balance of different enteral feeding strategies in human milk-fed versus formula-fed very preterm or VLBW infants as the trials and reviews did not contain sufficient data for subgroup analyses.

IMPLICATIONS FOR RESEARCH

Further randomised controlled trials could provide more precise estimates of the effects of early enteral feeding on important outcomes for very preterm or VLBWinfants. Trials should aim to ensure the participation of ELBW and extremely preterm infants as well as infants with evidence of compromised intrauterine growth so that subgroup analyses can be planned for these infants at highest risk of NEC. Masking caregivers and investigators to these interventions is unlikely
to be possible. Since the unblinded evaluation of NEC and late-onset infection is subject to surveillance and ascertainment biases, trials should aim to assess more objective outcomes, principally allcause mortality and long-term growth and development.

SIFT

The success of the large 'Antenatal Doppler Enteral Prescription Trial' (ADEPT) in assessing the effect of delayed versus early (within 48 h of birth) enteral feeding for growth-restricted infants has

generated interest and enthusiasm for further trials to assess enteral feeding strategies in very preterm or VLBW infants. In the UK and Ireland, the 'Speed of Increasing Feeds Trial' (SIFT) Group, a collaboration of service-user representatives, clinicians and trial unit experts, is undertaking a pragmatic randomised controlled trial in which 2500 very preterm or VLBW infants will be enrolled. The trial will compare advancing enteral feeds at either 30 ml/kg/day or 18 ml/kg/day. To enhance generalisability, human milk-fed and formula-fed infants will be eligible to participate and daily feeding logs will record the type of milk given. The primary outcome is death or moderate or severe disability at 2 years post-term and analyses will be by intention-to-treat. The trial is also powered to assess meaningful effects on in-hospital mortality and major morbidity, antibiotic usage and duration of hospital stay. We will conduct an economic evaluation to assess whether the intervention is likely to be cost-effective. SIFT is designed to run in parallel with another large UK multi-centre treial (ELFIN) that aims to assess the effect of prophylactic enteral lactoferrin supplementation for very preterm infants [*ELFIN Trial Investigators Group. Lactoferrin immunoprophylaxis for very preterm infants. Arch Dis Child Fetal Neonatal Ed 2013;98:F2–4.*].	
Best mode of enteral feeding in preterm infants has not been definitively determined, and the clinical effects of continuous nasogastric milk feeding versus intermittent bolus milk feeding have not been fully elucidated. These strategies are interesting because theoretically both continuous and intermittent feeding could have advantages and disadvantages. **Continuous enteral feedings** may improve energy balance by increasing energy absorption and lowering energy expenditure [*Grant J, Denne SC.1991*], contribute to improving growth, and favor feeding tolerance [*Toce SS, Keenan WJ 1987*]. However, it is possible that continuous feeding affects the cyclical release pattern of gastrointestinal tract hormoones (gastrin, gastric inhibitory peptide, and enteroglucagon), affecting metabolic homeostasis [*Aynsley-Green A, Lucas A,1990*], and interferes with lower esophageal sphincter function, encouraging the development of gastro-esophageal reflux (GER) [*Newell SJ, Sarkar PK,1988*]. **Intermittent feeding** is more physiological and promotes the cyclical release of gastrointestinal trakt hormones normally seen in healthy term infants [*Lucas A, Bloom SR,1986*]. This could be very important for gastrointestinal tract development [*Aynsley-Green A.1989*]. A recent meta-analysis of seven randomized controlled studies (511 patients) by Premji and Chessell found no differences in terms of time required to achieve full enteral feeds, somatic growth and incidence of NEC between infants who received continuous feeding compared to infants who received bolus feeding [*Premji SS, Chessell L.2011*]. However, it is noteworthy that the most recent study on this issue demonstrates that continuously fed infants grewand achieved full enteral feeding significantly faster than intermittently fed infants, and that this improvement was more evident in the smallest infants (birth weight ≤ 850 g) [*Dsilna A, Christensson K,2005*]. On the basis of this	**9.Continuous milk feeding versus intermittent bolus feeding in preterm infants** Carlo Dani , Simone Pratesi, Jacopo Barp, Italy 2013 Syst.Rev.

background, we decided to study the effects of continuous and intermittent bolus milk feeding on gut perfusion in two cohorts of AGA and SGA preterm infants, evaluating changes in splanchnic regional oxygenation (rSO2S) using NIRS, and changes in blood flow velocity (BFV) in the superior mesenteric arter (SMA) using Doppler ultrasonography [*Dani C, Pratesi S,2013*]. We found that existing evidence does not support the firm recommendation of one strategy among the many alternatives. However, although many areas remain to be investigated, it is probable that continuous feeding might be advantageous compared to intermittent feeding in favoring the faster establishment of full enteral feeding, and decreasing the risk of hypoxic–ischemic gut damage in preterm neonates in critical condition, especially SGA infants, by limiting their gastrointestinal oxygen requirement. However, it is noteworthy that the most recent study on this issue demonstrates that continuously fed infants grewand achieved full enteral feeding significantly faster than intermittently fed infants, and that this improvement was more evident in the smallest infants (birth weight ≤ 850 g) [*Dsilna A, 2005*].	
We identified nine randomised controlled trials in which 1106 infants participated. Few participants were extremely preterm (less 28 weeks' gestation) or extremely low birth weight (less than 1000 g). The trials defined delayed introduction of progressive enteral feeds as later than four to seven days after birth and early introduction as four days or less after birth. Meta-analyses did not detect statistically significant effects on the risk of NEC (typical RR 0.93, 95% CI 0.64 to 1.34; 8 trials; 1092 infants) or all-cause mortality (typical RR 1.18, 95% CI 0.75 to 1.88; 7 trials; 967 infants). Four of the trials restricted participation to growth-restricted infants with Doppler ultrasound evidence of abnormal fetal circulatory distribution or flow. Planned subgroup analyses of these trials found no statistically significant effects on the risk of NEC or all-cause mortality. Infants who had delayed introduction of enteral feeds took longer to establish full enteral feeding (reported median differences two to four days). We planned the following subgroup analyses: 1. trials in which most infants were exclusively formula-fed; 2. trials in which most infants were at least partially fed with human milk (maternal or donor); 3. trials in which most participants were of ELBW (less than 1000 g) or extremely preterm (less than 28 weeks' gestation); 4. trials in which participants were infants with intrauterine growth restriction, or infants with absent or reversed enddiastolic flow velocities detected on antenatal Doppler studies of the fetal aorta or umbilical artery. The evidence available from randomised controlled trials suggested that delaying the introduction of progressive enteral feeds beyond four days after birth did not reduce the risk of developing NEC in very preterm or VLBWinfants, including growth-restricted infants.	**10.Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants** Jessie Morgan, Lauren Young, William McGuire;UK, 2014 **Editorial group:** Cochrane Neonatal Group. We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2014, Issue 8), MEDLINE (1966 to September 2014), EMBASE (1980 to September 2014), CINAHL (1982 to September 2014), conference proceedings and previous reviews.

Delaying the introduction of progressive enteral feeds resulted in a few days' delay in establishing full enteral feeds but the clinical importance of this effect was unclear. The applicability of these findings to extremely preterm or extremely low birth weight was uncertain. Further randomised controlled trials in this population may be warranted.

No evidence that delayed introduction of progressive enteral feeds prevents necrotising enterocolitis in very low birth weight infants.

Evidence exists that feeding with artificial formula rather than human milk increases the risk of developing NEC [*Quigley 2014*]. This review focused on the comparison of delayed versus earlier introduction of progressive enteral feeding; that is, advancing the volume of milk feeds beyond minimal enteral nutrition levels. We addressed the effect of minimal enteral nutrition, the early introduction of small volume enteral feeds (up to 24 mL/kg/day) without advancing the feed volumes for at least five days versus enteral fasting in another Cochrane review [*Morgan 2013a*].

Evidence exists that artificial formula feeding increases the risk NEC[*Quigley 2014*]. The risk-benefit balance of enteral feeding strategies may differ between human milk-fed and formula-fed very preterm or VLBW infants. Currently there are insufficient data to comment on whether there is a differential effect of the timing of the introduction of enteral feeds depending on whether infants received human breast milk versus formula.

For this Cochrane review, we defined delayed introduction as later than four days after birth since some observational studies have found the risk of NEC to be lower when feeds are introduced five to seven days after birth [*Patole 2005*]. For ELBW or extremely preterm infants, itmay be more appropriate to define delayed introduction as more than seven days after birth (or even later). Small-intestinal motility is poorly organised before about 28 weeks' gestation resulting in a higher risk of feed intolerance. In addition, enteral feeds are often delayed in this population because of respiratory or metabolic instability or because of other putative risk factors for NEC, such as the existence of a patent ductus arteriosus, the use of non-steroidal anti-inflammatory drugs or the presence of an umbilical arterial catheter [*Boyle 2004*].

Implications for practice

The available data from randomised controlled trials do not proovide evidence that delaying the introduction of progressive enteral feeds beyond four days after birth reduces the risk of necrotising enterocolitis (NEC), mortality, and other morbidities in very preterm or very low birth weight (VLBW) infants. Delaying the introduction of progressive enteral feedsmay result in several days' delay in establishing full enteral feeds but the long-term clinical importance of these effects is unclear. Subgroup analyses of trials in which participating infants had evidence of intrauterine growth restriction or abnormal circulatory distribution or flow did not find any statistically significant effects.However, only limited data are available on the

effect of this intervention on outcomes for extremely preterm or extremely low birth weight (ELBW) infants.	
Background The introduction of enteral feeds for very preterm (< 32 weeks) or very low birth weight (< 1500 grams) infants is often delayed due to concern that early introduction may not be tolerated and may increase the risk of necrotising enterocolitis. However, prolonged enteral fasting may diminish the functional adaptation of the immature gastrointestinal tract and extend the need for parenteral nutrition with its attendant infectious andmetabolic risks. Trophic feeding, giving infants very small volumes of milk to promote intestinal maturation, may enhance feeding tolerance and decrease the time taken to reach full enteral feeding independently of parenteral nutrition. **Objectives:** To determine the effect of early trophic feeding versus enteral fasting on feed tolerance, growth and development, and the incidence of neonatal morbidity (including necrotising enterocolitis and invasive infection) and mortality in very preterm or VLBW infants. **Search methods** We used the standard search strategy of the Cochrane Neonatal Review Group. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 12),MEDLINE, EMBASE and CINAHL (1980 until December 2012), conference proceedings and previous reviews. **Selection criteria** Randomised or quasi-randomised controlled trials that assessed the effects of early trophic feeding (milk volumes up to 24 ml/kg/day introduced before 96 hours postnatal age and continued until at least one week after birth) versus a comparable period of enteral fasting in very preterm or very low birth weight infants. **Types of studies** Randomised or quasi-randomised controlled trials including cluster- randomised trials. **Types of participants** VLBW (< 1500 grams) or very preterm (< 32 weeks) newborn infants. **Main results** Nine trials in which a total of 754 very preterm or very low birth weight infants participated were eligible for inclusion. Few participants were extremely preterm (< 28 weeks) or extremely low birth weight (< 1000 grams) or growth restricted. These trials did not proovide any evidence that early trophic feeding affected feed tolerance or growth rates. Meta-analysis did not detect a statistically significant effect on the incidence of necrotising enterocolitis: typical risk ratio 1.07 (95% confidence interval 0.67 to 1.70); risk difference 0.01 (-0.03 to 0.05). **Authors' conclusions** The available trial data do not provide evidence of important beneficial or harmful effects of early trophic feeding for very preterm or very low birth weight infants. The applicability of these findings to extremely preterm, extremely low birth weight or growth restricted infants is	**11.Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants** Jessie Morgan, Lauren Young, William McGuire;UK, Australia 2013 **Editorial group:** Cochrane Neonatal Group.

limited. Further randomised controlled trials would be needed to determine how trophic feeding compared with enteral fasting affects important outcomes in this population.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses:

1. trials in which most infants were exclusively formula-fed;
2. trials in which most infants were at least partially fed with human milk (maternal or donor);
3. trials in which most participants were of ELBW (< 1000 grams) or extremely preterm (< 28 weeks);
4. trials in which participants were infants with intrauterine growth restriction, or infants with absent or reversed enddiastolic flow velocities detected on antenatal Doppler studies of the fetal aorta or umbilical artery.

Trophic feeding was generally started within the first three days after birth and continued for varying durations; either until infants were judged to be clinically stable (for example following endotracheal extubation or removal of umbilical catheters) or for pre-defined intervals, generally 7 to 10 days after birth. Feeding volumes ranged from about 12 to 24 ml/kg/day.

In most trials, infants received either expressed breast milk or formulamilk (diluted or full-strength) or amixture of breastmilk and formula. In two trials, infants received only formula milk [*Dunn 1988;Meetze 1992*]. Control infants received no enteral nutrition for at least one week after birth. Infants in both comparison groups received standard parenteral nutrition during the trial period. In most trials, milk was administered by intermittent bolus gavage feeds via oro or nasogastric tube. In Schanler 1999, participating infants were also allocated to either bolus or continuous feeding using a factorial design. In Troche 1995, infants weighing < 800 grams at birth received feeds via a continuous infusion whereas those weighing > 800 grams at birth received intermittent bolus feeds.

Summary of main results

The available data from randomised controlled trials do not proovide evidence that early trophic feeding compared to enteral fasting confers any substantial benefits for very preterm or very low birth weight (VLBW) infants. Although some trials reported that minimal enteral nutrition reduced the time taken to establish full enteral feeds, meta-analysis of all of the available data did not detect a statistically significant effect. The trial data do not suggest that minimal enteral nutrition is associated with important harms. Meta-analyses did not detect statistically significant effects on the incidence of necrotising enterocolitis, invasive infection or all-cause mortality. Only limited data on growth outcomes were found. Trials found inconsistent effects on short-term growth and meta-analysis did not reveal a significant difference in the time taken to regain birth weight. The clinical importance of any short-term effects is unclear as no longterm growth or developmental outcomes were assessed.

Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants

There is insufficient evidence to determine whether feeding very pretermor very low birth weight infants small quantities of milk during the first week after birth (early trophic feeding) compared with fasting helps bowel development and improves subsequent feeding, growth and development. Analysis of nine trials does not suggest that this practice increases the risk of a severe bowel disorder called 'necrotising enterocolitis'. Further trials could provide more robust evidence to inform this key area of care. **Implications for practice** The available trial data do not provide strong evidence that early trophic feeding has important effects on feed intolerance, growth or development. There is no evidence that trophic feeding has adverse effects. **Trophic feeding** (also referred to as minimal enteral nutrition, gut priming and hypocaloric feeding) was developed and adopted into clinical practice as an alternative to complete enteral fasting for very preterm or VLBW infants during the early neonatal periood (Klingenberg 2012). Early trophic feeding is conventionally defined as giving small volumes of milk (typically 12 to 24 ml/kg/ day) intragastrically starting within the first few days after birth, without advancing the feed volumes during the first week postnatally (McClure 2001). The primary aim of trophic feeding is to accelerate gastrointestinal physiological, endocrine and metabolic maturity and so allow infants to transition to full enteral feeding independent of parenteral nutrition more quickly. However, any beneficial effects may be negated if early trophic feeding increases the risk of necrotising enterocolitis in very preterm or VLBW infants. **Early trophic feeding**: enteral feeding with milk volumes up to 24 ml/kg/day (1 ml/kg/hour) beginning within four days after birth and continued for at least five days or until at least one week arter birth versus enteral fasting for the same period. Once progressive enteral feeding has started, infants should have received the same type of milk (breast milk or formula), the same route and mode of feeding (intragastric or transpyloric, bolus gavage or continuous) and the same rate of feed volume advancement in both groups.	
Background Milk feedings can be given via nasogastric tube either intermittently, typically over 10 to 20 minutes every two or three hours, or continuously, using an infusion pump. Although theoretical benefits and risks of each method have been proposed, effects on clinically important outcomes remain uncertain. **Objectives** To examine the evidence regarding the effectiveness of continuous versus intermittent bolus nasogastric milk feeding in premature infants less than 1500 grams. **Search methods** Searches were performed of the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 3, 2011), MEDLINE, CINAHL and HealthSTAR up to July 2011.	**12. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams** Shahirose S Premji, Lorraine Chessell , Canada 2011 **Editorial group:** Cochrane Neonatal Group.

Selection criteria
Randomised and quasi-randomised clinical trials comparing continuous versus intermittent bolus nasogastric milk feeding in premature infants less than 1500 grams.
Data collection and analysis
Two review authors independently assessed all trials for relevance and methodologic quality. The standard methods of the Cochrane Neonatal Review Group were used to extract data.
Investigators were contacted for additional information and/or clarification regarding six studies [*Macdonald 1992; Silvestre 1996; Toce 1987; Schanler 1999; Dollberg 2000; Dsilna 2005*].
See characteristics of included studies for details. Individual group standard deviation for data on days to full feeds from Macdonald 1992 (reported pooled standard deviations), subgroup data from Toce 1987; Schanler 1999; Dollberg 2000 and Dsilna 2005 were not available to include in this update.
Primary Outcomes:
a) feeding intolerance as measured by number of days of feeding interruptions and days on total parenteral nutrition (TPN);
b) days to regain birth weight;
c) age at full enteral feedings (days);
d) age at discharge to referral hospital or home (days);
e) somatic growth including rates of gain in weight, length, and head circumference;
f) necrotizing enterocolitis (NEC) including suspected and confirmed (Bell's Stage II or greater).
Secondary Outcomes:
a) Apnea
iv) conducting a subgroup analyses based on weight groups including < 750 grams, 750 to 999 grams, and 1000 to < 1500 grams.
Main results
Overall, the seven included trials, involving 511 infants, found no differences in time to achieve full enteral feeds between feeding methods (weighted mean difference (WMD) 2 days; 95% CI -0.3 to 3.9) . In the subgroup analysis of those studies comparing continuous nasogastric versus intermittent bolus nasogastric milk feedings the findings remained unchanged (WMD 2 days, 95% CI -0.4 to 4.1). There was no significant difference in somatic growth and incidence of NEC between feeding methods irrespective of tube placement. One study noted a trend toward more apneas during the study period in infants fed by the continuous tube feeding method compared to those fed by intermittent feedings delivered predominantly by orogastric tube placements [mean difference (MD) 14.0 apneas during study period; 95% CI -0.2 to 28.2]. In subgroup analysis based on weight groups, one study suggested that infants less than 1000 grams and 1000 to 1250 grams birth weight gained weight faster when fed by the continuous nasogastric tube feeding
method compared to intermittent nasogastric tube feeding method (MD 2.0 g/day; 95% CI 0.5 to 3.5; MD 2.0 g/day; 95% CI 0.2 to 3.8, respectively). A trend toward earlier discharge for infants less than

1000 grams birth weight fed by the continuous tube feeding method compared to intermittent nasogastric tube feeding method (MD -11 days; 95% CI -21.8 to -0.2). **Authors' conclusions** Small sample sizes, methodologic limitations, inconsistencies in controlling variables that may affect outcomes, and conflicting results of the studies to datemake it difficult tomake universal recommendations regarding the best tube feedingmethod for premature infants less than 1500 grams. The clinical benefits and risks of continuous versus intermittent nasogastric tube milk feeding cannot be reliably discerned from the limited information available from randomised trials to date. **P L A I N L A N G U A G E S U M M A R Y** There is no difference in time to achieve full feedings in low birth weight premature infants fed milk through a tube into the stomach either on a continuous basis or over 10 to 20 minutes every two to three hours. Premature infants born weighing less than 1500 grams are not able to coordinate sucking, swallowing, and breathing. Feeding into the gastrointestinal tract (enteral feeding) helps with gastrointestinal tract development and growth. Therefore, in addition to feeding through a tube into a vein (parenterally), premature infants may be fed milk through a tube placed either up their nose and into the stomach (nasogastric feeding) or through their mouth and into the stomach (orogastric feeding). Usually a set amount of milk is given over 10 to 20 minutes every two to three hours (intermittent bolus gavage feeding). Some clinicians prefer to feed premature infants continuously. Each feeding method has beneficial effects (e.g., achieve full feedings sooner) but can also have harmful effects (destructive inflammation of the gastrointestinal tract or necrotizing enterocolitis. There was no difference in time to achieve full feedings between feedingmethods regardless of tube placement. Reports of the incidence of destructive inflammation of the gastrointestinal tract (necrotizing enterocolitis) were similar. However, there is not enough evidence to determine the best feeding method for low birth weight premature infants. More research is required in this area.	
Objectives: To assess the clinical benefits and risks of (semi-)continuous versus intermittent nasogastric tube feeding in low birth weight infants. Continuous feeding is thought to improve energy efficiency, duodenal motor function, nutrient absorption and splanchnic oxygenation [*Grant J,1991; Toce SS,1987; de Ville K, 1998; Baker JH,,1997; Dani C,2013*]. However, a substantial portion of the nutrients provided could be lost to the delivery system [*Rogers SP,2010*]. In contrast, bolus feeding may result in a more physiological release pattern of gastrointestinal tract hormones and may stimulate gastrointestinal tract development and enhance protein accretion [*Aynsley-Green A,1989; Shulman RJ, Redel CA,1994; El-Kadi SW,2012*]. However, it may also adversely affect pulmonary function [*Blondheim O,1993*] and be more difficult for the immature gastrointestinal tract to handle ultimately	**13.Intermittent Bolus or Semi-continuous Feeding for Preterm Infants?** Lyanne W. W. Rövekamp-Abels, Jacomine E. Hogewind-Schoonenboom, Daphne P.M. de Wijs-Meijler, Margaux D. Maduro, Marijke C.

resulting in increased feeding intolerance and feeding-related apnoeas. **Methods:** Infants with a birth weight < 1750 grams and GA < 32 weeks were stratified according to birth weight and assigned to either semi-continuous (CON) or intermittent bolus (BOL) feeding. The primary endpoint was days to full enteral feeding (defined as 120 ml/kg/d). The endpoint of 120 ml/kg/d was selected because neonates who reached this amount were discharged from the NICU. We also collected data on feeding tolerance, weight gain, respiratory support and complications (sepsis, NEC and death). **Feeding protocol:** Enteral feeding started on the day of birth according to our MEF regime. Every four hours patients received MEF as a function of their BW—0.5, 1 or 2 ml (for BW 500-749 g, 750-1249 g and 1250-1749 g respectively). They were given their own mother's milk or formula if mother's milk was not available. In the absence of asphyxia or patent ductus arteriosus (PDA) on the day after birth, feeds were started at 24 ml/kg/d. Equal daily increments were given such that under ideal circumstances full volume feeds (120 ml/kg/day / ~100 Kcal/kg/day) were reached in 6 days. The PN was reduced inversely proportional to the increasing amount of feed administered. When 120 ml/kg/d EN was reached, PN was stopped. Slightly adapted standardized feeding regimes were followed in case of asphyxia or in children small for gestational age. In these adapter standardized feeding regime, the SGA infants or infants with PDA required 2 days longer to reach full volume feeds due to a less rapid increase in feed volume. **Ideally, in all studies "full enteral feeding" should be defined as enteral feeding of at least 150 ml/kg/d for at least 72 uninterrupted hours.** **Results:** There was no difference between the two groups (CON n= 121, BOL n=125) in days to reach full enteral feeding—7 (5-10) versus 6 (5-8) days, respectively, with a difference 1 [-0.05 to 2.1]. However, mean daily gastric residual volumes were significantly lower in the BOL group (4.8 versus 3.9 ml/d, difference 0.9 ml/d [0.1 to 1.7]), as was the total number of patients with feeding interruptions (76 versus 59, difference 16% [3% to 28%]). **Conclusions:** Bolus and continuous feeding are equally suitable feeding strategies for preterm neonates. However, intermittent bolus feeding might be preferable.	Jansen-van der Weide, Johannes B. van Goudoever, and Jessie M. Hulst, Netherland, 2015. RCT
	14.Koletzko B, Poindexter B, Uauy R (eds): Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, **2014,** vol 110, pp 201–214 (DOI: 10.1159/000358468

Table 1. Reasonable strategy to optimize enteral feeding practices in ELBW (<1,000 g) and VLBW (1,000–1,499 g) infants

	ELBW	VLBW
Preferred milk	HM*	HM*
First feeding	between 6 and 48 h of life	between 6 and 48 h of life
Initial feeding (MEF)	0.5 ml/kg/h or 1 ml/kg q2h	1 ml/kg/h or 2 ml/kg q2h
Duration of MEF	1–4 days	1–4 days
Feeding advancement	15–25 ml/kg/day	20–30 ml/kg/day
If continuous feeding	+0.5 ml/kg/h q12h	+1 ml/kg q8h
If q2h intermittent feeding	+1 ml/kg q12h	+1 ml/kg q8h
HM fortification	before 100 ml/kg/day	before 100 ml/kg/day
Target energy intakes	110–130 kcal/kg/day	110–130 kcal/kg/day
Target protein intakes	4–4.5 g/kg/day	3.5–4.0 g/kg/day

* Own mother's breast milk or donor HM, but adapted preterm infant formula may also be used if there is no access to HM.

)
Practice of Enteral Nutrition in Very Low Birth Weight and Extremely Low Birth Weight Infants
Thibault Senterre Department of Neonatology, University of Liege, CHU de Liege, CHR de la Citadelle, Liege , Belgium Reviewed by Christoph Fusch, Department of Pediatrics, McMaster University, Hamilton, Ont., Canada; Johannes B. van Goudoever, Department of Pediatrics, Free University Medical Center, Amsterdam, The Netherlands

A working group on feeding guidelines for VLBW infants was constituted in McMaster University, Canada. The group listed a number of important questions that had to be answered with respect to feeding VLBW infants, systematically reviewed the literature, critically appraised the level of evidence, and generated a comprehensive set of guidelines. These guidelines form the basis of this state-of-art review. A multi-disciplinary working group in McMaster University (comprised of staff neonatologists, fellows, nutritionists, nurse practitioners, nurses, lactation consultants, and occupational therapists) conducted a structured literature search, critically appraised the evidence, presented it to a wider group of neonatologists, and came up with practical suggestions to feed VLBWI—the basis for this review. There are some areas where there is limited evidence, and in these areas we have suggested reasonable approaches based on expert consensus.

We have stated the level of evidence (LOE) as per the Centre for Evidence-based Medicine, United Kingdom. The outline of the LOE for therapy trials is as follows:
1a Systematic review (with homogeneity) of randomized controlled trials (RCT)
1b Individual RCT with narrow confidence interval (CI)

15. Guidelines for Feeding Very Low BirthWeight Infants. Review 2015, Canada Sourabh Dutta *, Balpreet Singh, Lorraine Chessell, Jennifer Wilson, Marianne Janes, Kimberley McDonald, Shaneela Shahid, Victoria A. Gardner, Aune Hjartarson, Margaret Purcha, Jennifer Watson, Chris de Boer, Barbara Gaal and Christoph Fusch

2a Systematic review (with homogeneity) of cohort studies
2b Individual cohort studies and low-quality RCTs
3a Systematic review (with homogeneity) of case-control studies
3b Individual case-control studies
4 Case series, poor-quality cohort and poor-quality case-control studies
5 Expert opinion without explicit critical appraisal
If a minus sign is suffixed (e.g., 1a− or 1b−), it denotes either a single study with wide CI or a systematic review with troublesome heterogeneity.

Time to Reach Full Feeds

Suggestion

Aim to reach full enteral feeding (~150–180 mL/kg/day) by about two weeks in babies weighing <1000 g at birth and by about one week in babies weighing 1000–1500 g by implementing evidence-based feeding protocols. It may be noted that some babies, especially those less than 1000 grams, will not tolerate larger volumes of feedings (such as 180 mL/kg/day or more) and thus may need individualization.

Rationale

Reaching full enteral feeding faster results in earlier removal of vascular catheters, and less sepsis and other catheter-related complications (LOE 2b). Standardized feeding protocols improve outcomes in VLBWI. Reaching full feeds within a week is achievable—in an RCT on VLBWI, the median time to reach 170 mL/kg/day was 7 days after fast advancement of enteral feeding, with no increase in apneas, feed interruptions, and intolerance.

Frequency of Feeds

Suggestion

Administer three-hourly feeds for babies weighing >1250 g. There is not enough evidence to choose between two-hourly *versus* three-hourly feeds for babies weighing ≤1250 g.

Rationale

In an RCT, 92 neonates weighing <1750 g were allocated to either three- or two-hourly feeds [7]. The incidence of feed intolerance, apnea, hypoglycemia, and necrotizing enterocolitis (NEC) did not significantly differ, and nursing time spent on feeding was significantly less in the three-hourly group (LOE 2b).

Two retrospective studies on this issue were contradictory. In one that compared 2-h and 3-h enteral feeding in ELBW babies, the time to full enteral feeding, enteral morbidity, hospital stay, and growth parameters were similar in the two groups (LOE 4) [8]. In another, VLBWI (mean birth weight ~1200 g) fed twice hourly reached full feeds faster, received less prolonged TPN, and were less likely to have feeds held, compared to those fed three times hourly (LOE 4) [9].

Putting this limited information together, we propose that babies weighing ≥1250 g be fed three times hourly and those weighing <1250 g preferably twice hourly.

Trophic Feeds: Time of Starting, Volume, Duration

Suggestion

Trophic feeds are defined as minimal volumes of milk feeds (10–15

mL/kg/day). Start trophic feeds preferably within 24 h of life. Exercise caution in extremely preterm, extremely low birth weight (ELBW), or growth-restricted infants. If, by 24–48 h, no maternal or donor milk is available, consider formula milk. There is not enough evidence to recommend the maximum duration of trophic feeding before starting nutritional feeds.

Rationale

In a systematic review (nine trials, 754 VLBWI), the actual volume of trophic feeds ranged from 10 to 25 mL/kg/day; and onset from day one of life onwards. Early introduction of trophic feeds compared to fasting had a non-significant trend towards reaching full feeds earlier (mean difference − 1.05 days (95% CI −2.61, 0.51)) and no difference in NEC (LOE 1a−). More data is required before one can generalize these findings to extremely preterm, ELBW, or growth-restricted infants.

There was no subgroup analysis on formula milk. Among the included studies, there were two studies in which trophic feeding was provided exclusively by preterm formula (LOE 1b−). In both, the trophic feeding group had less feeding intolerance and reached full feeds faster without

increase in NEC. Hence, formula milk may be used after exhausting other options. We suggest a reasonable waiting period of 24–48 h for obtaining maternal or donor milk.

In a systematic review (seven trials, 964 VLBWI) on timing of introduction of nutritional enteral feeding to prevent NEC, early introduction of progressive enteral feeding (1 to 2 days of age) did not increase the risk of NEC (typical relative risk (RR) 0.92 (95% CI 0.64, 1.34)), mortality (typical RR 1.26 (95% CI 0.78, 2.01)), or feed intolerance (LOE 1a). We converted this into a practical suggestion of the maximum number of days for trophic feeding before introducing progressive enteral feeding.

Contraindications for Trophic Feeds

Suggestion

Withhold trophic feeds in intestinal obstruction or a setting for intestinal obstruction or ileus.

Asphyxia, respiratory distress, sepsis, hypotension, glucose disturbances, ventilation, and umbilical lines are not contraindications for trophic feeds.

Rationale

The studies included in a Cochrane review included VLBWI with asphyxia, respiratory distress, sepsis, hypotension, glucose disturbances, ventilation, and umbilical lines, without any excess adverse effects being reported (LOE 1a−).

Nutritional Feeds: Day of Starting, Volume, Frequency, Increase

Suggestion

In babies weighing <1 kg at birth, start nutritional feeds at 15–20 mL/kg/day and increase by 15–20 mL/kg/day. If the feeds are tolerated for around 2–3 days, consider increasing faster. For babies weighing ≥1 kg at birth, start nutritional feeds at 30 mL/kg/day and increase by 30 mL/kg/day.

Rationale A Cochrane review (four RCTs, 588 subjects) compared slow daily increments (ranging from 15 to 20 mL/kg/day) *versus* fast daily increments of enteral feeding volume (ranging from 30 to 35 mL/kg/day) (LOE 1a). Fast increment did not increase the risk of NEC (pooled RR 0.97 (95% CI 0.54, 1.74)), mortality (pooled RR 1.41 (95% CI 0.81, 2.74)), or interruption of feeds (pooled RR 1.29 (95% CI 0.90, 1.85)). The trials individually reported that the fast daily increment group regained birth weight and reached full feeds faster (LOE 1b and 2b). As there was no subgroup analysis of ELBW babies, we suggest starting with a lower feed volume in ELBW babies—as in the control arm (15–20 mL/kg/day)—until more studies are available. **Type of Milk for Starting Feeds** *Suggestion* The first choice is own mother's expressed breast milk or colostrum. This should preferably be fresh; if not, provide previously frozen milk in the same sequence in which it was expressed. Second choice: donor human milk. Third choice: preterm formula. *Rationale* Freshly expressed human milk has numerous benefits for preterm babies. Although there is no direct evidence comparing fresh *versus* frozen mother's milk, the use of fresh milk makes sense because of the depletion of commensals, immune cells, immune factors, and enzyme activity that occurs with freezing. Neonates who receive an exclusively human milk-based diet (mother's milk or donor human milk with human milk-based fortifier) have significantly lower rates of NEC compared to those who receive preterm formula or human milk with a bovine milk-based fortifier (LOE 1b). In another RCT, preterm infants who received an exclusively human milk diet (donor human milk and human milk-based human milk fortifier) had a lower incidence of NEC (21% *versus* 3%, $p = 0.08$) and surgical NEC ($p = 0.04$) compared to infants who received bovine milk-based preterm formula. The use of donor human milk (while continuing bovine milk-based fortifier) *versus* preterm formula as a substitute for mother's own milk does not reduce the rates of NEC. The prohibitively high cost of human milk-based human milk fortifier is often quoted as an obstacle to using an exclusively human milk diet; however, a cost-effectiveness analysis showed that use of exclusively human milk-based products resulted in shorter duration of hospitalization (less by an average of 3.9 days in neonatal intensive care unit (NICU)) and savings of $8167 per extremely premature infant ($p < 0.0001$) because of the reduction in NEC. **Feeding Small for Gestational Age (SGA) Babies with/without History of Absent/Reversed End Diastolic Umbilical Flow (AREDF)** *Suggestion* If the abdominal examination is normal, start feeding within 24 h of life, but advance slowly with volumes at the lowest end of the range. Advance feeds extremely slowly in the first 10 days among preterm	

SGA babies with gestation <29 weeks and AREDF. Make every effort to feed human milk, especially in SGA babies with AREDF and gestation <29 weeks.

Rationale

Mihatsch *et al*.fed 124 VLBWI (35 had intra-uterine growth retardation (IUGR)) with a standardized protocol (LOE 2b). There was no statistical difference in the age to reach full feeds in the IUGR and non-IUGR groups ($p = 0.6$). In a multiple regression model, increased umbilical artery resistance, brain sparing, Apgar scores, umbilical artery pH, and IUGR did not predict the age to reach full feeds. In an RCT on SGA preterm babies (gestation of 27–34 weeks) who had abnormal antenatal umbilical Doppler flows, the incidence of NEC and feeding intolerance was not significantly different ($p = 0.35$ and $p = 0.53$, respectively) between the early feeders ($n = 42$; median age 2 days) and delayed feeders ($n = 42$; 7 days) (LOE 2b).

In an RCT on preterm SGA infants, comparing minimal enteral feeding and no enteral feeding for five days, there was no difference in the rate of NEC ($p = 0.76$) and there was a trend towards shorter NICU stay in the enteral feeding group ($p = 0.2$) (LOE 2b).

In the Abnormal Doppler Enteral Prescription Trial (ADEPT) RCT, 402 preterm SGA infants (<35 weeks gestation, birth weight < 10th centile) with absent or reversed end diastolic umbilical blood flow and cerebral redistribution were allocated to early or late onset of enteral feeding (Day 2 or 6, respectively) (LOE 1b).The early feeding group reached full enteral feeds faster than the late feeding group (median (IQR) days: 18 (15–24) *versus* 21 (19–27), respectively; $p = 0.003$). There was no difference in the incidence of all-stage NEC (18% *versus* 15%, respectively; $p = 0.42$) and stage II–III NEC. Infants in the early feeding group had a significantly shorter duration of total parenteral nutrition (median difference 3 days, $p < 0.001$), a shorter duration of high dependency care ($p = 0.002$), and a lower incidence of cholestasis ($p = 0.02$). Eighty-six (21%) infants in this trial were below 29 weeks of gestation. The statistical test of interaction between treatment group and gestational age group (<29 weeks *versus* ≥29 weeks) was non-significant for age to reach full feeds ($p = 0.38$) and incidence of all stage NEC ($p = 0.47$), suggesting that the treatment effect was consistent across subgroups. The investigators published additional analysis from the ADEPT trial comparing infants of <29 weeks and ≥29 weeks of gestation. The former group took significantly longer to reach full feeds compared to the latter (median age 28 days (Inter-quartile range (IQR) 22–40) *versus* 19 days (IQR 17–23), respectively; hazard ratio 0.35 (95% CI 0.3, 0.5)) and had a significantly higher incidence of NEC (39% *versus* 10%, respectively; RR 3.7 (95% CI 2.4, 5.7)). Infants <29 weeks in this trial tolerated very little milk in the first 10 days. Exclusive human milk feeding was the only protective factor.

Feeding Babies on Non-Invasive Ventilation

Suggestion

Increase feeds cautiously. Do not rely on abdominal distension as a sign of feeding intolerance, especially in babies weighing <1000 g.

Rationale
Non-invasive ventilation can cause abdominal distension, and nasal continuous positive airway pressure (nCPAP) decreases pre-and post-prandial intestinal blood flow in preterm infants (LOE 4). Jaile *et al*.compared 25 premature infants on nCPAP with 29 premature infants not on CPAP (LOE 2b). Gaseous bowel distension due to CPAP developed in 83% of infants below 1000 g *versus* 14% of those weighing ≥1000 g. No cases of NEC were reported in the study; however, the sample size was too small to draw conclusions about NEC.

Feeding Babies with Systemic Arterial Hypotension

Suggestion
There is not enough evidence to make a suggestion.

Rationale
There is no published literature on feeding policies during systemic arterial hypotension.

Feeding Babies on Indomethacin or Ibuprofen

Suggestion
If the neonate is already on minimal feeds, continue to give trophic feeds until the indomethacin course finishes. If the neonate is fasting, introduce trophic feeds with human milk as per Section 3.
While there are no RCTs comparing feeding during indomethacin therapy *versus* ibuprofen, indirect evidence suggests ibuprofen may be the safer of the two.

Rationale
In the Ductus Arteriosus Feed or Fast with Indomethacin or Ibuprofen (DAFFII) trial, 117 infants (26.3 ± 1.9 weeks) who were on ≤60 mL/kg/day feeds and required treatment for patent ductus arteriosus (PDA) (75% to 80% received indomethacin) were randomized at 6.5 ± 3.9 days to receive trophic feeds or no feeds during the drug administration period [27]. Infants randomized to the trophic feeding subsequently required fewer days to reach 120 mL/kg/day (10.3 ± 6.6 days *vs*. 13.1 ± 7.8 days, $p < 0.05$). There is one retrospective study on 64 preterm infants (<29 weeks of gestation), half of whom had received indomethacin for PDA (LOE 4). There were no differences between the groups regarding feeding volumes, NEC incidence, or gastric residuals up to Day 7.
Ibuprofen is safer than indomethacin as it does not reduce mesenteric blood flow. In a meta-analysis of 19 studies (956 infants), NEC rates were lower in the Ibuprofen group (typical RR 0.68 (95% CI 0.47, 0.99)) (LOE 1a).

Assessment of Feed Tolerance

Suggestion
Do not check gastric residuals routinely. Check pre-feed gastric residual volume (GRV) only after a minimum feed volume (per feed) is attained. We suggest the following thresholds: <500 g: 2 mL, 500–749 g: 3 mL, 750–1000 g: 4 mL, >1000 g: 5 mL.
Do not check abdominal girth routinely.
Isolated green or yellow residuals are unimportant. Vomiting bile may indicate an intestinal obstruction or ileus. Withhold feeds in case of

hemorrhagic residuals, as hemorrhagic residuals are significant. If the problem of residual volumes persists despite slow bolus feeds, consider decreasing the feed volume to the last well-tolerated feed volume. Use the smallest volume syringe for checking residuals. Take care to aspirate gently. After a feed, nurse the baby in the prone position for half an hour. *Rationale* The rationale for 5 mL/kg is covered in Section 11. The criterion of 50% is a round figure approximately equal to the cutoff from the study by Cobb *et al*. Pushing back partially digested gastric aspirates may replenish acid and enzymes that aid in the digestive process. There is a paucity of data regarding the role of slow bolus feeding. In a physiologic study on pre-terms comparing a 120-min infusion of feeds compared to bolus feeds, the former was associated with faster gastric emptying, lower GRV, and more frequent duodenal motor responses (LOE 2b). Whether these theoretical advantages of slow bolus translate into clinical benefits is unclear, but there is a physiological basis for trying. In a Cochrane meta-analysis comparing continuous nasogastric *versus* intermittent bolus feeding in VLBWI, the continuous method resulted in a longer time to reach full enteral feeding (weighted mean difference (WMD) 3 days (95% CI 0.7, 5.2)), with no difference in growth or incidence of NEC (LOE 1a−). The narrower the diameter of the syringe, the less pressure is applied while pulling (as opposed to pushing) (LOE 4). Hence, smaller volume syringes are preferred. In an RCT, the decrease in the volume of gastric residuals was lower in the prone position than in supine, and the rate of decrease of gastric residual volume was highest in the first half hour after the feed.	
Synopsis - Necrotizing enterocolitis (NEC) is a multifactorial disorder that primarily affects premature infants. Human milk as compared to formula reduces the incidence of NEC. - Feeding practices such as minimal enteral nutrition (versus complete fasting) before progressive advancement of feeds, early introduction of feeds (before day 4 of life as compared to later), and a more rapid advancement of feeds (30–35 ml/kg/day as compared to 15–20 ml/kg/day) do not increase the incidence of NEC in preterm infants. - There is no evidence supporting continuous over intermittent tube feedings in preterm infants. - In a feed-intolerant preterm infant without any other clinical and radiological evidence of NEC, minimal enteral nutrition rather than complete suspension of enteral feeding may be an alternative. - Human milk-based fortifier as compared to bovine-based fortifier may reduce the incidence of NEC but additional studies are required. -The evidence is convincing that human milk feeding, as compared to formula feeding, reduces the incidence of NEC in preterm infants	**16. Feeding Practices and NEC** Manimaran Ramani, MD [Assistant Professor] and Namasivayam Ambalavanan, MD [Professor] Birmingham, UK, 2013

(LOE I – recommendation grade A) -Minimal enteral nutrition is a safe alternative to complete fasting before initiation of progressive feedings and does not increase the incidence of NEC in extremely preterm infants. In clinically stable VLBW infants, early introduction of progressive feeds and advancement of feeds at a faster rate (30–35ml/kg/day) is safe and does not increase the incidence of NEC (LOE I - recommendation grade B) -Based on the existing evidence, early advancements of feeding is safe and may be considered as an alternative to minimal enteral nutrition soon after birth in a clinically stable VLBW infant (LOE I – B). -Evidence indicates that both slow (15–20 ml/kg/day) and fast (30–35 ml/kg/day) advancement practices are safe and can be used in the preterm infants (especially larger VLBW infants) while advancing minimal enteral nutrition to full feeds. Randomized controlled trials are needed to determine the effect of slow versus fast feeding advancement on longer-term clinical outcomes of preterm infants and on the incidence of NEC and mortality in the subset of smaller ELBW infants (<750g) (LOE I – B). -Even though intermittent feeding may have some physiological advantages compared to continuous feeding, there is not enough evidence to recommend intermittent feeding over continuous feeding for reducing the risk of NEC, mortality or morbidity in preterm infants (LOE I - B). -In a feed-intolerant preterm infant without any other clinical and radiological evidence of NEC, minimal enteral nutrition rather than complete suspension of enteral feeding may be an alternatiive (LOE II-2 – I expert opinion). -Human milk-based fortifier as compared to bovine-based fortifier may reduce the incidence of NEC but additional studies are required (LOE I – B).	
Necrotizing Enterocolitis (NEC) Three systematic reviews (Boyd CA, 2007; Quigley MA, 2007; McGuire W, 2003) addressed specifically the effect of DHM versus formula on clinical outcomes. All of these reviews suggest that the use of DHM has a protective effect against NEC in premature infants. A meta-analysis of data from 5 trials demonstrated a significantly higher incidence of NEC in formula-fed infants (typical relative risk 2.5, with 95% confidence interval [CI] 1.2–5.1). The observed effect sizes were similar across 5 studies, and there was no statistical evidence of heterogeneity. The pooled estimate suggests that 1 extra case of NEC will occur in every 33 infants who receive formula milk. The systematic review and meta-analysis of Boyd et al in 2007 and an earlier systematic review and meta-analysis by McGuire et al in 2003 came to similar conclusions. There are limited data on the comparison of feeding with fortified DHM versus PF. Because fortification of HM is the present practice for preterm and particularly for VLBW infants, future studies should compare the effect of feeding with fortified DHM versus formula on the NEC incidence.	**17. Donor Human Milk for Preterm Infants: Current Evidence and Research Directions 2013** Sertac Arslanoglu, Willemijn Corpeleijn, Guido Moro, Christian Braegger, Cristina Campoy, Virginie Colomb, Tamas Decsi, Magnus Domellöf, Mary Fewtrell, Iva Hojsak, Walter Mihatsch, Christian Mølgaard, Raanan

	Shamir, Dominique Turck, and Johannes van Goudoever, ESPGHAN Committee on Nutrition.
Background: Necrotizing enterocolitis (NEC) is one of the most devastating diseases in the neonatal population, with extremely low birth weight and extremely preterm infants at greatest risk. **Method:** A systematic review of the best available evidence to answer a series of questions regarding nutrition support of neonates at risk of NEC was undertaken and evaluated using concepts adopted from the Grading of Recommendations, Assessment, Development and Evaluation working group. A consensus process was used to develop the clinical guideline recommendations prior to external and internal review and approval by the A.S.P.E.N. Board of Directors. **Results/Conclusions:** (1) When and how should feeds be started in infants at high risk for NEC? We suggest that minimal enteral nutrition be initiated within the first 2 days of life and advanced by 30 mL/kg/d in infants ≥1000g. (Weak) (2) Does the provision of mother's milk reduce the risk of developing NEC? We suggest the exclusive use of mother's milk rather than bovine-based products or formula in infants at risk for NEC.(Weak) (3) Do probiotics reduce the risk of developing NEC? There are insufficient data to recommend the use of probiotics in infants at risk for NEC. (Further research needed.) (4) Do nutrients either prevent or predispose to the development of NEC? We do not recommend glutamine supplementation for infants at risk for NEC (Strong). There is insufficient evidence to recommend arginine and/or long chain polyunsaturated fatty acid supplementation for infants at risk for NEC. (Further research needed.) (5) When should feeds be reintroduced to infants with NEC? There are insufficient data to make a recommendation regarding time to reintroduce feedings to infants after NEC. (Further research needed.) (*JPEN J Parenter Enteral Nutr*. 2012;36:506-523)	**18. A.S.P.E.N. Clinical Guidelines 2012: Nutrition Support of Neonatal Patients at Risk for Necrotizing Enterocolitis** Erica M. Fallon, MD; Deepika Nehra, MD; Alexis K. Potemkin, RN, BSN; Kathleen M. Gura, PharmD, BCNSP; Edwin Simpser, MD; Charlene Compher, PhD, RD, CNSC, LDN, FADA; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors; and Mark Puder, MD, PhD Journal of Parenteral and Enteral Nutrition Volume 36 Number 5 September **2012**
Comparison of hospital direct costs with and without specific morbidities in 2009 US$. BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis:	**19.Economic Benefits and Costs of Human Milk Feedings: A Strategy to Reduce the Risk of Prematurity-Related Morbidities in Very-Low-Birth-Weight**

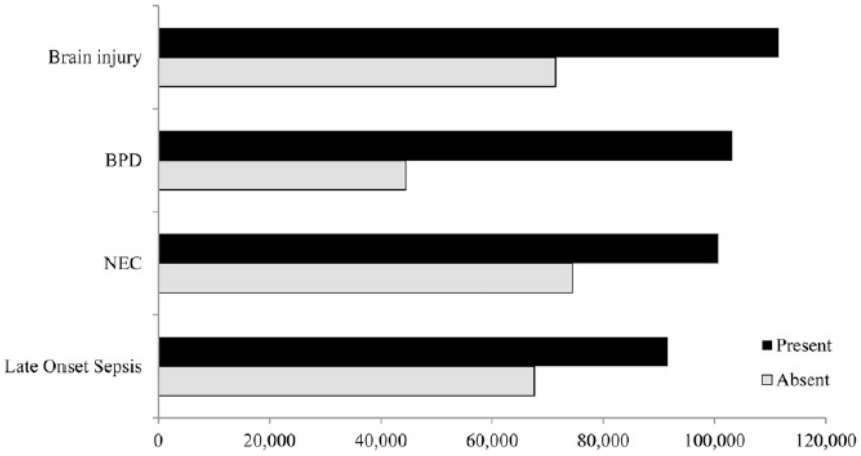


TABLE 1 Comparison of costs of preventable morbidities in VLBW infants[1]

Morbidity and authors	Type of costs	BW or GA	Cost as reported by authors	Year of costs	Cost inflated to 2011 US$
Brain injury					
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$12,045	2009	$13,305
BPD					
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$31,565	2009	$34,868
Late-onset sepsis					
Payne et al. (6)	Unadjusted costs	VLBW (401–1500 g)	$54,539 ($104,473 vs. $49,934)	1999	$90,316
Payne et al. (6)	Adjusted incremental cost	VLBW (401–1500 g)	$5,875, BW 401–750 g	1999	$9729
			$12,480, BW 751–1000 g		$20,667
			$9,583, BW 1001–1250 g		$15,869
			$6,276, BW 1251–1500 g		$10,393
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$10,055	2009	$11,107
NEC					
Medically managed only					
Bisquera et al. (7)	Unadjusted charges	VLBW (<1500 g)	$73,700	1992–1994	$144,910
Ganapathy et al. (7)	Adjusted incremental cost	≤28 wk GA	$74,004	2011	$76,716
Surgically managed only					
Bisquera et al. (7)	Unadjusted charges	VLBW (<1500 g)	$186,200	1992–1994	$366,110
Ganapathy et al. (8)	Adjusted incremental cost	≤28 wk GA	$198,040	2011	$205,299
Medically and surgically managed					
Johnson et al. (2)	Adjusted incremental cost	VLBW (<1500 g)	$15,440	2009	$17,056

[1] Costs inflated to 2011 US$ using the Consumer Price Index for medical care (9). BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; NEC, necrotizing enterocolitis; VLBW, very low birth weight.

TABLE 2 Impact of human milk on costs of preventable morbidities in VLBW infants[1]

Authors	Type of costs	BW	Morbidity	Cost savings of HM	Year of costs
Ganapathy et al. (8)	Incremental cost due to reduction in NEC: HM bovine	≤1250 g	NEC	Bovine milk associated with $8167 higher cost than HM	2011
Patel et al. (13)	Incremental cost, after controlling for sepsis: <25, 25–49.99, and ≥50 mL · kg^{-1} · d^{-1}	<1500 g	Sepsis	<25 mL · kg^{-1} · d^{-1} HM had $31,514 higher cost than ≥50 mL · kg^{-1} · d^{-1} HM and $20,384 higher cost than 25–49.99 mL · kg^{-1} · d^{-1} HM	2010

[1] BW, birth weight; HM, human milk; NEC, necrotizing enterocolitis.

To ensure adequate milk supply, NICUs need to supply at least 3 universal resources: hospital-grade breast pumps, breast pump collection kits, and disposable foodgrade storage containers. Jegier et al. 2013 demonstrated
that the cost to the institution to acquire 100 mL/d of human milk from the infant's mother is relatively low when the institution provides the mother with a hospital-grade electric breast pump collection kit and storage containers for the milk. Further, the downstream direct and indirect cost savings from the human milk feedings are likely to far exceed the hospital's costs to acquire human milk in most cases.
Our study team has conducted 2 studies to evaluate the maternal and institutional costs of providing human milk to VLBWinfants during the NICU stay. In a study of the maternal costs that included the breast pump rental, pump kit, and maternal opportunity cost, Jegier et al. 2010 found that the mean cost of providing 100 mL human milk

Tricia J. Johnson, Aloka L. Patel, Harold R. Bigger, Janet L. Engstrom, Paula P. Meier

ranged from $2.60 to $6.18 (in 2008 US$). The largest komponent of costs was maternal opportunity cost; however, this cost decreased over time as mothers became more efficient at pumping. In evaluating the institution's cost to acquire 100 mL of human milk from the biologic mother for different eoses and exposure periods, Jegier et al. 2010 demonstrated that the median cost to the institution ranged from $7.93/100 mL (in 2012 US$) for mothers who produced <100 mL/d of human milk to $0.51/100 mL for mothers who provided >700 mL/d. These data included the institution's cost of hospital-grade electric breast pumps, breast pump collection kits, and disposable food-grade storage containers. Additionally, the median cost for institutions to acquire human milk was substantially lower than donor human milk (cost per 100 mL = $14.84) after ~7 d of pumping and commercial formula (cost per 100 mL = $3.18) arter 19 d of pumping for all volumes of human milk pumped, except when <100 mL human milk was pumped per day. In fact, the institution's cost was less than donor human milk after 4 d of pumping and commercial formula after 10 d of pumping for women who pumped $400 mL/d of human milk.	

Ravijuhiste viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Grade of Recommendation: A. There is good research-based evidence to support the quideline (prospective, randomized trials). B. There is fair research-based evidence to support the quideline (well Designer studies without randomization). C. The quideline is based on expert opinion and editorial consensus. **Practice Recommendations** **Special Considerationd for Preterm Infant:** 1. For premature infants weighing < 1500 g and at risk for necrotizing enterocolitis (NEC), it is recommended that mothers be encouraged to supply breast milk for their infants (A). 2. Extremely low – birth weight (ELBW) and very low-birth weight (VLBW) infants may benefit from minimal enteral feeding starting slowly at 0,5-1,0 ml/kg/day to 20 ml/kg/day (B). 3. Advance nutritive feedings for VLBW and ELBW infants by a rate of 10-20 ml/kg/day (C).	**Enteral Nutrition administration. In A.S.P.E.N. enteral nutrition practice recommendations. Guideline summary NGC-7287.** Bibliographic Sourse(s): Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, Lyman B, Metheny NA, Mueller C, Robbins S, Wessel J. JPEN J Parenter. Enter. Nutr. **2009** Mar-Apr;33(2):149-58 (88 references).
Extremely premature infants often have an inadequate nutritional intake and demonstrate inhibited postnatal growth, which can be explained	**Care of extremely premature infants**

partly by undernutrition [*Stoltz Sjoström et al,2013*]. The children are unique when it comes to the need for nutrition and the nutrition during the first months of life plays a major role. In order to achieve normal growth and development, premature children ought to grow in accordance with the curve for normal foetal growth [*Niklasson, A et al,2008*]. Foetal growth is much faster than that of the newborn, which leads to extremely premature infants needing more nutrition than full-term children. A child who is born after 24 full weeks of pregnancy have passed and weighs around 700 g, for example, is expected to increase its body weight by five times over the next 3 ½ months of care in neonatal unit. The nutrition must not only result in normal growth, i.e. weight, height, head circumference and body composition, but also in normal growth and maturation of all organ systems.

The giving of breast milk should

be the first choice for enteral nutrition
be enriched on an individual basis to optimise the nutrition
be encouraged in the form of nursing following discharge.

If possible, the child ought to be given drops of its mother's colostrum or breast milk by mouth because it gives protection against infection and positively stimulates the sense of taste [*Hanson LA et al 2009]*. Breast milk is superior as nutrition for extremely premature infants, partly because it reduces the risk of developing necrotising enterocolitis (inflammation of the bowel). If the mother does not have her own milk, bank milk (donor milk) is the best alternative (following the parents' consent) [*Arslanoglu, S et al 2013*]. In order for the nutritional intake via breast milk to be sufficient, the milk needs to be analysed and almost always fortified [*Cuschel CA, 2004; De Halleux V, 2013*].

The enteral nutrition is escalated with the aim of achieving full enteral nutrition within 14 days of the birth.

Recommended nutritional intake:

Nutrient (kg/d)[a]	Day 0[b]	Day 4[c]	EN full dose[d]	TPN full dose[e]
Liquid (ml)	80-100	130-160	135-200	135-180
Energy (kcal)	50-60	105-125	115-135	90-115
Protein/aa (g)	2-2.4	3.5-4.5	4.0-4.5	3.5-4
Carbohydrates (g)	7-10	11-16	9-15	13-17
Glucose (mg/kg/min)	5-7	-	-	9-12
Fat (g)	1.0-1.5	4-6	5-8	3(-4)
DHA (mg)	-	-	12-60	11-60
Arachidonic acid (mg)	-	-	18-45	14-45
Na (mmol)	0-1	2-4	3-7	3-7
P (mmol)	0-1	1.0-2.5	2-3	2-3

Cl (mmol)	0-1	2-4	3-7	3-7
Ca (mmol)	0.5-1.5	2.2-2.7	3.0-3.5	1.5-2
P (mmol)	0.5-1.5	1.7-2.5	2-3	1.5-1,9
Mg (mg)	0-4	6-11	8-15	4,3-7,2
Fe (mg)	-	0	2-3	0,1-0.2
Zn (mg)	-	1-1.5	1.5-2.5	0.4-0.45
Cu (Mg)	-	70-110	120-200	20-25
Se (Mg)	-	2-5	2-7	2-5
Mn (Mg)	-	0-4	1.0-7.5	0-1
I (Mg)	-	10-30	10-50	10
Vit A (RE) (IE)	-	1 000-2 300	1 300-3 300	700-1 500
Vit D (IE)	-	220-600	400-1 000	40-160
Vit E (TE) (mg)	-	2.2-7	2.2-11	2.8-3.5
Vit K (Mg)	-	4.4-20	4.4-28	4.4-16
Vit C (mg)	-	13-35	11-46	15-25
Thiamine B1 (Mg)	-	140-300	140-300	200-350
Riboflavin B2 (Mg)	-	150-300	200-400	150-200
Pyridoxine B6 (Mg)	-	45-250	45-300	150-200
Niacin (NE) (mg)	-	0.4-7,0	0.4-5,5	4-7
Pantethine (mg)	-	0.3-2,0	0.3-2,1	1-2
Biotin (Mg)	-	1.7-12,0	1.7-16,5	5-8
Folate (Mg)	-	35-90	35-100	35-80
Vit B12 (Mg)	-	0.1-0.6	0.1-0/77	0.1-0.5

[a] Per kilo body weight and day for all units. The relevant weight is used for body weight except for the first few days when the birth weight is used until it has been achieved and passed.

[b] Here, day 0 is defined as the date of the birth, i.e. from the birth until the morning of the next day. The recommendation applies to a full day and needs to be individually adjusted down depending on the time when the child is born

[c] The child ought to be given a full dose of nutrition at least as of the fourth day of life (but still with some fluid restriction). The recommendation in this column is approximate and is based on 50 per cent enteral and 50 per cent parenteral nutrition. The exacta targets (which must be individually calculated) depend on the proportions of the parenteral supply of the nutrient in question, so the target will be slightly lower than stated if the
child receives a greater share of parenteral nutrition for example.

[d] Recommended intake for full enteral nutrition (EN).

[e] Recommended intake for total parenteral nutrition (TPN).

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#11	Add	Search **infant formula**	10735	03:18:18
#10	Add	Search **donor milk**	724	03:17:17
#9	Add	Search **breast milk**	34313	03:16:48
#8	Add	Search **human milk**	27873	03:16:33
#6	Add	Search **breastmilk**	757	03:15:25
#5	Add	Search **breastfeeding**	38635	03:14:42
#4	Add	Search **early enteral nutrition**	3006	03:14:10
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